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Review Article

Cleanroom Technology and Its Application in Pharmaceutical Production

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Abstract: The cleanroom is a contemporary invention. Although the design and administration of clean rooms has its origins in hospital infection control and dates back more than a century, modern civilisation requires a clean environment for industrial processes. A cleanroom is an environment with low levels of airborne microbes, dust, aerosol particles, and chemical vapours that is commonly used in manufacturing, including pharmaceutical products, scientific research, and aerospace semiconductor engineering applications. Cleanrooms are used in many different industries, such as microelectronics, nanotechnology, defence, pharmaceuticals, and biotechnology. Modern approaches to cleanroom technology design can help to minimise the contamination risks. More precisely, a cleanroom has a controlled level of contamination that is specified by the number of particles per cubic meter at specified particle size. Cleanrooms are necessary because people, production machinery, and the building struck generate contamination. As this article has demonstrated, these methods include using GMP validation phases to ensure rigorous testing, adhering to quality risk management to identify contamination sources, and applying computer-aided design techniques like computational fluid dynamics, which enable the use of predictive models to help identify contamination sources related to undesired air movement. Consequently, cleanroom technology is a preferred processing method that lowers the microbial burden and produces safe, high-quality final goods. The fundamentals of clean room technology and its use in the manufacturing of pharmaceuticals are covered in this overview.

Keywords: Cleanroom, Technology, Particles, Contamination, Airborne.

INTRODUCTION

Growth and globalisation have emerged as crucial terms in the current industrial development environment. The food, cosmetic, and pharmaceutical sectors are also impacted by a number of strict regulations. The type of product made and the countries to which it is intended for export determine these standards. As a result, the maker must adhere to FDA, GMP, or WHO standards. The design parameters needed for a certain clean room are determined by the production standards for that product [1]. These days, a wide range of businesses, including the defence sector, biotechnology, microelectronics, pharmaceuticals, and nanotechnology, employ cleanrooms. Cleanrooms can range in size from little to intricate multistory buildings with a lot of utilities and maintained equipment.

A cleanroom's primary purpose is to prevent contamination of the created product. The safety of the final product is crucial to the manufacturer's financial sustainability in the pharmaceutical industry. Therefore, it is necessary to identify a possible source of contamination, which may be the actual workplace. The development of new advanced technologies in several areas of human activity has raised the requirements for the quality of supply air. Temperature, humidity, pressure, and cleanliness are the primary operating parameters that define air quality. Conditions are taken into consideration while selecting settings to support each unique technical procedure. Both the maximum allowable number of viable microorganisms per unit of air capacity and the concentration of suspension particles per unit of air capacity are maximum criteria for air quality [2].

Cleanroom

A cleanroom is a specifically constructed space where a high fresh air rate and thorough filtration are used to limit the concentration of airborne contaminants. Additionally, cleanrooms are designed and operated to reduce the amount of particles that are introduced,

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produced, and retained within the space [3]. Thus, cleanrooms may be thought of as much regulated spaces where the air quality is tracked to guarantee that the cleanliness requirements needed for the production of medical, electrical, and pharmaceutical products are upheld. Other crucial elements like humidity, temperature, and pressure are also managed in the cleanroom.

There must be regulations governing the room's air quality. ISO 14644 is the most widely used standard. In terms of airborne particle levels in cleanrooms and clean zones, it is a document that defines standard classifications of air cleanliness. "A room where the concentration of airborne particles is controlled, where other pertinent parameters, such as temperature, humidity, and pressure, are controlled as needed, and where the room is designed and utilised to minimise the introduction, generation, and retention of particles inside the room" [4].

Importance of Cleanroom

An office building's air, which is conditioned for comfortable human occupation, still contains particles between 15 and 35 million particles per cubic metre. A particle 200 times smaller than a human hair can cause major damage to sensitive equipment. Aside from cleanrooms, it is impossible to create structures and devices that can resist the entry of dust particles. A single oversize particle settling at a critical point of a circuit board can cause the entire board to fail.

The lack of microbiological particles in the air, which might come into touch with goods at crucial stages of processing, is associated with air quality. One of the most crucial elements in ensuring that customers receive a safe product is air quality. Cleanroom technology is the greatest approach to ensure that the risks of air pollution are kept to a minimum. The need for cleanroom technology has grown over the past 20 years, especially in the pharmaceutical and electronics sectors. This technology's primary goal is to rid the air of dust, particles, and microorganisms. Cleanroom technology, particularly those methods intended to limit microbiological contamination, is being evaluated as a result of growing customer demand for better product quality and longer shelf life. New construction, processing, and packaging technologies combined with cleanroom technology provide safe and high-quality products.

The most significant pollutant in the cleanroom is often humans who work in or enter the room or processing area. Therefore, knowing how many individuals are entering and working in the clean room is crucial. The amount of air needed to dilute and eliminate the airborne dispersion of contaminants from workers' bodies will be directly impacted by this. Air quantity, cooling load, and contaminant dispersion are all directly impacted by clothing. Because there is less air interaction through the fabric of garments, it is particularly good at avoiding dispersion. Lowering the cleanroom's temperature is necessary since excessive temperatures can make employees uncomfortable. The standard cleanroom temperature is 20°C with a relative humidity of 40% ± 5%; however, for materials that are sensitive to moisture, the RH must be lowered to 25% ± 5%. Geographical location, manufacturing, and attire all affect these levels. As a result, dry bulb temperatures might vary between 18 and 22°C [5].

Cleanroom Technology

The technique that guarantees the control of microorganisms and particles in the numerous delicate pharmaceutical industry procedures is known as cleanroom technology. When microbiological inactivation via deep freezing or heat sterilisation is not practical, this approach should be taken into account. When a product needs a lengthy shelf life, cleanroom technology is utilised instead of preservatives. It's the economical technology. It needs to be included into the entire operation's sanitary chain, which always breaks at the weakest point.

Packaging is a crucial step in aseptic procedures; adopting cleanroom technology can reduce the chance of recontaminating the sterile product at this point. Highly filtered air, suitable airflow patterns and velocity, and enclosures dividing the cleanroom space from the outside environment are all components of classic cleanroom technology. Employees must dress appropriately for the cleanroom. The cleanroom area's surfaces and equipment should be cleaned according to approved protocols. The use of cleanroom technology for crucial steps in the manufacturing of pharmaceutical products is growing daily in the pharmaceutical sector. The purpose of cleanrooms is to safeguard both the staff and the product. The airflow, heat and contamination sources, exhaust location and air terminals, and the items in the room all interact intricately to determine cleanroom performance [6]. There are three basic categories into which cleanroom technology falls. When the cleanroom user progresses from purchasing a room to ultimately running it, these regions evolve in tandem with the technology.

- **Design and construction:** When planning and building a cleanroom, one must take into account the design standards, layout, materials, and services that will be provided.
- **Testing and monitoring:** Following installation, the cleanroom is tested to make sure it complies with the design specifications and observed to make sure it consistently meets the necessary standards.
- **Operation:** Following that, it is run to see if it is functioning well and to guarantee the safety of the finished product, that is, that the created product is free from contamination.

