Second Edition

Cleanroom Technology

Fundamentals of Design, Testing and Operation

William Whyte

WILEY

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Cleanroom Technology

Fundamentals of Design, Testing and Operation

Second Edition

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I dedicate this book to my sons Griogair and Murray who are both engineers and cleanrooms users.

About the Author

William (Bill) Whyte is an Honorary Research Fellow at Glasgow University. He has been involved with cleanrooms for over 45 years and has the useful dual qualifications of a BSc in microbiology and a DSc in mechanical engineering.

He has published over 130 reports and papers on contamination control and cleanroom design. He wrote the first edition of this book in 2001 and has also edited the book Cleanroom Design (second edition, 1999). He is a member of British and international standards committees writing the international cleanroom standards. He has extensive experience as an industrial consultant.

He has received the following awards for his work in Cleanroom Technology: Fellowship of the IEST, Honorary Life Member of S2C2, James R Mildon Award from the IEST, Michael S Korczyneski Grant from the PDA (twice), Parenteral Society Annual Award and the CleanRooms Hall of Fame Award.

Preface

The contamination-free conditions provided by cleanrooms are essential for much of modern manufacturing industry. Without cleanrooms, productswill become contaminated and either malfunction or infect people with bacteria. Cleanrooms are used for the manufacture of items used in computers, cars, aeroplanes, spacecraft, televisions, disc players and many other electronic and mechanical devices, as well as the manufacture of medicines, medical devices and foods.

Cleanroom technology can be divided into three parts: design, testing and operation of cleanrooms, and this book covers, in a holistic way, these three main facets. The book is intended to introduce people to these subjects or to update their knowledge. Those who teach 'cleanroom technology' either at college, or to their cleanroom personnel, may find this book useful, as it has been written with this in mind.

Most of the principles described in the book are those that are generally accepted within cleanroom industries. However, I have found areas where no sound advice exists and have had to develop guidance using my own knowledge and experience.

The first edition of this book has been well received and translated into several languages. However, new information on cleanrooms is now available and this edition contains a substantial amount of additional material. Each chapter has been updated. This might be by

the inclusion of more information, as in the chapter on the history of cleanrooms where information has been added about the early days of infection control in hospitals. However, Chapter 4 and 5, the chapters that contain information on cleanroom standards and guidelines, required extensive updating. Other chapters, such as Chapter 16, which discusses risk management, have also been extensively revised, especially the section on risk assesment. Other subjects that have been added are those on clean-build, determination of air supply volumes for non-unidirectional cleanroom, RABS (Restricted

Access Barrier Systems), contamination recovery test methods, entry of large items into a cleanroom, glove allergy problems, and how to develop a cleanrooom cleaning programme.

Acknowledgements

In the first edition of this book I acknowledged the help of (in alphabetical order) Neil Bell, Charles Berndt, Roger Diener, Gordon Farquharson, Gordon King, Lynn Morrison, Bob Peck, Martin Reeves, Hal Smith and Neil Stephenson. I also acknowledged the support of the Scottish Society for Contamination Control. Barbara McLeod read and commented on the script and Isabelle Lawson produced most of the drawings used in both editions of the book.

In preparing the second edition, I asked a number of experts in cleanroom technology to review the chapters that I had rewritten. Don Wadkins supplied information on clean-build contained in Chapter 8. R. Vijayakumar reviewed Chapter 9 on high efficiency air filters. Tim Eaton and Koss Agricola reviewed Chapter 16 on risk management. Roger Diener helped me rewrite Chapter 19 on the materials and the entry of machinery and equipment into a cleanroom. Chapter 20 on cleanroom clothing was revised with the assistance of Charles Berndt. The information on gloves in Chapter 21 was reviewed by Elizabeth Hill. My thanks go to all of these people whose help is much appreciated.

The photographs on the cover of this book are reproduced by permission of Lothian Health Services Archive at Edinburgh University Library, Micronova Manufacturing, International pbi, and Metron Technology. The permission to use other photographs, tables and drawings within the book is acknowledged at the end of each chapter.

Finally, I am most grateful to John Neiger for checking this edition from cover to cover with commendable thoroughness. John combines a considerable knowledge of clean air and containment technology with a passion for clear and understandable writing. This edition of my book has benefited greatly from his input.

1

Introduction

1.1 What is a Cleanroom?

It is clear that a cleanroom is a room that is clean. However, a cleanroom has a special meaning and it is defined in the International Organization for Standarization (ISO) standard 14644–1 as:

room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimise 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

The first two-thirds of the definition is, in essence, what a cleanroom is. It is a room that minimises the introduction, generation and retention of particles. This is achieved, firstly, by supplying it with an exceptionally large quantity of air that has been filtered with high efficiency filters. This air is used (1) to dilute and remove the particles, bacteria and chemicals dispersed from personnel, machinery and other sources within the room and, (2) to pressurise the room and ensure that no dirty air flows into the cleanroom. Secondly, a cleanroom is built with materials that do not generate particles or ‘outgas’ airborne chemical contamination and can be easily cleaned. Finally, cleanroom personnel use clothing that envelops them and

minimises their dispersion of particles and micro-organisms.

Figure 1.1 A cleanroom with personnel wearing cleanroom clothing

These and other similar measures that minimise the introduction, generation and retention of contamination in a cleanroom are discussed in this book. Cleanrooms can also control the temperature, humidity, sound, lighting, and vibration. However, these parameters are not exclusive to cleanrooms, and are therefore not discussed in any detail in this book.

1.2 The Need for Cleanrooms

The cleanroom is a modern phenomenon. Although the origins of cleanroom design and management go back for more than 150 years and are rooted in the control of bacterial infection in hospitals, the need for a clean environment for industrial manufacturing led to the modern cleanroom in the 1950s. Cleanrooms are needed because people, production machinery and the building structure all generate contamination. As will be discussed later in this book, people and machinery produce millions of particles, and conventional building materials can break up as well as 'outgas' chemical contamination. A cleanroom controls the dispersion of all this potential contamination to allow manufacturing to be carried out in a clean environment so that the correct quality and reliability of the product is achieved, and, in the case of healthcare products, the patient is not harmed.

The uses of cleanrooms are diverse and shown in Table 1.1 is a selection of products that are now being made in cleanrooms.

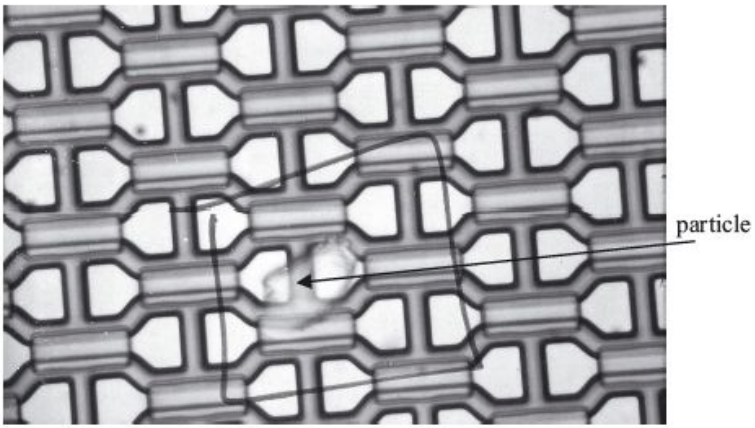
Table 1.1 Some cleanroom applications

Industry	**Product**
Electronics	Computers, flat screens
Semiconductor	Integrated circuits used in computer memory and control
Micromechanics	Miniature bearings, compact-disc players
Optics	Lenses, photographic film, laser equipment
Nanotechnology	A wide variety of products at nanometre size

Biotechnology	Antibiotics, genetically modified organisms (GMOs)
Pharmaceutical	Sterile pharmaceuticals
Medical Devices	Heart valves, cardiac by-pass systems, stents, catheters
Food and Drink	Brewery products, unsterilised food and drink

It may be seen in Table 1.1 that cleanroom applications can be broadly divided into two. Given in the top section of Table 1.1 are those industries where dust particles are a problem, and their presence, even in submicrometre size, may prevent a product functioning, or reduce its useful life.

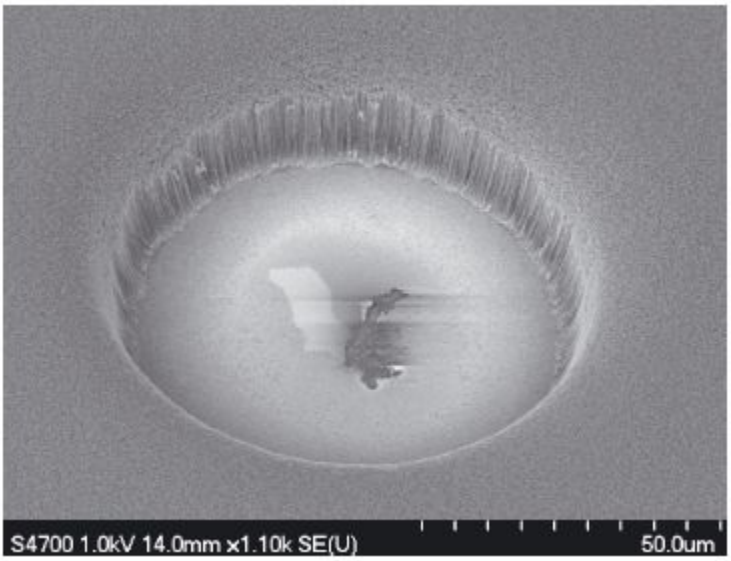
Figure 1.2 Contaminating particle on a semiconductor



A major user of cleanrooms is the semiconductor fabrication industry, where microprocessors are produced for use in computers, cars and other machines. Figure 1.2 shows a photomicrograph of a semiconductor with a particle on it. Such particles can cause an electrical short circuit and ruin the semiconductor. To minimise

contamination problems, semiconductors are manufactured in cleanrooms with very high standards of cleanliness.

Figure 1.3 Contaminating particle inhibiting carbon nanotube growth

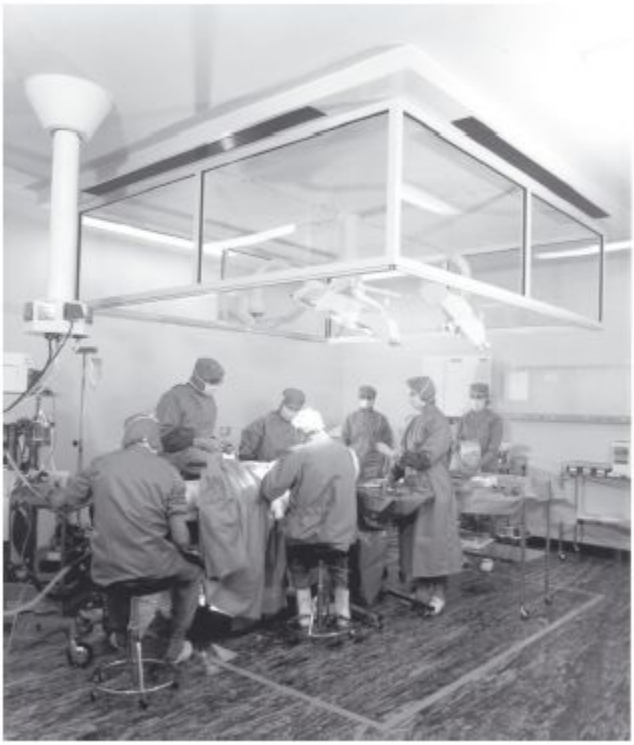


Shown in Figure 1.3 is a contamination problem in a nanotechnology application. The photograph shows a particle sitting in the centre of a field of carbon nanotubes that are growing upwards. The growth of nanotubes around the particle is inhibited by chemical contamination diffusing from the particle. Nanotubes beyond the edge of the area of inhibition are seen to have grown normally. In the photograph, the particle is approximately 10 μm micrometres across and the area of inhibition 70 μm in diameter. The nanotubes are only 2 to 3 nanometres in

diameter, so are difficult to distinguish one from another. 1 nanometre (nm) = 1/1000 micrometre (μm).

The bottom section of Table 1.1 shows manufacturers that require the absence of micro-organisms, as their growth in a product could lead to human infection. The healthcare industry is a major user of cleanrooms, as microorganisms or dirt must not be injected or infused into patients through their products. Hospital operating rooms also use cleanroom technology to minimise wound infection (Figure 1.4).

Figure 1.4 Unidirectional airflow system and occlusive clothing used in an operating room



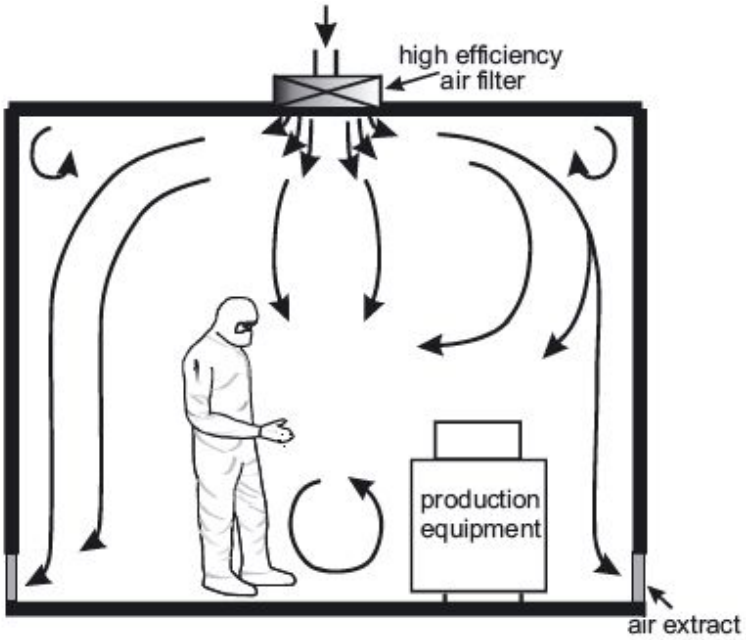
It may also be seen from Table 1.1 that many of the examples are recent developments and this list will certainly be added to in the future, there being a considerable and expanding demand for this type of room.

1.3 Types of Cleanrooms

Cleanrooms have evolved into two major types and they are differentiated by their method of ventilation. These are*non-unidirectional* and*unidirectionalairflow cleanrooms*. Unidirectional airflow cleanrooms were originally known as ‘laminar flow’ cleanrooms and

non-unidirectional flow cleanrooms as 'turbulently ventilated'. The use of the term 'laminar flow' was a mistake, as laminar flow has a meaning in physics and engineering that does not apply to the airflow in a cleanroom. Unidirectional airflow is the correct way of describing the airflow and is the term used in the ISO standards. Unidirectional airflow cleanrooms use very much more air than non-unidirectional airflow cleanrooms, and give superior cleanliness.

Figure 1.5 Non-unidirectional airflow type of cleanroom



The two major types of cleanroom are shown diagrammatically in Figures 1.5 and 1.6. Figure 1.5 shows a non-unidirectional airflow cleanroom receiving clean

filtered air through a high efficiency air filter and air diffuser in the ceiling. This air mixes with the room air and removes airborne contamination through air extracts at the bottom of the walls. The air change rates are normally equal to, or more than, 20 per hour, this being much greater than in ordinary rooms, such as in offices. In this non-unidirectional style of cleanroom, the contamination generated by people and machinery is mixed with and diluted by the supply air, and then removed.

Figure 1.6 Unidirectional airflow type of cleanroom

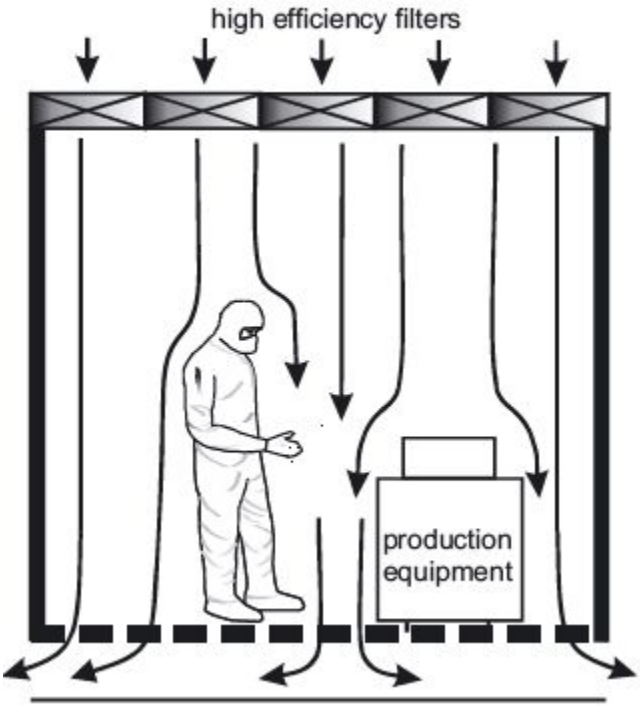
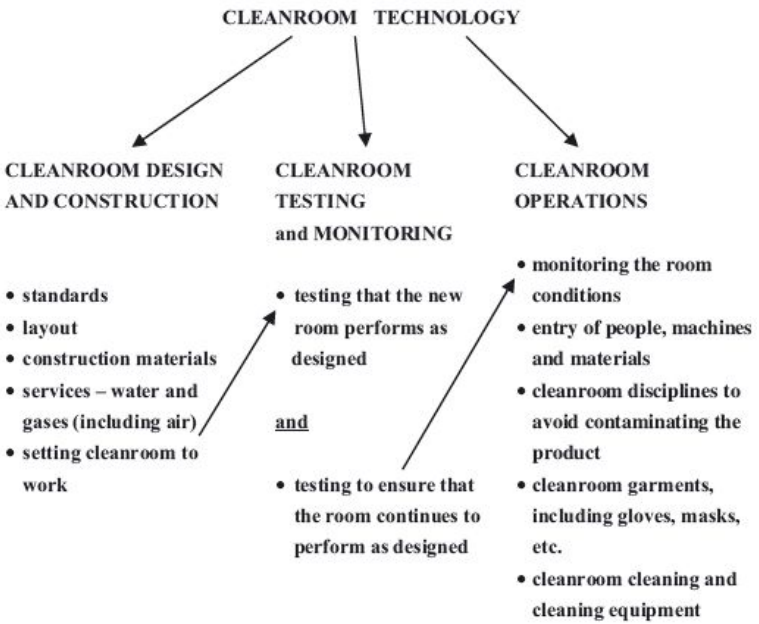


Figure 1.6 shows the basic principles of a unidirectional airflow room. High efficiency filters are installed across the whole ceiling and the air to the room is supplied through these. This air sweeps down through the room in a unidirectional way at a velocity generally between 0.3 m/s (60 ft/min) and 0.5 m/s (100 ft/min) and exits through the floor, thus removing the airborne contamination from the room. This system uses much more air than the non-unidirectional airflow cleanroom but, because of the directed air movement, it minimises the spread of contamination about the room and sweeps it out through grilles in the floor. An alternative configuration has the high efficiency filters installed across the whole of one wall with the air being removed at the opposite wall.

Separative devices, such as unidirectional airflow benches or isolators, are used in both non-unidirectional and unidirectional airflow cleanrooms. These give a localised supply of filtered air and enhanced air conditions where required, e.g. at the area where the product is open to contamination.

1.4 What is Cleanroom Technology?

Figure 1.7 Various parts of cleanroom technology and their interconnections



As can be seen in Figure 1.7, cleanroom technology can be divided into three broad areas. These areas can also be seen to parallel the application of the technology as the cleanroom user moves from firstly deciding to purchase a room to finally operating it.

Firstly, it is necessary to*design and construct* the room. To do this one must consider (1) the design standards that should be used, (2) what design layout and construction materials can be used, and (3) how services should be supplied to the cleanroom.

Secondly, after the cleanroom has been constructed it must be*tested* to check that it conforms to the stipulated design. During the life of the cleanroom, the room must also

be*tested and monitored* to ensure that it continually achieves the standards that are required.

Finally, it is necessary to*operate* the cleanroom correctly so that the manufactured products are not contaminated. This requires that entry of people and materials, garment selection, cleanroom disciplines and cleaning of the room are all correctly carried out.

These three fundamental elements of Cleanroom Technology are covered in this book.

Acknowledgements

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2

The History of Cleanrooms

2.1 The Earliest Years

Figure 2.1 Joseph Lister

It is clear that the first cleanrooms were found in hospitals. Joseph Lister's contribution to history was his realisation that bacteria caused surgical wound infection. The discoverer of microbes, Louis Pasteur, wrote that 'in the

field of observations, chance favours the mind that is prepared.' This is particularly apt when applied to Lister's discoveries. In 1860 he was appointed Regius Professor of Surgery at Glasgow University. Lister heard of Pasteur's experiments, which showed that boiling and exclusion of air from meat broth stopped decomposition. Lister realised that this might apply to hospital wounds. He had also read that carbolic acid (the old name for phenol) was being used to decontaminate sewage. The treatment not only suppressed the smell but when the sewage was spread on fields, cows no longer picked up enterozoal infections. In 1865 Lister tried carbolic acid on wounds with great success and in 1867 he used it with similar success in surgery. During surgery he used it on instruments, on the wound and on the surgeon's hands, and he attempted to prevent airborne infection by spraying it into the air. He found that these steps eliminated many bacteria and reduced infection in the operating room; this was the scientific basis for the first cleanrooms.

Shown in Figure 2.2 is a photograph taken in 1889 of a group of surgeons from the Aberdeen Royal Infirmary in Scotland using Lister's spray, which sprayed carbolic acid into the air of an operating room. This photograph is interesting from several points of view.

Firstly, Lister's spray is shown and this is of historical interest, although it probably did little to reduce airborne bacteria.

Secondly, shown in Figure 2.2 is the surgeon Ogston, who is the third figure from the right and famous as the discovery of 'staphylococci'. Ogston thought that his

patient's abscesses might be caused by bacteria and, using a microscope to look at the pus from abscesses, he found bacteria that had the appearance of either chains or bunches of cocci. When he introduced the pus into animals, abscesses developed with the same type of bacteria as found in the original abscess. He published this information in 1880 and 1881. The type of cocci that grew in chains had already been discovered and named 'streptococci' but the type he found in bunches had not and Ogston named them 'staphylococci', using the Greek word*staphyle* which means 'bunch of grapes'. Owing to the golden colour they exhibit when they grew into colonies, he named the bacteria*Staphylococcus aureus*. This type of bacteria are still a major cause of infections in hospitals, and in their methicillin resistant*Staphylococcus aureus* (MRSA) form, they are a major contamination control challenge.

Finally, it is interesting to observe the accepted mode of dress at that time. Although this photograph was probably posed, the clothing worn for actual surgery would have been of the same type, and operations were carried out without the protection of sterile (or even clean) clothing. The frock coat was a standard item of clothing in those days for surgeons and when the coat was too old it ended up in the operating theatre. An operation was a dirty job and a worn old coat was a suitable garment; it was faded with age, stained with blood and spotted with pus. The surgeon might wear an apron or gown, but this would be for the purpose of protecting the surgeon from blood and not the patient from the surgeon's bacteria.

Figure 2.2 A group of surgeons with the Lister steam spray (on table).

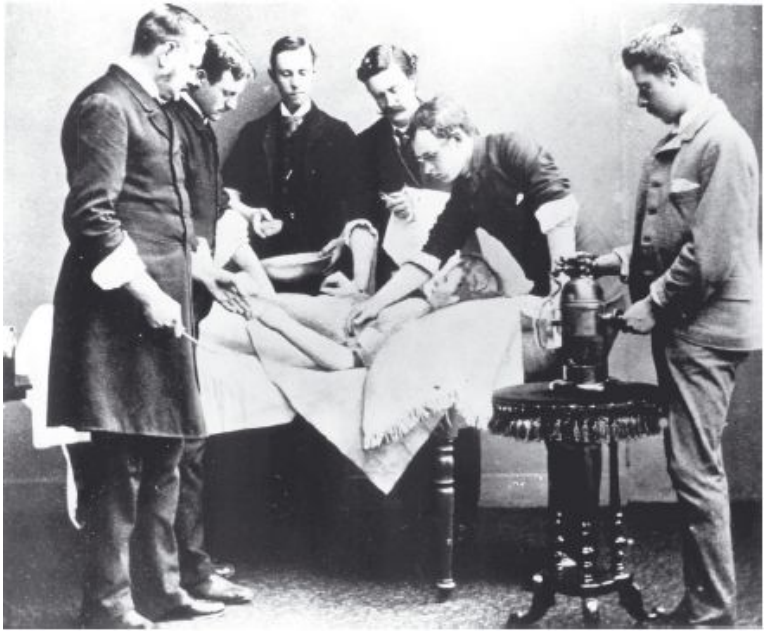
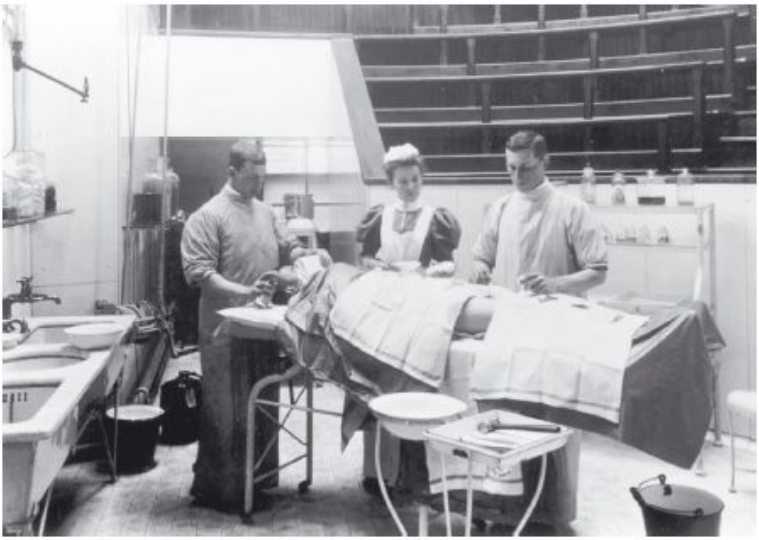


Figure 2.3 An operating room in the late 1890s.



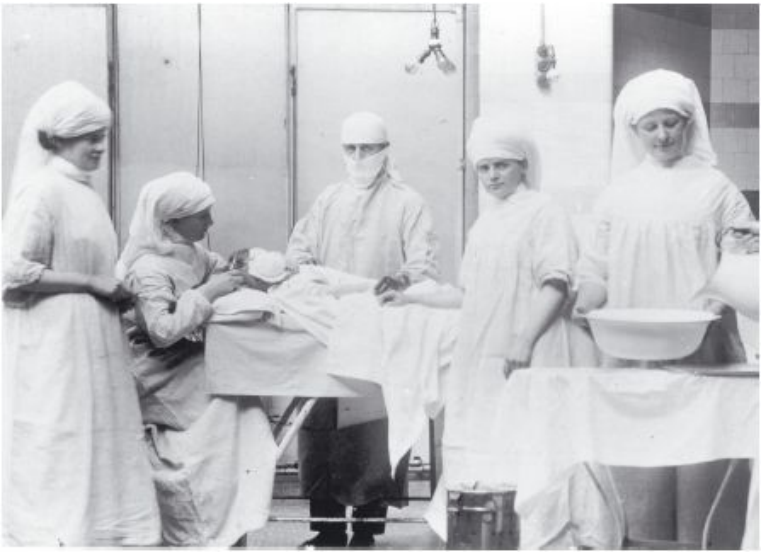
A photograph taken in the Royal Infirmary, Edinburgh, Scotland in the 1890s (Figure 2.3), shows a number of aspects of surgery that will interest anyone who works in a modern cleanroom. The gas lamp seen in the top left-hand side of the picture confirms the age of the photograph, as do many other aspects. The surgeons can be seen to be wearing gowns, but not gloves, hats or masks. In the background of the operating rooms is a gallery where the medical students would crowd in to see the operation without consideration of the bacteria they dispersed; the gallery is the reason that operating rooms are still called operating 'theatres' in many parts of the world. The floor is exposed wooden flooring, and the sinks, buckets and exposed pipes reflect a bygone age where little was known about contamination control.

Lister's reduction of wound sepsis was by an*antiseptic* method, as he used a disinfectant to kill the bacteria on

bandages, the hands of the surgeon and in the operating room environment. One of his former assistants, Sir William Macewen, who succeeded Lister as Professor of Surgery at the University of Glasgow, along with other surgeons in Germany and the USA, developed Lister's techniques into procedures known as*aseptic* techniques. These techniques sought not to kill bacteria that entered the wound, but rather to prevent them from getting there in the first place. Boiling of instruments and bandages was introduced and the surgeons and nurses ensured their hands were rigorously 'scrubbed' to remove bacteria. By the year 1900, surgical gloves, masks and gowns had been introduced. These could be steam sterilised before an operation, although at a lower temperature and pressure than used today. These methods were the basis of cleanroom techniques in the present.

Shown in Figure 2.4 is an operating room in the Royal Infirmary, Edinburgh, photographed around 1907. The contrast to the photograph in Figure 2.3 is very noticeable. Electricity has been installed, but of more interest is the fact that the surgeon is wearing gloves and a facemask. The face mask is below his nose, as it was not till the end of the 1930s that it was appreciated that it should go above the nose. There is also a terrazzo-type floor and tiled walls to facilitate disinfection and cleaning.

Figure 2.4 Operating room in 1907 showing aseptic precautions



2.2 Ventilated Operating Rooms

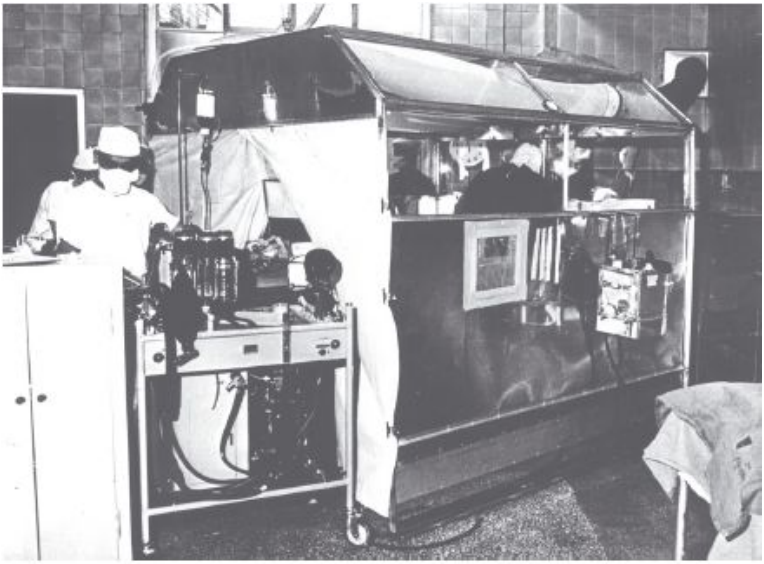
Although the operating rooms built before the 1950s had contamination control methods that were similar to modern cleanrooms, an important omission was positive ventilation with filtered air. Artificial ventilation was rarely used in hospitals in temperate climates until the 1940s and then more for comfort than for contamination control. It was only after the end of the 1939-1945 Second World War that ventilation in hospitals was clearly advocated for contamination control. The problems of airborne infection of people in crowded situations that occurred in wartime, e.g. in submarines, air-raid shelters and army barracks, were studied. Microbiological warfare required the airborne dispersion of micro-organisms and this was also studied. In addition, the airborne bacterial sampler was invented, and the ventilation of rooms and the

aerodynamics of particles were studied, all during the Second World War.

By the early 1960s, most of the principles that dictate the performance of non-unidirectionally ventilated rooms were known. Also established was the fact that people were the source of airborne bacteria, these being dispersed on skin particles. Open-weave cotton garments did little to prevent this dispersion and tightly woven fabrics were found to be necessary.

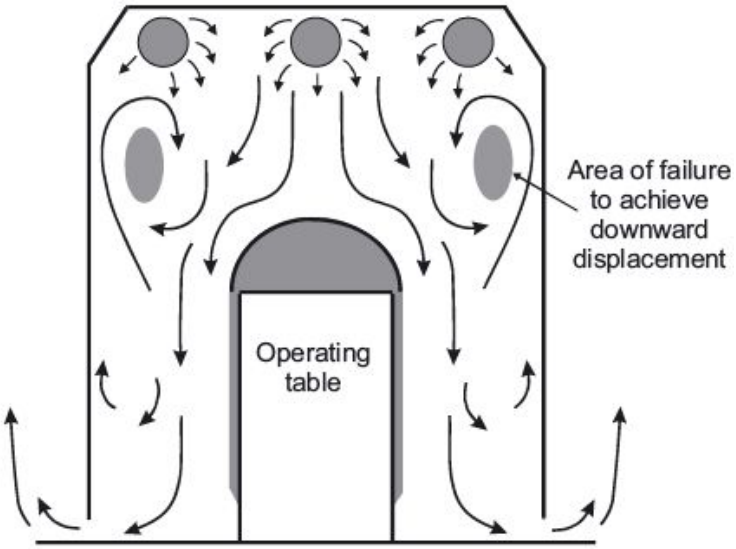
In 1960 Blowers and Crew attempted to obtain a downward 'piston' of air (unidirectional airflow, although they did not call it that) from an air diffuser fitted over the entire ceiling in an operating room in Middlesborough, England. Unfortunately, because of the thermal air currents from people and the operating room lamp, as well as movement of people, the low air velocity was disrupted; this made it impossible to achieve good unidirectional airflow. This was the situation when Professor Sir John Charnley (with assistance from Hugh Howorth) decided to improve the ventilation in his operating room at Wrightington Hospital near Manchester in England.

Figure 2.5 The Charnley-Howorth 'greenhouse'



Charnley was a pioneer of hip replacement surgery. He devised an operation to replace a diseased joint with an artificial joint made of plastic and metal. His initial operations gave a sepsis rate in the region of 10%. This was a major problem, and so he initiated a number of preventative measures. Using the knowledge that existed at the time (1961), he and Howorth attempted to perfect the 'piston effect' of a downward flow of air. Instead of using the whole of the operating room ceiling (as Blowers and Crew had done) they restricted it to a much smaller area and hence improved the downward flow of air. They used a 7 ft × 7 ft 'greenhouse' placed within the operating room. This is shown in Figure 2.5. Figure 2.6 shows the diagram Charnley published of the airflow in the 'greenhouse'; it can be seen that reasonable downward unidirectional airflow was achieved close to the operating table.

Figure 2.6 Section through Charnley's original 'greenhouse' system showing the airflow



Charnley and Howorth increased the air supply volume and incorporated design improvements using the knowledge gained from work on laminar (unidirectional) airflow systems in the USA and elsewhere. Charnley introduced improvements to the fabric and design of the clothing worn by the operating team to minimise the dispersion of microbes. He found that the improvements to the ventilation of the operating room and the clothing substantially reduced the concentration of airborne bacteria. These reductions were paralleled with reductions in the rate of deep hip infection from about 10% in 1959, when his operating room conditions were poor, to less than 1.0% by 1970 when all his improvements were complete. The Medical Research Council of the United Kingdom confirmed in the 1980s that the use of unidirectional

airflow enclosures with occlusive clothing would reduce the rate of joint sepsis to one quarter of that found in conventional non-unidirectional airflow operating rooms.

2.3 Early Industrial Cleanrooms

In engineering industries, similar advances were being made. The development of the first cleanrooms for industrial manufacturing started during the Second World War, mainly in an attempt to improve the quality and reliability of instrumentation used in guns, tanks and aircraft. It was realised that the cleanliness of the production environment had to be improved, or items such as bombsights would malfunction. Figure 2.7 is a photograph, taken in the nose of a B-17 bomber, of a Norden bombsight that was used in American planes in the Second World War to ensure accurate bombing. As there were gear wheels, ball bearings and a gyroscope that could cause inaccuracies if dirt were introduced, clean conditions were needed for manufacture.

Figure 2.7 Norden bombsight in the nose of a B-17 bomber

To achieve cleanliness it was assumed that cleanrooms were kept clean like people's homes. Surfaces like stainless steel, which did not generate particles, were used and kept clean. It was not appreciated that the airborne dispersion of large quantities of particles by machines and people needed to be minimised by supplying large quantities of clean air. For example, the dominant idea in a pharmaceutical production room was that it had to be kept free of microbes by the use of copious quantities of disinfectants. The walls were made suitable for this

purpose by being tiled, and the floor would be a terrazzo-type having a gully and drains to remove the disinfectant. Ventilation was very basic, there being few air changes per hour, and there was little in the way of air movement control within the room, or between the production area and outside areas. Personnel were dressed in cotton clothing similar to that used in the operating rooms of that era, and changing areas, if they existed, were very basic.

Work on nuclear fission, as well as biological and chemical warfare research carried out during the Second World War, were the driving forces for the development of High Efficiency Particulate Air (HEPA) filters to contain the dangerous radioactive, microbial or chemical contaminants.