Verifying the admission of individuals and supplies, staff attire, adherence to cleanroom regulations, and room cleanliness can all help to guarantee this [5].

Historical Background

The United States of America is where cleanroom history began. Cleanrooms are becoming more and more necessary in production facilities since the 1960s. Technical Manual 00-25-203, the first standard, was created in 1961 under an American Air Force directive. The guidebook provides information on entering, designing, and cleaning as well as the criteria for airborne particles. Two years later, Federal Standard 209—Clean Room and Work Station Requirements, Controlled Environments—was released. The first document governing cleanroom facilities was this one. Federal Standard 209 4 was established in 1966 and given the new designation 209A.

Each revision letter was then provided in alphabetical order: 1973 (B), 1987 (C), 1988 (D), and 1992 (E). International Organisation for Standards (ISO) 14644-1 formally superseded Federal Standard 209 in 1999. The European Union and a few other nations utilise ISO, which was formerly known as Cleanrooms and Associated Controlled Environments. Information about cleanroom requirements from around the world was gathered by the Institute of Environmental Science and Technology (IEST), which then published the following sections: 14644-2 (2000), 14644-4 (2001), 14644-4 (2001), 14644-5 (2004), 14644-7 (2004), 14644-8 (2006), and 14644-9 (Draft International Standard). Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones and Cleanrooms and Associated Controlled Environments-Biocontamination Control are now governed by ISO 14644 and 14698, respectively.

These days, as high-tech enterprises grow, there is a sharp rise in the need for cleanrooms. The semiconductor manufacturing sector, research labs, pharmaceutical institutions, hospitals, and other new product producers are all responsible for this rising need. These days, they are employed in many other sectors, including biotechnology, microelectronics, nanotechnology, pharmaceuticals, and the defence industry. Cleanrooms, where various goods are made, can range in size from tiny to massive multilevel complexes with intricately maintained utilities and equipment. The current state of cleanrooms is the result of several contributions and advancements from a wide range of commercial, industrial, scientific, and technical fields and projects. The development of cleanroom technology, which is essential to high-tech production, is the result of the convergence of demands in several industries, including manufacturing, healthcare, and military applications. Dust and other impurities were discovered in tiny mechanical and electromechanical devices during World War II. High-efficiency air filters were therefore created during the war to address the issues and subsequently made available for purchase for wider use.

Since electronics are now a commonplace in both the military and business, the first clean rooms combined filtered and conditioned air, controlled processes and behaviours, employee training, carefully chosen personnel clothing, construction design and materials, and physical isolation from other areas of the manufacturing facilities. Clean room procedures are becoming more and more commonplace, which has increased demand for standards and new advancements. With clean room technology at its heart, contamination prevention became a separate subject by the 1960s. As a result, new sectors and areas began to profit from clean room production. One of the key developmental dynamics in contamination control continues to be the confluence of demands that underpin previous advancements. Post-war events demonstrate the broad impact of military requirements and defence agency involvement in defining standards and procedures for processing cleanliness. Cleaning was pushed into both new and old sectors by factors including miniaturisation, growing complexity, and the necessity for utmost dependability in both military and commercial equipment and systems [5].

Cleanroom Standards

International standards are used to evaluate cleanroom cleanliness levels. ISO 14644 is the primary international standard [7]. Two international organisations are in charge of pharmaceuticals: the European Union (EU) and the US Food and Drug Administration (FDA). The cleanroom categorisation is one of the main distinctions between various inspectorate agencies. The FDA [8] uses the ISO 14644 cleanroom categorisation standard. A universal standard that applies to all businesses that employ cleanrooms, including electronics and medicines, is ISO 14644.In Europe, the EU GMP guide for standard cleanroom operation uses a grading system from A to D (however ISO 14644 is used for cleanroom validation). In its GMP rules, the World Health Organisation use the same grading scheme as Europe [9].

It should be possible to find a document demonstrating equivalency if firms operate in both the FDA and European markets. This is also significant since the EU GMP limits are slightly stricter than ISO 14644, and the two sets of maximal particle values are not equal. Redundant phrases from previous standards, such as "Class 100," which referred to the abolished Federal Standard 209E, should be avoided in order to show GMP understanding. The two tables that follow provide a comparison of the two standards. Pharmaceuticals that are filled aseptically, which have a higher risk of contamination, are listed in the first table. Pharmaceuticals that may undergo terminal sterilisation are listed in the second table [10].

FOR ASEPTIC FILLING

Table 1: Comparison of international standards for cleanrooms used for the aseptic filling of medicinal products

EU GMP Grade	ISO 14644 Class	Example of operation
A	5[1]	Aseptic connection, preparation and filling. Including the filling zone, stopper bowls, open vials.
B	7	Background environment for the critical zone for aseptic filling.
C	8	Preparation of components for sterilisation. Final formulation. Preparation of solutions to be sterile filtered.
D	9	Less critical manufacturing stages, such as equipment washing.

FOR TERMINAL STERILISATION

Table 2: Comparison of international standards for cleanrooms used for the filling of medicinal products which can be subject to terminal sterilisation

EU GMP Grade	ISO 14644 Class	Example of operation
A	5	Filling of products at an unusual level of risk
C	8	Filling of products
D	9	Preparation of solutions and components prior to filling

International Standards

Cleanrooms are categorised based on how clean the air is. In the design process, standards are crucial. Their use raises the bar for efficiency, quality, safety, and dependability. The United States of America is where cleanroom standards first emerged. In 1961, the American Air Force ordered the creation of the first standard. Technical Manual 00-25-203 was its title. Cleaning, designing, and entering were described. It also includes criteria for airborne particles. Federal Standard 209 was released two years later. It is the original document governing cleanroom operations. It was named "Clean Room and Work Station Requirements, Controlled Environments". The observed particle size was found to be greater than 0.5 meters. This was the case because, at the time, there was inadequate equipment for measuring smaller particles. Federal Standard 209 4 was revised and renamed 209A in 1966. Letters were then assigned to each of the subsequent revisions in alphabetical order: 1973 (B), 1987 (C), 1988 (D), and 1992 (E) [11].

Federal Standard 209 was formally superseded by ISO-14644-1, a standard released by the International Organisation for Standards in 1999. "Cleanrooms and Associated Controlled Environments" was the name of this ISO. All member states of the European Union as well as a few other nations utilise it. IEST—the Institute of Environmental Sciences and Technology—develops the standard that links all cleanroom requirements worldwide and publishes additional parts, including 14644-2 (2000), 14644-4 (2001), 14644-5 (2004), 14644-7 (2004), 14644-8 (2006), and 14644-9 (Draft International Standard) [11].