Figure 2.8 Gyroscope production room at Western Electric

Use of the same type of filters allowed cleanrooms to be supplied with very clean air, and low levels of airborne contamination to be achieved.

Rooms with large volumes of well-filtered air supplied by ceiling diffusers were built between 1955 and the early 1960s. In the early 1950s the Western Electric Company in Winston-Salem, NC, USA was having a major problem in manufacturing missile gyroscopes. About 99 out of 100 gyroscopes were being rejected, the problem being identified as dust. It was decided that a 'dust-free' production room should be built and this was designed by the AC Corporation and completed in 1955. Figure 2.8 shows the room soon after production started.

This may be the first production cleanroom built that recognised all of the basic requirements of a cleanroom. Personnel wore synthetic fabric clothing with a cap; they also had a locker room for changing clothes. Construction materials were chosen for ease of cleaning and to minimise the production of particles. Cracks and corners were minimised, the vinylcovered floors were coved onto the wall and the lighting was flushmounted to minimise dust accumulation. As can be seen in the back righthand side of the photograph, pass-through windows were used. The airconditioned supply was filtered through HEPA or 'absolute' filters that were capable of removing 99.95% of 0.3 μm particles, and the room was positively pressurised.

2.4 Unidirectional Airflow Cleanrooms

The watershed in the history of cleanrooms was the invention, in 1960, of the 'unidirectional' or 'laminar air'

concept of ventilation at the Sandia Laboratories, Albuquerque, New Mexico, USA. This was a team effort, but it is to Willis Whitfield that the main credit goes. Shown in Figure 2.9 is a photograph of Willis Whitfield in his original room that was built in 1961.

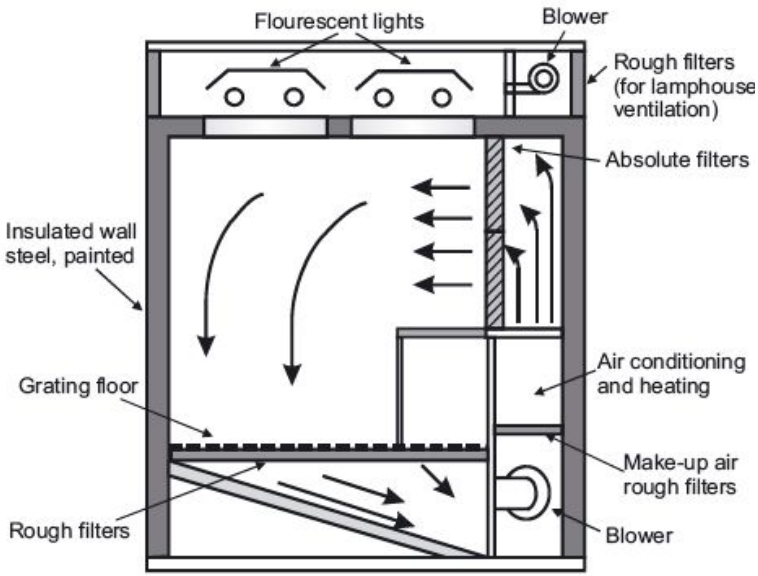
The room was small, being 6 ft wide by 10 ft long by 7 ft high (1.8 m × 3 m × 2.1 m). Instead of the air being supplied by ceiling diffusers and mixing with the room air in an uncontrolled manner, it was supplied by a bank of HEPA filters. This ensured that air moved in a unidirectional way from the filters, across the room, and out through the floor grilles.

Figure 2.9 Willis Whitfield in his original laminar air room

Shown in Figure 2.10 is a cross-sectional drawing of the original unidirectional airflow room. It may be seen that anyone working at the bench in the room should not

contaminate anything in front of them, as their contamination would be swept away.

Figure 2.10 A cross-section of the original unidirectional cleanroom



The invention at Sandia was publicised in*Time* magazine of April 13th 1962, and this article created a great deal of interest. The article was as follows:

'Mr Clean

Scientists at the Sandia Corp. in Albuquerque, where nuclear weapons are designed and assembled, have a passion for cleanliness. They have to. As weapons components are made smaller and still smaller, the presence of a single particle of dust can make larger and

still larger trouble. The strictest housekeeper in all Sandia is Texas-born Physicist Willis J. Whitfield, creator of the Whitfield Ultra-Clean Room. "I thought about dust particles," he says with a slight drawl. "Where are these rascals generated? Where do they go?" Once he answered his own questions Physicist Whitfield decided that conventional industrial clean rooms are wrong in principle.

The usual system in clean rooms, which are necessary for an everincreasing number of industrial operations, is to keep dust particles from being released. Smoking is forbidden; so are ordinary pencils, which give off graphite particles. People who work in the clean rooms are "packaged" in special boots, hoods and coveralls and are vacuum-cleaned before they enter. The rooms themselves are vacuumed continually. But despite all these precautions each cubic foot of their air still contains at least 1,000,000 dust particles that are.3 microns (.000012 in.) or larger in diameter. This is a vast improvement over ordinary air, but Whitfield was sure he could do better. Abandoning the idea of keeping dust particles from being generated, he decided to remove them as soon as they appear.

The Whitfield Ultra-Clean Room looks like a small metal house trailer without wheels. Its floor is metal grating. It is lined with stainless steel, and along one wall the workbench faces a 4 ft by 10 ft bank of "absolute filters" that remove all particles above.3 microns from a slow stream of air. Most clean rooms use their filters simply to clean up incoming air. Whitfield's trick is to make the clean air from the filters keep the room clean. It flows at 1

mph (a very faint breeze) across the workbench and past the people working at it. Workmen can dress in ordinary clothes and smoke if they desire. Dandruff, tobacco smoke, pencil dust and any other particles generated are carried away by the clean air, whisked down through the grating floor, and discharged outdoors. Every six seconds the room gets a change of ultra-clean air. No particles get a chance to circulate, and as a result, Physicist Whitfield's room is at least 1,000 times as clean as the cleanest of its competitor.'

The concept of unidirectional airflow cleanroom ventilation was very quickly adopted by a large variety of industries, as high-quality cleanrooms were urgently required.

Acknowledgements

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3

Cleanroom Classification Standards

3.1 The History of Standards

The first standard written for cleanrooms was published by the American Air Force on March 1961 and known as Technical Manual TO 00-25-203. This considered cleanroom design and airborne particle standards, as well as operating procedures such as: entry procedures; clothing; restriction of certain articles; cleaning of materials; procedures for cleaning the room. However, the standard that had the most influence on the design and operation of cleanrooms, and is the basis of the present ISO standard, ISO 14644-1:1999, was Federal Standard 209.

The Sandia Corporation team that invented the unidirectional airflow concept, aided by others from the USA military, industry and governmental agencies, produced the first Federal Standard 209 in 1963. This standard discussed both non-unidirectional airflow and unidirectional airflow cleanrooms. In the standard there is the first mention of a requirement to measure particles of ≥ 0.5 μm by means of optical particle counters; these instruments had just become commercially available. It is often asked why 0.5 μm was adopted as the standard size on which the Federal Standard was based. The answer is that it was the ‘art of the achievable’, this being the smallest size that could be accurately measured by the particle counters available at that time.

It has also been asked why 90 ft/min was suggested in the Federal Standard 209 as the velocity to be used in unidirectional airflow cleanrooms. It has been said that this was the velocity theoretically calculated to remove a particle dropped in front of the supply filter in the first 'laminar flow' room at Sandia Corporation. An alternative opinion given was that the only air supply fan available to Willis Whitfield gave this air velocity. I have discussed this with Willis Whitfield who said that the fan was capable of giving velocities of between 50 ft/min and 200 ft/min. When the room was run at high velocities, it was very noisy and expensive to maintain. When run at 50 ft/min, and with only one person in it, it was possible to obtain low particle counts. However, if several people were in the room, a velocity of about 90 ft/min to 100 ft/min was required to control the particle contamination. As he and his team were under pressure to produce data for the design of unidirectional airflow cleanrooms, and little time was available for a thorough scientific evaluation, this velocity was adopted.

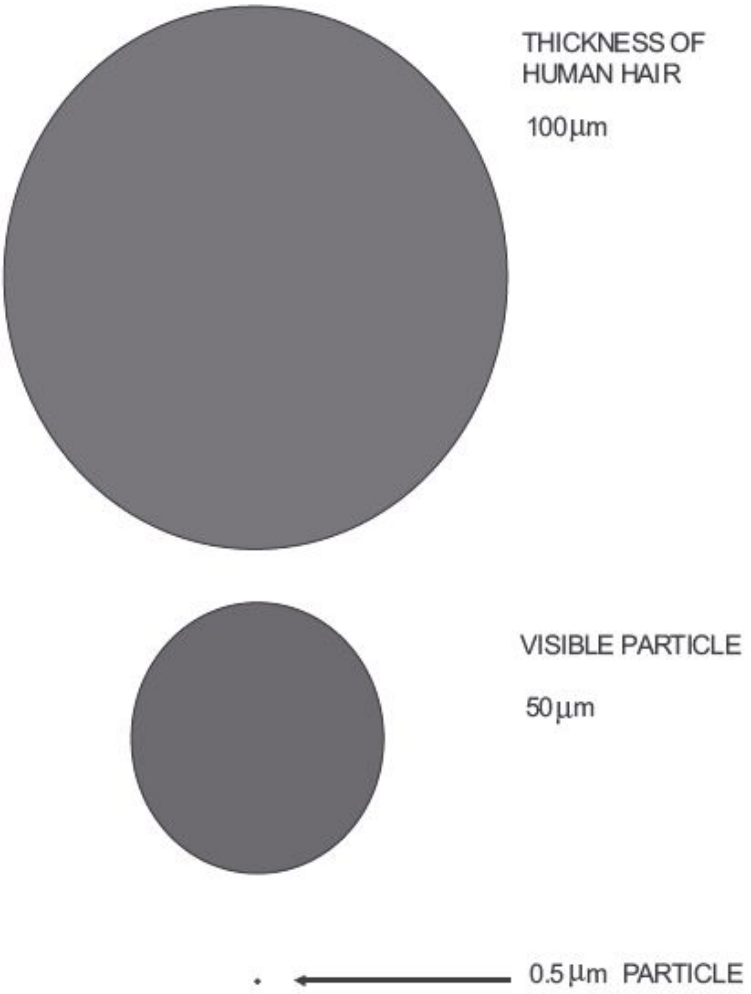
Another question asked about the Federal Standard, and hence about ISO 14644-1:1999, is about 'class limits'. These class limits give the maximum concentration of particles at each particle size for each cleanroom classification and are shown in Figure 3.2. It has been suggested that these limits were derived in some theoretical way. This is not so, the lines being obtained from the results of air sampling in a large number of cleanrooms.

Cleanroom standards have been developed to cater for the needs of the expanded cleanroom industry. These are discussed below.

3.2 The Basis of Cleanroom Standards

It is best to start this section of the chapter by giving some indication of the size of particles used in cleanroom standards. The unit of measurement is a micrometre, one micrometre (1 μm) being one millionth of a metre. The name 'micrometre' is often abbreviated to 'micron'. Shown in Figure 3.1 is a drawing comparing particle sizes. A human hair, a size that can be readily appreciated, is approximately 70–100 μm in diameter. Another size that helps to put particle sizes in a cleanroom into perspective is the size of particle that can be seen on a surface. This is approximately 50 μm in diameter, although this varies quite considerably depending on the acuteness of vision, the lighting intensity, the colour of the particle, and the colour of the background, and much smaller particles can be seen in optimal conditions.

Figure 3.1 Comparison of particle diameters



Cleanrooms are classified according to the cleanliness of the air inside them. The first classification of cleanrooms was contained in Federal Standard 209 of the USA. Although Federal Standard 209 was withdrawn in 2001, following the publication in 1999 of International Standard

ISO 14644-1, its classifications are still widely used. However, as ISO 14644-1 has now been adopted throughout the world, its cleanroom classifications are used in this book.

3.3 Federal Standard 209

The first Federal Standard 209 was published in 1963 in the USA and titled 'Cleanroom and Work Station Requirements, Controlled Environments'. It was revised in 1966 (209A), 1973 (209B), 1987 (209C), 1988 (209D) and 1992 (209E), and withdrawn in 2001. The cleanroom class limits are shown in Table 3.1. The actual class of a cleanroom is found by measuring the number of particles ≥ 0.5 µm in one cubic foot of room air, and determining which class limit is not exceeded; this is the cleanroom classification.

Table 3.1 Federal Standard 209 D class limits

Class	Particles / ft^3				
	≥ 0.1 µm	≥ 0.2 µm	≥ 0.3 µm	**≥ 0.5 µm**	≥ 5.0 µm
1	35	7.5	3	**1**	NA
10	350	75	30	**10**	NA
100	NA	750	300	**100**	NA
1,000	NA	NA	NA	**1,000**	7
10,000	NA	NA	NA	**10,000**	70
100,000	NA	NA	NA	**100,000**	700

3.4 ISO Standard 14644-1:1999

The International Organization for Standardization (ISO) has developed a series of cleanroom standards. These

cover a wide variety of important cleanroom issues such as classification, design, testing, operation and biocontamination. The first of the series, published in 1999, is ISO 14644-1 Cleanrooms and associated controlled environments Part 1: Classification of air cleanliness. This gives the cleanroom classification method. Other ISO standards in the series are discussed later in this chapter and in Chapter 4. Information on where to purchase ISO 14644–1 is also given in Chapter 4. Shown in Table 3.2 are the particle cleanliness classes given in ISO 14644–1:1999.

Table 3.2 Selected airborne particulate cleanliness classes for cleanrooms and clean zones shown in ISO 14644–1:1999

ISO Classification number (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with Equation 3.1)					
	≥0.1μm	≥0.2μm	≥0.3μm	≥0.5μm	≥1μm	≥5.0μm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

The ISO classification shown in Table 3.2 is based on the following equation:

Equation 3.1

$$C_n = 10^N \times \left[\frac{0.1}{D}\right]^{2.08}$$

where:

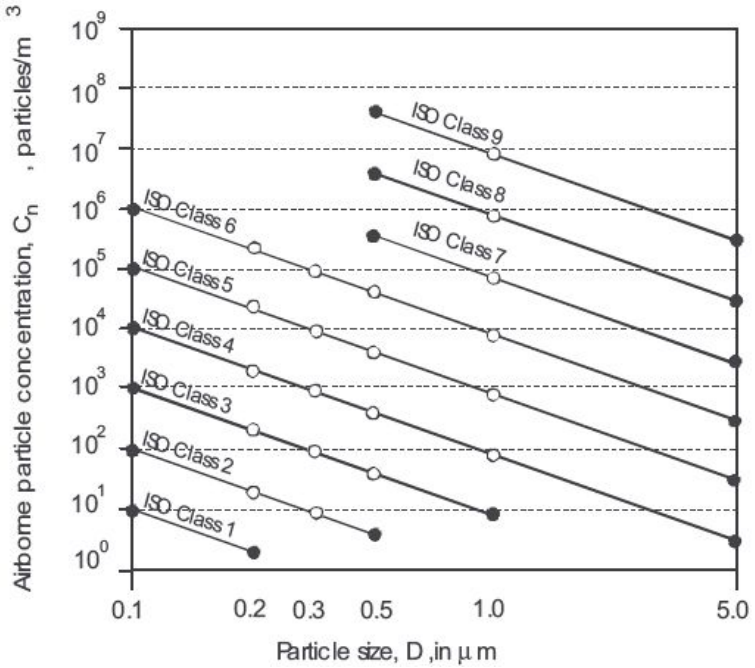
Cn	is the maximum permitted concentration (in particles/m^3 of air) of airborne particles that are equal to, or larger, than the considered particle size. C_n is rounded to the nearest whole number, using no more than three significant figures.
N	is the ISO classification number, which shall not exceed the value of 9. Intermediate ISO classification numbers may be specified, with 0.1 the smallest permitted increment of N.
D	is the considered particle size in µm.
0.1	is a constant with a dimension of µm.

It should be noted that Federal Standard 209 is the basis of ISO 146441:1999 and there is a relationship between the two classification methods. If the particle concentration/m^3 in the ISO standard is divided by 35.2 the count is converted to particles/ft^3, which is almost identical to the counts given in Federal Standard 209. The equivalent Federal Standard 209 classification to ISO 14644–1:1999 is shown in Table 3.3 at the 0.5 µm particle size, e.g. ISO Class 5 at 0.5 µm is equivalent to Federal Standard 209 Class 100 at 0.5 µm.

Table 3.3 Comparison between selected equivalent classes of FS 209 and ISO 14644–1:1999

ISO 14644-1 Classes	Class 3	Class 4	Class 5	Class6	Class 7	Class 8
FS 209 Classes	Class 1	Class 10	Class 100	Class 1000	Class 10 000	Class 6 100 000

Figure 3.2 Graphical representation of ISO-class concentration limits for selected ISO classes.



The same information contained in Table 3.2, but in a graphical form, is shown in Figure 3.2.

It should be appreciated that the airborne particle concentration of a cleanroom is dependent on the particle-generating activities in the room. If a room is empty, a very low particle concentration can be achieved, this closely reflecting the quality of air supplied by the high efficiency filters. If the room has production equipment in it that is operating, there is likely to be a greater particle concentration, but the greatest concentrations occur when the room is in full production with machinery and personnel all working and therefore all generating contamination. The classification of the room can therefore be carried out in these three different occupancy states which are defined in ISO 14644-1:1999 as follows:

As built: condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present

At-rest: condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present

Operational: condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon

ISO 14644-1:1999 also gives a method by which the classification of a cleanroom is measured. The method for determining the number of sampling locations, the sampling volume and how the airborne particles are

analysed and reported is discussed in Chapter 14 of this book.

ISO 14644-1:1999 also includes a method for specifying a cleanroom in terms of particles outside the size range given in Table 3.2. Smaller particles (≤ 0.1 μm), known in the standard as ultrafine particles, are of particular importance in the semiconductor and similar industries, and larger (≥ 5 μm) particles known as macroparticles are of interest in industries such as those parts of the medical device industry where small particles are of no practical importance. Fibres can also be specified. The M descriptor method employed with macroparticles uses the format:

M(a; b);c

where

a	is the maximum permitted concentration of macroparticles (expressed as macroparticles/m^3 of air);
b	is the equivalent diameter associated with the specified method for measuring macroparticles (expressed in micrometres);
c	is the specified measurement method.

An example would be: 'M (1 000; 10 μm to 20 μm); cascade impactor followed by microscopic sizing and counting'. M_{fibre} is used for fibres. A similar classification method is used with 'ultrafine' particles.

3.5 Pharmaceutical Cleanroom Classification

Cleanrooms used for pharmaceutical manufacturing have their own standards. The two most widely used are those published by agencies in the European Union and the USA. These are the most important guides, as other countries are covered by a mutual recognition system, or their local standards are more than adequately achieved by the requirements in the EU and FDA documents.

3.5.1 European Union Guidelines to Good Manufacturing Practice

The pharmaceutical 'standard' used in Europe is called 'The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use'. The most relevant part is Annex 1, which was most recently revised in 2008. These guidelines are often called the European Union Guidelines to Good Manufacturing Practice (EU GGMP). It is often called the EU GMP but as this does not appear to be the correct abbreviation it is not used in this book. It is available in various languages of the EU and information as to where they can be obtained is given in Chapter 4.

For the manufacture of sterile medicinal products, four grades of airborne cleanliness are given. The grade required is determined by the type of product and the part of the process that has to be protected from contamination. The grades given in Annex 1 of the EU GGMP are as follows:

'Grade A: *The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials,*

making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 - 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

Grade B: *For aseptic preparation and filling, this is the background environment for the grade A zone.*

Grade C and D: *Clean areas for carrying out less critical stages in the manufacture of sterile products.'*

Table 3.4 Maximum particle requirements for grades of airborne cleanliness given in EU GGMP

	Maximum permitted number of particles/m^3 equal to or greater than the tabulated size			
	at rest		in operation	
Grade	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	not defined	not defined

The airborne particulate classification of these grades is shown in Table 3.4. It may be see that the particle concentrations per m^3 are given both for particles ≥0.5 µm

and for particles ≥5.0 μm and they should be measured both 'at rest' and 'in operation'. The 'at rest' condition is defined in Annex 1 as *'the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present*.' The 'at rest' condition is the condition that is used to ascertain if the cleanroom is working correctly and the classification method is as given in ISO 14644-1:1999. 'In operation' is defined as *'the condition where the installation is functioning in the defined operating mode with the specified number of personnel working*.' The 'in operation' conditions may be measured during normal manufacturing operations or in simulated operations, '*and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices*.' The following information is given in Annex 1 about Table 3.4.

'For classification purposes in Grade A zones, a minimum sample volume of 1m^3 should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles Ů 5.0 μm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO 14644–1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles Ů5.0µm in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.'

Annex 1 should be consulted for information on how 'in operation' measurements in the cleanrooms should be carried out.

Table 3.5 Examples of cleanroom conditions required for different operations

Grade	**Examples of operations for terminally sterilised products**
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling
Grade	**Examples of operations for aseptic preparations**
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing.

Examples of operations to be carried out in the various grades of cleanliness are given in Table 3.5.

Microbiological monitoring is also required to demonstrate microbiological cleanliness in the cleanroom during production. The recommended limits are given in Table 3.6.

Table 3.6 Recommended limits for microbial contamination

Grade	Air Sample cfu/m^3	Settle Plates (diam. 90 mm), cfu/4 hours (b)	Contact Plates (diam. 55 mm), 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	-

Notes

(a) These are average values.

(b) Individual settle plates may be exposed for less than 4 hours.

Where an isolator is used to give additional protection against contamination, the air classification required for the cleanroom in which it is sited '*depends on the design of the isolator and its application*.' '*For asepticprocessing it should be at least grade D*.'

'Blow/fill/seal equipment used for aseptic production, which is fitted with an effective grade A air shower, may be installed in at least a grade C environment, provided grade A/B clothing is used. The environment should comply with the viable and non-viable limits 'at rest', and the viable limit only when in 'operation'. Blow/fill/seal equipment used for the production of products for terminal

sterilisation should be installed in at least a grade D environment.'

3.5.2 FDA Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (2004)

This document was produced in 2004 by the U.S. Food and Drug Administration (FDA). Information as to where it can be obtained is given in Chapter 4. Any pharmaceutical companies that produce sterile drugs for use in the USA, including countries outwith the USA, are inspected and approved by the FDA regulatory inspectors and must comply with the FDA Guidance.

The FDA Guidance contains a similar table to that given in Annex 1 of the EU GGMP for the required clean air classification. However, the FDA differs from the EU GGMP in that the processing areas need only conform to the required classification in the**operational** condition and not in the 'at rest' condition. They also do not require counting of particles ≥5 μm. The requirements are given in Table 3.7

Table 3.7 – Air classification[a]

Clean Area Classification (0.5 µm particles/ft^3)	ISO Designation[b]	≥ 0.5µm particles/m^3	Microbiological Active Air action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

Notes:

a	All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity
b	ISO 14644–1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c	Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d	The additional use of settling plates is optional.
e	Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

The FDA Guidance document identifies two clean areas of importance: the 'critical area' and the 'supporting clean areas' associated with it.

A**critical area** is described in the FDA document as:

'one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility. Activities conducted in such areas include manipulations (e.g. aseptic connections, sterile ingredient additions) of these

sterile materials prior to and during filling and closing operations.'

In a critical area, air is sampled at representative locations not more than 1 foot away from the work site, within the airflow, and should have a count of particles ≥ 0.5 μm of no more than 3520/m^3 during filling and closing operations.

The**supporting clean areas** are described in the Guidance as follows:

'Many support areas function as zones in which nonsterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred.'

The FDA recommends that during production the supporting clean area immediately adjacent to the aseptic processing line meets, at a minimum, Class 10,000 (ISO 7) standard. They also write that*'manufacturers canalso classify this area as Class 1,000 (ISO 6) or maintain the entire asepticfilling room at Class 100 (ISO 5). An area classified at a Class 100,000(ISO 8) air cleanliness level is appropriate for less critical activities (e.g. equipment cleaning).'*

In Appendix 1 there is information about isolators. The recommended clean air requirements are that*'the interior of the isolator should meet Class 100 (ISO 5) standards'* and that *'the classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g. transfer ports) as well as the number of transfers in*

and out of the isolator' but they write that 'a Class 100,000 (ISO 8) background is commonly used.'

In Appendix 2 information is given about blow-fill technology. The FDA Guidance considers that *'the classified environment surrounding the BFS machinery should meet Class 100,000 (ISO 8), or better'. 'Air in the critical area' i.e. where 'sterile products or materials are exposed (e.g., parison formation, container moulding or filling steps)' 'should achieve Class 100 (ISO 5) microbiological standards, during operations', and 'a well-designed BFS system should normally achieve Class 100 (ISO 5) airborne particle levels.'*

The FDA Guidance gives information about the requirements for various cleanroom tests. This will be discussed at appropriate places in this book.

3.6 Classification of Cleanrooms with Airborne Chemical Contamination

An international classification scheme for airborne chemical contamination was introduced in 2006 through the publication of ISO 14644–8:2006. This standard is called 'Cleanrooms and associated controlled environments Part 8: Classification of airborne molecular contamination'. The classification method used is based on what is called the 'ISO-AMC descriptor format' and is given in the following way:

ISO-AMC Class N(X)

Where, N is the ISO–AMC class, which is a logarithmic index of the measured concentration (c_X) of a group, or individual substance (known as X), measured in g/m^3. The index will fall within a limited range of 1 to −12.

Hence,

$$N = \log_{10} [c_x]$$

The types of the airborne chemical contamination considered in ISO 14644-8 fall into the following broad classification groups:

- acid (ac)
- base (ba)
- biotoxic (bt)
- condensable (cd)
- corrosive (cr)
- dopant (dp)
- total organic (or)
- oxidant (ox)
- any other group, or individual group of substances

The concentration of a given substance, or group of substances, is measured in the cleanroom and the classification determined. If, for example, the concentration of total organics (or) in the air of a cleanroom was found to be $10^{-4} g/m^3$, the classification of the room for organics would be 'ISO–AMC Class –-4 (or). If the concentration of condensable materials was $10^{-7} g/m^3$, the classification would be 'ISO–AMC Class −7 (cd).

3.7 Classification of Cleanrooms with Surface Contamination

At the time of writing this book, ISO standards are being developed for the classification of surface cleanliness in terms of chemicals and in terms of particles. These two standards are to be known as:

ISO 14644–9*Cleanrooms and associated controlled environments - Part 9: Classification of surface particle cleanliness*

ISO 14644–10*Cleanrooms and associated controlled environments - Part 10: Classification of surface chemical cleanliness.*

Acknowledgement

Table 3.2 and Figure 3.2, as well as extracts of ISO 14644–1, are reproduced by permission of the British Standards Institution.

4

Information Sources

It is important to be able to obtain current information about cleanrooms from the latest standards, books, recommended practices, magazines and other documents, as well as from cleanroom societies and the internet. This chapter gives the source of such information. Details of the sources were current when this book was published but contact information is continually changing. Readers are therefore advised to always check that the information they are using is up to date.

4.1 The International Confederation of Contamination Control Societies (ICCCS)

The ICCCS is a confederation of societies that have an interest in cleanroom technology. The present membership is as follows:

ASCCA: Associazione per lo Studio ed il Controllo della Contaminazione Ambientale, Italy

ASENMCO: Association of Engineers for Microcontamination Control, Russia

ASPEC: Association pour la Prevention et l'Etude de la Contamination, France

BCW: Belgian Cleanroom Workclub, Belgium

CCCS: Chinese Contamination Control Society, China

ICS: Irish Cleanroom Society, Ireland

IEST: Institute of Environmental Sciences and Technology, USA

JACA: Japanese Air Cleaning Association, Japan

RACC: Romanian Cleanroom Society, Romania

R^{3}Nordic: Renhetsteknik och Rena Rum, Denmark, Finland, Norway and Sweden

KACA: Korean Air Cleaning Association, South Korea

SBCC: Sociedade Brasileira de Controle de Contaminacáo, Brazil

SRRT: Schweizerische Gesellschaft für Reinraumtechnik, Switzerland

S2C2: Scottish Society for Contamination Control, Scotland

VCCN: Vereniging Contamination Control Nederland, The Netherlands

VDICCT: VDI Commission for Cleanroom Technology, Germany

Anyone who is interested in the design, testing or operation of cleanrooms is advised to join their local society to keep their cleanroom knowledge up to date. The contact information for the Secretary of ICCCS, and a

current list of the member societies with their contact details is available on the ICCCS web site: www.icccs.net.

4.2 The ICEB

Many people working in cleanrooms have the knowledge and expertise to claim to be cleanroom professionals but may wish to prove it with a certificate obtained by examination through a respected teaching institute. Towards this end, the ICCCS has set up the International Cleanroom Education Board (ICEB) to promote the preparation and accreditation of internationally -recognised educational courses for people who design and construct, test and monitor, operate, and work as operators in cleanrooms. These courses are given by member societies and are accredited within the 'Accreditation Guidelines' of the ICEB to ensure a high standard of course. Further information is obtained through the ICCCS web site: www. icccs.net, where there is a constantly updated list of ICEB accredited courses.

4.3 International Cleanroom Standards

4.3.1 ISO standards

A series of cleanroom standards has been produced by the International Organization for Standardization (ISO). The ISO Technical Committee that is responsible for writing these standards is TC 209, this being a committee of representatives from those national standards bodies that are members of ISO. Experts, nominated by the national standards bodies, write these standards through Working Groups designated by the TC and reporting to it. The

cleanroom standards that have been published, or are under development by the TC, can be found and indeed purchased at www.iso.org/iso/iso_catalogue.htm. At the time of publication of this book, the following standards, which are in two separate series, ISO 14644 and ISO 14698, are either published or are under development.

4.3.1.1 ISO 14644

This consists of the following parts, under the general title 'Cleanrooms and associated controlled environments':

Part 1: Classification of air cleanliness

This gives the airborne particle limits for different classes of cleanroom. It also gives the methods that should be used to measure the airborne particle concentration when testing a cleanroom to determine its class.

Part 2: Specifications for testing and monitoring to prove continued compliance with ISO14644-1

This gives information, including time intervals, for testing a cleanroom to show that it complies with the ISO 14644–1 standard.

Part 3: Test methods

This gives a description of the methods that should be used to test the cleanroom to show it is working correctly.

Part 4: Design, construction, and start-up

This gives general guidance as to how a cleanroom should be designed, constructed and made ready for handing over to the user.

Part 5: Operations

This gives general advice on how to run a cleanroom.

Part 6: Vocabulary

This is a compilation of all the definitions of terms that are listed in the individual parts of the ISO cleanroom standards.

Part 7: Separative enclosures (clean air hoods, gloveboxes, isolators and mini environments)

This gives information on enhanced clean air devices such as isolators and minienvironments.

Part 8: Classification of airborne molecular contamination

This gives a classification scheme for airborne concentrations of specific chemical substances (by individual, group or category) and gives test

methods.

Part 9: Classification of surface particle cleanliness

This gives a classification scheme and other information on surface particle contamination.

Part 10: Classification of surface chemical cleanliness.

This gives a classification scheme and other information on surface chemical contamination.

4.3.1.2 ISO 14698

This consists of two parts under the general title 'Cleanrooms and associated controlled environments-Biocontamination control':

Part 1: General principles and methods

This gives information on how to establish methods for risk management and how to measure micro-organisms in the cleanroom.

Part 2: Evaluation and interpretation of biocontamination data

This gives information on how to deal with the results obtained from measuring micro-organisms in a cleanroom.

The ISO 14644 and ISO 14698 standards discussed above are available throughout the world from the various national standard organisations. In some cases they are translated into the local language. For further information on the various ISO members world-wide and where standards can be bought locally, see: www.iso.org/iso/iso_members. In the UK, these standards have been adopted as British Standards and information about their availability can be obtained from:

BSI British Standards, Customer Services

389 Chiswick High Road

London

W4 4AL

United Kingdom.

Tel: +44 (0)20 8996 9001

Email: http://cservices@bsigroup.com

Web site: www.bsigroup.com

In the USA, the standards are available from the Institute of Environmental Sciences and Technology (IEST) at:

Institute of Environmental Sciences and Technology (IEST) Arlington Place One

2340 Arlington Heights Road, Suite 100

Arlington Heights, IL 60005-4516 USA

Phone: +1 847 981-0100

Email: http://iest@iest.org

Web site: www iest.org

4.3.2 Pharmaceutical standards

The two most commonly standards used in pharmaceutical cleanrooms are available from the European Union and the US Food and Drug Administration (FDA).

4.3.3.1 The European Union Guidelines to Good Manufacturing Practices (EU GGMP)

Pharmaceutical production in the European Union is regulated by a set of documents published by the European Commission and known as 'The Rules Governing Medicinal Products in the European Union'. These documents are available for free download at the following internet address:

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex.

The relevant document is 'Volume 4 Guidelines for good manufacturing practices for medicinal products for human and veterinary use', and Annex 1 of that volume is the document most relevant to cleanroom technology. Annex 1 was available at the time of writing as a free PDF download via the same internet address.

4.3.3.2 Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice

This FDA Guidance can be downloaded free of charge PDF from the web site of the FDA Center for Drug Evaluation and Research at the following internet address- http://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInfo rmation/Guidances/ ucm070342.pdf

4.4 Cleanroom Books

The following is a list of books (in alphabetical order) written in the English language that cover similar topics to this book. These are the books I know to be in print, or were recently printed, and should be available through the internet, bookstore, or requested through a library. I would be pleased to receive any other titles so that the list can be extended.

1.***Cleanroom Clothing Systems: People as a Contamination Source*** by B. Ljungqvist and B. Reinmuller (2004). PDA – DHI Publishing, IL, USA.

2.***Cleanroom Design (Second Edition)*** edited by W. Whyte (1999). Wiley, Chichester, UK.

3.***Clean Room Design, Minimizing Contamination through Proper Design*** by B. Ljungvist, and B. Reinmuller (1997). Interpharm Press, USA.

4.***Cleanrooms-Facilities and Practices*** by M. N. Kozicki with S. A. Hoenig, and P. A. Robinson (1991). Van Nostrand Reinhold, New York, USA.

5.**Conta*mination Control and Cleanrooms*** by A. Lieberman (1992). Van Nostrand Reinhold, New York, USA.

6.***Environmental Monitoring for Cleanrooms and ControlledEnvironments*** edited by Anne Marie Dixon (2006). CRC Press.

7.***Handbook of Contamination Control in Microelectronics*** edited by D. L. Toliver (1988). Noyes Publications, Park Ridge, NJ, USA.

8.***Isolator Technology*** by C. M.Wagner, and J.E. Akers (1995). Interpharm Press, Buffalo Grove, IL 60089, USA.

9.***Isolator Technology - a Practical Guide*** by T. Coles (1998). Interpharm Press, Buffalo Grove, IL 60089, USA.

10.***Introduction to Contamination Control and Cleanroom Technology*** by M. Ramstorp (2000). Wiley-VCH.

11.***Microbial Contamination Control in Pharmaceutical Cleanrooms*** by N Halls (2004). CRC Press.

12. Pharmaceutical Isolators edited by B Midcalf, W.M. Phillips, J.S. Neiger and T. Coles (2004). Pharmaceutical Press, London.

13.***Practical Cleanroom Design*** by R.K. Schneider (1995). Business News Publishing Company, Troy, MI, USA.

14.***Practical Safety Ventilation in Pharmaceutical and BiotechCleanrooms*** by B. Ljungqvist and B. Reinmüller (2006). PDA DHI Publishing, IL, USA.

4.5 Recommended Practices and Guides of the Institute of Environmental Sciences and Technology (IEST)

The IEST in the USA produce a large number of Recommended Practices (RPs) and Guides that cover many topics. They are an invaluable source of information and are available from:

Institute of Environmental Sciences and Technology (IEST)

Arlington Place One

2340 Arlington Heights Road,

Suite 100

Arlington Heights, IL 60005-4516

USA

Phone: +1 847 981-0100

Email: http://iest@iest.org

Web site: Web site: www iest.org

4.5.1IEST Recommended Practices (RPs)

The following RPs are available from the IEST. It should be noted that some of the RPs have been updated several times and the most current edition should be obtained. Also, Recommended Practices are continually being written and current information as to what is available may be obtained from the IEST website.

IEST-RP-CC001: HEPA and ULPA filters

This covers the basic provisions for HEPA and ULPA filter units. The RP provides performance information for 11 filter types, defines six construction grades, and includes a filter selection guide.

IEST-RP-CC002: Unidirectional flow clean-air devices

Covers definitions, procedures for evaluating performance, and major requirements of unidirectional flow clean air devices.

IEST-RP-CC003: Garment system considerations in cleanrooms and other controlled environments

Provides guidance for the selection, specification, maintenance and testing of garments used in cleanrooms.