Today there are standards:

- ISO 14644 - standard for Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones
- ISO 14698, Cleanrooms and associated controlled environments – Bio contamination 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”
- San PiN 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)”

For a long time, cleanroom technology has been employed to construct and renovate pharmaceutical industry facilities. Cleanrooms for pharmaceuticals ensure product quality. It is first and foremost a microbiological defence against environmental influences and product mixing. Certain items, such as injections, vaccines, and some kinds of ointments, are subject to regulations that promote the sterilised aseptic sector. Special advancements in cleanroom technology are linked to the dissemination of industrial Good Manufacturing Practice (GMP) standards. GMP is a set of regulations, standards, and guidelines that outline how medications, medical equipment, food, and supplements are made. GMP regulations initially appeared in the pharmaceutical business in the United States in the 1960s. Later, they spread to Western Europe, Southeast Asia, and other areas. In Russia, there are comparable international standards, such as GOST P 52249 2004.

The translation of EU GMP is the same. OST 42-510-98 took the place of the previous Russian regulation LD 64-125-91, which was the first GMP to be published in Eastern Europe.

General Conditions

The manufacturing of sterile pharmaceutical items must adhere to a number of unique specifications that reduce the possibility of microbial contamination. The operating experience, training, and work attitude of the people determine how these regulations are implemented. Quality support, manufacturing process preparation and fulfilment, as well as their meticulous development and validation, are particularly high claims. Controlling the production backend or the final product cannot be regarded as a special sterility tool or other product quality attributes. Manufacturing of sterilised drugs must be done in cleanrooms, sometimes known as "clean zones," with air chambers for staff access and for transferring supplies and equipment. Standards require that cleanrooms maintain a certain level of purity. Air must pass via the appropriate efficiency filters. The detachable cleanrooms are where the original product and package preparation and filling must be completed. Cleanrooms for producing sterile goods are categorised based on environmental standards to reduce the possibility of product contamination. In exploitative conditions, a certain amount of environmental purity is necessary for every working action [12].

Cleanroom Zoning

When producing pharmaceuticals that have been sterilised, there are four different kinds of clean zones. The product type and a production step that must be shielded from contamination determine the grade.

- Local zone (A). For processes that carry a significant risk to the quality of the product, such as filling, closure, ampoule, and bottle opening zones. Laminar air flow, which has a comparable velocity of 0.36 to 0.54 m/s, is typically utilised in these areas.
- The B-zone, which is encircled by the A-zone, is utilised for aseptic fulfilment and preparation.
- C and D are clean zones for less accountable sterilisation product production phases [13].

Cleanroom Classification

According to standards, cleanrooms are separated into many classes. Table 3 displays the equivalency of classes from several international standards. There is a specific categorisation (table 4) for the production of sterile goods, with grades A through D that correspond to activity categories (tables 3 and 4).

Table 3: Class limits for Federal 209D and ISO Standards [14].

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 ft3 (for illustration purposes) while all others are per m3.

Table 4: Air particle classification system for the manufacturing of sterile products [12]

Grade	Maximum permitted number of particles per m3 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) The number of air changes should be proportional to the room size, equipment, and personnel in order to achieve the B, C, and D air grades. The right filters, such HEPA for grades A, B, and C, should be installed in the air system.

b) After the 15 to 20 minute "clean up" phase, the at-rest state should be received unattended.

c) The outcomes of particle and microbiological monitoring should be subject to appropriate alert and action limitations. Operating procedures should specify remedial action in the event that these limitations are exceeded.

The nature of the product and the production process determine the need for other factors like temperature and relative humidity. Purifying classes are unrelated to these factors.

Table 5: Terminally sterilized products [12]

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 6: Aseptic parameters [12]

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

Remarks: Components should be handled in a category D environment or higher after washing. Sterile beginning material handling should typically be carried out in a grade a setting with a grade B backdrop. In a grade C environment, solutions that will be sterile filtered throughout the process should be prepared; in a grade A environment with a grade B backdrop, materials and products should be prepared if they are not filtered. Aseptically prepared items should be handled and filled in a grade a setting with a grade B backdrop. When the product is exposed and not filtered later, the preparation and filling of sterile ointments, creams, suspensions, and emulsions should be done in a grade A environment with a grade B backdrop. In the operating condition, it is necessary to regulate the cleanliness of the zones by particles. Additionally, microbial control must frequently be made at an aseptic manufacture. Table 7 displays the suggested levels.

Table 7: Recommended limits for microbial contamination in the operation state (average values) [12]

Grade	Air sample, cfu/m3	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	-

Observations:

(a) A single settle plate may be left out for fewer than four hours. Colony-forming unit, or CFU. The outcomes of control determine the extent of the warning and the course of action for particle and microbe contamination. In the event that these restrictions are exceeded, you should also include provisions for remedial action [12].

Contamination Sources

Contamination can come from a variety of sources, including surfaces, workers, and process equipment. The most significant contaminant in a pharmaceutical cleanroom is bacteria. Nearly all of these originate from the individuals present. Therefore, we need to know how many individuals are using the rooms for work. The amount of air needed to dilute and eliminate the airborne dispersion of contaminants from their bodies will be directly impacted by this. The amount of air and contaminants spread by the occupants in the room will be influenced by how well they are dressed for the cleanroom. The kind of clothes also affects the cooling burden. There is less air interaction via the clothes fabric the better the clothing prevents dispersion. The high temperature will make the staff uncomfortable, and they will probably need cooler room temps. Ordinary cleanroom temperatures are 20°C and 40% ± 5% relative humidity. Lower RH of 25% ± 5% is necessary for materials that are sensitive to moisture. These levels are also influenced by manufacturing, location, and attire. As a result, dry bulb temperatures can range from 18 to 22°C [13].

Process equipment is another important source of particle pollution. Prior to imposing restrictions on removing particles once they have entered the cleanroom, the primary goal should be prevention by removal of the particles at their source. This will guarantee a more economical design. Entering the cleanroom with an external airborne pollution is a common issue. That may occur if poorly detailed material from the outside enters the cleanroom and causes airborne contamination. Therefore, building holes should be kept to a minimum. In order to avoid this issue, the chamber was shut. When workers, tools, or supplies are dispersed through poorly constructed airlocks and restrooms, contamination may also enter. Air or surface pollution is possible. Pharmaceutical cleanroom suites are made up of several cleanrooms used for various manufacturing procedures. As product materials and packaging components are processed in separate rooms, environmental control standards gradually rise. It keeps

going until the product is ready to be filled, closed, and sealed. The best quality condition is necessary. When labelling and inspecting a sealed package, less environmental conditions are needed. Different air supply rates and the use of unidirectional flow units or isolators at the essential locations achieve different environmental control standards [13].

Prevention of Contamination

Microbiological contamination is the biggest threat to pharmaceutical cleanrooms. Here, bacteria can spread through direct touch and the air. Cleaning and disinfection procedures, together with personnel practices, can reduce the dangers associated with direct contact [15]. Air pollution can occur from both air entering the cleanroom and from people in the cleanroom putting contaminants into the airstream. Many contamination issues in the pharmaceutical sector can be resolved by improving airflow and supply. The management of airborne microorganisms in cleanrooms is based on four concepts [16].