IEST-RP-CC004: Evaluating wiping materials used in cleanrooms and other controlled environments

Describes methods for testing wipers used in cleanrooms for characteristics related to cleanliness and function.

IEST-RP-CC005: Gloves and finger cots used in cleanrooms and other controlled environments

Describes tests for evaluating gloves and finger cots for use in cleanrooms.

IEST-RP-CC006: Testing cleanrooms

Describes tests to determine the performance of cleanrooms.

IEST-RP-CC007: Testing ULPA filters

Describes a test procedure for production testing of ULPA filters for particle penetration and pressure drop.

IEST-RP-CC008: High efficiency gas-phase adsorber cells

Covers the design and testing of modular gas-phase adsorber cells for use where high efficiency removal of gaseous contaminants is required.

IEST-RD-CC011: A glossary of terms and definitions relating to contamination control

Gives terms and definitions used in the recommended practices.

IEST-RP-CC012: Considerations in cleanroom design

Makes recommendations regarding factors to consider in the design of cleanroom facilities.

IEST-RP-CC013: Calibration procedures and guidelines for selecting equipment used in testing cleanrooms and other controlled environments

Covers procedures for calibrating and verifying instruments used for testing cleanrooms and determining the intervals of calibration.

IEST-RP-CC014: Calibration and characterization of optical airborne particle counters

Covers procedures for calibrating and characterising the performance of optical particle counters (OPCs).

IEST-RP-CC016: The rate of deposition of nonvolatile residue in cleanrooms

Provides a method for determining the rate of deposition of nonvolatile residue on surfaces in cleanrooms.

IEST-RP-CC018: Cleanroom housekeeping – operating and monitoring procedures

Provides guidance for maintaining the correct level of cleanliness in a cleanroom and establishing housekeeping procedures, with tests for establishing the frequency and effectiveness of housekeeping.

IEST-RP-CC019: Qualifications for organisations engaged in the testing and certification of cleanrooms and clean-air devices

Defines qualification standards for organizations that test and certify cleanrooms, clean-air devices, HEPA- and ULPA-filtered systems and associated components. It also establishes professional categories and levels of competence to be used for qualifying personnel who test cleanrooms.

1EST-RP-CC020: Substrates and forms for documentation in cleanrooms

Provides guidance to establish the suitability of substrates and forms used in cleanrooms for the purpose of documentation.

1EST-RP-CC021: Testing HEPA and ULPA filter media

Discusses test methods for physical and filtration properties of HEPA and ULPA filtration media.

1EST-RP-CC022: Electrostatic charge in cleanrooms and other controlled environments

Discusses methods for specifying and evaluating the effectiveness of techniques for controlling electrostatic charge.

1EST-RP-CC023: Microorganisms in cleanrooms

Provides guidelines for the control and quantitative measurement of viable air and surface contamination.

1EST-RP-CC024: Measuring and reporting vibration in microelectronics facilities

Discusses equipment used in the manufacture, measurement and inspection of integrated circuits and other industries sensitive to vibration and sound.

1EST-RP-CC026: Cleanroom operations

This provides guidance for maintaining cleanroom integrity at all times, including during routine maintenance, modifications and equipment replacement. It

also provides a basis for preparing standard operating procedures and outlines test procedures for verifying cleanliness of cleanroom apparatus and surfaces.

1EST-RP-CC027: Personnel practices and procedures in cleanrooms and controlled environments

Provides a basis for establishing personnel procedures and the development of training programmes.

IEST-RP-CC028: Minienvironments

Provides a framework for describing minienvironments for microelectronics and similar applications.

1EST-RP-CC029: Automotive paint-spray applications

Provides recommended procedures for controlling dirt in paint-spray operations.

IEST-RP-CC031: Method for characterizing outgassed organic compounds from cleanroom materials and components.

Describes a method for characterising organic compounds outgassed from materials or components in cleanrooms and other controlled environments.

IEST-RP-CC032: Flexible packing materials for use in cleanrooms and other controlled environments.

Presents a systematic selection method to achieve the protective environment required for the product. It covers

acceptable materials, seals, material properties, compatibility of packaged product environment, and related topics.

1EST-RP-CC034: HEPA and ULPA filter leak tests

Covers definitions, equipment and procedures for leak-testing filters in the factory where they are produced, and in the cleanroom.

4.5.2 IEST Guides

The following Technical Guides are available to complement ISO 14644–1 and ISO 14644–2:

IEST-G-CC1001: Counting airborne particles for classification and monitoring of cleanrooms and clean zones

This guide provides information on methods used to sample air in clean environments using a discrete-particle counter to determine concentrations of airborne particles.

IEST-G-CC1002: Determination of the concentration of airborne ultrafine particles.

This guide supplements the coverage of procedures for determining the concentration of ultrafine particles as provided by ISO 14644–1.

IEST-G-CC1003: Measurement of airborne macroparticles.

This guide covers the sampling of macroparticles, these being the larger particles to be found in cleanrooms.

IEST-G-CC1004: Sequential-sampling plan for use in classification of the particle cleanliness of air in cleanrooms and clean zones. This guide expands the coverage of sequential sampling introduced in ISO 14644–1.

4.6 Cleanroom Journals and Magazines

Controlled Environments: This magazine is published by:

Vicon Publishing, Inc.

4 Limbo Lane

Amherst, NH 03031

USA.

Tel: +1-603-672-9997

Web site: www.cemag.us

CleanRooms: This magazine is published by:

CleanRooms

PennWell

1421 S Sheridan Road

Tulsa, OK 74112 USA.

Web site: http://cr.pennnet.com

Cleanroom Technology: This magazine is published by*:*

HPCi Media Ltd

Paulton House

8 Shepherdess Walk London N1 7LB UK

Tel: +44 (0) 20 7549 2566

Web site: www.cleanroom-technology.co.uk

Journal of the Institute of Environmental Sciences and Technology

This is emailed to members of IEST. It covers a wider field of interest than cleanrooms, but usually has at least one article about cleanroom-related matters in each issue. It is available from:

Institute of Environmental Sciences and Technology (IEST) Arlington Place One

2340 Arlington Heights Road, Suite 100 Arlington Heights, IL 60005-4516

USA

Email: http://iest@iest.org

Web site: http://www iest.org

European Journal of Parenteral and Pharmaceutical Sciences

This is a quarterly journal of the European Sterile Products Confederation (ESPC). It usually has articles concerned with contamination control in pharmaceutical manufacturing and is available from:

European Journal of Parenteral and Pharmaceutical Sciences

Euromed Communications Ltd

The Old Surgery

Liphook Road Haslemere

Surrey GU27 1NL United Kingdom

Tel: +44 (0) 1428 656665

Email: http://info@euromed.uk.com

Web site: www.euromed.uk.com

PDA Journal of Pharmaceutical Science and Technology

The Parenteral Drug Association (PDA) publishes this journal. It usually has articles concerned with contamination control in pharmaceutical manufacturing. It is available from:

Parenteral Drug Association

Bethesda Towers

4350 East West Highway, Suite 150

Bethesda, MD 20814, USA

Tel: +1 (301) 656-5900

Web site: www.pda.org

4.7 Sources of Pharmaceutical Cleanroom Documents

Pharmaceutical and Healthcare Sciences Society

This Society has a selection of books, Technical Monographs and videos. The following PHSS Technical Monographs are relevant to cleanrooms:

PS Technical Monograph No. 2 (revised 2002): Environmental Contamination Control Practice

PS Technical Monograph No. 14 (2005): Risk Management of Contamination (RMC) During Manufacturing Operations in Cleanrooms

PS Technical Monograph No. 16 (2008): Best Practice for Particle Monitoring in Pharmaceutical Facilities

The PHSS can be reached at the following address:

Pharmaceutical and Healthcare Science Society 6a Kingsdown Orchard

Hyde Road

Swindon

Wiltshire, SN2 7RR

United Kingdom

Tel: +44 (0)1793 824254

Email: http://info@phss.co.uk

Web site: www.phss.co.uk

Parenteral Drug Association

This society has a selection of books, monographs and videos. The PDA

can be reached at the following address:

Parenteral Drug Association

Bethesda Towers

4350 East West Highway, Suite 150

Bethesda, MD 20814,

USA

Tel: +1 (301) 656-5900 Web site: www.pda.org

4.8 Training Videos/DVDs

Training videos/DVDs on contamination control are available in various languages from the following company:

Micron Video International

3 Links House

Dundas Lane

Portsmouth, Hants, PO3 5BL

United Kingdom

Web site: www.mvitraining.com

5

Non-unidirectional Airflow and Ancillary Cleanrooms

There are two fundamentally different designs of cleanroom, namely those with unidirectional airflow and those with non-unidirectional airflow. This chapter deals mainly with the non-unidirectional airflow type of cleanroom, although some of its design features are the same as those for unidirectional airflow cleanrooms and will therefore be discussed.

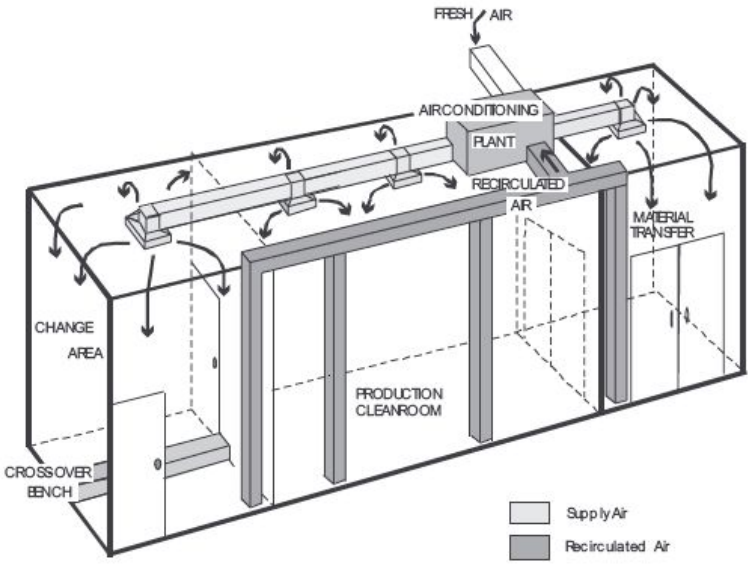
The designs of ancillary cleanrooms, which are the cleanrooms outside the main cleanroom and normally designed as non-unidirectional airflow cleanrooms, are also discussed in this chapter. The ancillary cleanrooms discussed are the cleanroom changing area, where people change out of their outdoor clothing and into cleanroom clothing, and the materials transfer area through which items that are required in the cleanroom are brought in and out.

5.1 Non-unidirectional Airflow Cleanrooms

The ventilation principles of non-unidirectional airflow cleanrooms are similar to those found in most air conditioned rooms, such as offices and shops, where the air from an air conditioning plant is supplied to the room though diffusers in the ceiling. Figure 5.1 shows the layout of a simple non-unidirectional airflow cleanroom.

In a non-unidirectional airflow cleanroom, the supply air moves in a random way throughout the room, mixing with the airborne contamination, diluting it, and removing it through low-level air extracts round the walls. The ventilation method of non-unidirectional airflow cleanrooms is fundamentally different from that of unidirectional airflow cleanrooms where the air enters through filters across the whole ceiling, or wall, and flows in a unidirectional manner through the room. Unidirectional airflow cleanrooms are discussed in the next chapter.

Figure 5.1 A simple non-unidirectional airflow cleanroom



A cleanroom differs from an ordinary air conditioned room in a number of ways. These main differences are as follows:

- the air supply rate is much greater;
- high efficiency air filters are used to remove very small particles and are normally placed immediately before the diffusers through which the air enters the cleanroom;
- the air movement within the cleanroom is designed to assist the removal of contamination from areas that must be particularly clean i.e. critical areas;
- the cleanroom is pressurised with respect to adjacent areas to prevent the ingress of potentially contaminated air from outside the cleanroom through doors, hatches, gaps and leaks;
- construction materials and finishes are chosen to minimise particle shedding and facilitate frequent cleaning.

5.1.1 Air conditioning plant and air distribution system

Figure 5.2 Cleanroom air conditioning plant

A normal air conditioned room, such as an office or shop, will be supplied with sufficient air to achieve comfort

conditions, i.e. to achieve the correct temperature and humidity, and the number of air changes required may be in the region of 2 to 10 per hour. However, a typical non-unidirectional airflow cleanroom is likely to have between 10 and 100 air changes per hour. The higher volume of air dilutes the contamination dispersed in the room and reduces it to below the particle concentration of the specified ISO 14644–1 class.

Shown in Figure 5.2 is a photograph of a typical air conditioning plant used to supply air to a cleanroom. It contains heating and cooling batteries, a humidifier, fan and filters.

Figure 5.3 Diagram of a typical air distribution system used in a cleanroom. A/C = air conditioning

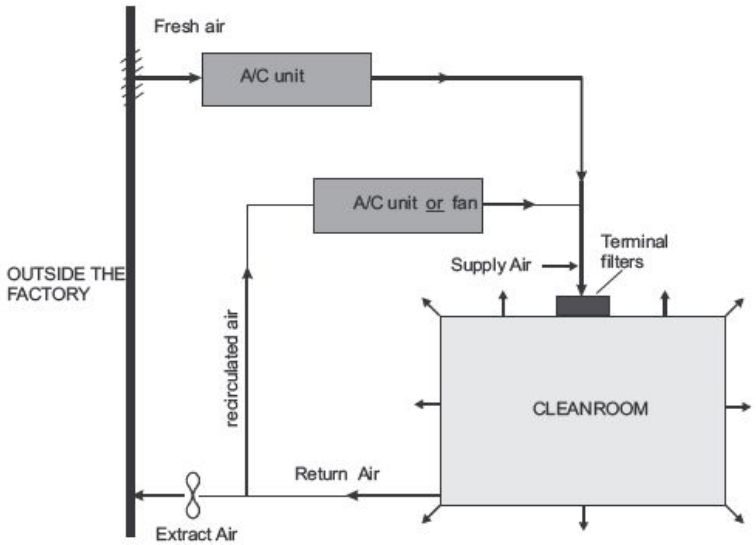


Figure 5.3 gives a layout of a typical air distribution system used in a cleanroom in association with an air conditioning plant. Most of the air from the cleanroom is recirculated through an air conditioning plant but some is extracted to the outside. If the cleanroom generates large amounts of heat, the recirculated air will have to pass through an air conditioning plant to adjust the temperature and humidity, mix with conditioned fresh air, and enter the cleanroom through high efficiency filters. If the cleanroom does not generate large amounts of heat, and therefore the recirculated air does not need much cooling, sufficient air conditioning can be achieved by the conditioned fresh air, and the air from the cleanroom recirculated only by a fan. Another alternative design commonly used in small-to-medium sized cleanrooms is one in which the air recirculated from the cleanroom is mixed with fresh air that does not pass through an air conditioning plant. The mixed air then passes through an air conditioning plant before entering the cleanroom.

It is necessary to provide fresh, outside air to the cleanroom for the health of personnel working there, but fresh air is also required to pressurise the cleanroom against contamination from less-clean adjacent areas. Without the addition of fresh air, the same amount of air would be supplied as extracted, and therefore there would be no excess supply air to pressurise the room. Normally, between 2% and 20% of the total air supply is fresh air, with air-tight rooms requiring a smaller percentage. Also, because larger rooms receive more air than smaller rooms, but do not have proportionally more cracks round doors etc. they generally require a lower percentage of fresh air. If air is additionally extracted to remove undesirable or

toxic contamination from around machinery or processes, and it is discharged directly to the outside, then the fresh air supply will have to be increased to compensate. Excess air supplied to the cleanroom is either extracted by a fan to the outside, or allowed to find its way out of the cleanroom suite via pressure relief flaps, door gaps, hatches etc. to the rest of the factory or laboratory.

5.1.2 Air supply volumes

Air change rate per hour is a common way of describing the air supply to a non-unidirectional cleanroom as this measure determines the extent to which the airborne contamination is diluted. The more air changes per hour, the cleaner the non-unidirectional room. The air change rate is calculated as follows:

Equation 5.1

$$Air\ changes/\ hour = \frac{air\ volume\ rate\ (m^3\ /\ hour)}{volume\ of\ room\ (m^3)}$$

Given in Table 5.1 is the number of air changes that may be required to obtain a given cleanroom classification. As is shown in Equation 5.1, the number of air changes per hour is dependant on the volume (size) of the cleanroom and hence, for the same quantity of dispersed contamination from people and machines, in order to obtain the same particle classification, cleanrooms that are small will require air change rates at the upper end of the range given in Table 5.1, and larger rooms will require those at the lower end. Also, as will be explained in the

next few paragraphs, cleanrooms with high levels of dispersion of contamination from people and machines will need a higher air change rate, and vice versa.

Table 5.1 Air change supply rates for cleanrooms

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

The air changes given in Table 5.1 are 'best guesses' based on experience of designing cleanrooms. Choosing the correct air change rate for a cleanroom is a difficult task, and to ensure that the airborne concentration is not exceeded during use, the design engineer will often provide more air than required to the cleanroom. This results in a cleanroom that is cleaner than is necessary and more expensive to build and run. However, if the dispersion rate of contamination from the people or machinery turns out to be higher than originally anticipated, the specified airborne classification may be exceeded, and this can be a difficult problem to correct after the cleanroom has been built. To assist in the correct choice of air supply volumes the following should be considered.

Although air changes per hour are commonly used to design a cleanroom, the airborne cleanliness of a non-unidirectional airflow cleanroom is determined from the air supply rate (m^3/s, $m^3/hour$ or ft^3/min) and the

generation of contamination in the room i.e. from production machinery and personnel. The airborne conditions in a cleanroom are determined by the following equation.

Equation 5.2

$$Airborne\ concentration\ /m^3 = \frac{number\ of\ particles\ (or\ microbes)\ dispersed\ /\ s}{air\ volume^{*}\ to\ room\ (m^3\ /\ s)}$$

* including any contributed from clean air devices within the room

This equation can only be used with a non-unidirectional airflow system as it requires the room air to be well mixed, as occurs in a non-unidirectional airflow cleanroom (not unidirectional airflow). It also assumes that the air supply does not contribute to airborne contamination in the room and that therefore the high efficiency supply filters are sufficiently efficient for the purpose, and have been checked for leaks.

It can be deduced from the above information that a non-unidirectional airflow cleanroom is dirtier if (a) less air is supplied, (b) more people are in the cleanroom, (c) cleanroom garments are used that are less effective in preventing dispersion of contamination from people, and (d) there is more contamination from production machinery and processes. A further factor is that if there is a clean air device in the cleanroom that takes its air from the cleanroom and discharges filtered air back into it, this can work the other way and improve the quality of air in the cleanroom. All these variables should therefore be

taken into consideration when determining the air supply to a non-unidirectional flow cleanroom.

The airborne concentration measured in the ‘as built’ occupancy state should always be low as, by definition, the production machinery is not working and personnel are not present (although the testers are usually present). The airborne particles and microbe-carrying particles must therefore come from the people testing the room, or from leaking filters. With correctly functioning filters the airborne contamination concentration should be very low. Similarly, the airborne particle concentrations in the ‘at rest’ occupancy state are likely to be low if there is no machinery working. However, in the ‘operational’ occupancy state, a full compliment of personnel will be present and the machinery will be working. Hence, many more particles and microbes will be dispersed and it is quite common to find that the airborne concentration of contaminants will be 10 to 100 times greater than the room ‘at rest’. The ‘operational’ occupancy state is the condition that determines the required air supply. Therefore, it is the particle concentration limit in the operational state that must be given in the brief to the design engineer. These requirements can be ascertained by reference to ISO 14644–1

The present state of knowledge of cleanroom technology requires that an informed guess must be made as to the required number of air change per hour required for a cleanroom. However, this guess will be more informed if an experienced design engineer is chosen who has already designed cleanrooms of a similar size and layout, with a

similar number of personnel and type of manufacturing machinery in the cleanroom.

5.1.3 High efficiency air filters

A cleanroom uses air filters that are much more efficient than those used in offices etc. Cleanroom filters would be normally be better than 99.97% efficient in removing particles greater than about 0.3 μm from the room's air supply. These filters are known as High Efficiency Particulate Air (HEPA) filters, although Ultra Low Penetration Air (ULPA) filters, which have an even higher efficiency, are used in microelectronic fabrication and similar cleanrooms. Most cleanrooms use HEPA or ULPA filters, but in the lowest standards of cleanrooms they are not essential. In an ISO Class 8 room, bag-type filters, with an efficiency near to 90% against particles ≥ 0.5 μm can be used, two filters in series being preferred.

In most cleanrooms, HEPA or ULPA filters are installed at the point where the air is discharged into the room (see Figure 5.1). In normal air conditioning systems in offices etc., the final air filters are usually placed as the last component in the air conditioning plant and the filtered air is distributed by air ducts to the air supply diffusers. However, particles may be drawn into the air supply ducts at joints, or come off duct surfaces and pass into the room. The filters in cleanrooms are therefore placed in a terminal position of the air supply ducts that supply a cleanroom. In lower standards of cleanroom, such as ISO Class 8, the particles that enter, or come from, the ducts will be a small proportion of the total airborne count and filters are occasionally installed in the traditional position just after

the central air conditioning plant. Another reason for the use of terminal filters is the large air volume supplied to a cleanroom. This requires a very large area of filtration and it is more practical to distribute the filtration across all the supply air outlets rather than to concentrate it at the central plant. High efficiency air filters are described in greater detail in Chapter 9.

5.1.4 Air movement within non-unidirectional airflow cleanrooms

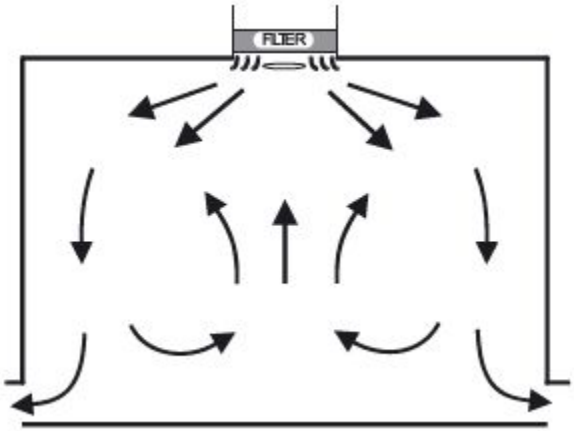
The type, number and placement of air supply diffusers, as well as extract grilles, must be considered in a non-unidirectional airflow cleanroom so as to ensure the cleanest conditions. It is possible to supply the air to a cleanroom with, or without, an air diffuser.

Figure 5.4 Four-way ceiling diffuser

Air diffusers are used in many non-unidirectional airflow rooms at the point where the supply air enters a room i.e. just after the terminal high efficiency filter. Diffusers are designed to minimise draughts and ensure good air mixing. They should therefore be selected so that they are sufficient in number and size to give good mixing and draught-free conditions; although this requirement is largely dictated by the size and nominal face velocity of the air filters (usually 0.45 m/s). Shown in Figure 5.4 is a photograph of a 4-way type of diffuser, which distributes air in four directions.

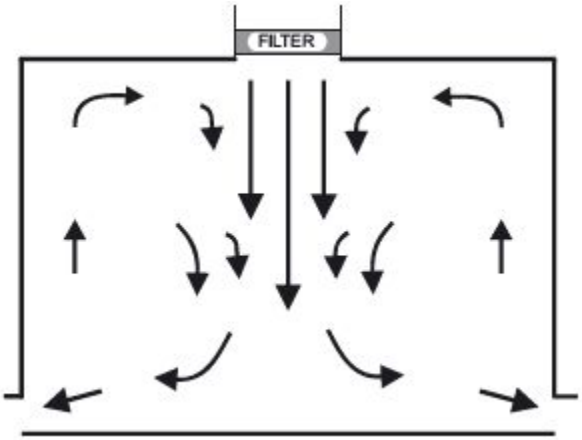
The expected air movement in a cleanroom using a 4-way diffuser is given in Figure 5.5 and this air movement will ensures an efficient mixing of the supply air with the room air.

Figure 5.5 Airflow conditions produced by a ceiling diffuser



As shown in Figure 5.6 when diffusers are not used the supply air is ‘dumped’ down directly from the air filter into the cleanroom. This method will give good contamination control conditions under the filter but the conditions elsewhere will be below average.

Figure 5.6 Airflow conditions produced by a ‘dump’ system



It is my opinion that air diffusers should be used in non-unidirectional airflow cleanrooms. If enhanced conditions are required at critical areas, then it is better to ensure good air mixing in the cleanroom by means of diffusers and to use separative enhanced clean air devices at the critical areas.

If the ‘dump’ method is chosen, then the supply air filters should preferably be distributed evenly about the room, although there may occasionally be an advantage in grouping the filters together to protect an area that must be

kept clean. However, if grouping is employed, it should be remembered that the rest of the cleanroom away from the area under the filters will almost certainly be of a lower standard and, as the classification of the cleanroom is determined by the dirtiest part, the classification may be lower than expected.

It is normal practice in cleanrooms to site the air extract grilles at a low level around the walls. This is considered to be preferable to siting them at high-level as the 'throw' of clean air from the diffuser is likely to be along the ceiling so that some of the air is drawn straight into the high level exhaust grilles and is therefore not available to mix with the room air to dilute the contamination. Although this does occur to an extent, it must be understood that in non-unidirectional airflow cleanrooms, the air does not move in straight lines and a reasonable amount of air mixing will occur with the rest of the room, even when there are high level exhausts. In the case of the air being supplied without the use of a diffuser, the air will be thrown to the floor and some of it will short circuit to the low level exhausts. Therefore, to ensure efficient mixing of air in a cleanroom, it is generally better to provide air supply diffusers and use low-level extracts. However, if this is difficult to achieve, the use of an air supply without a diffuser, and high level exhausts may give reasonably satisfactory results.

5.1.5 Room pressurisation and air movement control between rooms

A cleanroom must be designed to ensure that contaminated air does not enter the room from adjacent dirtier areas. Air

should therefore always move from the cleanroom to less-clean adjacent areas. To ensure that the movement is in the correct direction, the airflow can be observed by smoke, water vapour or streamers; these methods are discussed in Section 12.2. However, although these methods are satisfactory for setting up a cleanroom prior to hand-over, they are not a long-term monitoring possibility. To monitor a cleanroom, it is normal practice to monitor that the cleaner areas are more positively pressurised than the less-clean adjacent areas and that hence the air will move in the correct direction.

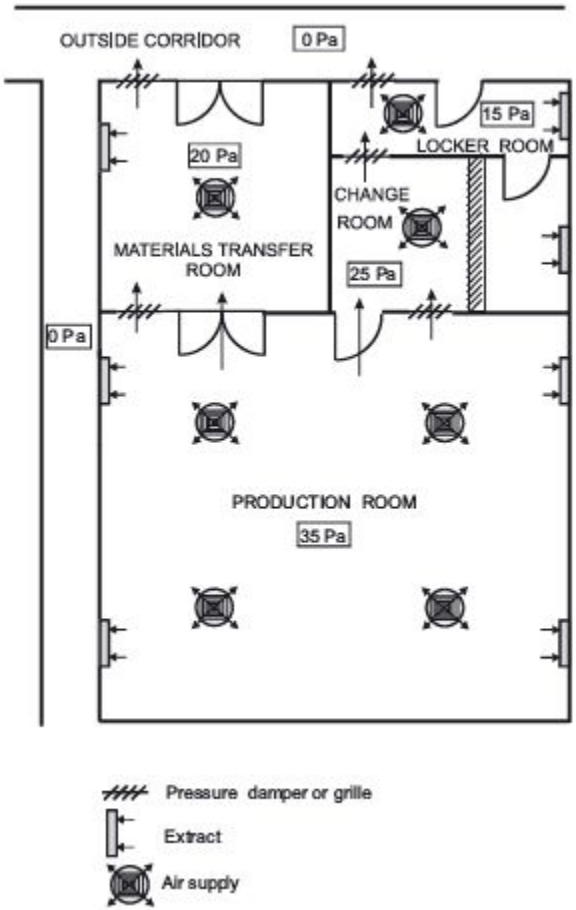
If a cleanroom is at a higher pressure than an adjacent area, then air will flow from the cleanroom to the adjacent area. Differential pressures of 10 Pa between two cleanrooms, and 15 Pa between a cleanroom and an unclassified area, are reasonable minimum design pressures (12Pa = 0.05 inches water gauge). Where practical difficulties arise in achieving these pressures, e.g. where there is a process tunnel connecting the two areas, a minimum pressure differential of 5 Pa is acceptable according to ISO 14644–4. However, if this value is used, a thorough validation of the airflows out of the cleanroom should be undertaken.

In a cleanroom suite, the air pressures should be set up so that the air moves from the clean to the less-clean areas. This means that the highest pressure is normally in the production area. Figure 5.7 shows a cleanroom suite where the production room is set at a pressure of 35 Pa compared to the outside corridor. This is necessary to give 10 Pa pressure difference between the production room and the change room, 10 Pa difference between the change room

and the locker room and 15 Pa difference between the locker room and the outside corridor, making a total pressure difference of 35 Pa.

Because a 35 Pa pressure difference is established between the production room and the outside corridor, the same pressure difference is available across the material transfer room. The material transfer room can therefore be 15 Pa less than the production room and 20 Pa greater than the outside corridor. This pressure differential is greater than required but quite acceptable. However, if too large a pressure difference is used, then extra energy costs will be incurred. Other problems may also be experienced including difficulties in opening or closing doors against the pressure, and 'whistling' through cracks.

Figure 5.7 A simple cleanroom suite showing pressures and airflow between areas



5.1.6 Construction materials and finishes

Another indication that a room is a cleanroom is shown by its construction materials and finishes. Cleanrooms should be constructed to minimise air leakage out of the room and, to achieve this, good quality constructional systems should be used. The internal surface finishes should also be sufficiently tough to resist chipping or powdering when

impacted, or abraded. The surface finish should also be smooth, easy-to-clean, and not harbour dirt in cracks. Construction materials and surface finishes are discussed in Chapter 8 of this book.

5.2 Ancillary Cleanrooms

Adjacent to the main production cleanroom there will be other cleanrooms. The number and type of these rooms will vary according to what is being produced within the cleanroom suite and the complexity of the process. In the simple cleanroom shown in Figure 5.1, there is one room for personnel to change their clothing, and one to bring materials in and out of the production room. In other cleanrooms there may be additional rooms to prepare materials required for the production room, and there may also be additional clothing change, materials transfer, production, and storage areas.

5.2.1 Clothing change area

Rooms used for changing into, and out of, cleanroom clothing vary in design. The number of rooms in the change area, and whether these rooms are divided into two or more zones by cross-over benches, will vary. The design of the change areas may also be made more complicated if separate change rooms are provided for males and females. Sometimes, lockers for outdoor clothing and valuables are provided outside the change area, and sometimes inside.

Figure 5.8 shows the plan view of a one-room change area which can have either one or two zones. In this type of

room, personnel come into the room, take off their excess clothing, change into cleanroom garments and exit directly into the cleanroom; all of the change procedures are carried out in the one room. A cross-over bench is often provided to divide this room into two zones. This bench provides a seat for personnel to change footwear or don overshoes. It also divides the room into two zones of cleanliness, the area adjacent to the outside corridor being used for dirtier functions. A single room is popular in the more economically-designed cleanroom. It is also successfully used in high quality cleanrooms with high numbers of staff, such as in the microelectronics industry. Sometimes, an airlock is additionally provided in this design to minimise the transfer of contamination from the change area into the production

Figure 5.8 One-room change areas

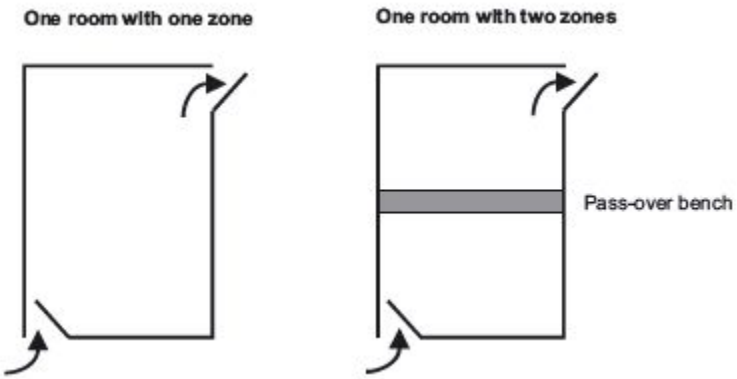
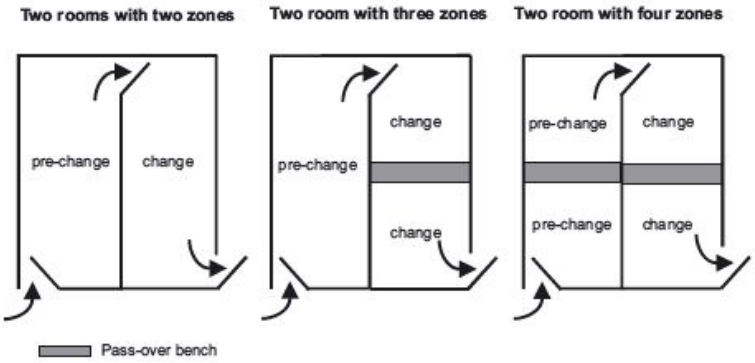


Figure 5.9 shows three possible designs of a two-room change area. These rooms and zones can also be built ‘in line’. Change areas that have the greater number of rooms and zones allow a more secure method of ensuring that the

outside of the cleanroom clothing is not contaminated, but more time has to be devoted to changing.

Figure 5.9 Two-room change areas with, or without, cross-over benches



Procedures used to change in and out of cleanroom clothing are discussed in detail in Chapter 21, which should be consulted for an explanation as to how change rooms are used.

Consideration should be given to where cleanroom garments are stored if they are to be re-used on re-entry. They should be stored so that contamination is minimised. In higher quality cleanrooms, clothing hangers are provided under unidirectional airflow. An example of this is shown in Figure 5.10.

Other methods require the provision of lockers, pegs for clothing bags, or pigeon holes (with separate ones for footwear). Further information is given in Section 19.3. Some change areas, especially those where cleanroom

garments are changed at every entry, have a separate area through which personnel leave the cleanroom.

Air showers are sometimes provided between the change areas and the cleanroom. Personnel enter the air shower and turn round as air jets play on their cleanroom clothing.

Figure 5.10 Cleanroom clothing under a vertical unidirectional airflow

An air shower is designed to remove particles from clothing and hence reduce dispersion in a cleanroom. However, their use is controversial. I have studied the particle dispersion from people after showering, as well as the airborne particle count in the cleanroom, and it appears that air showers do little, or nothing, to reduce contamination. However, they do have a psychological

effect of reminding personnel that they are entering a special area. This benefit, however, should be balanced against the production time lost while using, or waiting to use, the air shower.

Cleanroom flooring and mats that remove dirt from shoes should be placed on the change areas floor. Where they are placed, and the type used, varies. More information is contained in Chapter 18 and Chapter 19.

5.2.2 Materials transfer area

Figure 5.1 shows a materials transfer area. This is built as an airlock and allows materials to be transferred into the cleanroom with the minimum of contamination. Information as to how these are used is given in Chapter 20.

A materials transfer airlock may be divided into two zones by a cross-over bench. However, a bench should not be provided if it is an obstacle to large equipment being brought into the room. The materials transfer airlock will minimise the transfer of contamination from the outside corridor to the production room, and give a clean environment suitable for unwrapping the materials transferred into the production room. It should therefore be ventilated.

Airlock doors are often interlocked to ensure that both doors cannot be opened simultaneously. This minimises the direct exchange of air from the outside corridor to the production room. Airlocks can also have indicator lights fitted outside the doors to show if anyone is in the room.

Acknowledgement

Figure 5.10 is reproduced by permission of Roger Diener.

6

Unidirectional Airflow Cleanrooms

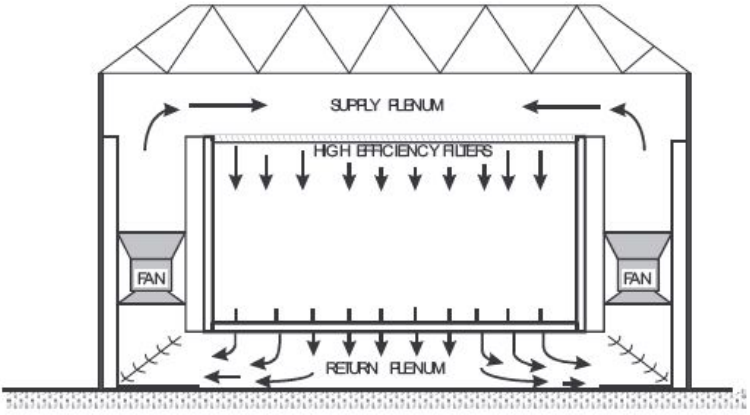
Non-unidirectional airflow cleanrooms are designed in the manner described in the previous chapter and may achieve clean conditions during manufacturing as low as ISO Class 6, but ISO Class 7 or greater are more likely. To obtain rooms better than ISO Class 6 during operation, more efficient removal of generated particles is required. This is best achieved by a unidirectional flow of air.

6.1 Types of Unidirectional Airflow Cleanrooms

Unidirectional airflow is used in cleanrooms when low airborne concentrations of particles or micro-organisms are required. The unidirectional type of cleanroom was previously, and incorrectly, known as a ‘laminar flow’ cleanroom. The older term should not be used, as the airflow is not ‘laminar’ in the scientific sense but ‘unidirectional’. Unidirectional airflow in a cleanroom is throughout the entire air space, in one direction which can be either horizontal or vertical, and at a uniform velocity that is normally between 0.3 and 0.5 m/s. Figure 6.1 is a diagrammatical representation of a cross-section through a typical vertical unidirectional airflow cleanroom. It may be seen that air is supplied from a complete bank of high efficiency filters that forms the ceiling of the cleanroom. The air then flows down through the room like an air piston, thus efficiently removing all airborne contamination. It exits through the floor, mixes with some

fresh air brought in from outside, and recirculates back to the room through the high efficiency filters.

Figure 6.1 Vertical unidirectional airflow cleanroom



Airborne contamination dispersed from people, machinery, and processes is immediately removed by this flow of air, whereas nonunidirectional airflow systems rely on mixing and dilution. In an empty room with no obstructions to the unidirectional airflow, contamination can be efficiently removed by air velocities lower than those mentioned above. However, in an operating cleanroom, machines cause obstructions to the airflow, and people move about. These factors disrupt the airflow and turn it into non-unidirectional airflow so that higher concentrations of contamination may be established in these areas. A velocity in the region of 0.3 m/s to 0.5 m/s is necessary so that disrupted unidirectional airflow can quickly reform.

The higher the velocity in the room, the lower the particle concentration is likely to be. However, unidirectional airflow cleanrooms with higher velocities are more expensive to run. A velocity at the lower end of the suggested range is more appropriate for a cleanroom with few personnel and few machines. I have studied the effect of velocity in a variable-velocity unidirectional airflow room that was in the operational state. The velocity was varied from 0.1 m/s to 0.6 m/s (20 ft/min to 120 ft/min) and it was shown that a velocity greater than 0.3 m/s was required to give stable unidirectional airflow and low particle and microbial concentrations. Increasing the air velocity above this value, in stages up to 0.6 m/s, gave lower airborne counts, but only according to the 'law of diminishing returns'. The information obtained from the experiments was interpreted as suggesting that a velocity of 0.3 m/s gives the best return for effort, but if a cleanroom has a high density of machinery, or personnel, a higher velocity would be needed to give low levels of airborne contamination.

Unidirectional airflow is correctly defined in terms of air velocity, as the higher the velocity the cleaner the room. The measure of air changes per hour should not be used as it is related to the volume of the room. This is demonstrated by the fact that a change in ceiling height will change the air changes but not the air velocity, or the level of airborne contamination.

The volume of air supplied to a unidirectional airflow cleanroom is many times greater (10 to 100) than that supplied to a non-unidirectional airflow cleanroom.

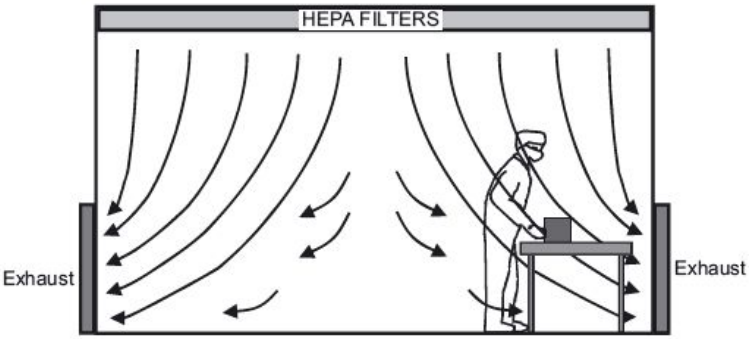
Unidirectional airflow cleanrooms are therefore very much more expensive to build and run.

Unidirectional airflow rooms are of two general types, namely, horizontal flow and vertical flow. In the horizontal system, the airflow is from wall to wall and in the vertical system it is from ceiling to floor.

6.2 Vertical Unidirectional Airflow Cleanrooms

A vertical flow unidirectional airflow cleanroom is shown in Figure 6.1. This shows the air flowing down through the complete area from the ceiling to the floor. However, unidirectional airflow rooms are also designed so that the air leaves through extract grilles distributed around the wall at floor level. This type is illustrated in Figure 6.2. The use of wall extracts is recommended in rooms that are not too wide, with 6 metres suggested as a maximum width. Care must be taken with this design. The route that the air takes to get to the extracts is the reason for the problem. Airflow of the type shown in Figure 6.2 gives poor unidirectional airflow in the centre of the room and an airflow that is not vertical in the rest. As the width of the room increases, the airflow will tend towards the horizontal and personnel may contaminate the product if they are positioned between the centre of the room and the product. Also, as the size of the cleanroom increases so will the air volume supply rate, but the wall area will not increase proportionally and it may be difficult, with the limited area available for the exhausts situated round the room, to obtain a velocity appropriate for comfort and engineering design requirements.

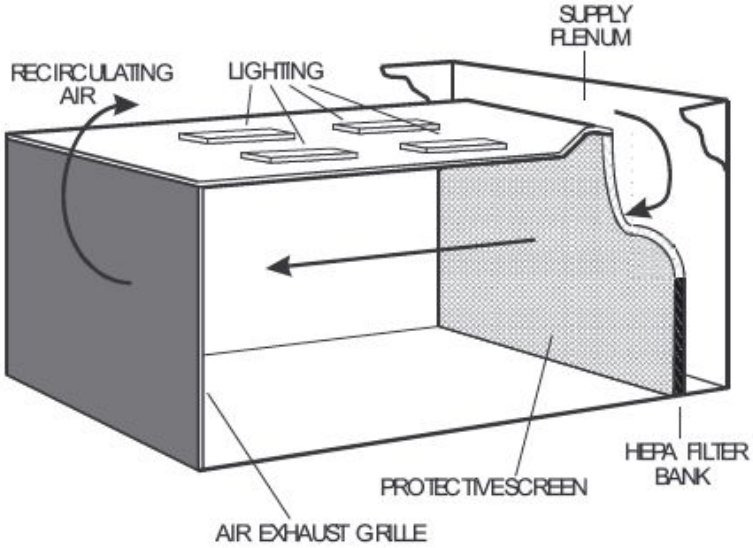
Figure 6.2 Vertical unidirectional airflow cleanroom with exhausts in the wall



6.3 Horizontal Unidirectional Airflow Rooms

Figure 6.3 shows a typical design of a horizontal unidirectional airflow cleanroom. In this design, the air enters through a wall of high efficiency filters, flows across the room, and exits on the other side. The air is then returned to a ventilation plant and back through the air filters.

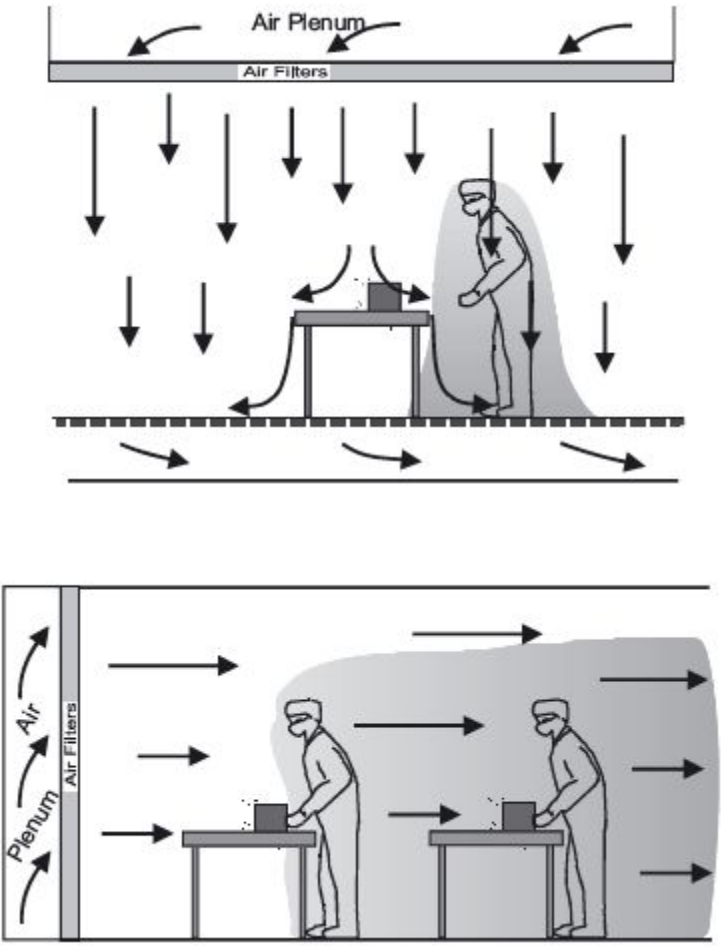
Figure 6.3 Horizontal unidirectional airflow cleanroom



The area of a wall in most rooms is usually smaller than that of the ceiling, and hence a horizontal room will cost less in capital and running costs than a vertical one. The horizontal flow type of cleanroom is not as popular as the vertical type. The reason for this is illustrated in Figure 6.4, which compares how the two systems deal with a contamination source.

Any contamination generated close to the filters in a horizontal airflow cleanroom will be swept across the room and could contaminate any work taking place downwind. Generally speaking, a vertical flow of air gives better contamination control (as shown in Figure 6.4) because the contamination dispersed from personnel is less likely to reach the product.

Figure 6.4 Dispersion of contamination in vertical and horizontal unidirectional airflow cleanrooms



If a horizontal flow cleanroom can be arranged so that the most critical operations are close to the supply filters and

the dirtier ones at the exhaust end, then this type of room can be a success. The following works well:

1. a faulty component, requiring repair, enters the end of the room away from the filters;

2. the component is dismantled in stages as work progresses towards the filters;

3. the most susceptible-to-contamination repair is carried out next to the supply filters;

4. the component is reassembled and then packaged on its way back up the other side of the cleanroom;

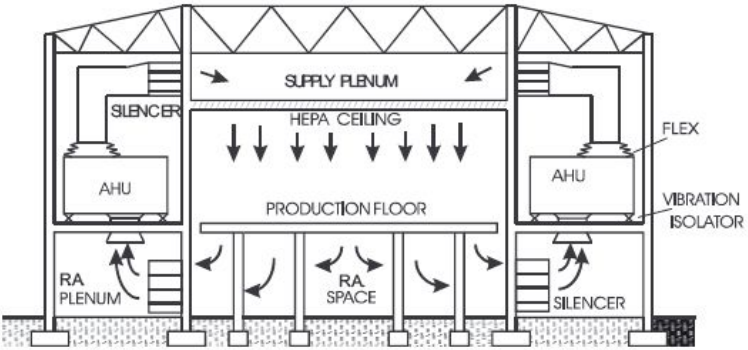
5. the repaired component exits out of the room, on the opposite side from the entering components.

A horizontal flow type of cleanroom can also be successful if the machine or process is placed close to the filter bank and no-one is allowed to pass between the filter bank and machine, especially when production is in progress.

6.4 The Application of Unidirectional Airflow

Unidirectional airflow cleanrooms are used in semiconductor manufacturer and similar applications. The design of semiconductor cleanrooms has evolved over several years, but a design still used by semiconductor manufacturers and other similar applications is shown in Figure 6.5.

Figure 6.5 Vertical unidirectional airflow cleanroom often used in semiconductor manufacturing



The air flows downwards, in a unidirectional way, from a ceiling of high efficiency filters and out through the floor of the cleanroom. As the manufacturing of semiconductors is sensitive to vibration, anti-vibration measures are incorporated.

Some cleanroom designs return the air from just below the floor, while others (similar to the type shown in Figure 6.5) use a large basement, that basement also being used for services. There are also designs that have both the sub floor and a basement below. The design shown in Figure 6.5 is often called a 'ballroom' type because of its size. It can be over 1000 m^2 in floor area and some rooms are large enough to hold two football fields. It is expensive to run but adaptable. Figure 6.6 shows a photograph of a typical 'ballroom' cleanroom before production equipment was installed.

In the ‘ballroom’ type of cleanroom, a complete ceiling of high efficiency filters provides clean air throughout the whole room, irrespective of need, and the machinery stands throughout the room. However, the best quality air is only really necessary where the product is exposed to airborne contamination, and lesser quality air should be acceptable in other areas.

Figure 6.6 Ballroom type of cleanroom

Figure 6.7 Plan views of three types of vertical unidirectional airflow cleanrooms

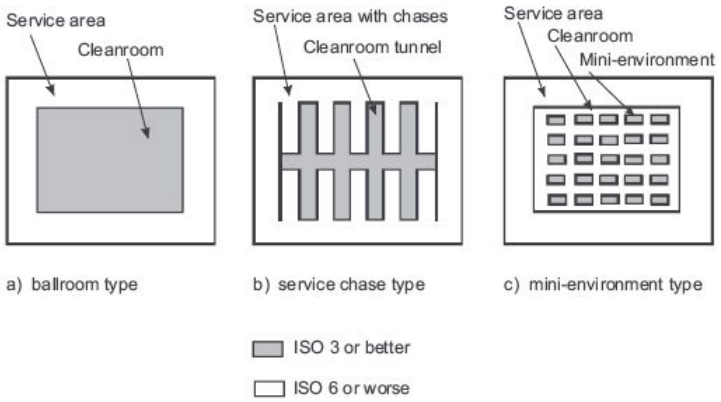


Figure 6.8 Cleanroom tunnel

By confining high quality air to where it is required, less expensive unidirectional airflow cleanrooms have been designed. One such design is where service chases with

lower cleanliness standards are interspersed with cleanroom tunnels. This concept is shown in Figure 6.7(b), and a photograph of a cleanroom tunnel is shown in Figure 6.8.

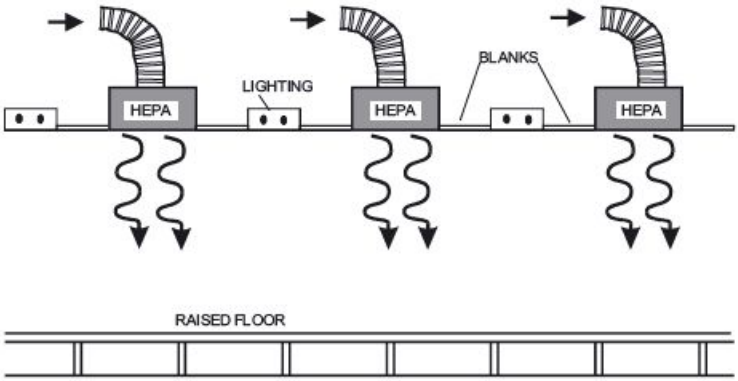
Service technicians can gain access to bulkhead-fitted machinery through the service chases without entering the clean space where the product is exposed. Less expensive and lower quality air conditions are provided in these service chases. It is also possible in the ballroom type of design to divide up the 'ballroom' with prefabricated walls and to provide clean tunnel and service chases. These walls can be dismantled and reassembled in a different configuration should the need arise.

Another design of cleanroom uses mini-environments. The minienvironments are enhanced clean air devices that protect the exposed product by bathing them in the highest quality of clean air so that they can be situated in a cleanroom with a lower quality of air. This concept is shown in Figure 6.7 (c) and is explained in Chapter 7.

Service chases and other less critical areas of the cleanroom are normally supplied with lesser quantities of air and have a lower standard of air cleanliness. This can be achieved by reducing the ceiling filter coverage by means of ceiling blanks. This method is shown diagrammatically in Figure 6.9. If this method is used, it is probably best to distribute the filters evenly around the ceiling. If the filters are grouped together in lines or rectangles, the areas under the filters will have better quality air, but the surrounding areas will have poorer quality air. As cleanroom classifications are determined by

the worst particle counts, this design may result in a poorer classification. Another alternative is to use 100% filter coverage and reduce the overall air velocity. This design is likely to give better air movement than a filter ceiling with less than 100% coverage and hence will give lower particle counts. However, it will be more expensive to build.

Figure 6.9 Reduced ceiling filter coverage to give non-unidirectional airflow conditions



If the cleanroom design uses an air supply plenum then the unfiltered air in the plenum above the filters will be at a higher pressure than the air in the cleanroom. Unfiltered air can therefore leak from the supply plenum into the cleanroom through joints in the structure that are either unsealed or badly sealed. This problem is discussed in Chapter 11 and shown in Figure 11.1. Such problems can be overcome if the area above the ceiling is below the pressure of the cleanroom. This can be achieved by using individual supply ducts to each filter and utilising the fact that the pressure in the cleanroom is greater than that of the surrounding area including the plenum, or by using

individual fan-filter units that draw air from the plenum, thus ensuring that the pressure in the plenum is negative with respect to the cleanroom.

Acknowledgements

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7

Separative Clean Air Devices and Containment Zones

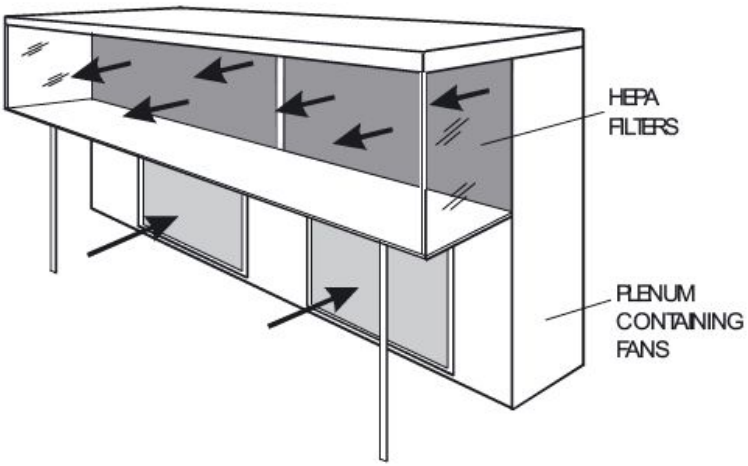
Separative clean air devices are used in cleanrooms to provide a higher quality of air (and, in some types of device, protection from contact with personnel) at critical areas in the cleanroom. Types of enhanced clean air devices that are available are: unidirectional airflow cabinets and enclosures, restricted access barrier systems (RABS), isolators and minienvironments.

7.1 Unidirectional Airflow Devices

Shown in Figure 7.1 is a drawing of a horizontal unidirectional airflow cabinet (or workstation), this being the simplest of the separative clean air devices. The operator sits at the bench and works with materials, or at a process, on the bench top. The air flows towards the person and hence the contamination dispersed into the air by the person is kept downwind of the critical process.

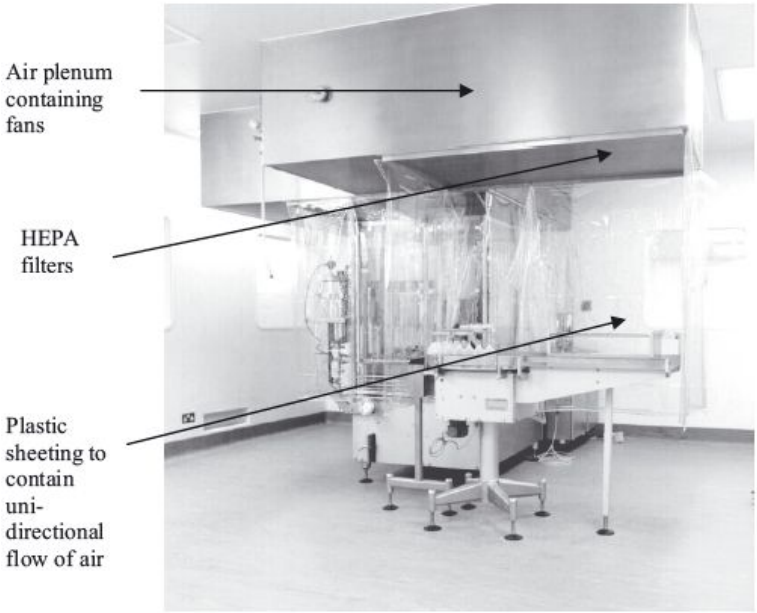
The use of a unidirectional airflow device should reduce the airborne particle and microbial contamination by at least ten-fold and may reduce it by more than a hundred-fold. However, it will not reduce contact contamination when personnel touch the product. Where contact contamination is a problem, separative devices such as mini-environments, isolators and RABS should be used. These are described later in this chapter.

Figure 7.1 Horizontal unidirectional airflow cabinet



A variety of styles of unidirectional airflow enclosures is also available. These vary in size to accommodate any size of production machinery. Figure 7.2 shows a vertical unidirectional airflow enclosure placed over a filling machine. The airflow in the surrounding cleanroom is non-unidirectional but the product is protected from contamination by being processed in a unidirectional flow of air in the enclosure.

Figure 7.2 Vertical unidirectional airflow workstation



7.2 Mini-environments, Isolators and RABS

To obtain better contamination control than provided by unidirectional airflow cabinets and enclosures, 'mini-environments', 'isolators', and 'restricted access barrier systems (RABS)' can be used.

7.2.1 Mini-environments

Mini-environments are similar in design to isolators that are discussed in the next section but 'mini-environment' is the term normally used for a separative device in the semiconductor and similar industries. A mini-environment uses a physical barrier (usually plastic sheet or glass) to isolate the critical manufacturing area from the rest of the cleanroom so that the rest of the cleanroom can be

provided with a lower quality of air. A mini-environment also separates the personnel from the manufacturing process so they cannot contaminate the product, or process, by touch.

Figure 7.3 shows a diagram of a unidirectional airflow cleanroom with a service chase but*without* a mini-environment. In this design, unidirectional airflow gives the best condition (shown as white in Figure 7.3 and designated ISO Class 3) in those parts of the cleanroom where the operators move products, such as silicon wafers, from machine to machine. Lesser quantities of air are provided in service chases (shaded area and designated ISO Class 6), from which the bulkhead-fitted machines are serviced.

Figure 7.3 Design of unidirectional airflow system with a service chase

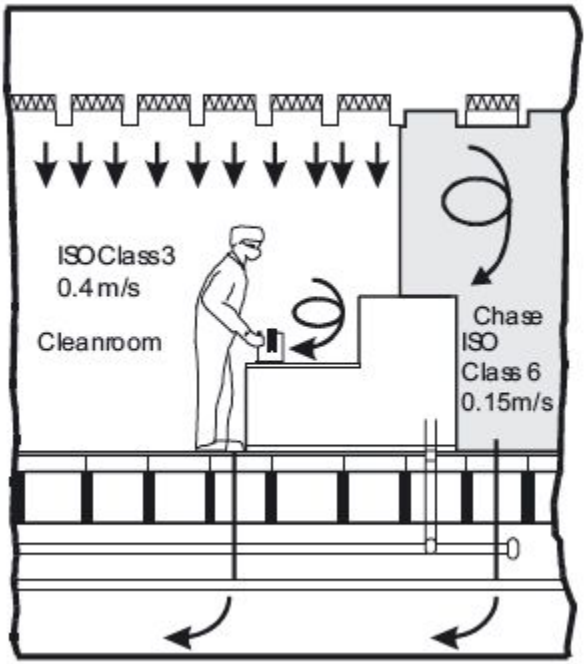
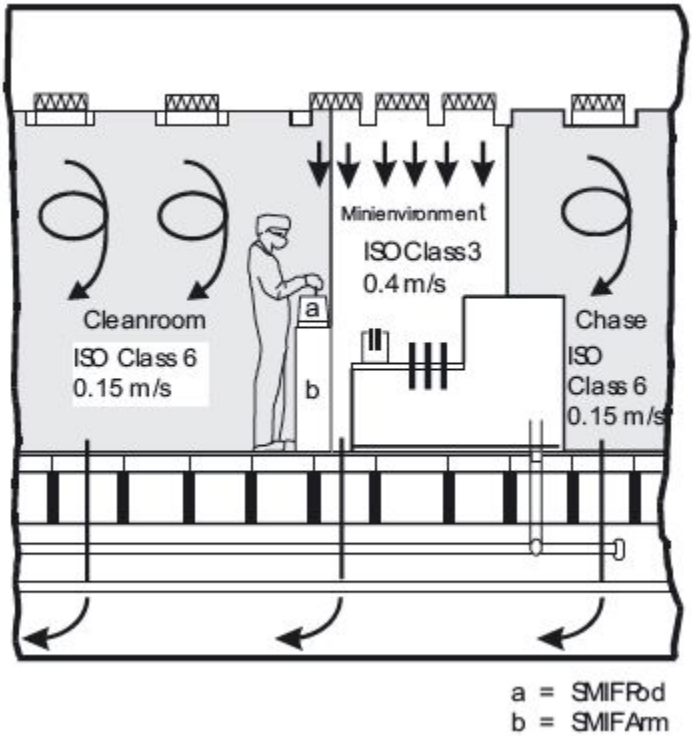


Figure 7.4 is a diagram of a cleanroom design that uses mini-environments. The mini-environment (shown as white and designated as ISO Class 3) provides the highest quality of environment over the product. A lesser quality of environment (ISO Class 6 or poorer) is provided in both the production areas and the service chase. The total air supply volume for a cleanroom is therefore much less when mini-environments are used.

Figure 7.4 Semiconductor fabrication room with a SMIF isolation system



In Figure 7.4 the air velocity in the mini-environment is shown as 0.4 m/s (80 ft/min), this being the velocity associated with low particle counts in occupied cleanrooms. However, as there are no personnel within the mini-environment causing disruption of the unidirectional airflow, and if the machinery is not disrupting the air flow then a lower air velocity may suffice. The minimum velocity that is suitable will have to be determined by use of air visualisation techniques described in Section 12.2.

As well as using a mini-environment to isolate the area where the silicon wafers are exposed, the wafers can also be transported between processing machines in specially

designed carriers (SMIF Pods), which prevent the wafers being contaminated by personnel and the air outside them. These pods are slotted into the machine through a Standard Mechanical Interface Format (SMIF). The wafers are processed and loaded back into a carrier which is then detached and taken to another machine and loaded into its interface. The transfer of the carrier can be done by a person, but automatic overhead handling systems are also used.

Various types of mini-environment, with different methods of accessing the wafers into the production machines, have been developed. As long as these are well designed, particularly with respect to the transfer port and the container that contains the wafers, they should work well.

7.2.2 Isolators

Isolators have similar design concepts to mini-environments and are used in pharmaceutical and similar types of manufacturing. Isolators can be used to either:

1. protect the product from contamination,

2. personnel from toxic compounds,

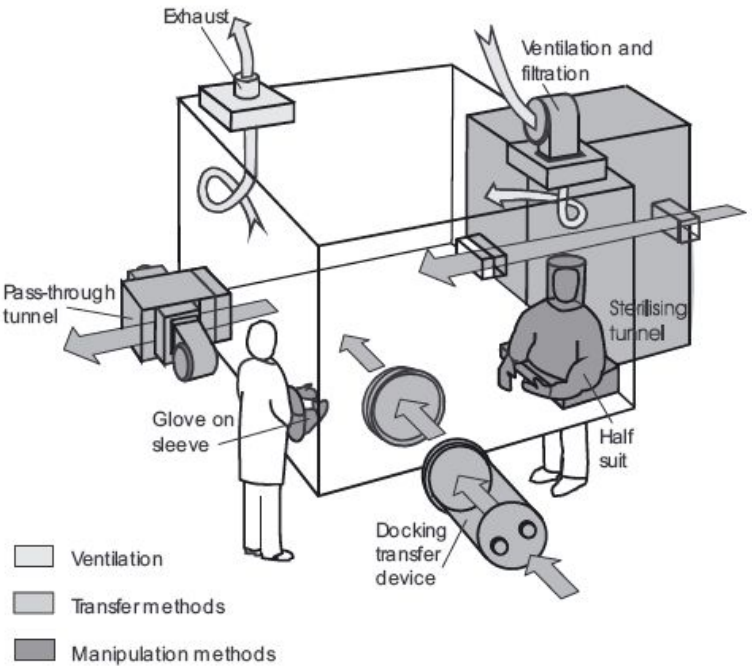
3. both of the above.

These attributes can be achieved by isolators that are positively or negatively pressurised with respect to the cleanroom in which they are sited. The cleanliness of the product, or process, inside will be maintained by using a

positively pressurised isolator. Internal pressures can range from 20 to 100 Pa compared to those outside the isolator depending on the design. Where hazard containment is required, a negative pressure system is used. Typical pressures range from −80 Pa down to −250 Pa.

Isolators can be purchased with various design attributes of the type shown in Figure 7.5. The type of transfer device selected for transferring items in and out of an isolator depends on the application. Figure 7.5 shows two types of pass-through sterilising tunnels, and a transfer-docking device.

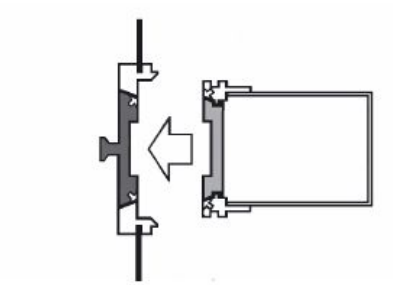
Figure 7.5 An isolator with its various components



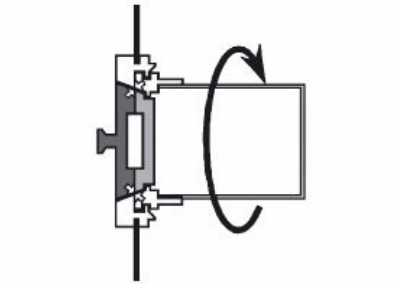
Different types of transfer device are described and classified in ISO 14644-7. They range from simple doors (Type A) to transfer-docking devices (Type F). Transfer-docking devices are the most effective way of transferring materials between sterile isolators without the materials becoming contaminated. They may also be used to connect individual isolators. The sequence shown in Figure 7.6 illustrates the operating principles of a transfer-docking device.

Figure 7.6 Operation of a transfer-docking device

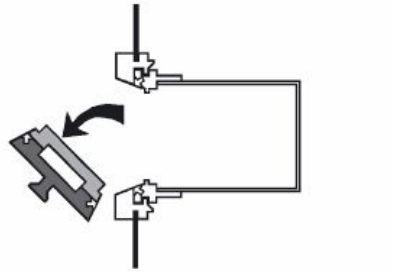
Step 1 Container (or transport isolator) approaches closed isolator port.



Step 2 Container docks with port and rotates to lock and enclose exposed faces. At the same time the interlock is released on the isolator door.



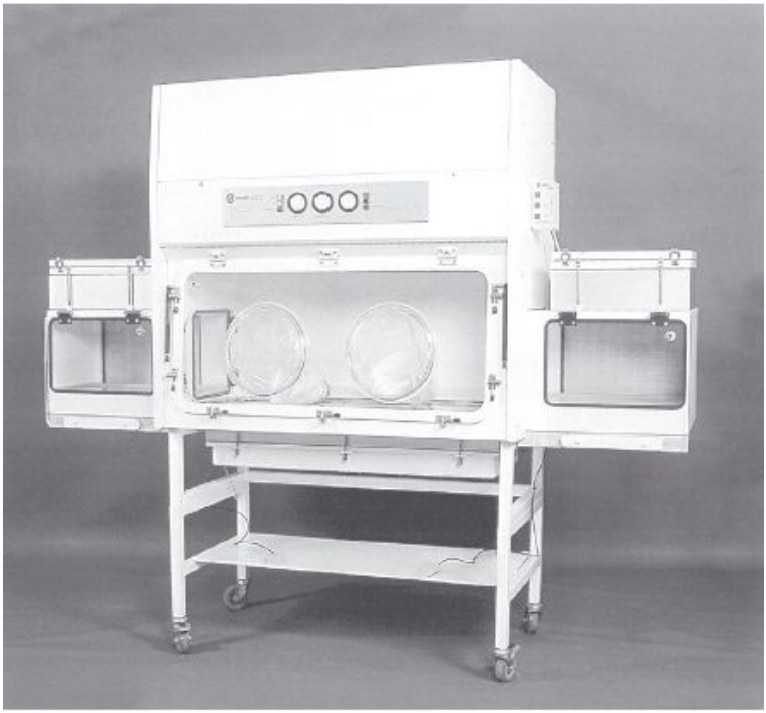
Step 3 Door into isolator is opened to allow free communication between the two enclosed volumes.



Double door transfer chambers are used where materials are taken into and out of the isolator from the surrounding area, which is usually a lower grade cleanroom. They can be provided with an appropriate combination of

interlocked doors and filtered air to ensure that potentially contaminated air cannot pass into or out of the isolator during material transfers. Disinfectant sprays or wipes are used to control surface contamination on materials going in, and interlock timers are used to ensure sufficient time for disinfectant action and for an effective purge with filtered air. Figure 7.7 illustrates an isolator with transfer chambers on each side.

Figure 7.7 Isolator with transfer chambers on either side



When the manufacturing process is continuous, as in large scale manufacturing, it is more convenient if the product is

transferred out of the isolator continuously. This can be done by using a final 'holding' isolator to receive the product, or by means of an aerodynamically-designed 'mouse hole' or transfer tunnel, with an outward flow of air (see Figure 7.5).

Most isolators require people to manipulate products within the isolators. This is achieved by the use of glove ports or half suits. These two methods are illustrated in Figure 7.5. Figure 7.8 also shows an isolator being used with a half suit.

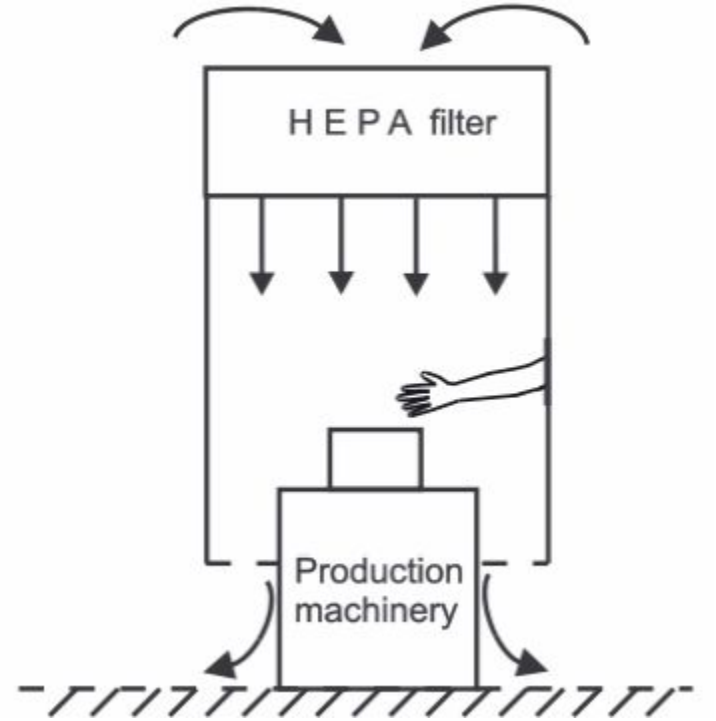
Figure 7.8 View of a half suit and the inside of an isolator

7.2.3 Restricted access barrier systems (RABS)

RAB systems are similar in design to isolators but have design attributes that bring them closer to the design of unidirectional airflow workstations. The use of a RAB system removes some of the difficulties associated with access into an isolator for cleaning, setting up of machinery, and the transfer of materials.

Shown in Figure 7.9 is a drawing of a simple RAB system. The air flows in a unidirectional way from the high efficiency filters in the top, down over the critical production area, and out at low level in a similar way to that in a unidirectional workstation. The area through which the air exits is relatively large, and there can therefore only be a small pressure difference between the interior space of the RABS and the surrounding area.