These Include:

- Using HEPA filters to filter the air entering the cleanroom.
- A sufficient number of room air changes to dilute the air in the cleanroom.
- The flow of air, which keeps any particles suspended and, ideally, moves them away from the vital zone.
- Airflow that is directed.

This pertains to two domains. First, a cleaner area and a less clean area should have a positive pressure difference (contamination cannot migrate upstream against the pressure differential). Second, to blow pollution away from important places when localised protection is needed. A well-defined environmental monitoring program, practical monitoring techniques, and particle counters are used to evaluate cleanroom settings for contamination sources. A policy or justification and related standard operating procedures should have comprehensive documentation of the program [17]. According to GMP requirements and cleanroom standards, rooms must be maintained at varying pressures to ensure that each cleanroom has a unique set of circumstances. To stop an undesirable air flow from a lower location to a higher area, contaminant transfer can be minimised. Show us that achieving a reasonable relative room pressure level and its subsequent support presents key design, commissioning, and operating challenges using a complicated pharmaceutical processing suite with many rooms.

According to the requirements, cleanrooms should have a room pressure differential of 10–15 Pa. These parameters are easily controlled, reachable, and seem to stop the spread of infection. Although it's useful to know that cleanroom regulations could specify a pressure differential of 10 or 15 Pa, this rule is only a tool. When there is no unfavourable air flow between the suite's rooms, the pressure differential is irrelevant. However, this remark is not acceptable and cannot be made clearly. With isolators, the same thing may occur. However, because of the limited controlled environment in this instance, the displacement impact of gloves is significant and needs to be considered when choosing and identifying pressure differences. For isolators, typical pressure differentials range from 15 to 60 Pa. The cleanroom's exhaust may exit through an airlock or changing area on a nearby hallway outdoors, where the pressure is two levels lower than in the room. A pressure differential of more than 30 Pa can make it difficult to open and close swing doors and create "whistling" through the door gaps. Manufacturing equipment that exceeds the limits of room pressure is another potential issue. One way to demonstrate it is by looking at a tunnel process that involves filling, sterilising, and washing a component as it moves from a component preparation facility into an aseptic filling room. Air will move between the two locations that the tunnel connects due to the pressure differential. This air flow has the potential to cause hot patches, alter the hot air oven's heating characteristics, and harm the tunnel. Variations in the pressure differential will result in variations in the air flow volume. Efficiency changes and challenges with system validation may result from this. The flow through the tunnel must be restricted by some kind of masking since it crosses across sections of tunnel barriers with varying pressures. If it doesn't, however, an excess of air will be directed to the region with the greatest pressure. Another option is to install a well-masked tube to the supply air. Equation 1 may be used to compute this. There are two methods for sealing cleanrooms in a suite, which are referred to as "closed door" and "open door" options. In situations when airlocks are inconvenient or impractical to install, such as in hospital operating rooms, the "open door" alternative has been devised and is very useful [13].

Each room is provided with the amount of air required by regulations for cooling needs or for dilution of contaminants. The exhausts in the rooms are modified to provide the proper pressure differential. It is feasible to install automated dampers that are controlled by the room pressure or to manually adjust the extract air. The "closed door" option has the advantage of being straightforward and likely to function with minimal issues. If each room's air supply and extract are balanced, the amount of air that moves between spaces will be reduced. As previously said, one of the most crucial things is to ensure that the rooms are constructed in an airtight manner to reduce the amount of air that escapes the room envelope. However, it is difficult to stop air from moving from a high-pressure location to a low-pressure area through the door gaps. We can determine how much air leaks via tiny holes and gaps by using formula 1.

$Q = A.\alpha \sqrt{\Delta p}$, …… (1)
Where,
Q – air volume (m3/s),
A – area of air leakage (m2),
Δp – pressure difference (Pa), and
α – coefficient of discharge (0.85).

If the door's precise dimensions are provided, an estimate of leakage may be made; nevertheless, the overall amount of leakage will rely on how well the building details are done. Furthermore, until the room is put into operation, this data cannot be known. Therefore, it's important to make sure the air handling system can handle more leakage than is anticipated.

According to the calculations, the suite's air flow should be directed appropriately, for instance, from cleaner to less clean regions. Peter Robertson, who was previously at the University of Glasgow's Building Services Research Unit, has computed this solution to the air distribution control needs. About 0.69 m3/s of air must be sent to the filling room and roughly 0.63 m3/s to the solution preparation room in order to ensure that the air distribution throughout the suite is directed correctly. These volumes relate to air movement control and do not account for the amount of air needed to dilute the airborne pollution or for the cooling load. More air can be drawn from the room or added to the door to provide protection [13].

Isolating Technology

Human effect on processing zones is reduced by the use of separating equipment. Aseptic production can significantly reduce the possibility of environmental microbiological contamination of the final product. All forms of transfer units and isolators must adhere to strict air quality standards. It's also important to think about any leaks or damages brought on by an insulator's materials or design elements. Transfer devices come in a variety of configurations, ranging from single- or double-door models to fully sealed systems that perform sterilisation.

The primary possible cause of pollution is the movement of materials inside and outside of an insulator. An insulator's area is meant to be used for procedures that pose a high risk to production quality. Concurrently, it is intended that working zones be arranged in an insulator without laminar air flow. The design of an insulator and its placement determine the requirements for air purity in the surrounding environment. At the very least, zone D corresponds to aseptic manufacturing and this environment needs to be managed. Insulators may only be put into use after validation, which should take into account all important aspects of isolating technology, such as the integrity of the insulator, the order in which it is processed, the technology of transfer, and the quality of the air both within and outside the insulator. Establishing the current control procedure, which includes regularly testing for leaks in an insulator, is essential.

Blowing-Filling-Hermetic Sealing Technology

The "blowing - filling - hermetic sealing" apparatus is a unique piece of equipment. One continuous work cycle creates packages that are sealed after being filled with a product. One automated complex handles all of these tasks. If employees will be wearing clothing applied in zones A and B, the "blowing-filling-hermetic-sealing" apparatus, which is utilised in aseptic manufacturing zone A with an efficient air flow, can be set up in zone C. In a maintained state, the environment should only include microorganisms, but in an equipped state, it should match the established criteria of particles and microbes. Zone D should be the minimum location for the "blowing-filling-hermetic sealing" equipment used in the production of sterilised items. The design and certification of the equipment; the certification and reproducibility of the "clearing on a place" and "sterilisation on a place" processes; the cleanroom parameters where the equipment is located; operator and clothing training; and actions in a critical zone of the equipment, such as performing connections and building up in aseptic conditions prior to the filling beginning, all require special attention [18].

Personnel

Cleanrooms should continue to employ a minimal number of people. For aseptic manufacturers in particular, it is crucial. Outside of clean zones, inspections and control should be carried out. Regular training on the production of sterile goods, including the fundamentals of hygiene and microbiology, should be provided to all employees working in such areas, including those involved in clearing and maintenance services. Workers who have not received such training but who must enter a cleanroom (such as those working in construction or maintenance services) require extra care when it comes to instruction and supervision [13].