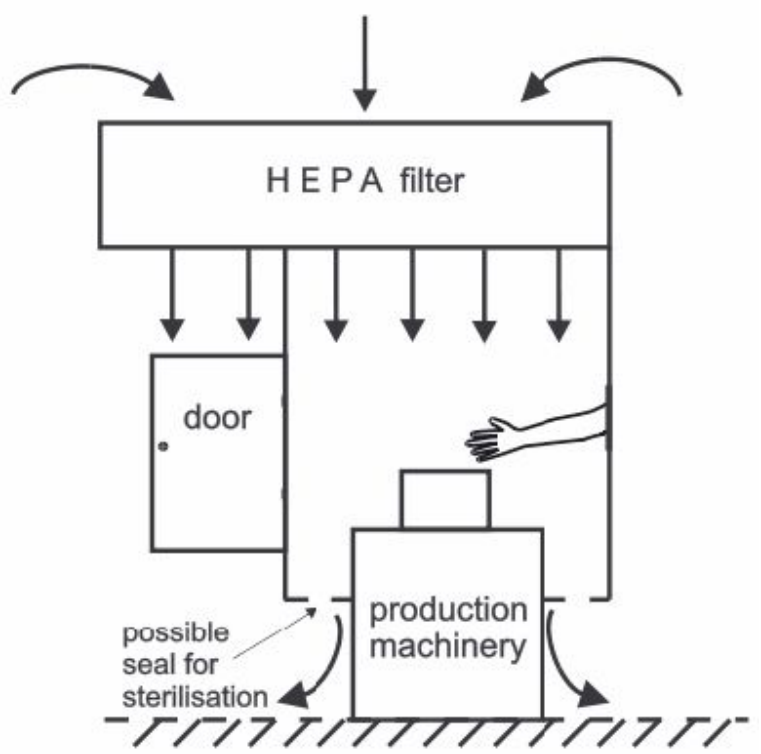
Figure 7.9 Simple RAB system



In a unidirectional airflow enclosure, of the type shown in Figure 7.2, personnel can pass through the hanging plastic

curtains and handle the product. In a RAB system the walls are solid, being made from sheets of glass or plastic, and mounted on either the production machine bedplate, or the floor. Access to the area during production is only by use of gauntlets, sleeves/gloves, or half-suits, thus minimising contact of personnel with the product.

Figure 7.10 RAB system with door protection and optional sealing method for vapour sterilisation



When production is complete, and the process equipment has to be dismantled, cleaned, sterilised if required, and set

up ready for the next batch of product, access can be obtained by opening doors in the walls. The doors are closed during production. Access doors make RABS easier to use than an isolator. To give more protection against the transfer of airborne contamination into the RABS when a door is open, a unidirectional flow of air on the outside of the RABS can protect the area round the open door. This design is shown in Figure 7.10.

As with isolators, in microbiologically clean pharmaceutical areas, the inside of a RABS has to be capable of being disinfected or made sterile. Sterilisation is normally carried out by means of a suitable sterilising gas or vapour, such as hydrogen peroxide vapour. However, it may require hours to complete the sterilisation cycle. Disinfection can be carried out by wiping down the various surfaces with a disinfectant such as alcohol. Cleaning and machine assembly can therefore be carried through the open door, the door closed, and, after the unidirectional airflow is established, production started.

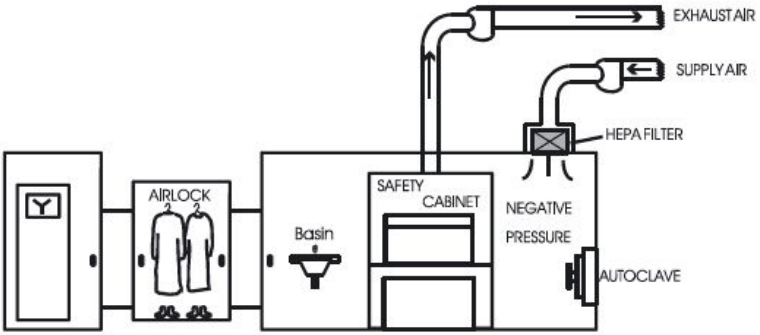
When gaseous sterilisation of the RABS is required, it is necessary to ensure that it is air tight, and that the area where the air would pass out of the system must be closed. This is shown as a dashed line in Figure 7.10. It is interesting to note that the design of the RABS shown in Figure 7.10 comes close to that of an isolator.

7.3 Containment Zones

Cleanrooms are used to prevent the contamination of articles produced in the room. However, some manufacturing processes produce toxic chemicals or

dangerous bacteria and these must not be allowed to escape and harm people. This can occur, for example, in the pharmaceutical industry where highly active pharmaceuticals, such as hormones, must be kept free of contamination but must not reach the operator. Other examples are found in the biotechnology industry where rooms are required to contain, for example, genetically-engineered micro-organisms. Also, microbiological laboratories dealing with dangerous micro-organisms require that the personnel working in them, or the people passing near them, are protected from infection.

Figure 7.11 Microbiological containment room



The technology associated with the design of these containment rooms is similar to that used in cleanrooms, as containment rooms are often cleanrooms with containment properties.

Figure 7.11 is an example of a containment room that might be used for working with micro-organisms dangerous to the health of personnel. It may be seen that

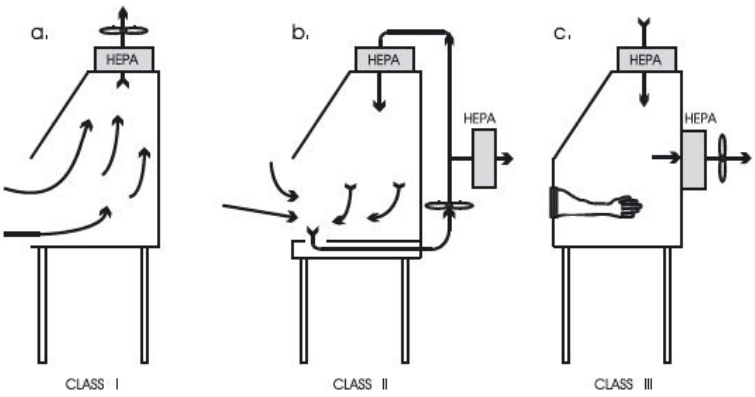
clean air is supplied to the room, but more air must be extracted so that the room will be under a negative pressure and air will always flow into the room. The air that is extracted from the room must be filtered through a high efficiency filter before being discharged to the outside environment. In Figure 7.11 this is done through the microbiological safety cabinet. Indeed within the type of containment room shown in Figure 7.11 there is very often likely to be a safety cabinet.

Shown in Figure 7.12 is a diagrammatic representation of the three basic types of microbiological safety cabinet that are available, showing their airflow and isolation principles. For microbes where there is not a very high safety risk, a Class I or Class II cabinet is used. If it is not critical that the conditions inside the cabinet are cleaner than in the surrounding area, a Class I cabinet may be chosen, as this retains contamination inside by drawing the surrounding room air in. However, if cleaner conditions than the room are required then a Class II cabinet is used. This type gives a flow of filtered air over the product, while still ensuring a flow of air into the cabinet. For high-risk microbiological agents, a Class III cabinet would be used. The design of a Class III cabinet is very similar, to that of some designs of negative pressure isolator.

Microbiological safety cabinets may be adapted for other applications. If they are to be used as safety cabinets to provide protection against toxic chemicals, they should therefore be designed so that any potential contamination is restricted to areas that are readily accessible for cleaning. If they are to be used as safety cabinets for use with radioactive substances they must be provided with

suitable radiation protection in the form of lead lining and lead-acrylic or lead-glass visors.

Figure 7.12 Microbiological safety cabinets



Another feature that may be found in containment rooms is an airlock to allow people to change into special clothing and to minimise airflow out of the containment room. A pass-through autoclave may be available to allow the sterilisation of material contaminated in the room.

Other containment rooms may be of a higher or lower standard, depending on the toxic, chemical or microbiological hazard in the room. Less-hazardous rooms would not use an airlock or pass-through autoclave. Rooms in which the hazard is high would use a Class III type of cabinet or a negative pressure isolator, and may provide a shower area between the air lock and the room. In particularly hazardous situations, personnel would wear suits supplied with filtered air.

Acknowledgements

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8

Construction and Clean-build

8.1 Constructional Materials and Methods

A cleanroom requires a higher standard of construction and can be distinguished from other structures in the following ways:

- it should be built with airtight walls and ceilings;
- the internal surface finishes should be smooth and suitable for easy and frequent cleaning;
- the internal surface finishes should be sufficiently tough to resist chipping or powdering when impacted or abraded;
- the internal surface finishes should resist the attack and penetration of process chemicals, cleaning agents, disinfectants and water;
- in some cleanrooms, electro-dissipative construction materials are required;
- in some cleanrooms, construction materials that give a minimum of 'outgassing' of chemicals are required.

Cleanrooms are maintained at a positive pressure with respect to adjacent areas. If the construction is poor and the joints not well sealed, then the structure may leak too much. It may then be necessary to pressurise the room by excessive amounts of fresh outside air. It is not good economic sense to waste air that has to be expensively filtered and air conditioned. Attempting to seal up the structure during the 'snagging' part of the construction will not be as successful as making it airtight during construction. If a cleanroom leaks by more than the amount found by the design calculations for the air

conditioning system, additional fresh air capacity may be required, including replacement of the fresh air conditioning plant by one of higher capacity. A particularly difficult problem of sealing exists with containment cleanrooms that are maintained at a negative pressure. They must be airtight, or dirty unfiltered air will be drawn into the room through cracks, joints and service penetrations in the fabric.

The materials that are used for the construction of a cleanroom should be smooth on the surface facing the inside of the cleanroom. There should be no pores or roughness that will retain contamination. The finished construction should be free of ledges and easily wiped free of any contamination that is deposited. The butts and joints, on the inside of the cleanroom, should not show openings that may harbour, and then disperse, dirt.

The surface finish in a cleanroom must not break up easily and disperse chips or particles of material. A conventional material that is often used in houses and offices is plasterboard that is nailed to stud partitions, and the joints taped or filled, and painted. If the plasterboard is struck heavily, the outer layer may be breached and powder released. This is unacceptable in a cleanroom, and therefore if this type of construction is used, the plaster surfaces must be suitably covered or coated so that they are resistant to impact.

Cleanroom surfaces, especially floors, should be able to withstand liquids used in cleanrooms. Some processes use strong acids or solvents that will attack surfaces. Cleanrooms, where micro-organisms cause contamination,

will require disinfection. Disinfectants are normally in an aqueous solution and the contact time needs to be several minutes for adequate disinfection; therefore water penetration is possible if construction materials are not suitable. Similar problems can occur when surfactant solutions are used for cleaning the surfaces in the cleanroom. It is therefore necessary to ensure that penetration of water does not occur, as it can cause degradation of the structure and can produce damp conditions that are suitable for microbial growth. It should, however, be noted that it is incorrect to suggest that micro-organisms sitting in dry conditions in cracks and pores will multiply. Micro-organisms are aquatic in nature, and unless free water is available, or the relative humidity is very much higher than normally found in a cleanroom, growth will not occur.

An electrostatic charge can be generated by rubbing two dissimilar surfaces together and can this can give two problems in cleanrooms. Firstly, the charge will attract particles from the air and those deposited particles may give a contamination problem. Secondly, electrostatic discharge from surfaces to certain products can cause component failure. Construction materials that minimise this problem may be necessary in cleanrooms where such susceptible products are processed.

Some chemicals can ‘outgas’ from the materials used in construction of cleanrooms. These outgassed chemicals can cause what is termed ‘molecular’ or ‘chemical’ contamination. Outgassing is also occasionally called ‘off-gassing’. In some cleanrooms, such as those required for manufacturing semiconductors or optical surfaces, the

deposition of outgassed chemicals onto the product may be unacceptable. Where this is a problem, construction materials that do not outgas will be required.

Cleanrooms can be constructed in various ways. However, despite the fact that some construction methods will not fit easily into either group, the building techniques are now discussed under two headings: conventional and modular.

8.1.1 Conventional building techniques

Conventional building techniques, suitably modified, can be used in cleanroom construction. The building used to contain the cleanroom suite will be conventionally constructed with a floor, ceiling and external walls. Inside that structure, internal walls will be built to create the various rooms of the cleanroom suite. These are constructed using conventional techniques employing bricks or blocks, and may be finished using wet plastering or dry lining methods.

The dry finishing method is the most popular method as this employs less site time, is more easily repaired, and allows electrical and other services such as air ducts to be run behind. At its simplest, wall studs are erected and these are lined with plasterboard. The boards are taped, primed and painted. The paint is sprayed on and will be chosen to give good impact resistance, e.g. an epoxy-based paint. To assist cleaning, wall to wall corners are best constructed with 25 mm (1 inch) to 50 mm (2 inch) radii. The corner where the wall meets the floor would normally be finished with a 100 mm (4 inch) quarter-round coving. With an epoxy paint finish, this conventional construction method

is only suitable for lightly used cleanrooms of about ISO Class 8 or 9, or for approach corridors or controlled areas outside the cleanroom. A considerable improvement in the quality and appearance of a cleanroom built by this method can be achieved by lining the floor, walls and ceiling with fully welded 2 mm thick heavyduty flexible vinyl sheet.

Another finish would comprise rigid sheets or panels of cleanroomcompatible materials fixed to a conventional studded wall frame. The panels will be about 3 mm to 12 mm ($^1/_8$ inch to $^1/_2$ inch) thick, depending on their strength and rigidity and, because the studs will give additional rigidity, they are thinner than those required for the studless system used in modular construction.

Figure 8.1 Cleanroom change area showing good use of curves

The following wall panels are suitable and are available from a variety of specialist suppliers:

- Panels laminated with an outer cleanroom-compatible surface and an inner strengthening core. Outer surfaces can be (a) mild steel that is galvanised and either powder-coated or enamelled, (b) plastic sheet, (c) aluminium that is either anodised, powder coated or enamelled. Inner core materials can be plaster, composite board, plywood, honeycombing, etc.,
- Glass-reinforced epoxy sheets,
- Mild steel sheets that are galvanised and either powder coated or enamelled,
- Aluminium sheets that are anodised, powder coated or enamelled,
- Stainless steel sheets, with or without a suitable paint finish.

Many other combinations and materials can be used, as long as they fulfil the criteria defined in the first section of this chapter.

8.1.2 Modular construction

Modular construction is a type of construction where components are delivered ready-made and assembled on site to produce a cleanroom structure. A large variety of modular components is available from firms that specialise in manufacturing such systems. Inevitably, the most easily assembled, best looking and most robust system, with the least likelihood of contamination problems, will be the most expensive. It is therefore necessary to choose wisely, balancing the quality and cost of the construction with the advantages it brings. The two principal types of modular system are:

- studless wall systems,
- framed wall systems.

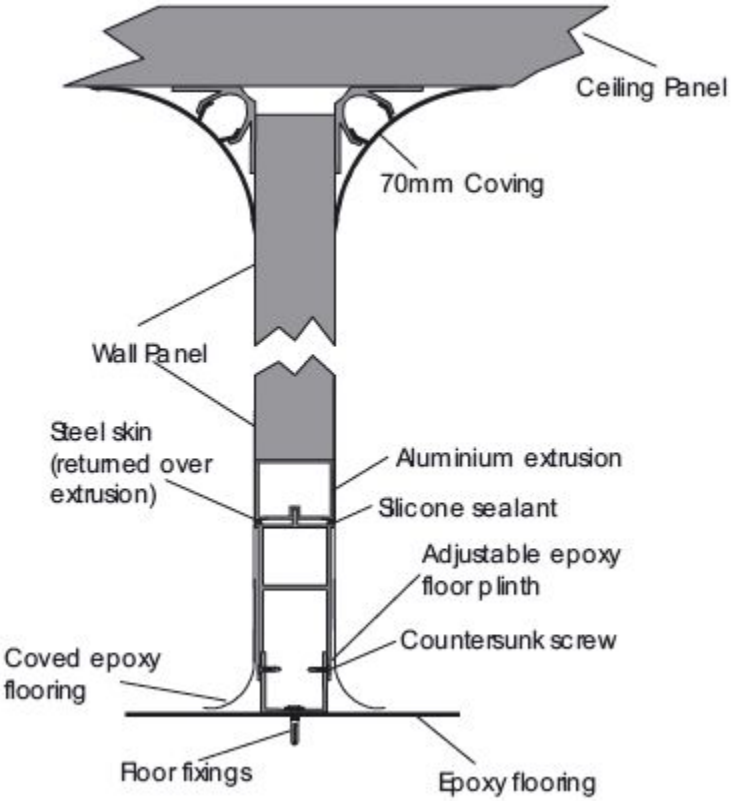
8.1.2.1 Studless wall systems

These are normally assembled from wall panels that are about 50 mm (2 inches) thick to give suitable rigidity. The panels are, slotted into ceiling and floor mounted tracks and butted together. The tracks are usually anodised aluminium extrusions. Figure 8.2 shows a drawing of the ceiling and floor details of a system of this type.

The wall panels are laminated from outer layers of a cleanroomcompatible surface and an inner strengthening core. The outer surfaces can be plastic sheet, aluminium that is either anodised, powder coated or enamelled, or

suitably treated mild steel. Inner core materials can be plaster, composite board, plywood, honeycombing, etc.

Figure 8.2 Cross-section of ceiling and floor details of a modular system



8.1.2.2 Framed wall systems

The frames are built from special aluminium profile extrusions. The uprights and cross members are clipped or bolted together and clad with wall panels either on one

side (single skin) or on both sides (double skin). Wall panels used in this type of construction will be made of the same types of material as already described, although they will be thinner.

Framed systems are also used for enclosures to isolate process machinery from the rest of the room. Minienvironments, or RABS, as well as safety screens around machinery, are examples of this. Lightweight extrusions are connected together to give a framework round the machinery and panels made of aluminium sheet, glass or clear plastic are glazed into the frames with special easy-to-clean gaskets.

8.1.3 Doors, windows, floors and ceilings

8.1.3.1 Doors and windows

The most popular types of cleanroom door are made from dimensionally stable cores, seamlessly faced and edged with glass reinforced plastic, hard plastic laminate or mild steel that has been suitably treated and coated. The use of door fittings such as door handles is kept to a minimum to assist cleaning and minimise the transfer of hand contamination. Where fittings have to be used, they should have no dirt traps and be easy to clean.

Doors are usually hung to open inwards so they are kept closed by the positive pressure of the cleanroom. However exceptions are made, for example, where it is necessary for personnel to push the door open with their bodies because they are carrying materials. In such cases, a self-closer should be fitted.

Doors are often manufactured with fine tolerances to minimise air leakage. This is of special importance in a negatively-pressurised containment cleanroom where the entry of contamination from outside the room has to be minimised.

Doors may be glazed, which is particularly useful in the materials transfer airlock so that it can be seen if it is occupied. If glazing is required, the glazing should be flush and any gaskets should be designed for easy cleaning. Doors that are made entirely of glass are also available.

Windows are frequently specified in cleanroom walls. They take away the need for visitors, wishing to see the cleanroom, to enter it and to introduce unnecessary contamination. They also allow management to see what is going on inside without having to go through the time consuming process of changing into and out of cleanroom clothing. Windows should be glazed using easy-to-clean gaskets.

8.1.3.2 Floors

Concrete is the most common floor foundation in cleanrooms. A smooth, impervious and durable surface then has to be added. This should be slip resistant and resistant to spilled chemicals. In some cleanrooms it may also require to have good electrostatic properties or minimal outgassing properties.

A commonly used surface covering is heavy-duty flexible vinyl sheeting joined by welding. A less common surface covering is terrazzo, which is very durable and therefore

suitable in situations that require such durability. Vinyl sheet can be manufactured to be electrically conductive for use where this is desirable. In unidirectional airflow rooms, where the air passes through the floor, it would be common to find that the floor is made of perforated floor panels placed on pedestals, the panels allowing the air to pass though.

The floor to wall joints would normally be coved with some type of corner profile. An exception to this may be where machines are used to clean the floor.

8.1.3.3 Ceilings

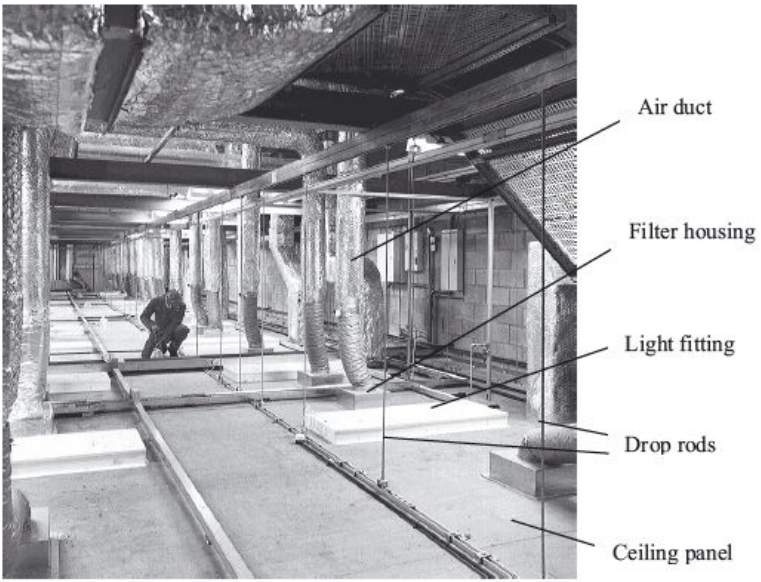
It would be unusual in a cleanroom to have anything other than a false ceiling. The need for access to air conditioning ducts and other services, and the use of terminal filters and recessed lights that are integrated with the ceiling, dictates the use of a suspended or supported ceiling.

In non-unidirectional airflow cleanrooms the ceilings are either suspended or self-supported. The flush mounted light fittings and air filter housings, being recessed into the ceiling void, are sited to avoid any supporting structures, and the remaining area is filled with blank panels. Figure 8.3 shows a suspended cleanroom ceiling, suitable for walking on, with the various components built into it.

All the light fittings, filter modules and blank panels must be well fitted to ensure a minimum of air leakage. If top-quality components are not used, a suitable mastic or other means can be used to seal all the joints.

In a unidirectional airflow cleanroom, most of the ceiling area consists of filters. The ceiling framework is assembled from special extruded aluminium sections and the filters are inserted into housings in the framework. This is discussed in Section 9.6 of this book.

Figure 8.3 Suspended cleanroom ceiling



8.2 Outgassing and Electrostatic Properties

In semiconductor and similar areas, the use of construction materials that allow chemicals to 'outgas' can give contamination problems. For example, the heavy duty vinyl sheeting used for flooring (and sometimes walls and ceilings as described earlier) has a significant amount of plasticiser added to make it flexible. Plasticisers usually come from the chemical group known as phthalates.

Phthalates will evaporate from the vinyl and this is why soft vinyl products become hard over time. Evaporation is slow, but the area of the floor is large. It is therefore necessary to specify specially formulated vinyl sheeting wherever very low emissions of volatile chemicals are required. It is also necessary to ensure that suitable wall and ceiling panels are specified, and that sealants and adhesives that do not outgas are chosen.

It should be noted that the materials used for the air conditioning plant and air distribution ductwork should not outgas, e.g. silicon mastic should be avoided. The same applies to cabling and high efficiency filters.

Test methods are available to ascertain the outgassing properties of materials. These accelerate the outgassing of chemical contamination and assess the amount that is likely to condense onto a surface.

8.3 Clean-build

When a cleanroom has just been built, it must be handed over to the client in a clean condition. During the building of a cleanroom, materials will be delivered to the construction site in a far from clean condition, left in the staging area to collect more dirt, and then used to build the cleanroom. There is also the high probability that construction methods will add to the contamination. This dirt must not end up in the product and to minimise this possibility two options are open. Firstly, after the cleanroom has been built, a thorough clean is carried out. This is often known a ‘final super clean'. Information on how cleanrooms should be cleaned is given in Chapter 22

of this book and the cleaning of cleanrooms is not discussed any further in this chapter. A second additional option is to use a 'cleanbuild' technique to minimise the amount of dirt built into the cleanroom. The remainder of this section is devoted to describing this technique, which employs the following methods:

1. The materials used in the construction are delivered in a timely manner when needed for use and stored in a way to minimise contamination;

2. packaging of the construction materials is removed and surface cleaning carried out before the materials are brought into the building;

3. the generation of contamination from the building process and personnel within the cleanroom is minimised;

4. cleaning is carried out during construction.

Even when using the clean-build method, a 'final super clean' should always be carried out after the cleanroom construction has been completed. Clean-build is often employed in semiconductor and similar high-quality cleanrooms. Where cleanrooms of ISO Class 7, and dirtier are constructed they are unlikely to need the clean-build method.

8.3.1 Advantages and disadvantages of clean-build

The main advantage of using clean-build is that dirt is not built into the cleanroom structure and the leaking-out of dirt with time should be minimal. Also, if future changes

to the use of the cleanroom require internal walls to be moved, or the structure of the cleanroom needs to be opened up to allow access of new production equipment, contamination problems caused by these actions should be minimised. No one has demonstrated that there are lower rates of product contamination when clean-build is used. However, anyone who has seen materials delivered to the construction site and left in the mud and rain for weeks, before being fitted into a cleanroom, will feel that at least some aspects of clean-build should be employed in cleanroom construction.

The disadvantages of clean-build are the additional cost and time taken in construction. Additional costs are said to be between 1% and 5% of the total cost. If a 'final super clean' is used as an alternative to cleanbuild, the cost of the 'final super clean' will not be more than 1%. The clean-build method requires a large expenditure on gloves, overshoes, mats etc. for the construction personnel, but the largest part of the cost is in the non-productive time of construction staff putting on contamination control clothing, the cleaning of construction materials and tools, and carrying out other requirements.

8.3.2 Clean construction protocol

Clean-build is carried out by dividing the construction process into stages, these stages requiring increasingly more effective contamination control measures as the project gets closer to completion. IEST RP 12 gives an example of how this might be done by providing a clean-build protocol. It is unlikely that any one protocol will work for all cleanrooms owing to the different

construction methods and construction sequences, and it is likely that a suitable protocol will have to be developed for each cleanroom built.

The first stage of clean-build can start after the 'drying out' of the shell of the building. This is the first stage that allows the perimeter of the clean area within the building to be secured by the use of partitions. Tasks to be carried out at this first stage are the electrical, plumbing, painting, joinery, and similar work to the shell of the building, as well as the installation of air conditioning plant and associated ductwork. No special garments are normally required for construction personnel at this stage, although boots must be clean and a discipline enforced to ensure that this is so. The only entry to the clean area will be through a controlled entrance. Temporary transfer areas may need to be built for personnel, as well as for materials to be stored under cover before being cleaned and brought into the clean area. Materials needed in the clean area should be stored until required and, when required, they should be unpacked before being brought into the clean area. No packaging material is allowed into the clean area, especially cardboard, wood, paper and plastic foam. Before materials are brought into the clean area, gross contamination should be removed by wiping with lint-free wipes, or by vacuuming and then wiping. Basic disciplines are required from personnel to reduce contamination. Regular cleaning within the clean area must be carried out.

The second stage of the clean-build starts when the materials used to construct the cleanrooms are brought into the clean area. Cleanroom interiors i.e. walls, ceilings and floors are fitted, along with electrical and other services

required for the cleanroom and the manufacturing process. If possible, the clean area should be pressurised against contamination from outside. If the clean-build technique is used in cleanrooms where there is a separate fresh air conditioning plant this should be switched on with its primary filters fitted (but no terminal HEPA or ULPA fitted). If there is a single air conditioning plant then this should be switched on with its primary filters fitted. During this stage, personnel will be required to wear shoes dedicated to the clean area, or overshoes, and they should not be allowed into the clean area with noticeably dirty clothes. Packaging materials will already have been removed from the materials, and these materials are wiped down with lint-free wipes as they are brought in. The clean area will be continually cleaned using suitable cleaning methods. Disciplines should be used to ensure that contamination is not introduced by inappropriate building techniques that generate substantial contamination e.g. sawing wood, welding, drilling holes etc. These should be carried out in special areas, or measures taken to minimise the spread of contamination.

The third stage of the clean build will start when the erection of the cleanroom is complete. During the third stage, the HEPA or ULPA filters are installed and integrity tested, and the air conditioning plant is balanced. The mechanical and electrical services that control the manufacturing processes are completed and a further thorough clean carried out with the same intensity as for a ‘final super clean’. From this point on the same contamination control disciplines and measures should be employed as will be employed when the cleanroom is in

production. This third stage will end with the cleanroom being tested in the ‘as built’ condition.

The final stage of clean-build starts after the ‘as built’ testing of the cleanroom has been satisfactorily completed. The production equipment is installed and connected to the required electrical power supplies and other services. This stage ends with the testing of the cleanroom in the ‘at rest’ condition to demonstrate that the cleanroom is fit to be handed over to the client.

8.3.3 Optimising the work sequence

An important part of a clean-build is the planning of the work sequence. The dirty work must be carried out first and the clean work last. Unfortunately, this is not always possible and, where dirty work is carried out in clean conditions, protective measures should be used to reduce contamination.

8.3.4 Temporary storage and ‘clean down’ facilities

The storage of construction materials can be a problem. Materials that are delivered and left outside the building can become grossly contaminated. Storage should, therefore be inside the building or, if no suitable area is available, temporary structures should be built. The storage areas need to be planned and managed well so that materials can be accessed in the correct order for the construction of the cleanroom.

8.3.5 High purity piping

The installation of high purity piping, both for gases and liquids, requires special attention. While most piping subcontractors are fully qualified to install systems in electropolished stainless steel, plastic, copper etc, the techniques needed to ensure a contamination-free supply of fluids for a cleanroom manufacturing process may be beyond their knowledge. It may therefore be best to employ a third-party expert who understands these requirements to advise on installation and to provide testing services to validate the purity of the fluids delivered through the pipework.

Acknowledgements

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9

High Efficiency Air Filtration

9.1 Air Filters used in Cleanrooms

The air supplied to a cleanroom must be filtered to ensure the removal of particles and micro-organisms. Until the early 1980s, only High Efficiency Particulate Air (HEPA) filters were used to filter cleanroom air, as these were the most efficient air filters available. A HEPA filter will remove at least 99.97% of the most easily penetrating particles. Today, HEPA filters are still used in most cleanrooms to remove micro-organisms and inert particles in the supply air.

The manufacture of integrated circuits and other devices has now evolved to a level where more efficient filters than HEPA filters are required to ensure that fewer particles pass through the air filters and into the cleanroom. More efficient filters are used and these are known as Ultra Low Penetration Air (ULPA) filters. An ULPA filter will remove at least 99.999% of the most easily penetrating particles. These filters are constructed and function in the same way as a HEPA filter.

It is generally accepted that:

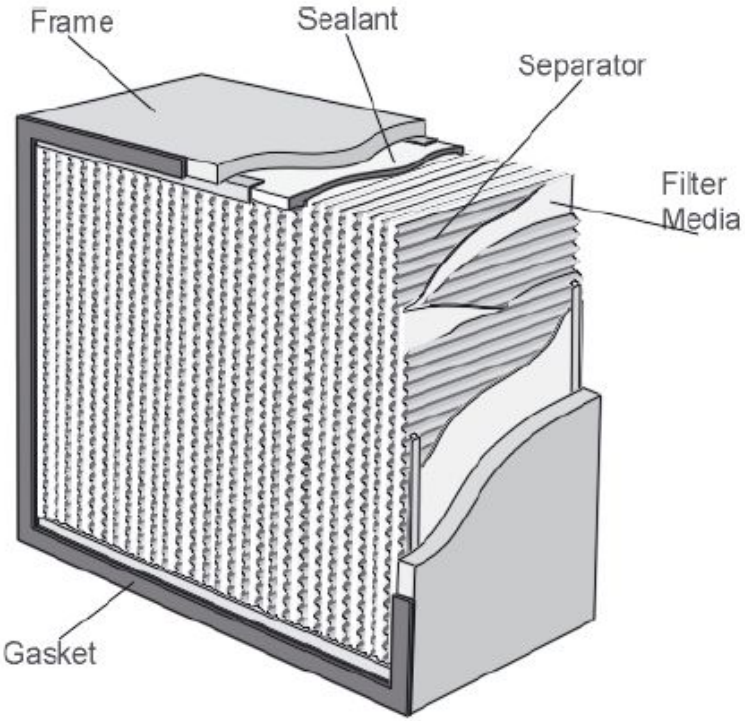
- for cleanrooms of ISO Class 6 and poorer quality, HEPA filters are used with non-unidirectional ventilation to meet the cleanroom classification.

- for ISO Class 5, HEPA filters that completely cover the ceiling are used to supply unidirectional airflow down through the cleanroom.
- for ISO Class 4 or lower, ULPA filters should be used with unidirectional airflow.

9.2 The Construction of High Efficiency Filters

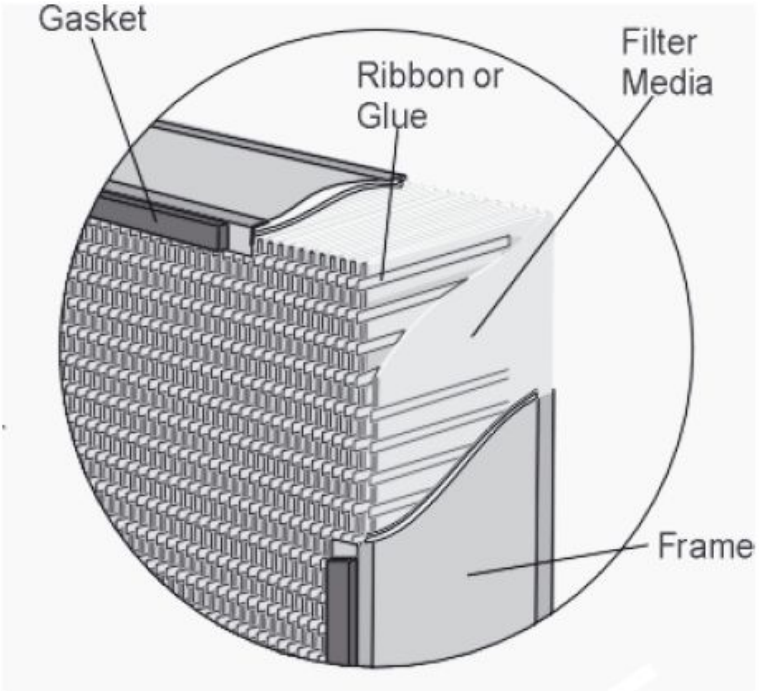
High efficiency filters are usually constructed in two ways, i.e. deep-pleated and mini-pleated. In a deep-pleated filter, which is an older type of construction method, filter paper is drawn from rolls and folded back and fore continuously to form filter packs that are either 15 cm (6 inches) or 30 cm (12 inch) deep. To allow the air to pass through the paper and to give the filter pack strength, a corrugated sheet of aluminium foil is used as a separator between each fold or pleat. This pack of filter media and separators is then glued into a frame of a plastic, wood or metal. A cross-section of a filter made by this traditional method is shown in Figure 9.1.

Figure 9.1 Deep-pleated high efficiency filter with separators



High efficiency filters are now most commonly available in the mini-pleat form. Aluminium separators are not used in this method of construction but the paper medium folds are held ‘open’ by ribbons, glued strings, or raised dimples in the media and the completed pack then assembled into a frame. This method of assembly, shown in Figure 9.2, allows 2.5 to 3 times more pleats than the deep-pleated filters and can therefore be made more compact.

Figure 9.2 Sectioned view of a mini-pleat filter



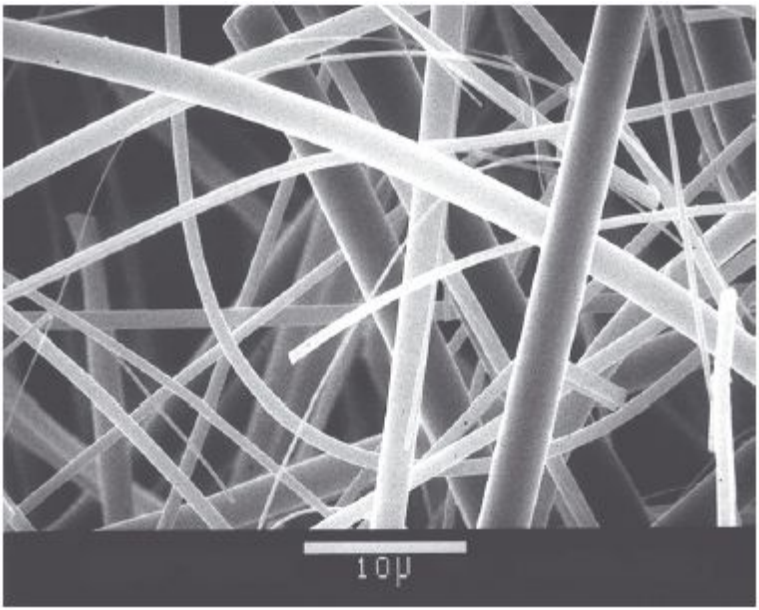
The pressure drop across a filter is dependent on the air velocity through the filter media and its type of construction. The nominal air velocity through the whole filter is usually 0.45 m/s, although the velocity through the filter media is only about 1 cm/s to 2 cm/s. At this velocity, the pressure drop across the filter will vary according to the thickness of filter media, and the type of media used. It is usual that the higher the efficiency of the filter the higher the pressure drop, although the higher pressure can be compensated for by using a greater length of filter media. The initial pressure drop across high efficiency filters is likely to be between 120 Pa and 170

Pa. When the pressure drop reaches 2.5 to 3 times the original pressure, the filters are normally replaced.

9.3 Particle Removal Mechanisms

A high efficiency filter is designed to remove particles of about 1 μm and smaller. High efficiency filters will remove larger particles but it is not good economic sense for them to be used for this purpose. Much less expensive pre-filters can be used to remove the larger particles but these filters are not discussed in this chapter. High efficiency filter media is made of glass fibres ranging in diameter from about 0.1 μm to 10 μm, with spaces between fibres that are often very much larger than the particles captured. An ULPA filter will have more fine fibres than a HEPA filter.

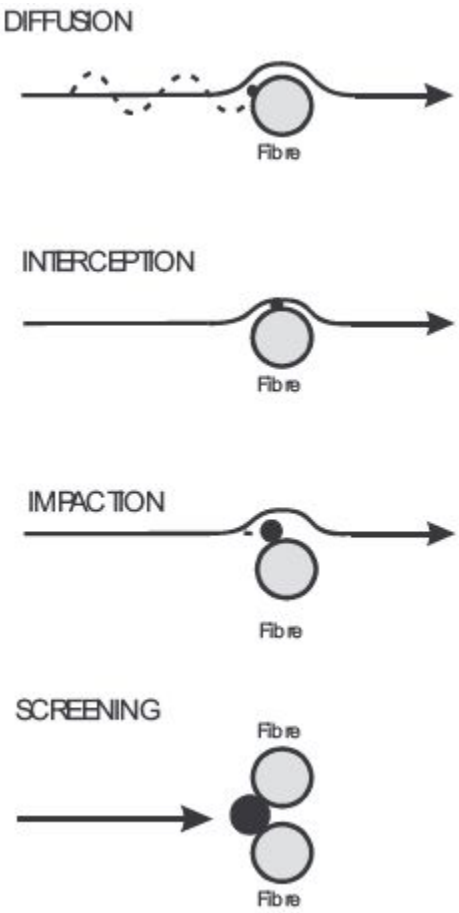
Figure 9.3 Photomicrograph of high efficiency filter media



These fibres criss-cross randomly throughout the depth of the filter media and do not give a controlled pore size. A photomicrograph of high efficiency filter media is shown in Figure 9.3 with a 10 μm scale shown at the base of the photograph.

As airborne particles move through the filter paper, they bump into the fibres, or into other particles that are already stuck to the fibres. When a particle bumps into either a fibre or a previously captured particle, strong forces, such as the van der Waals force, are established between the captured particle and the fibre or particle that has captured it so that the particle is retained. These forces are also the reason why captured particles are not released from a filter into the air supply to a cleanroom.

Figure 9.4 Particle removal mechanisms



The three main mechanisms involved in the removal of small particles in filter media are diffusion, interception and impaction. The fourth, screening, which can also be called sieving or straining, is of less importance as it occurs only with larger particles sizes that should already have been removed by the pre-filters placed before the

high efficiency filters. These four mechanisms are shown diagrammatically in Figure 9.4. It is generally believed that electrostatic effects are unimportant in high efficiency filters and for that reason are not included in the figure.

In the process of capture by*diffusion* (also known as Brownian movement), very small particles move about randomly. This random motion is caused by constant bombardment by other small particles and by the molecules of the gas in which they are suspended. The resulting random paths taken by these smallest of particles make it more likely that they will bump into the fibres of the filter, or previously captured particles.

If a particle strikes a fibre as it passes by in the airstream, it will be captured and retained by a process known as*interception*.

In the process of capture by*impaction*, a particle with sufficient mass (and therefore momentum) leaves the airstream and goes straight on to strike a fibre as the airstream turns around it.

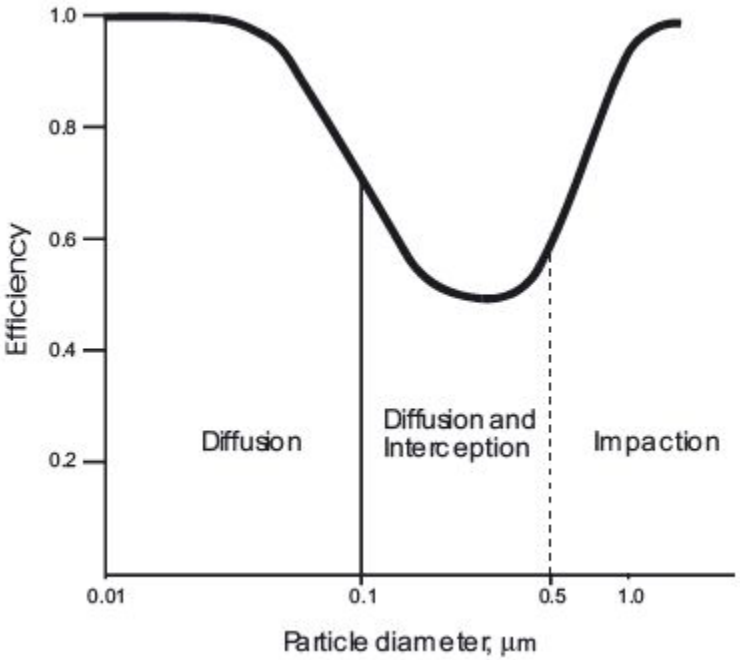
The final mechanism of filtration, which is known as*screening*, sieving or straining, occurs when the spaces between the fibres are smaller than the particles that are being captured.

A high efficiency filter is dependent on the first three of the mechanisms described above to remove particles in the air. The largest size of particle is removed by inertial impaction, the medium size by direct interception and the smallest by diffusion. The information shown in Figure 9.5

is the combined outcome of these mechanisms. This figure shows the classical removal efficiency curve for a HEPA-type filter and the lowest removal efficiency for a particle size of about 0.3 μm. The Most Penetrating Particle Size (MPPS) normally lies between 0.1 μm and 0.3 μm. Particles larger that the MPPS are removed more efficiently, and it should be noted that so are particles smaller than the MPPS, this latter effect being caused by diffusion.

The curve gives a rather simplistic approach, as the particle size that has the lowest removal efficiency (maximum penetration) depends on variables such as the density of the particle and the type of filter medium.

Figure 9.5 Classic efficiency curve for an air filter (from early work over 50 years ago)



9.4 Testing of High Efficiency Filters

High efficiency filters are tested in the factory where they are manufactured to ensure they have the correct efficiency against test particles. There are a number of tests used for this purpose. The best known are:

9.4.1 Military Standard 282

This USA test uses thermally-generated particles of dioctyl phthalate (DOP) with a mass median diameter (MMD) of 0.3 µm to test the efficiency of HEPA filters. This diameter is equivalent to a count median diameter (CMD) of 0.19 µm. Other oils such as poly-alpha olefin (PAO) or dioctyl

sebacate (DOS) are also used. The oil is heated so that it vapourises, and when the vapour leaves the generator it meets air and condenses to form particles of the required size. The efficiency against this challenge is determined.

9.4.2 IEST Recommended Practices

The Institute of Environmental Sciences and Technology (IEST) has developed several Recommended Practices for testing and classifying HEPA and ULPA filters (IEST-RP-CC001, 007, 034). Filter classification is based on testing according to Mil Standard 282 methods described above, or by measurements using particle counters. In the particle counter test method (RP 007), the filter efficiency is determined for the particle size range of 0.1 μm to 0.2 μm, using either a nearly monodisperse aerosol and a detector, or a polydisperse aerosol and a particle counter. The choice of the aerosol material is left to the user; several are recommended. In both methods of classification, the aerosol size used for determining the filter efficiency is near the MPPS.

9.4.3 European Standard EN 1822

This standard has largely replaced the Eurovent 4/4 method of testing high efficiency filters and is used for both HEPA and ULPA filters. It gives a method for both testing the particle removal efficiency and for classifying the filter.

An important departure of this test method from methods described above is the determination of the MPPS for the filter media being tested, and the measurement of the

removal efficiency of the filter at that particle size. As discussed in Section 9.3, each type of filter media has a particular size of particle that will pass through the filter most easily, that size being determined by such variables, as the fibre sizes, packing density of the filter media, and air velocity. It is logical therefore to test the filter at the MPPS, which is normally between 0.1 μm and 0.3 μm.

The first stage of this test method is to determine the MPPS of the flat sheet filter medium used in the filter. This is carried out at the face velocity that will correspond with that produced by the filter when working at its given flow rates. The efficiency of the complete filter can then be determined in two ways:

- Leak testing (local efficiency). The filter media of the complete filter is scanned to determine the amount of leakage through pinholes in the filter medium when the filter is operating at its rated flow.
- Overall efficiency. The efficiency of the complete filter is determined when the filter is operating at its rated flow.

The filter is then classified by its overall and local efficiency against particles of its specific MPPS. This classification is shown in Table 9.1.

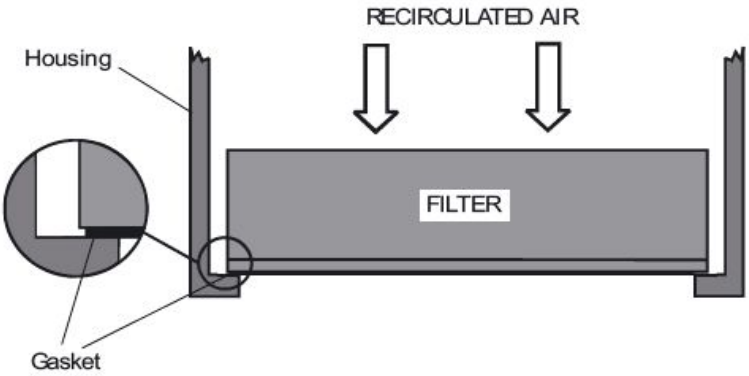
Table 9.1 Classification of filters according to the EN 1822.

Filter class	Overall value efficiency (%)	Overall value penetration (%)	Leak test Efficiency (%)	Leak test penetration (%)
H 10	85	15	–	–
H 11	95	5	–	–
H 12	99.5	0.5	–	–
H 13	99.95	0.05	99.75	0.25
H 14	99.995	0.005	99.975	0.025
U 15	99.999 5	0.000 5	99.997 5	0.002 5
U 16	99.999 95	0.000 05	99.999 75	0.000 25
U 17	99.999 995	0.000 005	99.999 9	0.000 1

9.5 Scan Testing of High Efficiency Filters

Air that is supplied in a non-unidirectional airflow cleanroom through diffusers in the ceiling is well mixed with the room air. Some pinhole leaks in the filters may be tolerated, as long as they are not great enough to significantly reduce the overall efficiency of the filtration system and affect the required air cleanliness (see Table 9.1). This tolerance is possible because the small numbers of particles passing through the filter are well mixed with the room air. This is not the case in unidirectional airflow systems, where a leak can release a unidirectional stream of particles into the close proximity of the process or product. To prevent these pinhole leaks, the filters should be scanned in the factory by introducing a test aerosol upstream of the filter and scanning the whole downstream face using a probe in overlapping passes to search for leaks. This method is very similar to that described in Chapter 14 of this book, which describes the scanning that has to be carried out when a filter has been installed in a cleanroom.

Figure 9.6 Traditional neoprene gasket sealing method



When a high efficiency filter leaves the factory where it has been manufactured and tested, it should be fit for the purpose required. If it has been properly packed, transported, and installed by personnel who are familiar with the delicate nature of filter media, then the filter's integrity should be maintained. To check this, the filter's integrity will be tested using the scan method described in Chapter 14.

To ensure that there is no ingress of unfiltered air into the cleanroom, the filter must be fitted into a well-designed housing. The housing must be of sound construction and particular attention must be paid to the method of sealing between the housing and the filter.

Neoprene rubber gaskets are commonly fitted to the filter frame as seals. This method of construction is illustrated in Figure 9.1. When the filter is fitted into the filter housing

the gasket presses down, compressing onto the flat face of the housing and preventing leakage of contaminated air (Figure 9.6). This method is normally successful, but insufficient tightening, distortion of the filter frame or housings as supplied or when tightening up, and poor or old gaskets, can cause leakage. Better-designed housings overcome these problems.

Figure 9.7 Ceiling grid with channel for a fluid seal

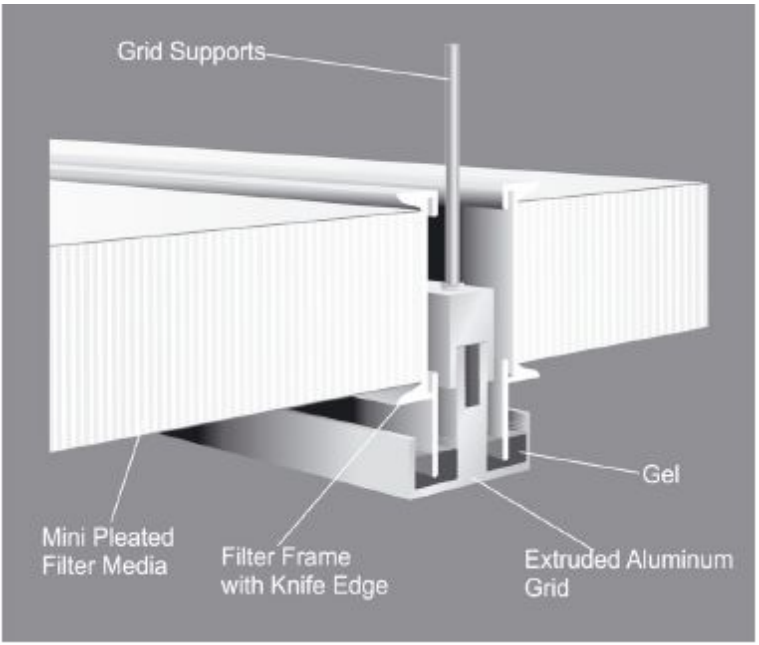


Figure 9.7 shows a typical system that would be used in a unidirectional airflow cleanroom. The ceiling grid has a continuous channel filled with the fluid seal, which is a jelly-like substance that will not flow out of the channel. A knife-edge, fitted to the filter frame, mates into the channel

of sealant. The fluid flows round the knife-edge to give a perfect seal that prevents particles by-passing the filter through the housing. Fluid seal systems are also available for use in non-unidirectional cleanrooms where there is no ceiling grid. There are also systems where the gel seal is in the filter and the knife-edge in the housing.

9.7 Removal of Airborne Chemical Contamination

High efficiency air filters are provided in cleanrooms to remove particles and microbe-carrying particles. However, the air supplied to the cleanroom may be a source of airborne chemical contamination and, in cleanrooms where airborne chemical contamination is a problem, methods of removal must be used. When the air recirculates through the air conditioning plant there is an opportunity to remove some of the contamination produced within the cleanroom. A minority of the air supplied to a cleanroom will be drawn from the outside environment and this can also be a significant source of airborne chemical contamination, especially if the cleanroom is situated in an area of pollution. The air is treated in the air conditioning plant using the following methods:

- adsorption onto materials such as activated carbon, ion exchange compounds etc.,
- photoelectron ionisation and electrostatic ion removal,
- catalytic photo-oxidation.

Acknowledgements

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Evanite Fiber Corporation. Table 9.1 is reproduced by permission of the British Standards Institution.

10

Cleanroom Testing and Monitoring

When a cleanroom has been built and is about to be handed over to the purchaser, or when an existing cleanroom is reopened after being shut down for modifications that could cause changes to its contamination control characteristics, it will be tested. This initial type of testing is to establish that the cleanroom is working correctly and achieving the contamination standards that it has been designed to fulfil. These standards are laid down in ISO 14644-1 with the methods used to test a cleanroom being given in ISO 14644-3. A secondary function of this initial testing is to establish the initial performance of the room so that this can be adopted as a 'benchmark'. When the room is checked in the future, and a contamination problem is encountered, deviations from the original conditions may be found, and the possible reasons for contamination thus ascertained. The final and indirect reason for carrying out initial testing of a cleanroom is to familiarise and train the staff who will monitor and run the room. This may be their most important, and possibly only, opportunity to understand how their cleanroom works and to learn the test methods used to ensure that the cleanroom continues to perform correctly.

When it has been shown that the cleanroom fulfils the ISO 14664-1 cleanroom classification set down at the design stage, it is necessary to regularly check the room at the time intervals set by ISO 14644-2, to ensure that the room

continues to comply with the standard. Many cleanrooms are built and passed over to the user with little or no effort being put into ensuring that over their many years of use the correct level of cleanliness continues to be achieved. Routine testing must therefore be carried out so that the customer who buys a product is assured that it is fit for the purpose for which it is intended.

As well as checking the cleanroom to show that it is working correctly when first installed, and at regular intervals to show that it complies with ISO 14644-1, it may be necessary to regularly monitor the room during production. This may not be required in lower quality cleanrooms, but in higher quality rooms it may be necessary to monitor the room to ensure that the correct cleanliness conditions are maintained during production. This testing may be either continuous, or at intervals that are much shorter than those laid down in ISO 14644-2.

Most of the tests carried out to test the initial performance, or to demonstrate continued compliance to ISO 14644-1 or monitor the cleanroom during production are identical, although it is normal to find that the initial testing is more thorough and extensive.

10.1 Principles of Cleanroom Testing

To show that a cleanroom is working satisfactorily it is necessary to demonstrate that the following principles have been satisfied:

- The air supplied to the cleanroom is of sufficient*quantity* to dilute or remove the contamination generated in the room.

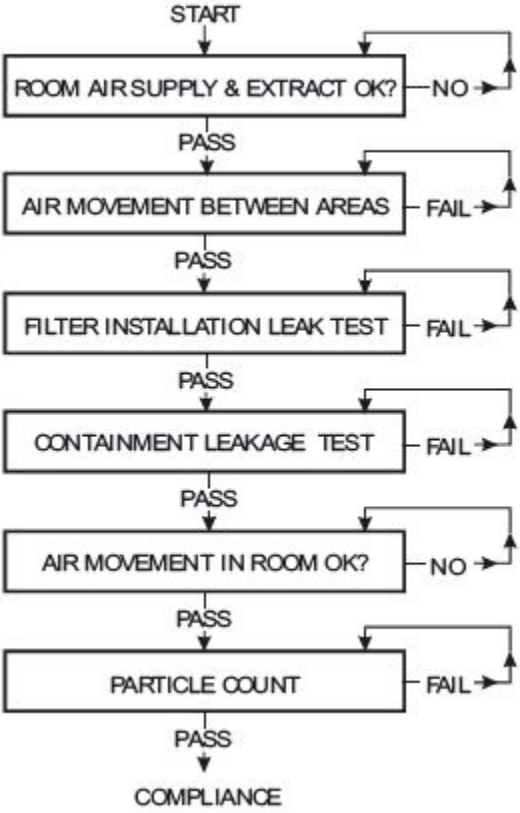
- The air within the cleanroom suite moves from clean to less-clean areas to minimise the adverse movement of contaminated air. Air should move in the correct direction through doorways and the fabric of the room.
- The air supplied to the cleanroom is of a*quality* that will not add significant amounts of contamination to the room.
- The air movement within the cleanroom should ensure that there are no areas within the room with high concentrations of contamination.

If these principles are satisfied then the concentration of particles, and where necessary microbe-carrying particles, should be measured to ascertain that the specified cleanroom standard has been achieved.

10.2 Cleanroom Tests

To ensure that the requirements in Section 10.1 are fulfilled, the tests shown in Figure 10.1 should be carried out. The order of testing given in Figure 10.1 is that usually carried out during the initial testing of a new cleanroom but subsequent testing may be carried out in a less structured way.

Figure 10.1 Cleanroom test sequence



10.2.1 Air supply and extract quantities

In the case of non-unidirectional airflow cleanrooms, the air supply and extract volumes should be measured. In the case of unidirectional airflow cleanrooms the air velocity should be measured.

10.2.2 Air movement control between areas

It is necessary to demonstrate that the airflow between areas is in the correct direction. The air direction through

doorways, hatches, etc. should be from clean to less-clean and the pressure differences between areas should be correct.

10.2.3 Filter installation leak test

The high efficiency air filter, and its housing, should be checked to ensure that no airborne contamination passes into the cleanroom through (a) a damaged filter (b) a leak between the filter and its housing or (c) a leak in any other part of the filter installation.

10.2.4 Containment leak testing

Testing should be carried out to show that airborne contamination is not entering the cleanroom by passing through its construction materials, such as walls or ceilings. Examples of the occurrence of containment leaks and a description of containment leak testing are given in Chapter 12.

10.2.5 Air movement control within the room

The type of air movement control test is dependant on whether the cleanroom is of the unidirectional or non-unidirectional airflow type. If the cleanroom is non-unidirectional, it is necessary to check that there are no areas, especially at the critical zone, with insufficient air movement. Visualisation tests and decay or recovery tests can be used. If the room has unidirectional airflow, it is necessary to check that the air velocity and direction throughout the room, especially at the critical areas, is that specified in the design.

10.2.6 Airborne particles and microbial concentrations

If the above tests are satisfactory then final measurements will be carried out to ascertain that the concentration of particles and, where appropriate, micro-organisms complies with the design specification laid down for the cleanroom.

10.2.7 Additional tests

In addition to the above requirements, it may be required in some cleanrooms to measure particles on surfaces. Information about this is given in ISO 14644-9. The concentration of chemicals in the air and on surfaces in the cleanroom may also need to be measured, and information is given in ISO 14644-8 and ISO 14644-10, respectively.

As well as the contamination control tests discussed in this chapter, it may be necessary to satisfy one or more of the following requirements:

- temperature,
- relative humidity,
- heating and cooling capabilities of the room,
- sound levels,
- lighting levels,
- vibration levels.

These requirements are not considered in any detail in this book, as they are tests that may be required in air conditioned rooms other than cleanrooms. Information on these tests are available in various building services textbooks and in Guides provided by the American Society of Heating, Refrigeration and Airconditioning Engineers

(ASHRAE) in the USA, and the Chartered Institute of Building Services Engineers (CIBSE) in the UK, as well as by professional societies in other countries.

10.3 Testing in Relation to Room Type and Occupation State

The type of testing to be carried out in a cleanroom depends on whether the room has unidirectional, non-unidirectional, or mixed airflow (a mixed flow room is one that is ventilated by non-unidirectional airflow but has unidirectional airflow cabinets, workstations, minienvironments, RABS, or isolators within the room). The tests required, with respect to the type of cleanroom, are discussed in the chapters that follow.

Tests can be carried out in the cleanroom when it is (a) 'as-built' i.e. empty, (b) 'at rest' i.e. the room fitted with machinery that may be operating but with no personnel present or (c) 'operational'. These occupancy states are defined in Section 3.4 of this book. When the cleanroom is being handed over to the user, the initial testing is usually carried out in the 'as built' condition. Similarly, when the cleanroom is checked throughout its life to demonstrate that it complies with ISO 14644-1, it will be normally tested in the 'at rest' occupancy state; this will demonstrate that the cleanroom is working correctly. However, if the cleanroom is being monitored to demonstrate that the conditions in the room are acceptable for production, the testing will be done in the 'operational' occupancy state. The type of test for each of the occupational states is very similar, and any special requirements are described in next few chapters.

10.4 Re-testing to Demonstrate Compliance

It is necessary to ensure that a cleanroom performs satisfactorily throughout its life and continues to comply with its cleanroom classification. The cleanroom must therefore be checked at regular intervals, these intervals being more frequent in higher-quality rooms. ISO 14644-2: 2000 gives the maximum time intervals that a cleanroom should be left before being tested to show it still complies with ISO 14644-1. These maximum time intervals are listed in Table 10.1 along with the type of test to be carried out.

Table 10.1 Schedule of tests to demonstrate continuing compliance

Test Parameter	**Class**	**Maximum Time Interval**
To demonstrate compliance by particle counting	≤ ISO 5	6 months
	> ISO 5	12 months
Schedule of additional tests		
Airflow velocity or volume	all classes	12 months
Air pressure difference	all classes	12 months
Schedule of optional tests		
Installed filter leakage	all classes	24 months*
Airflow visualisation	all classes	24 months*
Recovery	all classes	24 months*

Containment leakage	all classes	24 months*

*= suggested time interval

The one test that must be carried out to demonstrate that a cleanroom continues to comply with ISO 14644-1 is airborne particle counting. This must be carried out at a maximum time interval of 6 months for a cleanroom with a classification equal to, or less than, ISO Class 5, or 12 months if the classification is over ISO Class 5. Particle counting is normally carried out in the 'at-rest' state but may also be carried out in the 'operational' state. If the installation has a continuous, or frequent, particle and air pressure difference monitoring system, then ISO 14644-2:2000 allows the time interval to be extended.

Where the application requires them, 'additional' tests to demonstrate compliance may be added. These are air velocity or volume, and air pressure difference testing. These must be tested at maximum intervals of 12 months, although, as with particle counting and air pressure difference, the time interval can be extended if continuous, or frequent, monitoring is used.

ISO 14644-2:2000 also allows 'optional' tests to be included in the testing if agreed by customer and supplier. These should be at a maximum interval of 24 months. However, in this case these are only suggested time intervals. The optional tests are as follows:

- filter integrity leakage tests;
- airflow visualisation tests to show that the air movement within the cleanroom is correct;

- recovery test to show that any contamination dispersed into the air is removed efficiently;
- containment leakage test to show that air moves in the correct direction through the cleanroom fabric, i.e. from clean to less-clean.

Information on all of the above tests is discussed in subsequent chapters of this book.

It should be noted that ISO 14644-1:1999 and ISO 14644-2:2000 were being revised at the time of publication of this book and there may be changes to the classification and testing requirements. It is advised that the new edition of the standard is referred to when it is published.

The information given in the subsequent chapters of this book about cleanroom testing is mainly taken from the ISO 14644 series of standards. However, it will be found that pharmaceutical regulatory expectations (contained in documents such as the EU GGMP and the FDA Guidance) may have more stringent requirements. Where this occurs, the regulatory requirements should be used. Where there is no advice in the pharmaceutical documents on the testing methods to be followed, the methods laid down in the ISO 14644 series of standards will normally be accepted by the regulators.

10.5 Monitoring of Cleanrooms

The time intervals for the tests to be carried out to show that a cleanroom continues to comply with ISO standard 14644-1 are provided in ISO 14644-2. In cleanrooms of a high standard, where cleanliness is a vital part of the production process, e.g. pharmaceutical manufacturing,

further testing or monitoring, may be required. This will be carried out to show that during production the cleanroom conditions are correct, and under control.

The parameters that are most likely to be monitored are:

- air pressure differences,
- air supply volumes,
- airborne particle counts,
- and, where appropriate, microbiological concentrations.

Air pressure difference and air volume supply can be measured and recorded continuously by measuring instruments. This might be necessary in high quality cleanrooms such as ISO Class 4, and better. If monitoring is done in cleanrooms of poorer quality, the time interval might be daily, weekly, monthly, three monthly or six monthly, the interval being shorter the cleaner the cleanroom classification.

Particle counts can be measured and recorded using the same criteria as were discussed in the previous paragraph. It should be noted that when particle counts are monitored, it is not expected that this should be done at the number or layout of positions required by ISO 14644-1 for classification. Fewer positions can be selected and they need not be distributed evenly around the cleanroom. Monitoring positions should be selected that are important to the manufacturing process e.g. close to where the product is at risk of being exposed to contamination.

Acknowledgement

Table 10.1 is compiled from information given in ISO 14644-2: 2000 and reproduced by permission of the British Standards Institution.

11

Measurement of Air Quantities and Pressure Differences

A cleanroom must have sufficient clean air supplied to it to dilute and remove the airborne contamination generated within the room. In a nonunidirectional airflow type of cleanroom the cleanliness classification is directly dependent on the air supply volume and quality; the greater the volume of clean air supplied in a given time, the cleaner the room. In a unidirectional airflow type of cleanroom, the cleanroom classification is dependent on the air supply velocity. The volume or velocity will have been decided at the design stage. It will therefore be necessary, before the cleanroom is handed over to the client, and at regular intervals throughout the cleanroom's life, to show that the air quantities are correct.

To ensure that the air in a cleanroom suite always leaks from the cleanest cleanroom into the less clean surrounding cleanrooms and from there into the unclassified surrounding building, the rooms are pressurised, with the highest pressure being in the cleanest room. The movement of air and the required pressure differences to achieve this are discussed in Section 5.1.5 of this book.

11.1 Air Quantities

When the construction of a cleanroom suite is nearing its end, commissioning will start, and the accurate measurement and adjustment of the air supply and extract

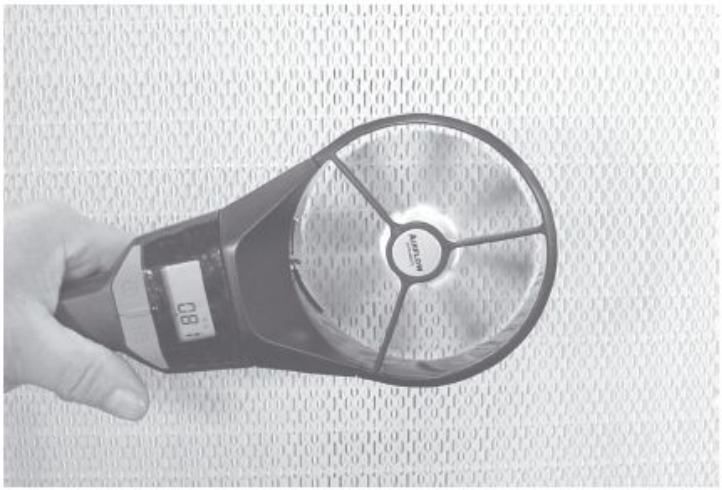
volumes to each cleanroom must be carried out. It is then necessary to check at regular intervals that the air supplied to the cleanrooms is correct. This testing is normally carried out using air volume measuring hoods and anemometers.

11.1.1 Instruments used to measure air velocities and volumes

11.1.1.1 Vane anemometer

This type of anemometer works like a windmill, and the higher the air velocity the faster its vanes will turn. Each turn of the vanes is measured and the frequency converted into a velocity. A typical vane anemometer is shown in Figure 11.1

Figure 11.1 Vane anemometer



Vane anemometers are robust instruments but if the air velocity is about 0.2 m/s (40 ft/min) or less, the mechanical friction within the revolving assembly may prevent the vanes from moving freely, thus causing the instrument to give an inaccurate reading.

Vane anemometers have either a pointer on a scale or digital readout. A pointer type anemometer gives an instant reading, but a digital type can average the velocity over a longer period. Averaging the velocity can be a useful feature, as the velocity of cleanroom air fluctuates, and it may otherwise be difficult to obtain the correct average velocity. Use of an averaged digital reading also avoids optimistic readings, where the highest result can be taken as the correct result.

11.1.1.2 Thermal anemometers

Thermal anemometers measure velocity by employing the cooling effect of air passing through the head of the instrument. Different types exist but one example is shown in Figure 11.2.

Figure 11.2 Thermal Anemometer

Most types of thermal anemometer use a bead thermistor, the cooling of which is related to the air velocity. The air velocity is measured by the amount of electrical energy required to maintain the bead at a constant temperature. To compensate for any variation in the air stream temperature an additional unheated thermistor in the probe is incorporated in the circuitry.

In some makes of thermal anemometer, the probe can be placed at the end of a telescopic extension. This enables the anemometer to be used for measuring velocities within an air supply duct. It also enables staff using anemometers in cleanrooms to position themselves where they will not influence the direction and velocity of the air stream being measured.

Low velocities can be measured with more confidence using thermal anemometers, and they are therefore suitable

for use within the cleanroom space to investigate air flows. They are less robust than vane anemometers but with reasonable care they will give long service.

11.1.2 Measuring hoods

Figure 11.3 Hood being used over an air supply diffuser in a cleanroom

Measuring hoods of the type shown in Figure 11.3 are used routinely to measure the air volumes within the cleanroom. The hood is placed over a supply diffuser or terminal air filter to gather the air which is then measured at the outlet. It should be noted that the type of supply diffuser may

affect the pattern of the air exiting the outlet and influence the measurement. In particular, the circling air from a swirl diffuser gives a higher air velocity at the outer edge of the outlet and this can causes high readings.

11.1.3 Measurement of air quantities in cleanrooms

11.1.3.1 Unidirectional airflow cleanrooms

The cleanliness of a unidirectional airflow cleanroom is influenced by the velocity of the unidirectional air and hence the velocity should be measured and not the airflow supply rate. ISO 14644-3 suggests that the number of points at which the velocity should be measured should be the square root of 10 times the filter area of the ceiling (or wall) in square metres, and should be not less than 4. These measuring points should be evenly spread over the filter bank.

The air velocity is normally measured by an anemometer close to the filter face but far enough away to allow the unevenness and jetting of the airflow from the filter to become more uniform. This is a particular problem with the vane anemometer, which, if it is placed directly against the filter face, will give a velocity reading that is about 25% too high. ISO 14644-3 suggests that the airflow should be measured 15 cm to 30 cm from the filter face. A distance of 15 cm will be found to give accurate readings.

11.1.3.2 Non-unidirectional airflow cleanrooms

The cleanliness of a non-unidirectional airflow cleanroom is dependent on the air supply volume. The greater the air

supply volume, the cleaner the room. The air volume supplied to a cleanroom can be checked by use of a measuring hood or anemometer. A measuring hood gives a direct measure of the air supply volume and this method has been described in Section 11.2.3. However, if an anemometer is used to determine the air supply volume, the following method should be employed.

In a non-unidirectional airflow cleanroom the air is supplied from filters in the ceiling, often through an air diffuser. If air is supplied through a diffuser it will exit in a multi-directional way and with varying velocities. The average air velocity is therefore impossible to measure. To overcome this, the diffuser should be removed and the average air velocity at the filter face measured using an anemometer placed 15 cm from the filter face. The average can be obtained by taking measurements at various points across the 'active' part of the filter face, i.e. the filter media and not the frame, or by scanning over the 'active' part of the filter face. The area of the 'active' part of the filter face is then measured and the air supply volume calculated using Equation 11.1.

Equation 11.1

$$\text{Air supply volume } (m^3/s) = \text{average air velocity } (m/s) \times \text{filter face area } (m^2)$$

As explained in Chapter 5, the cleanliness of a non-unidirectional cleanroom is more accurately determined by the air supply rate (m^3/s or m^3/h.) than by the air changes per hour. However, it is common to report

the air supply in terms of air changes per hour. Knowing the air supply rate and the volume of the cleanroom, the air changes per hour can be calculated by means of Equation 11.2.

Equation 11.2

$$\text{Air changes per hour} = \text{air volume supplied per hour } (m^3/h) \div \text{volume of room } (m^3)$$

Example:*The air is supplied to a cleanroom through eight terminal filters with an active filter face of 0.585 m × 0.585 m.i.e. a surface area of 0.342 m^2. The average face velocity of the filter measured 15 cm away from the filter face is 0.45 m/s. The cleanroom has a size of 8 m × 8 m × 3.5 m. What are (1) the air supply volume and (2) the air changes per hour?*

(1) Using Equation 11.1,

Air volume supplied from each filter (m^3/s) = surface area of filter (m^2) x average air velocity at filter face (m/s) = 0.342 × 0.45 = 0.154 m^3/s

The air supply from all 8 filters = 0.154 × 8 = 1.232 m^3/s = 4435 m^3/h

(2) Volume of room = 8 m × 8 m ×3.5 m = 224 m^3

However, it is known that the air supplied to the room is 4435 m^3/h

Therefore, using Equation 11.2,

Air changes/hour = 4435 ÷ 224 = 19.8

11.2 Differential Pressure Tests

It is necessary to ensure that air in a cleanroom suite moves from clean to less-clean areas, and not vice-versa. Measurement of pressure is an indirect measurement of this, as air will flow from an area of high pressure to an area of lower pressure. Higher quality cleanrooms should therefore have a higher pressure than adjacent less-clean areas. The units used to measure pressure differences are Pascals, although other units such as inches water gauge are sometimes used (12 Pa = 0.05 inches water gauge). A pressure difference of 10 Pa is generally accepted as that which should be established between two cleanrooms and 15 Pa between a cleanroom and an unclassified room.

Problems can occur when trying to achieve a pressure difference between areas connected by a large opening, such as a supply tunnel. To achieve the suggested pressure drop it may be necessary to use very large air quantities through the tunnel, even where the area of the opening has been restricted. An alternative is to use a lower pressure difference and ISO 14644-4 suggests that this can be as low as 5 Pa. To use this lower pressure difference is perfectly reasonable as long as the primary requirement is achieved, i.e. the airflow is always in the correct direction as shown by smoke visualisation tests. It may, however, be difficult to convince everyone of the correctness of this argument, and it may be necessary to conform to the higher pressure difference.

11.2.1 Instruments for measuring pressure differences

A manometer capable of reading pressure differences in the range of 0-60 Pa (0-0.25 inch water) is required for measuring the pressure difference between clean areas. This is usually an inclined manometer, magnehelic gauge, or electronic manometer.

Inclined tube manometer This works by the higher air pressure pushing a liquid up a graduated inclined tube. The change in gradient in the inclined manometer, shown in Figure 11.4, enables it to measure small pressure differences up to about 60 Pa and then much larger pressure differences up to 700 Pa as the tube moves round into the vertical direction. The manometer can thus be used for two very different cleanroom applications, namely for measuring the pressure difference between two areas, which might be 10 or 15 Pa, or for measuring the pressure drop across a high efficiency air filter which might be anything between 100 Pa to 500 Pa.