Designing and Implementing Pharmaceutical Cleanrooms

Protecting the product from contamination is the clean room's primary function. In the pharmaceutical sector, the product's purity determines both the patient's life and the manufacturer's reputation. Determining the possible sources of contamination makes it crucial. These might include the production staff, process equipment, raw materials, and working facilities. Therefore, you should consider that successful cleanroom operation—good housekeeping—requires control of the operating processes in the room, which implies that the raw materials, process equipment, and production staff are all necessary.

When seeking a definition of the term "cleanroom," the IES Recommended Practice provides perhaps the most concise explanation of these elements:

"A cleanroom is a room in which the following: • air supply • air distribution According to Federal Standard 209B or the most recent version, "airborne particle concentrates are controlled to meet appropriate cleanliness levels through the regulation of construction materials, operating procedures, and air supply filtration" [19].

Pharmaceutical facilities cannot design their cleanrooms separately. It is difficult to adopt the solution of using clean places. Both building and working there are costly endeavours. The phrase "cleanroom" really refers to a broad variety of spaces, from those with basic housekeeping and environmental controls to aseptic spaces with laminar flow air distribution, complete changing of working clothes, and the most rigorous cleaning and sterilising conditions. The design department must resolve the most challenging issues: minimising risk while maximising cost. It refers to the degree of cleanliness necessary to reduce the possibility of product contamination while also creating a facility that is cost-effective to build and operate without raising the price per unit of the product [19].

Purpose and Strategy of Design

The following succinctly describes the design goals of a pharmaceutical cleanroom suite in a production facility:

- The atmosphere outside the cleanroom suite is excluded. 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 optimising the arrangement and connection of individual rooms; Containment of hazards arising from the product; Control of product-to-product cross-contamination; Removal or dilution of contamination arising from the manufacturing process; and Protection of personnel.
- The operation's overall security through management of personnel and material admission and exit;
- The best possible working environment for staff
- Provision of process plant and equipment to guarantee safe and simple usage, as well as good access for maintenance;
- Particular product environmental requirements, such as low relative humidity for powder filling
- Good observation of the room's circumstances

Each of these points is significant, and cleanrooms should be planned to support and enhance each other. For this reason, it is essential to investigate every demand and create the answer in a systematic way.

Here is a summary of a simple phased plan: Analyse production phases; create process flow diagrams; specify room-related activities; and provide environmental quality standards. Determine the demands for accommodations; create layouts and schemes; quantify production, process, and space requirements; create room association diagrams; create designs and specifications; and carry out the comprehensive design and construction process. Because of a facility's physical size, scale, and complexity, these stages can be performed at various levels of detail. Determining the roles and duties of all parties involved is always crucial, as is ensuring that the responsible parties have the necessary experience [13].

Layout of Cleanroom

Cleanroom Design

Cleanrooms are constructed as a group of rooms with specific purposes in the pharmaceutical production industry. The 'clean changing area' is where employees of this manufacturing company would enter the suite of cleanrooms. This room is used to take off factory clothing, wash hands, and put on the proper cleanroom attire. Components and raw materials, including containers, would enter through the appropriate entrance airlocks. Procedures are implemented in these airlocks to reduce the possibility of external contamination entering the cleanrooms. In the "solution preparation" room, solutions are ready to be transferred, either directly or indirectly, to the "clean filling" room for filling operations using pipelines or mobile containers. In the "component preparation" room, primary containers and closures would be cleaned and prepped before being manually moved to the filling stage or moved by a conveyor system. In the "clean filling" room, containers are packed and filled beneath the unidirectional flow clean zone. Product containers that have been filled and packaged exit the cleanroom suite via the terminal sterilisation autoclave. Employees would exit the suite through the changing room, where the cleanroom protective suite would be taken off, at the conclusion of a workday [13].

A standard set of cleanrooms set up for a product's manufacturing using the aseptic filling method. The following significant variables are mentioned in the differences in the process requirements: The rooms are divided between aseptic and clean rooms. The oven, autoclave, and transfer hatch for goods entering the aseptic suite, as well as the division of the "solution preparation" and "aseptic filling" rooms, serve as barriers between them. Because the environmental management of the clean and aseptic suites differs, a separate and more precise changing room control is provided for the aseptic suite. Additionally, the unidirectional flow workstation can be replaced by the isolator.

The amount of contaminants discharged into the space is typically the most challenging factor in achieving the proper degree of cleanliness of the interior environment.

- The standard of the room's air supply.
- The amount and mode of room air delivery, such as unidirectional flow,

conventional/turbulent ventilation, or a combination of the two.

- The degree of pollution that enters the space from nearby places. Although many of the same problems apply when using isolators, contamination from outside the isolated volume is often reduced [13].

Changing Room

The contemporary cleanroom necessitates that management give instructions to employees. Therefore, there should be a sufficient level of discipline among employees and operators to maximise the whole contamination control effort. Employee impact begins in the transitional sections where people should migrate from "black" to "grey" to "white" zones. In the "black" zone, staff members change and store their outerwear. Individual lockers are often provided in these rooms. Wet and bulky outdoor apparel and shoes should be stored. The floor should be cleaned quickly and frequently. Contamination control should be used to safeguard entrances.

It's possible that the "black" zone changing room is situated apart from the cleanrooms. They could be near the employee's building entrance. When appropriate, specialists may be held in the "grey" region. It is necessary to have distinct areas for men and women if personal household attire is swapped out for uniform pants. When a complete clothing change is used, a personal, lockable locker will be needed. The process then moves on to the actual storage and usage of cleanroom apparel, where the installation will be based on the choice of clothing and how often it is changed. There should be facilities in the "grey" area for employees to "scrub-up" and take off their makeup. Distributing cleanroom clothing may be a different reality.

Simple rails with hangers or vertical laminar flow control cabinets are two possible configurations. The flooring that leads to the "white" region has to be contaminated-free. Employees change into their cleanroom shoes in the "white" section. An air flow from the "white" zone's "clean air" through the "grey" and "black" zones would be ideal for the entire shifting environment. Additionally, the changing area has to include supplies for handing out sterile, cleaned clothes, masks, gloves, and tools for gathering soiled objects so they can be cleaned. Showers are available for both regular and emergency usage. They are located in locations where there is a chance that dangerous chemicals will contaminate employees [20].

Material Distribution Technology

Although the mobility of materials is crucial to the pharmaceutical technical process, their entry and exit from cleanrooms must be managed to prevent contamination. Clean conditions must be maintained during the manufacturing and packaging of raw materials. Instead of using paper for envelopes, use polythene or comparable materials. Before materials enter the cleanroom, any paper that is required must be taken out and its contents thoroughly cleaned. Airlocks are required for the transport of materials. Additionally, if at all feasible, customised cars or trolleys should be employed not to go from "grey" to "white" regions with a vehicle.

When pallets are utilised, they should always be made of plastic. Smaller materials can be moved via air lock hatches with the use of specialised trays. To prevent contamination from moving from the "grey" to the "white" areas, it could be required to install distinct conveyors with dead plate transfers at the cleanroom entrance point. In order to support the absence of particles once in the production process, fluid materials may need to be filtered at the point of usage. It must be acknowledged that while working with a particle matter, certain powder-based procedures like tableting and vial filling are employed. In certain cases, preventing the entry of foreign particles may be the answer. Reducing the dangers of explosions to both the environment and humans is crucial [20].

Air Supply

The number of particles of a certain size measured in a given volume of air at a specific location is directly connected to airborne particulate pollution because of clean air technology. Therefore, the air supply, air distribution, and filtration—the first three components of the cleanroom definition—are tightly related. Filtration needs are influenced by cleaning decisions. Additionally, supply air amounts are influenced by the filtering needs. It should be evident from examining these topics independently that choices made about one will have an impact on the others.

The air volume in each location is influenced by the size of the air handling facility and the quantity of utilities like power, steam, and chilled water. Additionally, they will ascertain the dimensions of the plant rooms and services zones required to fit generating equipment and ducts. The amount of air to be provided to each room must be determined at the outset of the HVAC design. Therefore, we should be able to determine whether or not the air volume is important for dissipating the heat load in the space. The vague nature of cleanroom design typically disappoints engineers who have been taught to compute their ideas accurately. The requirements for validation to reach the required class limits are sufficiently precise. However, there isn't a formula that can relate air change rates to cleanliness levels. In this case, the designer will use his expertise to gather precise information regarding the nature of the equipment, the number of participants, the character of the operations in the room, and the state of the room where the test will take place. He should then determine how much air is needed. Prior regulations recommended a minimum number of air changes but did not advocate

for cleanliness. For example, it was hourly changes. Regretfully, this resulted from misinterpretation and was frequently interpreted as a comprehensive need in thorough specifications [20].

The use of overpressure plays a significant role in preventing particle collection in cleanrooms. Pressure gradients can be created in suites of rooms with varying degrees of cleanliness. Adjacent rooms typically have a pressure differential of around 12 Pa. Increased overpressure can cause noise in the cracks and make it harder to open doors. In cleanroom blocks with multiple cleanroom classes, it is required to provide the 5 Pa pressure differential between adjacent rooms. Therefore, more pressure is sustained in spaces that are cleaner. As a result, the most vulnerable locations experience the largest overpressure, which supports and reduces the spread of contamination from room to room. There are several methods for producing gradients. For example, each room can be constructed to a fixed overpressure independently of the others by carefully calculating its air flow rates, or air can be distributed from room to room by passing it through pressure relief dampers and transfer grilles [20].

Although the first approach reduces the chance of cross-contamination, it is difficult to support in balance if HEPA filters block at different rates and to balance initially. Once accomplished, the second way becomes autonomous since it is participatory. By increasing the supply air flow rate when filters are blocked by a manually operated damper in the main supply duct or by a constant volume damper, the system characteristics are quickly sustained. Areas of greatest sensitivity are shielded by the lowest negative pressure in negative pressure cascades, which function in an equal and opposite manner. To avoid a net influx of contaminated air, a positive pressure zone should be used to protect the order of arrival in a containment suite [20].

Air Distribution

In the cleanroom, there are two recognised forms of air distribution. First, a conventional design is turbulent flow. It is utilised in cleanrooms when terminal outlets only make up a portion of the ceiling space and are positioned to accommodate general room transfers or specific process needs. Extracts might be found at the low level of the walls or at the ceiling. Although they are predictable, air flows cannot be guaranteed. Installing HEPA filters in terminal housings can result in cleanliness levels as high as Class 1000 [20].

Second, facilities that require Class 100 and superior conditions—especially when "in use" testing is necessary—need a unidirectional downflow (laminar flow) air distribution. Particle transmission may be predicted more easily with a vertical air flow of available velocity 0.45 m/s from a 24 completely filtered ceiling since there are no dead zones where contamination might grow [20].

Table 8: Air change rates for clean room

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

The location of air exhaust becomes more important as cleanliness levels rise. Exhaust air grilles installed in the ceiling or high up in the walls may support Class 100,000 cleanliness requirements. Low-level extraction becomes crucial when cleanliness levels increase. If unsightly cleanroom implementations need to be avoided, double-skin walls or ducting placed in service chases must be used. The last prerequisite is airflow predictability. Systems can be created in this situation to shield the operator and the product from contamination.

However, it should be noted that even in laminar downflow sections, turbulence must be reduced because the entry of humans, machinery, and the ceiling structure itself into the airstream will impact such areas. Horizontal unidirectional airflow is another option. Because air quality rapidly deteriorates the farther one is from the filter bank, its usage is currently considerably less common. The airflow across the room is stopped at each operation, which reduces direction predictability and introduces pollution that persists throughout subsequent processes. In spaces where product safety is the sole option, horizontal laminar flow is still often utilised.

The main benefits include:

- Greater loading capacity, which leads to a longer service life;
- Reduced pressure drop, which results in less system resistance.
- Reducing the chance of off-gassing, minor leaks, and friction when using separators.

Understanding the relative efficacy of HEPA fillers is crucial. Throughout the production process, every filter will undergo at least one test. Efficiency and leak testing for filters are outlined in several legislation. Efficiency testing can confirm general effectiveness but are unable to spot potentially dangerous flaws. They cannot be maintained throughout transit or modification until an overall instruction is given indicating that the required efficiency has been achieved.

As a result, the qualifier will consistently request that leak tests be installed in order to carry out the system validation. The filter media is not the only source of improved output. Factory sealed cassette filters that include both the filter and the housing have been widely manufactured recently, until they were always placed into constant housings as part of the room ductwork system using a "fluid" seal. A higher replacement cost and a loss of room integrity during filter changes are two of the biggest drawbacks of factory control over the challenging filter seal and lower initial cost. Pharmaceutical industries don't often utilise cassette filters. For maximum effectiveness, filters should be positioned as close to the extract point from the room as feasible. In order to reduce contamination, ductwork is run more carefully. It is necessary to replace filters without compromising the ducting system's structural integrity. In order to prevent replacing and dispersing any pollutants gathered on the media, filters require certain frame and bagging procedures. We refer to it as "safe change" [20].

Remove the Cover

Stretch the plastic bag, open the filter from the exterior of the canister, grab the handle of the filter through the middle of the bag, and pull the filter out about halfway. In a concertina pattern, feed the bag over the filter's end. d. Slide the filter out on the table and hold it by the supports away from the concertinered bag. e- Cut the rear on the centre line after heat-sealing three lines across the bag. It is now safe to dispose of the encased soiled filter. Return the bag to the first swage. f- Put a fresh filter in. Over the old bag and second swage, feed the beaded edge of the new bag with the new filter. g- The new bag's location above the second swage must not be disturbed when the old bag is removed. h. Move the old bag below the slide filter into the unit and lift the filter to the top of the bag. Note that the old bag is not wedged between the clamping frame and the filter's bottom. i- Clamp the filter. As previously, move the old bag to the very end of the new bag's heated seal and cut it off. j. Flatten the sack into a roll. Put the cover back on and fasten it [20].