Figure 11.4 Inclined tube manometer

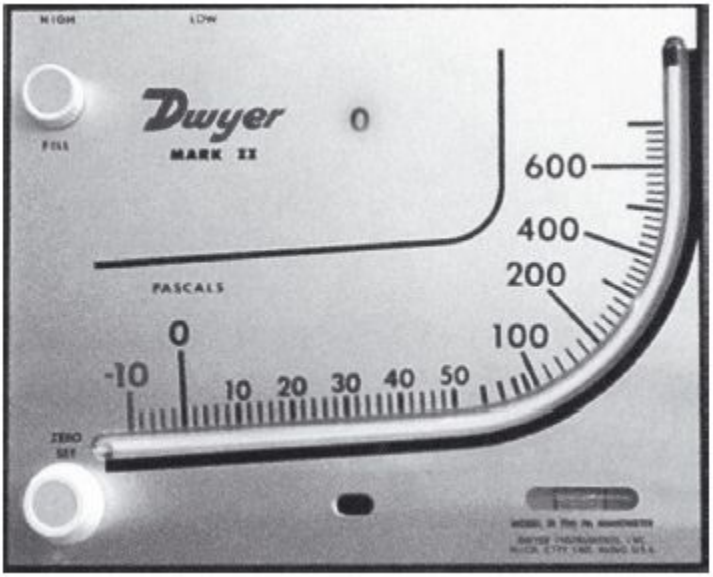


Figure 11.5 Magnehelic pressure gauge

Magnehelic gauge This is shown in Figure 11.5 and works by the pressure acting on a diaphragm. This moves an indicating pointer, the movement being relayed and amplified through a magnetic linkage.

A panel of inclined gauges or magnehelic manometers is often mounted on the outside of a cleanroom so that the pressure differences can be easily seen and checked. Pressures can also be relayed electronically from manometers to a building management system.

Electronic manometer This can work in various ways but is distinguished from the previous two types of manometer

by using electronic means to give a digital pressure reading. Electronic manometers are convenient for field measurements, being compact, robust and portable. A typical electronic manometer is shown in Figure 11.6.

Figure 11.6 Electronic micromanometer

11.2.2 Methods of checking pressure differences

To check the pressure differences between clean areas, the air conditioning plant must be supplying and extracting the

correct volumes of air and all doors in the cleanroom suite must be closed. If a pressure difference needs adjusting, the air extract volume from the room must be reduced to increase the pressure, and opened to decrease it. These adjustments are best carried out by a specialised firm, as a change in pressure in one room is likely to give changes in the pressure differences between other rooms of the cleanroom suite.

If manometers are not permanently installed, a tube from a pressure gauge is passed under the door, or through an open by-pass grille or damper, into the adjacent area. The end of the tube must be sufficiently distant from the door so that no pressure is registered from air movement through the door crack, and care should be taken not to block the tubing by twisting or trapping it. A reading of the pressure difference may then be taken.

Acknowledgement

The photographs shown in Figures 11.4 and 11.5 are reproduced by permission of Dwyer Ltd.

12

Air Movement Control: Containment, Visualisation and Recovery

It may be necessary when testing a cleanroom to demonstrate that the airflow within a cleanroom, or between cleanrooms, is correct. This can be demonstrated by the following tests:

1. containment leak testing to show that no airborne contamination comes from less-clean areas into the cleanroom,

2. visualisation methods to show that air moves in the correct direction,

3. recovery tests to show that in non-unidirectional airflow cleanrooms the airborne contamination is quickly removed after contamination.

These tests are now discussed.

12.1 Cleanroom Containment Leak Testing

To show that a cleanroom is working correctly, it is necessary to demonstrate that no contamination infiltrates into the cleanroom from dirtier adjacent areas. Airborne contamination can come into a cleanroom from less- clean adjacent areas and pass through doors and hatches, as well as through holes and cracks in the walls, ceilings and other parts of the cleanroom fabric. If a cleanroom is pressurised correctly with respect to all adjacent areas, then air will

flow out to areas of lower pressure and contamination will not enter the cleanroom. However it is possible that adjacent areas such as air plenums or dirty areas connected to the cleanroom by service ducts, and at a higher pressure than the cleanroom, can contaminate the cleanroom.

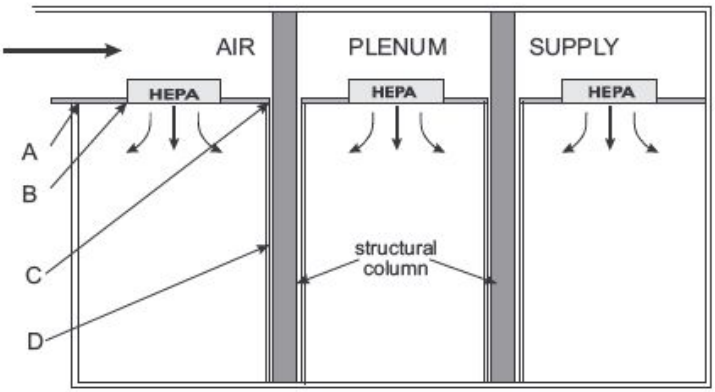
An example of such a problem is shown is Figure 12.1. It can be seen in this drawing that the supply air plenum of a vertical airflow unidirectional system contains unfiltered air at a higher pressure than the cleanroom. Contamination can be pushed into the cleanroom at the (a) ceiling-to-wall inter- face, (b) ceiling-to-filter housings and ceiling-to-lighting interfaces, (c) ceiling-to-column interface, and (d) through the cladding of the ceiling support pillars. Other infiltration problems are associated with service plenums and the entry of services into the cleanroom. For example, electrical sockets and switches and other service outlets, can be connected by conduits and ducts to dirty areas that are at a higher pressure than the clean-room. Contamination control in a negatively-pressurised containment room is particularly difficult as the negative pressure will draw in contamination from other adjacent areas and therefore the construction must be leak-proof.

12.1.1 Containment leak testing for checking infiltration

It is a relatively simple matter to check that air is flowing in the correct direction through an open door, or through the small gaps around a closed door. This is done by generating smoke and observing where the airflow takes it. However, to ensure that there is no unwanted flow of airborne contamination through the cleanroom fabric it is

necessary to check cracks around the walls, ceiling and floor. This will normally be at the overlapping edges or butted joints, as well as at service penetrations through the clean- room fabric.

Figure 12.1 Infiltration problems with an air supply plenum



A - ceiling-to-wall interface
B - ceiling-to-filter housing and ceiling-to-lighting interface
C - ceiling-to-column cladding interface
D - column cladding

A test dust or smoke can be introduced into the areas from which the contamination is thought to arise and possible places of infiltration scanned with a particle counter. This is not a simple task. Where the contamination originates may be unknown, and it is often difficult to find places to release test smoke. In these cases, it should be sufficient to scan for particles, relying on the natural contamination that comes from the adjacent contaminated areas to show up any problem. If no particles show up in these circumstances, then the problem is unlikely to be serious.

Containment leak testing should be done in the cleanroom prior to hand- over to the user, or after major reconstruction work has been completed. The ISO cleanroom standard 14644-2: 2000 lists the 'containment leak' test as an 'optional' test and suggest a re-testing interval of two years (see Table 10.1).

12.2 Air Movement Control within a Cleanroom

As part of the testing procedure to ensure that a cleanroom is working correctly, the movement of air within the room should be checked. It is necessary to ascertain that there is sufficient air movement within the room to either dilute, or remove, airborne contamination and hence prevent a buildup of contamination.

In a**non-unidirectional airflow** cleanroom, air is supplied and mixed in a random manner. Good mixing should be demonstrated in all parts of this type of cleanroom to ensure that contaminants will be removed through the air extracts. It is particularly important in critical areas, where the product is exposed to the risk of contamination, to demonstrate good mixing.

To ensure the cleanest conditions are obtained in a**unidirectional airflow** cleanroom, critical areas must be supplied with air coming directly from the high efficiency filters. However, problems may be encountered because of:

- heat rising from the machinery and disrupting the airflow;
- obstructions preventing the supply of air getting to the critical area;

- obstructions, or the shape of machinery, turning the unidirectional air-flow into non-unidirectional random airflow;
- contamination being entrained into the clean air.

Because of these potential problems, it is necessary to demonstrate that contamination coming from people or other contamination sources does not enter the critical area. Visualising the airflow will demonstrate whether, or not, any of these problems exist, and the extent to which they are likely to cause an increase in contamination in the critical area.

12.2.1 Air movement visualisation

There are a number of methods that can be used to visualise the flow of the air in a cleanroom. These can be grouped under the following headings:

1. streamers,

2. smoke or particle streams,

3. measurement of air velocity and direction.

Figure 12.2 'FlowViz' nylon thread streamer on an anemometer

12.2.1.1 Streamers

The types of streamer that are used to visualise airflow are usually threads or tapes. The best types are those that have a very high surface area to weight ratio. These are more easily carried by the airflow and can be easily seen. Small recording tapes can be used or loosely spun threads. A useful way of using a streamer is to attach it onto the end of an anemometer. It can then be used to ascertain the direction of airflow when the velocity is being measured at a particular place. Streamers can also be used by attaching a number of them onto a grid similar to the one discussed later, in Section 12.2.1.3.

Streamers will indicate the direction of airflow but, because of their weight, they do not flow exactly in the same direction as the air. This is a problem that increases as the air velocity decreases. A horizontal flow of air with

a velocity of about 0.5 m/s (100 ft/min) is required to get a typical streamer to stream at 45° to the horizontal, and a velocity of about 1 m/s (200 ft/min) for it to stream almost horizontally i.e. in line with the air stream.

12.2.1.2 Smoke or particle streams

There are a number of methods suitable for generating clouds or streams of smoke or particles to show the airflow in cleanrooms. Smoke generators of the type that use glycol or glycerine-based fluids are commonly used. These generators are similar or identical to smoke generators used in discos and in the theatre. They are considered to cause little or no harm to the health of the operator, although the risk to the product would have to be assessed. Shown in Figure 12.3 is a small smoke generator of this type. It is inexpensive and will produce a continuous cloud of smoke, the amount de- pending on the size of the generator.

Figure 12.3 Instrument for producing a cloud of smoke

Figure 12.4 Instrument producing wisps of smoke to check air flow under door

Hand-held smoke-generators are also available that use glycol or glycerin to produce wisps of smoke. An example of this type is shown in Figure 12.4 where the airflow under a door is being checked.

Using one of the smoke generating methods described above, the air- flow in the room can be visualised and areas found where the air movement is poor. Single ‘puffs’, ‘streams’, ‘multiple streams’, or ‘clouds’ can be used. Sufficient information may be obtained by witnessing the air movement, but a permanent record can be preserved by the use of a video camera.

The use of smokes may not be acceptable in some cleanrooms where smoke deposited on surfaces is a contamination hazard. In this situation, water vapour can be used as a contamination-free alternative and produced

by using frozen CO_2 (dry ice) or liquid nitrogen water vapour generating systems, or by nebulising water.

The solid CO_2 systems work by using electric heating elements in a sealed vessel to bring water up to near boiling temperature. The dry ice is then either lowered or dropped into the water. The dry ice, which has a surface temperature of minus 79 °C, is turned directly into a gas by the hot water and produces water vapour that is forced out of a nozzle in the vessel with the CO_2 gas.

Liquid N_2 boils at a very low temperature of minus 196 °C. The low temperature of the N_2 gas drops the temperature of the air and causes the moisture in the air to condense out. Shown in Figure 12.5 is the water vapour produced when liquid nitrogen is released from a Dewar vessel through a tube. The quantity and quality of the water vapour can be improved by using an apparatus that boils off water which is then condensed in the jet of very cold nitrogen.

The third alternative method produces water vapour by using a nebuliser or fogger. Figure 12.6 shows a photograph of nebulising apparatus producing water vapour.

Figure 12.5 Water vapour generated by liquid nitrogen

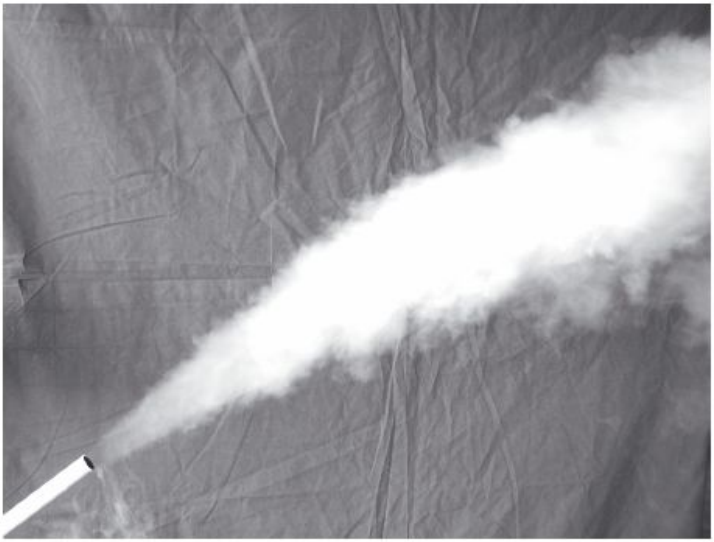
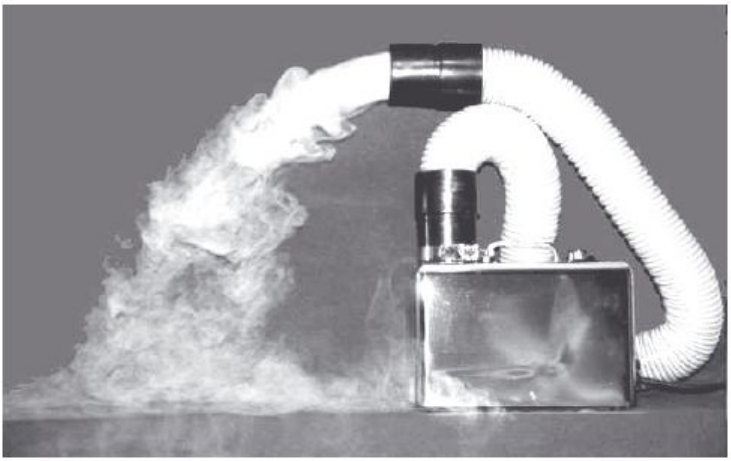


Figure 12.6 Nebulising apparatus producing water vapour



In**non-unidirectional** airflow cleanrooms it will be found that test streams will quickly disperse into the cleanroom

air. However, non- unidirectional airflow cleanrooms depend on the random flow of air mixing thoroughly with any contamination and removing it through the exhausts. If the test smoke is dispersed quickly, then this demonstrates that the clean- room ventilation is working well. Areas where the smoke does not disperse are areas where airborne contamination will build up and it is important that these areas should not be critical areas where product is exposed. If necessary, the mixing action of the air flow can be improved by adjusting the air supply diffusers, removing an obstruction, moving a machine, or finding another similar solution.

In the majority of cleanrooms,**unidirectional** airflow will be used to protect critical areas where product is exposed to potential contamination. This may be in the form of a complete unidirectional airflow room, or in the form of a unidirectional airflow cabinet or enclosure. When the airflow is unidirectional, the air moves in straight lines, the smoke disperses much less than in non-unidirectional air flow and, therefore, the airflow is much easier to see. In a unidirectional airflow system, the air coming from the filters should, ideally, flow unimpeded to the critical area and no particles and microbe-carrying particles from people and machines should be found in the critical areas. Both the FDA Guidance and the EU GGMP give good advice as to what is required.

The FDA Guidance suggests that*'Proper design and control preventsturbulence and stagnant air in the critical area. Once relevant parametersare established, it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air*

contaminants (e.g., from an adjoining lower classified area). In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. The studies should be well documented with written conclusions, and include evaluation of the impact of aseptic manipulations (e.g., interventions) and equipment design. Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes.'

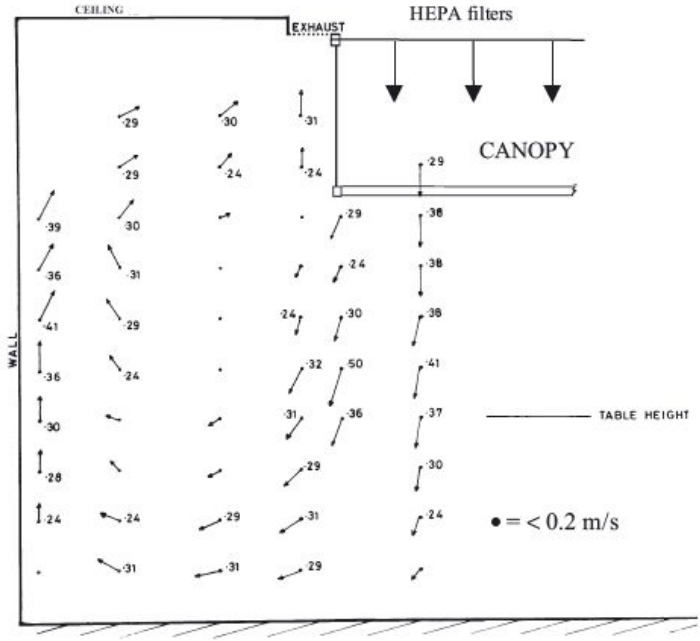
In the EU GGMP there is a requirement to show that airflow patterns do not present a contamination risk. It suggests that '*care should be takento ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.'*

A useful method of visualisation in unidirectional airflow is to use a pipe of about 2.5 cm (1 inch) diameter with 2 to 3 mm diameter holes bored in line, about every 10 cm (4 inches). The pipe is set up on stands and sup- plied with a smoke from a generator. Either a generator of the type used in discos or theatres (Figure 12.2), or the type used to generate a test challenge for a filter integrity test, can be used. The generator will probably require an air pump to push the smoke through the holes in the pipe. The continuous smoke streams issuing out of the pipe holes gives good visualisation of the unidirectional airflow. Still pictures can be taken of the airflow, but because of the diffusion of the smoke they are generally not very clear

(and hence not shown here). A video taken of the smoke movement gives the best representation of the airflow. The video pictures can be improved if the room lighting is switched off and the smoke highlighted with beams of light.

12.2.1.3 Air velocity and direction

Figure 12.7 The direction and velocity of air coming from the supply filters to the exhaust of a partial-wall unidirectional canopy



A permanent record of the airflow within the cleanroom can be obtained by measurement of the velocity and

direction over a section of the area of interest. Setting up a grid in the room helps with this. Stands can be used with strong thread, such as 4 pound nylon used by fishermen, strung across the stands.

The thread is marked at given intervals, e.g. 10 or 20 cm (4 inches or 8 inches), so that points are available for measuring air velocity and direction. Measurement can be done using a multidirectional anemometer that will give the air velocity either in the X and Y axes, or in the X, Y and Z axes. These anemometers are expensive and a simple thermal anemometer with a streamer attached to give the air direction will give reasonable results, especially if the airflow is unidirectional.

Figure 12.7 shows a two-dimensional representation of the velocity and direction of the unidirectional airflow coming out from the filters in a unidirectional airflow canopy. This system had a filter supply area of 3 m × 3 m (10 ft x 10 ft) and partial sidewalls that stopped 2 m (6 ft) from the floor, rather than coming down to near floor level. The air exhaust was in the ceiling around the outside of the canopy. Only half of the system is shown, the other half being a mirror image. The lengths of the arrows shown in the figure denote the magnitude of the air velocity. This drawing shows that the unidirectional downflow of air had a sufficiently high velocity to reach the table, and that the airflow paths to the exhaust prevented contamination from round the outside of the canopy being entrained into the clean area, and hence contaminating any work being carried out on the table in the clean area.

12.3 Recovery Test Methods

The visual methods described in the previous section are qualitative methods that can be used to show that sufficient clean air gets to the critical areas. A quantitative approach, namely a recovery test, can also be used for this, the methods being described in ISO 14644-3 and the EU GGMP.

12.3.1 ISO 14644-3 recovery test methods

ISO 14644-3 contains a description of methods that can be used to obtain information on how quickly contaminated areas will recover from being contaminated. This is done by measuring the decay rate of airborne particles, the faster the decay the more clean air is demonstrated to get to the area being tested and the better the cleanroom is working. This decay method is considered to be only applicable in non-unidirectional airflow cleanrooms and not in unidirectional airflow cleanrooms. ISO 14644-3 contains two test methods known as ‘cleanliness recovery performance’ and ‘cleanliness recovery rate’. These can be carried out in the ‘as built’ or ‘at rest’ operational states.

12.3.1.1 Cleanliness recovery performance test

Test particles, usually of the type generated by a particle generator used for testing filters or for visualizing air is introduced into the area being tested. Once the particles have mixed with the surrounding air, the airborne particle count is measured at regular intervals as the concentration decays. A useful endpoint is one tenth, or one-hundredth, of the original concentration, and the times taken to reach these endpoints is used as the index of the efficiency of ventilation.

12.3.1.2 Cleanliness recovery rate

The cleanliness recovery rate is ascertained by measuring the effect of ventilation on the rate of decay of test particles introduced into the cleanroom, and can be calculated from the following equation:

Equation 7.1

$$\text{Cleanliness recovery rate} = -2.3\times\frac{1}{t}\log_{10}\left[\frac{C_1}{C_0}\right]$$

where

t = time between first and second measurement,

C_0 = initial measurement,

C_1 = concentration after time t.

12.3.2 Example of a calculation of cleanliness recovery tests

Recovery tests were carried out in a non-unidirectional airflow cleanroom. Air was supplied through terminal HEPA filters that had been tested for integrity, and therefore did not contribute particles to the air in the room. In this example, the air conditioning plant was turned off, a 5 second burst of test particles was introduced into the flow of a fan brought into the room to thoroughly mix the air. The air supply was then turned on and airborne particles measured at the point in the room where the product was assembled. The particle counts were measured over time and the results are shown in Table 12.1.

Table 12.1 Particle concentration with respect to time

Particle concentration	Time (min)
100 000	0
50 000	2
10 000	6.5
5000	8.5
1000	13

The cleanliness recovery performance and the cleanliness recovery rate can now be calculated.

Cleanliness recovery performance It may be seen from Table 12.1 that the time for the particle concentration to drop 10-fold from 100 000 particles to 10 000 was about 6.5 minutes and 100-fold to 1000 in about 13 minutes. These are the results required by ISO 14644-3.

Cleanliness recovery rate The time for the particle concentration to drop from 100 000 to 1000 is shown in Table 12.1 to be 13 minutes.

$$\therefore \text{Cleanliness recovery rate} = -2.3 \times \frac{1}{13} . \log_{10} \left[\frac{100\,000}{1\,000} \right]$$

$$= -2.3 \times 0.077 \times 2$$

$$= -0.35 \text{ /min} = -21.3 \text{ /hour}$$

The cleanliness recovery rate is therefore 21.3/hour.

12.4 Recovery Rate Requirement in the EU GGMP

The EU GGMP states that 'The particulate conditions given in the table (Table 3.4 in this book) for the "at rest" state should be achieved after a short "clean up" period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.'

The requirement in the EU GGMP is tested in a similar way to the tests described above. However, artificial test particles are not introduced into the cleanroom but natural-occurring particles are used. The concentration of airborne particles is measured by a particle counter (usually particles ≥0.5 μm) immediately after production ceases and personnel withdraw. The time is then measured for the particle concentration to decay to the concentration required in the 'at rest' state for the grade of cleanroom being investigated. The time should be less than 15 to 20 minutes.

Acknowledgement

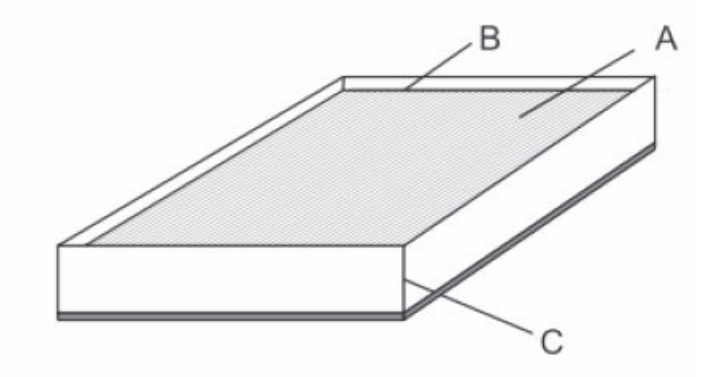
Figure 12.6 is reproduced by permission of Clean Air Solutions.

13

Filter Installation Leak Testing

Part of the cleanroom testing programme is to determine that high efficiency filters, and the housings into which they are fitted, are not leaking and allowing airborne contamination to enter the cleanroom.

Figure 13.1 Leakage areas in a high efficiency filter



A - filter media (often at the fold)
B - filter media to case cement area
C - frame joints.

High efficiency filters that are to be installed in the cleanroom will have been tested in the manufacturer's factory and packed so that they should arrive at the construction site undamaged. This is not always so. Damage may also occur when the filters are unpacked and fitted into the filter housings. Leaks may also arise during use.

The typical fault areas of an installed filter are shown in Figure 13.1, and these will allow contaminated air to leak through the filter and into the cleanroom.

In addition to the leaks in the filter there may be leaks between the filter gasket and the filter housing, and the contaminated air can leak past the gasket and into the cleanroom. This problem is shown in Figure 13.2. To minimise this type of leakage, gel seal types of filter housing as shown in Figure 13.3, may be used. However, they are more expensive.

Figure 13.2 Filter gasket leaks

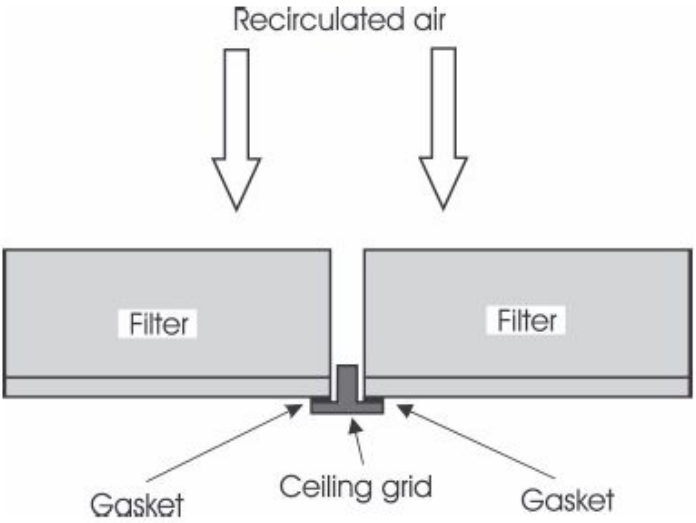
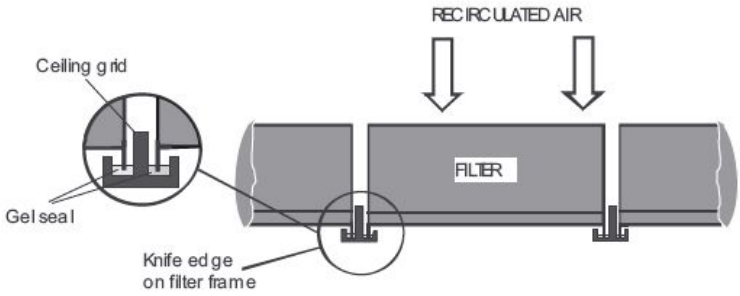


Figure 13.3 Filter housing gel seal method



Testing a high efficiency filter and its filter housing for leaks into a cleanroom is carried out using an artificial test aerosol. This is produced by an aerosol generator and injected into the ductwork system so that there is a suitable challenge concentration upstream of the high efficiency filter. Any problems are found by scanning the filter system on the downstream cleanroom side for test particles that leak through.

13.1 The Use of Aerosol Test Challenges

Before discussing the choice of artificial test aerosols that are available for testing filters, it is appropriate to consider whether it necessary to carry out filter leakage tests in all grades of cleanrooms.

It is fairly common in less stringent quality cleanrooms (occasionally in ISO Class 7 and frequently in ISO Class 8) not to carry out filter leak tests. ISO Class 8 rooms may not use high efficiency filters in a terminal position in the supply duct, but bag-type filters positioned after the air conditioning plant. In this case it will not be possible to carry out leak tests of the type described in this chapter. It

is also argued that if the correct air classification standard is achieved within the cleanroom, then a small leakage of unfiltered air through the filter system has little influence, and is acceptable. This viewpoint is perfectly valid in non-unidirectional airflow cleanrooms where the supply air is well mixed with the room air, and localised high concentrations of contamination arising from a damaged filter are avoided. In a unidirectional airflow system, especially in a separative clean air device, where the distance from the high efficiency filter to the critical area may be small, a hole in a faulty filter could give a unidirectional stream of contaminated air, which may give a localised and unacceptably high particle count at the critical area. Unidirectional airflow systems are therefore normally always tested for filter leaks.

13.2 Artificial Aerosol Test Challenges

The following sections describe the test aerosols that are used for testing filter installations in cleanrooms and describe how they are generated.

13.2.1 Suitable oils for aerosol generators

Dioctyl phthalate (DOP) is the original oily liquid that was used as the test aerosol for testing filters and gave its name to the DOP test, as it is sometimes called. Because of its potentially toxic effects, it is no longer used in many countries and similar oils, such as Shell Ondina EL mineral oil or polyalpha olefin (PAO), or diethylhexyl sebacate (DEHS) which is also known as dioctyl sebacate (DOS), are now specified.

13.2.2 Cold aerosol generators (Laskin nozzles)

To create a cold-generated test aerosol, air is passed at high pressure (20 psi) through a nozzle designed for this purpose known as a Laskin nozzle. The air shears oil drawn from a reservoir. Fine particles, with a mass median diameter of about 0.5 μm, and a count median diameter of about 0.25 μm, are ejected at a small positive pressure.

The output of one Laskin nozzle is relatively small (about 0.4 g/min) and is only sufficient to test challenge a small volume ventilation system such as a separative clean air device. The air volume that can be tested will depend on the concentration of the test challenge used, but with a single Laskin nozzle, air ventilation systems supplying up to about 0.5 m^3/s (1000 ft^3/min) of air can be tested when the filter penetration is measured by a photometer. Multiple nozzle systems are therefore necessary when larger volume systems are tested with a photometer. However, it should be noted that Laskin nozzles in a multi-nozzle format require a large air pump for what is normally a portable system.

Another possibility is to use a single particle counter in place of a photometer. A concentration of 10 μg/l of test aerosol produced by a Laskin nozzle will give a challenge particle count of about $3 \times 10^{10}/m^3$ ($10^9/ft^3$), and so by using particle counter it should be possible to scan for filter leaks in most cleanrooms. A further possibility is to use a thermal generator. This is explained in the next section.

13.2.3 Thermal aerosol generators

Because of the difficulty of generating sufficient challenge from Laskin nozzles, thermal aerosol generators are often used. These also have the advantage of not requiring air pumps to produce particles, although pumps are required to push aerosol into positively-pressurised ducts and air plenums found downstream of the fans in air conditioning plants and separative devices. Thermal generators use a gas, such as CO2 or nitrogen as a carrier. Suitable oil, of the type described in section 13.2.1, is injected into a heated evaporation chamber at a measured rate. The vaporised oil then condenses into the carrier gas at the exit nozzle as a fine aerosol with a mass median diameter of about 0.4 μm and a count median diameter of about 0.3 μm. The aerosol is much more concentrated than that produced by a Laskin nozzle and the amount of aerosol that can be produced is much greater. Therefore the thermal generator is much more suitable for larger installations.

Generators of the type shown in Figure 13.4 will produce around 10 to 50 g/min of aerosol, this being sufficient to test air ventilation systems of up to about 40 m^3/s (85 000 ft^3/min) when using a photometer.

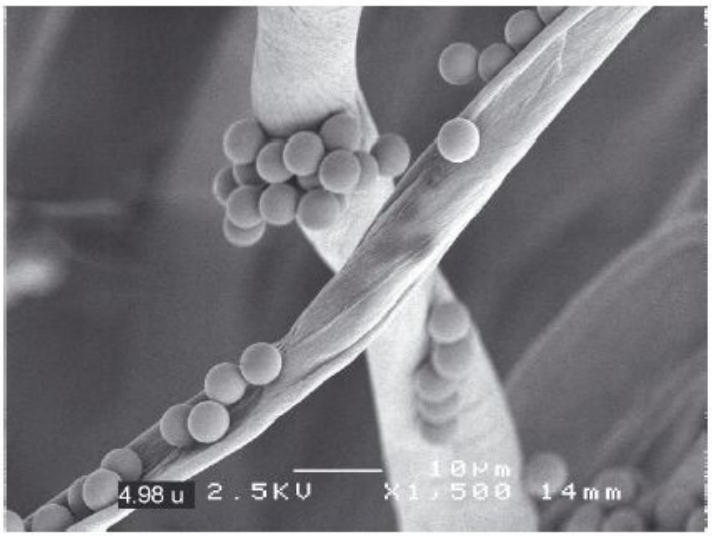
Figure 13.4 Thermal aerosol generator

13.2.4 Microspheres

In some cleanroom situations, such as semiconductor manufacturing, inert test particles are specified. This is done to ensure that there is no possibility of 'outgassing' of chemical products that are harmful to the process from any test aerosol left on the filter. The most commonly used inert test aerosol is microspheres and a photograph of these on filter fibres is shown in Figure 13.5. They are available as monodispersed suspensions in a wide range of diameters so that an appropriate size can be chosen for leak testing. The size of spheres used for filter integrity testing is similar to the size of particles used by the manufacturers to test filters and the most penetrating particle size, and is between 0.1 μm and 0.3 μm. For the sake of clarity, the spheres shown in Figure 13.5 are much larger than these sizes. The suspensions are diluted and aerosolised, and the penetration of the microspheres

through the filter is measured by scanning the filter face using a probe attached to a particle counter. Measurement of the upstream challenge concentration, where a particle counter is used, is described in 13.3.2.

Figure 13.5 Photograph of microspheres on filter fibres.



13.3 Apparatus for Measuring Aerosol Penetration

13.3.1 Photometer

A typical photometer is shown in Figure 13.6. A probe is used to scan the filter for leaks of test aerosol and 28 l/min (1 ft^3/min) of air is drawn from the filter face through a tube and into the photometer. The photometer has an area where light is concentrated and the particles in the test aerosol are drawn through it. The particles scatter light in

this area and the light produced is collected and converted into an electrical signal. Photometers usually measure an oil concentration of between 0.0001 µg/l and 100 µg/l. A photometer calculates the overall**mass** concentration of the particles, and is entirely different from a discrete-particle counter which counts and measures the size of individual particles.

Figure 13.6 A typical photometer

A photometer has an advantage over a particle counter in that it can measure the upstream challenge concentration and this can be set as the 100% reading by flicking a switch. The sample tube is then moved to the downstream side of the filter and the instrument switched to an appropriate scale that indicates the % leak penetration through the filter. When the specified maximum leak penetration through the filter, e.g. 0.01%, is exceeded this

shows on the scale, and, if required, triggers an audible alarm.

13.3.2 Discrete-particle counters

Discrete-particle counters of the type normally used to count and size particles in the air of cleanrooms can be used to carry out filter leak testing. However, the particle counter must be able to run in a continuous measuring mode. When a particle counter is used to measure leaks in filters, the upstream particle challenge count is likely to be outside the range of the instrument and a diluter will have to be purchased to dilute the upstream sample. When a particle counter is used to test filters, then the method described in ISO 14644-3 should be employed.

13.4 Methods of Testing Filters and Filter Housings

One of the test aerosols described in the previous section 13.3 should be introduced into the air supply ductwork system upstream of the filter. The point of introduction should be at a position sufficiently distant from the filter to give enough mixing to achieve an even concentration across the back of the filter. If there is any doubt as to the thoroughness of the mixing, the uniformity of the aerosol concentration immediately upstream of the filter should be checked. When an even concentration of test aerosol challenge has been obtained, the following test methods are employed.

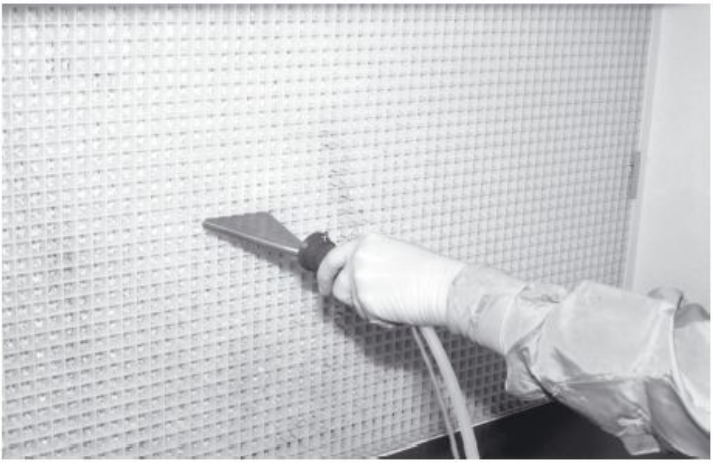
13.4.1 Scanning methods

Before starting to test the integrity of filters, it will be necessary to consider smoke alarms. Aerosol (smoke) from the generator, especially if it is introduced into the cleanroom itself to test separative clean air devices, can set off smoke alarms. The possibilities and consequences of smoke alarms going off should be considered. It is best to turn them off prior to testing rather than suffer the embarrassment of the arrival of the fire brigade or, worse still, the damage that would result from a dousing from water sprinklers.