Materials of Construction

Any pharmaceutical building project's success is determined by the facility's "quality," which is determined by an individual's assessment, rather than by the process and services upkeep. The designer must give careful consideration to the installation or application's details and material choices. In addition to the evident need for appropriateness, it is crucial to account for the substantial service loads sometimes imposed in a pharmaceutical application while evaluating structural options for a project. Regular penetration for holes and slots is accepted by the structure. Engineers should use caution when designing floors, particularly when there are movement linkages, to ensure that the integrity of the applied floor is not jeopardised. The selection of building technique affects a few outside variables. The location of the facility, flexibility, and economical solutions are the main determinants. First and foremost, building materials are influenced by a facility's location, which affects not only the accessibility of raw materials and installation expertise but also the rigorous adherence to building standards. The main requirement of facility managers is flexibility. Solving many issues at once is really challenging. For example, building a facility that satisfies modern performance standards, adapting to quick changes in equipment, and updating without requiring a complete overhaul.

Even if there are several needs to meet, you should look for alternatives that are economical. At the detail design stage, a final engineering study is necessary to ensure that the solutions given operate at the optimal price per unit. Places of production need to be "fit for purpose." The designer must maintain a balance between risk and cost while choosing the right building technology and materials. Danger of materials degrading and contaminating the technical process and project cost control. Traditional building construction methods are used to construct cleanrooms. A good and sufficient compromise between something that is perfect everywhere and something that can be built owing to budget and schedule constraints must be provided by every system.

The quantity of air leakage into or out of the cleanroom suite is directly influenced by the construction quality of the space, and this type of leakage should be avoided. When choosing windows and doors, dirt traps must be avoided. The building envelope must incorporate the air conditioning system, services, and technology. Additionally, air ducts should be cleanable and airtight. When manufacturing operations change, it is common to arrange renovations for pharmaceutical cleanrooms and technical equipment. The provision of service access above the cleanroom and vertical service ducts in the walls will make it easier to modify the services. Although replacing items is more challenging, using premade walls might be beneficial [20].

Operating Procedures

Operational procedures in cleanroom facilities are the subject of the final part of the statement that was mentioned at the beginning of section 4. Given that the user bears full responsibility and the designer cannot have any effect, it is crucial to provide a comprehensive overview of all contamination control-related issues. A number of cleanroom operations, including sanitisation, validation, and basic clothing, can have an impact on the production process.

Control and Maintenance of Cleanroom Areas

Careful primary selection, first cleaning by removing packaging, and proper housekeeping procedures throughout the processing of the materials are all necessary to regulate the raw materials entering the cleanroom. Stainless steel and other non-shedding

materials can be used in technological equipment to reduce contamination. Motors and drives are examples of moving parts that can be packaged or taken out of the clean room completely. The largest source of contamination in the production process is manufacturing personnel. It shows the relative amounts of contamination during the course of the working day. Additionally, it illustrates how human movement affects the manufacturing and cleaning processes. The room may be verified in three states in accordance with the standards:

- "As built," a test primarily used to determine whether the cleanroom builder has fulfilled his contractual duties
- "At rest" is a test in which the space is completely furnished and prepared for production, but no machinery is operating and no staff is present.
- "In use," a test conducted with the room completely functional [13].

Testing "at rest" at 6 a.m. and testing "in use" at noon or 8 p.m., when the cleaners are at work, shows a significant variation in the number of particles in the area, as can be immediately determined. It is crucial to realise that in order to attain the desired levels of cleanliness, building technologies and norms must be followed. Before beginning the design process, engineers need also have a clear understanding of how the space will be used and executed. However, there are other instances where safeguarding employees from the product is required. In many ways, cleanroom technology has evolved to offer this protection. To ensure the necessary degree of protection, controlling work may be conducted in safety cabinets or isolators, or negative pressure rooms may be utilised for secondary containment of enclosed production processes [20].

Cleanroom Clothing

Personnel are the main source of contamination in the cleanroom, as was previously established. However, this issue is not as significant as it formerly was. Since there are many different types of clothing available nowadays that provide enough protection for the item. Because cleanrooms inherently function at high levels of performance for both product integrity and operator safety, the appropriate use of cleanroom gear in the pharmaceutical business is becoming increasingly important. In addition to protecting the environment from the workers, cleanroom apparel needs to be made with the strictest specifications.

Table 9: Cleanroom clothing applications

Cleanroom class	Coveralls	Headgear	Footwear	Coats/ frocks	Hands
1	Yes	Full hood and mask	Long over boots	No	Powder and lint free
10	Yes	Full hood and mask	Long over boots	No	Powder and lint free
100	Yes	Full hood, mask as required	Long over boots	No	Powder and lint free
1000	Yes or coat	Hood or snood	Long over boots 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 tap	Overshoes	Yes	As required

It may be noted that the above recommendations are based on a density of one person per 9 m2 of floor space [20]. The usage of one-piece working suits, often with integrated hoods, knee-length overboots, and gloves, is now required by facilities. Streetwear and outside footwear should be kept in changing rooms by cleanroom workers. Additionally, they must hide their faces. Clothes must be made entirely of synthetic materials. If the garment is made of antistatic material, be sure to assess both its fundamental capacity to keep particles out of the clothing and its actual antistatic performance. The entire garment should be loose enough to boost pressure and lessen internal friction, and the openings should be sized to minimise emissions for proper fit.

Cleaning Instructions

Initially, a wet and dry hoover cleaner must be used to clean the floor. To start, the dry vacuum cleaner must be used to get rid of any dust or debris that is visible. Using wet mops on the cleanroom floor is the second step. A sticky roller works well for sanitising surfaces and getting rid of germs. After that, using a specialised floor scrubbing machine with rotating brushes to clean the floor is advised. The cleaning solution should not be combustible or hazardous, it should dry quickly, and it shouldn't damage the surfaces in the cleanroom.

General Cleanroom Regulations

The successful operation of a cleanroom is governed by a set of minimal standards. Everyone involved in cleanroom operations should agree to abide by the rules. Keys, watches, rings, matches, lighters, cigarettes, and other personal belongings should all be kept in the personal locker outside the dressing room. If valuables like wallets are never taken off of the cleanroom clothes, they can be permitted inside. Eating, smoking, chewing gum, and wearing makeup are all prohibited. Only ballpoint pens and authorised cleanroom paper are permitted in the cleanrooms. The use of hand dryers with HEPA filters is advised. Every

instrument and container used during the cleaning procedure needs to be as thoroughly cleaned as the surfaces in the cleanroom.

Gloves or finger cots (a medical device used to cover one or more fingers) must be worn before touching any object or surface that has not been thoroughly cleansed. Every tool needs to be set up on a cleanroom towel that has been certified for the cleanroom class. Those who are physically unwell, particularly those with stomach or respiratory conditions, are not allowed to enter the cleanroom. Additionally, it is prohibited to run, walk quickly, sit on tools or work tables, take off things from cleanroom clothing, use cleanroom clothing outside of the cleanroom, and wear filthy or damaged suits [21].

Measurement of the Airborne Particles

The quantity of particles in the cleanrooms may be estimated using specialised equipment. One such gadget is a particle counter or detector. Aerosol particle counters are utilised in pharmaceutical cleanrooms. They are used to measure the size of airborne particles and assess the quality of the air. As was previously noted, the number of particles per cubic metre is strictly limited in cleanrooms. Therefore, a cleanroom is evaluated in accordance with the classification criteria using an aerosol particle counter. A lot of particle counters have alarms to stop contamination of the production process. Additionally, building automation can incorporate this monitoring system. It can capture contaminated times to assist staff in maintaining cleanroom air quality. The most common method of preventing contamination is to detect it early on. To keep an eye on various cleanroom conditions, a serial selection system or a single remote particle counter is required. A portable particle counter with great sensitivity can locate the source of particle emissions [22].

Risk Assessment

The official implementation of quality risk management is a relatively recent addition to contemporary cleanroom architecture. This is now expected by regulations. The most crucial guideline document for incorporating risk assessment into the design process is ICH Q9 [23]. The FDA accepted ICH Q9 in 2010 after it was included into EU GMP in 2008. When designing and building cleanrooms and clean air devices, it is important to use risk management and risk assessment concepts as early as feasible. A well-considered risk management strategy can help reduce contamination hazards and prevent costly design mistakes [24]. The cleanroom design process should ideally start with a project risk assessment, which will provide a wealth of information to take into account during the design stage [25]. Hazard Analysis and Critical Control Points (HACCP) and Failure Modes and Effects Analysis (FMEA) are examples of appropriate risk assessment methodologies. Every validation step (the steps were described before) should take risk into account.

On-Going Compliance

Every stage of a new facility is examined, but according to ISO 14644-2: Specifications for testing and monitoring to show continuing compliance, an existing cleanroom's operational status is confirmed every six months or every year. Both the "at rest" and "in operation" occupancy states are used for cleanroom verification, which should take into account the following factors:

- The class of air purity;
- Variations in room pressure;
- HEPA filter leak test installed;
- Air velocity (for unidirectional airflow) or air flow rate (for turbulent airflow) [26].

CONCLUSION

As a result of pollution from people, raw materials, completed goods, lodging facilities, processing plants, and equipment, air is a transporter of poisons and microorganisms. With cleanroom technology, specific environmental conditions may be established in the processing area. Cleanroom certification, design, and construction can be difficult. The main issue facing the pharmaceutical industry is preventing excessive contamination that might endanger the medication being handled in the cleanroom. Reduced contamination hazards can be achieved via the use of contemporary cleanroom technology design techniques. As this article has demonstrated, these strategies include using GMP validation phases to ensure rigorous testing, adhering to quality risk management to identify contamination sources, and applying computer-aided design techniques like computational fluid dynamics, which enable the use of predictive models to help identify contamination sources related to undesired air movement. Because it lowers the microbial burden and produces safe, high-quality final goods, cleanroom technology is therefore a preferred processing method.

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REFERENCES

1. Gaurav A. Chaudhari, Dr. Suhas H. Sarje. (2015). Clean Room Classification for Pharmaceutical Industry. International Journal of Engineering and Technical Research (IJETR); 3(4):241-244.
2. Kitain M. (2010). Cleanrooms in Pharmaceutical Production. Building Services Engineering. Mikkeli University of Applied Sciences. :1-36.
3. Farquharson G. (2002). Clean Rooms and Associated Controlled Environments. Pharm Tech Eur. 14:43-47.

4. Eaton T. (2019). Pharmaceutical Cleanroom Classification using ISO 14644 and the EU GGMP Annex 1; Part 2: Practical application. European Journal of Parenteral and Pharmaceutical Sciences; 24(4): 1-11.
5. Gupta A, Kaur M, Kaur A. (2017). Cleanroom Technology and Its Application in Food Proceesing. Novel Food Processing Technologies, Editor, Vikas Nanda and Savita Sharma, New India Publishing Agency, New Delhi, India.:323-357.
6. Stribling D. (2000). Airflow modelling in contamination control. Cleanroom Technol.: 30-31.
7. ISO 14644-1. (1999). "Cleanrooms and Associated Controlled Environments— Part 1: Classification of Air Cleanliness," (ISO, Geneva, Switzerland).
8. Food and Drug Administration. (2004). Guideline on Sterile Drug Products Produced by Aseptic Processing, Food and Drug Administration, Rockville.
9. Euradlex. (2009). The Rules Governing Medicinal Products in the European Community, Annex 1, published by the European Commission, Brussels, Belgium.
10. WHO. (1999). Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Good manufacturing practices and inspection. Geneva, World Health Organization, 2.
11. Karvonen J. (2008). Clean room courses.
12. EU-GMP. (1997). Guidelines for the manufacture of sterile medicinal products. EU GMP.
13. Wiley J and Sons. (2001). Cleanroom design. Edited by W. Whyte. Second edition. Chichester.
14. ISO 14644-1. (1999). Classification of airborne particulates. Part of its annexes.
15. Sandle T. (2012). Cleaning and Disinfection. In Sandle, T. (Ed.). The CDC Handbook: A Guide to Cleaning and Disinfecting Cleanrooms, Grosvenor House Publishing: Surrey, UK.: 1-31.
16. Howorth FH. (1987). Prevention of Airborne Infection in Operating Rooms. Nat News Brit J Theatre Nursing. 24:13-15.
17. Sandle T. (2011). 'Environmental Monitoring' in Saghee MR., Sandle T. and Tidswell EC. (Eds.): Microbiology and Sterility Assurance in Pharmaceuticals and Medical Devices, New Delhi: Business Horizons. :293-326.
18. GOST R 52249. (2004). Rules of manufacturing and quality inspection of medical agents. Good manufacturing practice for medicinal products (GMP).
19. IEST RP 012. (1993). Consideration in cleanroom design. Contamination Control Division (WG-CC012). Suite 400, Schaumburg, IL 60173.
20. Graham Cole. (1998). Pharmaceutical production facilities: design and applications. London, UK.
21. Fadden RM. (2010). A Basic Introduction to Clean Rooms. Coast wide Laboretories, Staples Inc.
22. Light House World Wide Solutions. (2022). Airborne Particle counters and how they work. 1-10.
23. ICH Q 9. (2006). Quality risk management. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH, Geneva.
24. Sandle T. (2011). 'Risk Management in Pharmaceutical Microbiology' in Saghee MR., Sandle T. and Tids well EC. (Eds.): Microbiology and Sterility Assurance in Pharmaceuticals and Medical Devices, New Delhi: Business Horizons.:553-558.
25. Akers JE. and Agalloco JP. (2002). Aseptic Processing, Elephants, Blind Men and Sterility. PDA J Pharm Sci Tech. 56:231-234.
26. ISO 14644-2. (2000). Cleanrooms and associated controlled environments – Part 1: Specifications for testing and monitoring to prove continued compliance with ISO14644-1, ISO, Geneva, Switzerland.

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