If an air diffuser is fitted after the filter, this should be removed to give access to the filter face. The normal scanning method is to use a sampling probe together with a photometer or discrete-particle counter, to scan over the whole filter face. The perimeter of the filter is scanned for gasket leaks and then the filter face is scanned. The probe is normally held about 3 cm from the filter and the filter scanned with overlapping strokes (Figure 13.7).

The velocity of scan and size of probe is important. If the probe passes slowly over a hole it will pick up more particles and find more faults. A quick run over the filter will not be sufficient to pick up all faults, and this should be guarded against. A scan speed of not more than 5 cm/s is reasonable but a method is given in ISO 4644-3 to calculate the correct size of probe and the correct scan velocity.

Figure 13.7 Scanning a filter



If a photometer is used, the concentration of the challenge aerosol is measured behind the filter and adjusted to a suitable concentration. The concentration suggested in ISO 14644-3 is between 20 μg/l and 80 μg/l. The photometer is then set so that the upstream concentration becomes the 100% reading and the percentage penetration is then read directly from the photometer scale. A concentration that exceeds 0.01% of the test challenge introduced upstream of the filter is generally considered to indicate a leak.

13.4.2 Testing filters in large unidirectional airflow rooms

The problem with checking a filter bank in the ceiling of a large unidirectional airflow room is that the area is so large that testing will take a considerable time. This may be several days for a large semiconductor fabrication cleanroom. It is therefore useful to use methods that reduce the time. For example, several probes connected to photometers or particle counters can be placed on a

motorised trolley at a suitable height below the filter bank, and scanning carried out by moving the trolley about the room.

An alternative method is to scan each filter and its casing on a rig nearby and then install it carefully into its housing in the ceiling. It is then only necessary to check the periphery of each filter for filter-to-housing leaks when all the filters are in place and the ventilation system switched on.

13.5 Repair of Leaks

The ISO 14644-3 standard accepts that repairs can be made to any part of the filter as long as it is acceptable to the customer. Leaks will normally come from the gasket, the filter pack to casing joint, and the filter media. If the leak comes from the gasket, the filter should be removed and either reseated correctly, or the gasket renewed, or the filter replaced. If a leak comes from between the filter media pack and frame then an effective repair can often be achieved using a material such as silicon mastic. If the leak comes from a small area of the filter media then this can also usually be repaired with a material such as silicon mastic. However, it is difficult to achieve a repair of a large area and, because of blockage, this may have an adverse effect on the uniformity of air flow. In a non-unidirectional airflow cleanroom, the air supply will quickly mix with room air, and hence be diluted, and a less than perfect repair can be tolerated. However, in unidirectional airflow, especially if the air is supplied directly to a critical area, the filter would normally be renewed.

Acknowledgements

Figure 13.5 is reproduced by permission of Thermo Fisher Scientific. Figures 13.4 and 13.6 are reproduced by permission of DOP Solutions.

14

Airborne Particle Counts

The most important test used to ensure a cleanroom is working correctly is the measurement of the airborne particle concentration. Before proceeding with this measurement, the tests described in Chapters 10 to 13 should have been carried out and shown to be satisfactory i.e. air supply volume, pressure differential, air movement within and between cleanrooms, and filter integrity tests. It is then necessary, as a final test, to show that the airborne particle concentration does not exceed the particle class limit in the agreed occupancy state, or states.

14.1 Airborne Particle Counters

A ‘particle counter’ is used to count and size the particles in the air of a cleanroom. This is often called a ‘discrete-particle counter’ to distinguish it from the photometer used to test for installed filter leaks. A particle counter both counts and sizes each particle in the air sample, whereas a photometer simply measures the mass of airborne particles. In this chapter, for the sake of simplicity, the former instrument is called a ‘particle counter’.

A particle counter is an essential tool for testing and running cleanrooms. Good second hand models are often available at a modest price, so that no cleanroom should be without one. Figure 14.1 shows a typical particle counter.

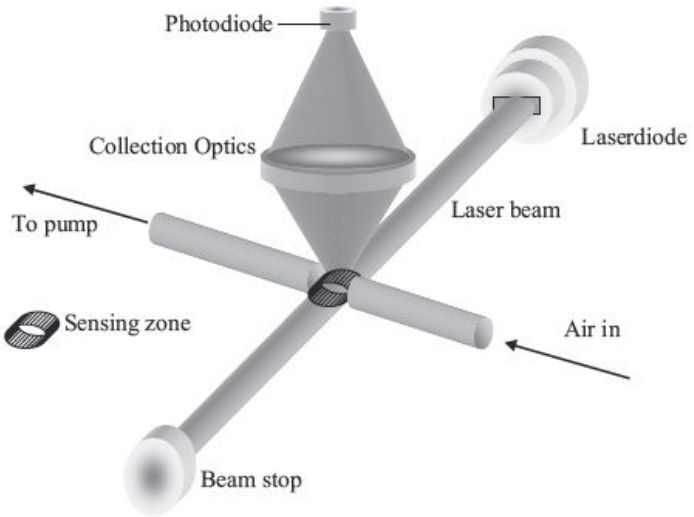
Figure 14.1 Airborne particle counter

Particle counters of this type, size and count particles in the range of 0.3 μm–10 μm. The most commonly available particle counters will sample 28 l/min (1 ft^3/min) of cleanroom air and count particles down to either 0.3 μm or 0.5 μm. High-sensitivity models can count particles down to 0.1μm and some instruments can sample 50 or 100 l/min.

Figure 14.2 shows how a particle counter works. The light source is typically a laser diode. The light scattered from each discrete, particle in the air that is being sampled is concentrated by a lens system and converted by the photodiode into an electrical pulse. The amplitude of the pulse is proportional to the particle size and the number of

pulses at each particle size gives the particle concentration at that particle size. Particles are normally counted on an 'equal to or greater than' size basis i.e. 'cumulatively', and therefore the particle counter counts all particles equal to and greater than the size or sizes that the instrument is set to detect. This cumulative method of measurement is specified in cleanroom standards.

Figure 14.2 Detection method typically used in a particle counter



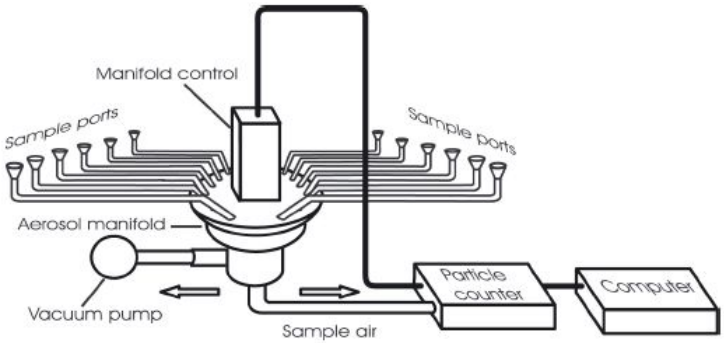
14.2 Continuous Monitoring Apparatus for Airborne Particles

In high quality cleanrooms, where the product is very susceptible to airborne particle contamination, continuous monitoring of the air is used during production to check

for deviations from the required airborne particle cleanliness. In lesser quality cleanrooms it may be considered unnecessary to sample continuously and a technician with a portable particle counter can carry out the testing at weekly, monthly or yearly intervals, depending on the required cleanliness of the room. The cleaner the room the more frequent the counting should be.

There are two main methods of continuous sampling. These are often called 'sequential' and 'simultaneous'. A*sequential monitoring* system, which is also known as a 'manifold' system, is shown in Figure 14.3

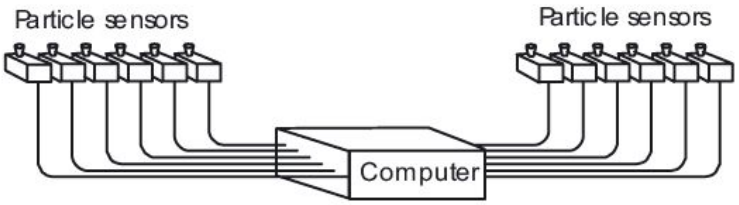
Figure 14.3 Sequential monitoring system



In this system the cleanroom is fitted with sampling tubes that run to sampling ports at the points to be sampled. A sample of air is taken from each collection point in turn and transported through the sampling tubes to a manifold, and then to a particle counter, where the particles are counted. If we consider a manifold system with 12 sampling tubes, the rotating manifold is arranged so that

one tube, the active tube, is connected to particle counter, whilst the other eleven tubes are connected to the external vacuum pump. When the particle counter has drawn the necessary volume for the sample, then the manifold system rotates so that the next sample tube becomes the active tube and the previous one becomes one of the eleven that are connected to the vacuum pump. This ensures that there is a more or less constant flow of air down each sample tube.

Figure 14.4 Simultaneous monitoring system



A*simultaneous monitoring* system is shown in Figure 14.4 and this system uses small sensors to continuously size and count particles in the air at various points of the room. This system is also called a 'point-of-use' system.

Figure 14.5 shows a typical point-of-use sensor, its size being compared to a pen. Information on the number and size of airborne particles measured by sensors is transmitted by electrical signals through a cable to a computer where it is analysed.

Both methods of monitoring use software packages to analyse the results. These can calculate either the overall average count of each particle size in the room, or the

average count of each particle size at each sampling point. They can also register any results that are greater than an 'alert' or 'action' value set into the computer. Other information can also be obtained.

It would appear that the simultaneous monitoring system is the best system, as air is continuously sampled at the chosen sampling places and no high counts missed. However, it is also the most expensive. The sequential method may deposit particles on the inner surfaces of the tubing that runs to the particle sampler, as well as within the manifold.

Figure 14.5 Point-of-use sensor used in simultaneous sampling

These losses can be reduced if care is taken in the design of the system, mainly by minimising the length of the tubes. Studies have shown that when small particles ≥ 0.5 μm are sampled, the losses caused by deposition are small

and usually acceptable, especially if increases in particle counts are sought rather than absolute values. Losses by deposition of larger particles ≥ 5 μm are considered to be unacceptably high in anything but the shortest lengths of tubing.

14.3 Particle Counting in Different Occupancy States

The airborne particles in a cleanroom can be measured in three occupancy states. These are defined in ISO 14664-1 as:

- *As built*: condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present
- *At-rest*: condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present
- *Operational*: condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon

There can often be a considerable time delay between the cleanroom being completed by the building contractor and products being manufactured in the room. However, the contractor will wish to be paid for building the cleanroom and it is common practice to check that the room in its 'as-built' state is satisfactory and, if it is, to pay all or most of the contract price. The problem with checking the 'as-built' state is that as there is no equipment working, nor personnel in the room, there is no generation of airborne particles. Thus, the airborne particle concentration will be very close to that of the filtered air supply. In practice, one or more people are required to test the room

and they will increase the particle count. However, the particle count will still be much lower than when the room is ‘operational’. The user will certainly wish the cleanroom to perform satisfactorily in the occupied state, when the machines and people are dispersing particles. It should therefore be made clear in the building contract which occupancy state (or states) should apply for contractual testing.

If a cleanroom has been designed properly and the cleanroom tested when empty, i.e. in the ‘as-built’ state, then there is a ‘rule of thumb’ assumption that can be applied. This is that the ‘as built’ room will be between one or two class of cleanliness cleaner than when ‘operational’. This is not always correct, but it should be possible, by the use of tests carried out in the ‘as-built’ state, to predict how likely it is to conform to the class limit in either the ‘at-rest’ or ‘operational’ state. The important confirmatory tests are the filter integrity and the quantity of air supplied. Because of the directed airflow in a unidirectional system, the correct standards are likely to be achieved if the filters have no particles leaking through them or by-passing them, and the air velocities are correct. In a non-unidirectional cleanroom, the achievement of the correct standard in its ‘operational’ state is less certain, as it is dependant on the air supply volume being sufficient to dilute the contamination dispersed from machines and people. Section 5.1.2 should be consulted for additional information. However, this is unlikely to be a problem if an experienced cleanroom designer has been used. It is more normal to find that the designer has overdesigned, and the cleanroom ends up cleaner than expected.

After the contractor has handed over the cleanroom, the equipment will be installed and commissioned and particle counts taken in the 'at rest' state. When production starts the particle contamination can then be measured in the 'operational' state. The 'operational' occupancy state is the most relevant state to be measured, as it reflects the actual contamination when the manufacturing area is working. This state is also likely to give the highest particle count.

14.4 Measurement of Particle Concentrations

The standard of a cleanroom is defined by the concentration of airborne particles, at a given size or sizes that should not to be exceeded in a given occupancy state. These class limits are given in ISO 14644-1 and shown in Table 3.2, and Figure 3.2 in Chapter 3.

To classify a cleanroom, it is necessary to take sufficient samples of air to have confidence that the airborne particle concentration of the room is within the limits set by the standard. The number of sampling locations is determined by the size of the room, the larger the room, the more the number of sampling locations that must be used. The air sample must also be of a sufficiently large volume to give confidence in the results. This is determined by the cleanliness of the cleanroom, the cleaner the room the larger the sample required. The methods for determining the number of sampling locations and the minimum air volumes are laid down in ISO 14644-1: 1999, and are explained below. The acceptance criteria that must be met for a cleanroom to achieve a given classification are also given in the ISO 14644-1: 1999 and are described below. However, anyone wishing to test a cleanroom must

purchase the ISO 14644-1: 1999 standard (see Section 4.3.1. for information). It is also necessary to check that ISO 14644-1 is the latest version as this standard is being revised at the time of publication of this book and the testing method may be changed in the new edition.

14.4.1 Sample locations and number

ISO standard 14644-1: 1999 gives a formula by which the minimum number of locations can be calculated. This is as follows:

$$N_L = \sqrt{A}$$

where,

N_L is the minimum number of sampling locations (rounded up to a whole number) and A is the area of the cleanroom, or clean air controlled space, in m^2.

The ISO standard requires that the samples are evenly distributed around the cleanroom and placed at the height at which the work is carried out.

14.4.2 Airborne sampling volume

It is necessary to determine the minimum volume of air to be sampled at each location. Because there are fewer particles in cleaner rooms, a larger air sample will be required to be confident that the results are within particle class limits given in ISO 14644-1: 1999. This standard

requires that the air volume should be large enough to count 20 particles of the largest particle size specified, when the concentration is at the class limit being considered.

The following formula is used to calculate the minimum volume:

$$V = \frac{20}{C} \times 1000$$

where,

V is the minimum single sample volume per location, expressed in litres;

C is the class limit (number of particles/m^3) for the largest considered particle size specified for the relevant class;

20 is the defined number of particles that could be counted if the particle concentration were at the class limit.

One or more samples can be taken at each location. The volume sampled at each location should be at least two litres, and the minimum sample time should be at least one minute.

14.4.3 Acceptance criteria

The ISO standard 14644-1: 1999 considers that a cleanroom has met the required classification:

1. the average particle concentration at each of the particle measuring locations falls below the class limit;

2. when the total number of locations sampled is less than 10, the calculated 95% Upper Confidence Limit (UCL) of the particle concentrations is below the class limit.

14.5 Worked Example of ISO 14644-1 Test Method

To show the application of the ISO 14644-1: 1999 method, the following is taken as an example:

A cleanroom is 4m × 5m in floor size. It should comply with ISO Class 3 in the 'as built' state at a particle size of ≥ 0.1 μm, which is 1000/m^3.

The calculations are as follows.

14.5.1 Number of locations

The area of the cleanroom floor is 4m × 5m. Therefore, the number of sampling locations $= \sqrt{4 \times 5} = 4.47$. The minimum number of locations, rounded up to the nearest whole number, is therefore 5.

14.5.2 Minimum air sampling volume

$$\text{The minimum sampling volume} = \frac{20}{\text{class limit for the given particle size}} \times 1000$$

The class limit for a particle size of ≥ 0.1 μm in an ISO Class 3 room is 1000/m^3.

$$\therefore \text{Minimum volume} = \frac{20}{1000} \times 1000 = 20 \text{ litres}$$

Using a particle counter with a sampling rate of 28.3 l/min i.e. 1 ft/min, a 42 second sample will be required for each location. However, ISO 14644-1 requires a minimum sample time of 1 minute.

14.5.3 Sampling results

A minimum of five locations must be sampled in this example to fulfil the requirements laid down in the ISO 14644-1: 1999 standard. A sample set of results is given in Table 14.1.

Table 14.1 Particle counts at locations in the cleanroom

Sampling Location	Number of particles ≥ 0.1 ìm /m3
1	580
2	612
3	706
4	530
5	553

The results are one minute samples and only one sample is given at each location, although averages of multiple samples or one longer sample can be used. All of the results shown are below the class limit for the ISO Class 3 room, i.e. $1000/m^3$ for particles ≥ 0.1 μm. The first part of the ISO requirement is therefore satisfied. If the class limit is exceeded then the ISO standard accepts that further sampling can be performed at additional evenly distributed

sampling locations. The results from this further sampling are regarded as definitive.

As less than nine samples were taken in our example, it is now necessary to show that the 95% UCL does not exceeded the class limit. This is done using the following method. Firstly, the 'overall mean of the averages' is calculated by the equation:

$$\text{Mean of the averages (M)} = \frac{\text{Sum of individual location averages}}{\text{Number of individual location averages}}$$

The mean of averages in this example is calculated from the individual results given in Table 14.1, as only one sample has been taken at each location. The value can be calculated as follows:

Mean of the averages for particles ≥ 0.1 μm (M)

$$= \frac{580+612+706+530+553}{5} = 596$$

Using a 'mean of the averages' equal to 596, the standard deviation of the means is now calculated as follows:

Standard deviation (s.d.) =

$$\sqrt{\frac{(580 - 596)^2 + (612 - 596)^2 + (706 - 596)^2 + (530 - 596)^2 + (553 - 596)^2}{5-1}}$$

$$= \sqrt{\frac{256 + 256 + 12100 + 4356 + 1849}{4}}$$

$$= 69$$

where 5 in the denominator is the number of individual locations sampled.

The 95% UCL is now calculated using Table 14.2.

Table 14.2 Student's t distribution for the 95% UCL

Number of Locations	2	3	4	5	6	7-9
t	6.3	2.9	2.4	2.1	2.0	1.9

As the number of locations is 5, Table 14.2 gives a value of 't' of 2.1.

The 95% UCL is now calculated using the equation:

$$95\%\text{UCL} = M + \left[t \times \frac{\text{s.d.}}{\sqrt{n}} \right]$$

where, n = number of locations

$$\therefore \text{95\% UCL for particles} \geq 0.1\ \mu\text{m} = 596 + \left[2.1 \times \frac{69}{\sqrt{5}} \right] = 661$$

From these calculations it may be seen that the calculated value of the 95% UCL is less than the required class limit of 1000. The cleanroom is therefore within the required class limit.

The above set of results meets the second part of the ISO 14644-1 acceptance criterion, as the calculated 95% UCL is below the class limit. However, a large variation of the results or an unusually low (or high) result may cause the 95% UCL to exceed the class limit. An example of this is five sampling locations that gave counts of 926, 958, 937, 963 and 214. The 95% UCL of these results can be calculated to be 1108 particles/m^3. This cleanroom does not pass the acceptance criterion because of the one*low* result. If such a single 'outlier' is the cause of failure, and the reason can be found, then the ISO standard gives a method to treat and correct this problem. Such reasons are typically a mistake made during the sampling, or a sample point directly under a jet of clean air coming from an air supply terminal.

The simplest way to avoid problems caused by the use of the 95% UCL is to test more than nine points in the room. The time involved in additional sampling is often less than that required for the calculation of the 95% UCL.

Acknowledgements

Figure 14.1 is reproduced by permission of Particle Measuring Systems. Figure 14.2 was drawn by Bob Latimer of HACH. Figures 14.3 and 14.4 have been redrawn from drawings supplied by Particle Measuring Systems. Figure 14.5 is reproduced by permission of

HACH. Extracts of ISO 14644-1: 1999 are reproduced by permission of the British Standards Institution.

15

Microbial Sampling

In some biocleanrooms, such as those used by pharmaceutical and medical device manufacturers, the microbial population, as well as the particle population, has to be controlled. People are normally the only source of micro-organisms in a cleanroom. Measuring micro-organisms in the 'as built' or the 'at rest' operational conditions will therefore be of little value, as by definition no people should be in the cleanroom. However, when a cleanroom is fully operational, micro-organisms are continually dispersed from people in the room. It will then be necessary to monitor the cleanroom to demonstrate that the pre-determined concentration is not exceeded.

It is common to sample the air and surfaces of the cleanroom, as well as the personnel working in the cleanroom. Examples of the microbial concentrations that should not be exceeded in a cleanroom are given in the EU GGMP (shown in Table 3.6) and the FDA Guidance (shown in Table 3.7). Both are discussed in Section 3.5.

15.1 Microbial Sampling of the Air

Several types of sampler exist for counting micro-organisms in the air in cleanrooms. These samplers are sometimes known as 'volumetric' air samplers because a given volume of air is sampled, thus distinguishing them from settle plate sampling, where micro-organisms are deposited, mainly by gravity, onto nutrient agar plates.

This is also why 'volumetric' sampling is sometimes known as 'active' sampling. Many types of sampler have been invented for sampling micro-organisms in the air. In cleanrooms, the most popular types are those that impact micro-organisms onto nutrient agar media and those that collect micro-organisms by membrane filtration.

15.1.1 Impaction onto agar

Impaction samplers commonly used in cleanrooms employ either inertial impaction or centrifugal forces to remove micro-organisms from the air. Both these methods impact the microbe-carrying particles onto a nutrient agar surface. Agar is a jelly-type material to which nutrients are added in order to support microbial growth. Micro-organisms landing on a nutrient agar surface will multiply. If left at a suitable temperature for sufficient time, just one deposited micro-organism will multiply sufficiently for a visible colony, a few millimetres in diameter (or larger), to grow. Agar sample plates are normally incubated for 48 hours at 30 °C to 35 °C and a further 72 hours at 20 °C to 25 °C to give sufficient time for moulds to grow. Colonies are then counted, and hence the number of microbe-carrying particles that have been deposited from a known volume of air can be ascertained.

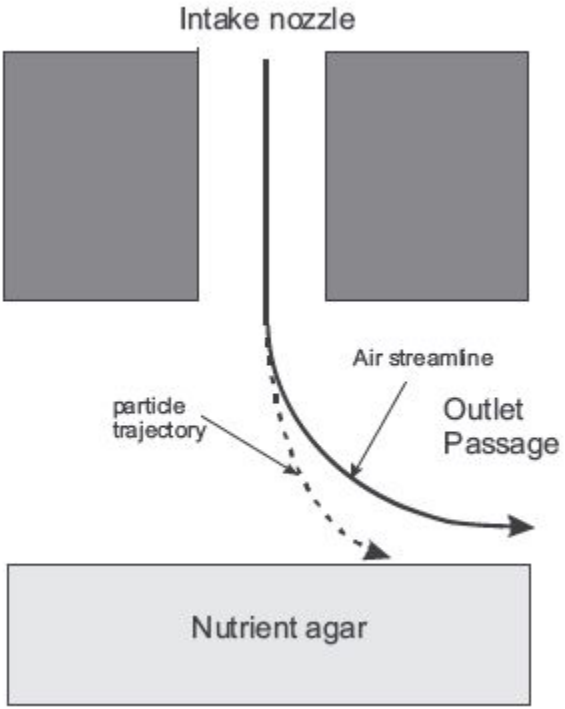
15.1.1.1 Inertial impaction samplers

These samplers will typically sample 30 to 180 litres/min (approximately 1 ft^3/min to 6 ft^3/min) of air, although one brand of slit sampler can sample up to 700 litres/min (25 ft^3/min). In the cleanest cleanrooms airborne microbial concentrations of 1/m^3 and less are required to be

measured (see Tables 3.6 and 3.7). For these very low microbial concentrations a sampler that samples a larger volume of air will reduce the sampling time. Therefore a sampling volume of at least 100 l/min (approximately 3 ft^3/min) is desirable.

Inertial impactors use the principle shown in Figure 15.1. Air containing microbe-carrying particles is accelerated through a small slit or hole. The velocity is high enough (about 20 m/s) to ensure that as the air turns through 90° the microbe-carrying particles leave the air stream and impact onto the nutrient agar surface. When incubated at a suitable temperature for a specified time, each microbe-carrying particle on the surface of the nutrient agar will grow to form a microbial colony. The colonies can then be counted and the number of microbe-carrying particles in a given volume of air can be determined.

Figure 15.1 Airflow within a slit-to-agar or hole-to-agar sampler.



A sampler that draws air through multiple holes, i.e. a sieve, and impacts the microbe-carrying particles onto a nutrient agar surface is shown in Figure 15.2. The outer sieve with its multiple holes has been removed to show a dish containing nutrient agar onto which the microbe-carrying particles are impacted.

15.1.1.2 Centrifugal air samplers

In this type of sampler (Figure 15.3) the air is drawn into the front of the sampler by a rotating vane. Centrifugal force then throws the microbe-carrying particles onto a nutrient agar surface. The impaction surface is in the form

of a plastic strip with rectangular recesses into which nutrient agar is dispensed. After sampling, the strip is removed from the sampler and incubated so that the number of microbe-carrying particles can be ascertained.

Figure 15.2 SAS inertial impaction air sampler

Figure 15.3 RCS Centrifugal sampler

15.1.1.3 Membrane filtration

Another method used to sample micro-organisms in cleanroom air is membrane filtration. A membrane filter is mounted in a holder, a vacuum is applied and a known amount of air drawn through it. The microbe-carrying particles contained in the air passing through the membrane will be filtered out. One such system is shown in Figure 15.4. The membrane is removed from the filter holder and placed on top of nutrient agar, incubated, and the microbe-carrying particles that grow into colonies are counted.

A membrane filter with a grid printed on the surface will assist in counting the micro-organisms. Filters made from gelatine can also be used. The gelatine retains moisture, and it has been reported that this assists in preventing death of the micro-organisms by desiccation.

Figure 15.4 Membrane holder with filter

15.2 Microbial Deposition onto Surfaces

15.2.1 Settle plate sampling

In the previous section of this chapter, volumetric microbial sampling of the air in cleanrooms has been described. However, volumetric sampling of airborne micro-organisms is an indirect measurement of the likelihood of micro-organisms depositing on, or into, products manufactured in the cleanroom. The direct method is by settle plate sampling.

As will be discussed in Section 20.2, micro-organisms in the air of occupied cleanrooms are usually carried on skin particles. These microbecarrying particles are, in

cleanroom terms, of a substantial size and have an average equivalent particle diameter of about 12 μm. They can therefore deposit, by gravity, onto surfaces at an average velocity of about 0.46 cm/s.

In settle plate sampling, Petri dishes containing nutrient agar are opened in the cleanroom and exposed for a given period of time, thus allowing microbe-carrying particles to deposit onto them. Petri dishes, 90 mm in diameter (internal area 64 cm^2) are frequently used but in high quality cleanrooms, with their attendant low airborne contamination, larger 140 mm (internal area 154 cm^2) Petri dishes are more appropriate. The number of microbe-carrying particles deposited on the agar surface over several hours of exposure is then ascertained. Four to five hours is a useful period, as it coincides with the time personnel are in the cleanroom. There is also little loss of micro-organisms caused by desiccation.

Petri dishes must be about two-thirds to three-quarters full of nutrient agar to minimise desiccation. The microbial deposition rate can be reported as the number of microbe-carrying particles depositing onto the area of a Petri dish in a given time. This rate can also be reported more scientifically as the number deposited per hour, per 100 cm^2.

15.2.2 Calculation of the likely airborne contamination

If the exposed area of a product and the time that it is exposed to airborne microbial contamination during manufacture is known, then the product's likely microbial contamination rate can be calculated. Using the number of

microbe-carrying particles deposited on a settle plate in a given time and proportioning the areas and times of exposure, the contamination rate can be calculated from the following equation:

$$\text{Contamination rate} = \text{Settle plate count} \times \frac{\text{area of product}}{\text{area of settle plate}} \times \frac{\text{time product exposed}}{\text{time settle plate exposed}}$$

Example: A 140 mm settle plate (154 cm^2 area) was laid close to where containers are filled and the microbial count on the settle plate after four hours of exposure was 3. The number of microbe-carrying particles likely to deposit into the product, which has a container with a neck area of 1 cm^2, when they are open during filling for an average of 10 minutes is therefore:

$$3 \times \frac{1}{154} \times \frac{10}{60 \times 4} = 0.0008$$

The microbial contamination rate of the product is therefore likely to be about 0.0008 i.e. 8 containers in 10 000.

15.3 Microbial Surface Sampling

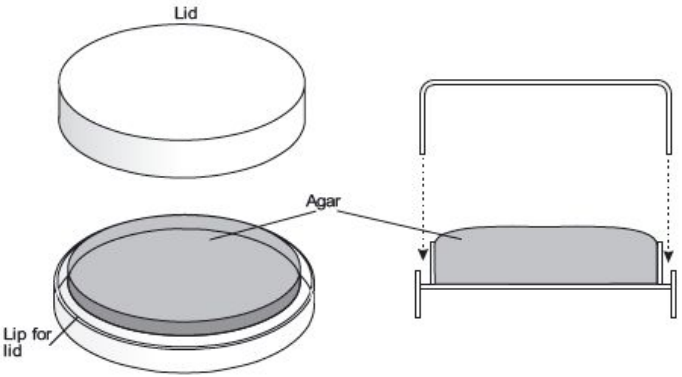
Several methods are available for microbial sampling of surfaces, but two are commonly used in cleanrooms. These are contact sampling and swabbing.

15.3.1 Contact surface sampling

Contact plates and strips are used when the cleanroom surface to be sampled is relatively flat. If plates are used, then RODAC (Replicate Organism Detection And Counting) dishes of the type shown in Figure 15.5 are used. These dishes are normally 55 mm in diameter with the inner dish covered by a lid resting on the lip. Pouring 15.5 ml to 16 ml of nutrient agar medium into the central chamber fills it and gives an agar meniscus that stands proud of the rim.

The nutrient agar surface is rolled over the cleanroom surface to be sampled. Microbe-carrying particles will stick to the surface of the agar and when the dish is incubated for a suitable time and temperature, these will grow into colonies that can be counted. Some disinfectants that are used in cleanrooms leave residues that may stop the growth of micro-organisms on the surfaces to be sampled. Chemicals that neutralise the action of these disinfectants should be incorporated into the nutrient agar to prevent this occurring.

Figure 15.5 RODAC contact plate



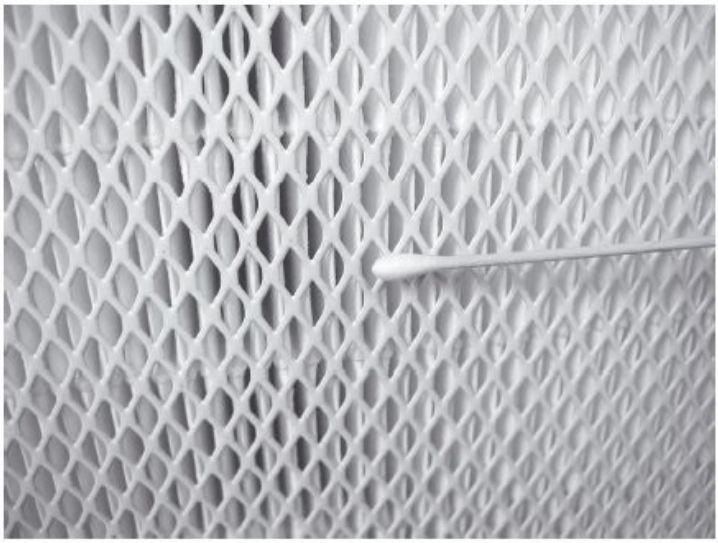
Agar contact strips of the type shown in Figure 15.6 are also used to sample surfaces. These strips are removed from their container and applied to the surface to be sampled. Microbe carrying particles stick to the agar surface and their number is ascertained by counting the colonies that grow during incubation.

Figure 15.6 Contact strip

15.3.2 Swabbing

To sample uneven surfaces, a commonly used method is the application of a bud swab made from a material such as cotton. At its simplest, a sterile swab is randomly rubbed over the cleanroom surface to be sampled (as shown in Figure 15.7) and then rubbed over a nutrient agar plate. The plate is then incubated and the microbial count determined. To improve the efficiency and reproducibility, the swab should be dampened with a sterile liquid such as saline, and a known surface area sampled. An alternative method is to shake the swab in liquid, pass the liquid through an appropriate filter and then count the number of microbe-carrying particles that have been removed from the swab into the liquid.

Figure 15.7 Swabbing a filter grille with a bud swab



15.4 Personnel Sampling

Personnel are the primary source of micro-organisms in a cleanroom, and it may be necessary to monitor them to ensure that there are no unusually high carriers or dispensers of micro-organisms working within the cleanroom. It may also be necessary, when unusually high concentrations of micro-organisms are found in the air, or on surfaces, or within the product, to find the person who is the source. The methods commonly used are:

- Finger dabs. The person's fingers tips, or their gloved fingers, are pressed or wiped on a nutrient agar plate and the number of microorganisms ascertained.
- Contact plates or strips. The person's garments are sampled by pressing the plate or strip onto the clothing. This is best done as the person is about to come out of the cleanroom.

- Body box. If a person wearing normal indoor clothing undertakes a series of prescribed exercises within a body box, then the dispersion rate of airborne micro-organisms for that person can be ascertained. (See Section 20.6.2.)

Acknowledgements

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16

Operating a Cleanroom: Managing the Risk from Contamination

The initial chapters of this book describe how a cleanroom is designed and constructed. Further chapters describe the tests required to ascertain that a cleanroom performs correctly when new, and throughout its life. In the final seven chapters I shall discuss how cleanrooms should be operated to minimise the risk of contamination. This chapter introduces the topic by considering the risk of contamination from the sources and routes within a cleanroom, and how these risks may be controlled and minimised.

To control contamination in a cleanroom, it is necessary to manage the various risks. Risk is defined in ISO 14644-6 as ‘the ‘combination of the probability of occurrence of harm and the severity of that harm’. Harm can be considered in a cleanroom as the amount of contamination that is transferred from a hazard to the product, where a ‘hazard’ is a source of contamination.

A number of systems exist for managing and assessing risk but the ones that are the most applicable to cleanrooms are the*Hazard Analysis andCritical Control Point (HACCP)* method and the*Failure Mode and EffectAnalysis (FMEA)* method, preferably in its*Failure Mode and Effect and Criticality Analysis (FMECA)* format. However, these methods need some reinterpretation and modification for application to cleanrooms, and this has been done in the

Risk Management of Contamination (RMC) system that is described in the PHSS Technical Monograph No 14. Information on where to obtain this document is given in Chapter 4. The RMC method, contains the following basic steps:

1. Identify the sources and routes of contamination in the cleanroom.

2. Assess the risks from these sources and routes and, where appropriate, introduce or improve control methods to reduce the risks.

3. Establish a monitoring programme using valid sampling methods to monitor the hazards, or their control methods, or both. Establish alert and action levels with measures to be taken, when required, if these levels are exceeded.

4. Verify, on a continuing basis, that the contamination control system is working well by reviewing product contamination rates, environmental monitoring results, risk assessment methods, control methods and monitoring limits and, where appropriate, modify them accordingly.

5. Establish and maintain appropriate documentation.

6. Train the staff.

These steps will now be discussed.

16.1 Step 1: Identification of Sources and Routes of Contamination

16.1.1 Sources of contamination

Examples of sources of particle and microbial contamination in a cleanroom are as follows:

- dirty areas adjacent to the cleanroom,
- unfiltered air supply,
- cleanroom air,
- cleanroom surfaces,
- people,
- machines and ancillaries,
- raw materials
- containers,
- packaging.

Areas adjacent to the cleanroom are likely to be less clean than the production cleanroom. The material airlock and clothing change areas will be contaminated by the activities going on in these areas, and the contamination in the outside corridors may not be controlled. The air supplied to a cleanroom, if not correctly filtered, is a source of contamination. Air in the cleanroom is also a source and contains contamination dispersed into it, mainly from people and machines.

The floor, wall, ceiling, tables, trolleys and other surfaces in the cleanroom are examples of surface sources. The contamination on them is mostly derived from personnel touching them, or contamination depositing on them from the air. If these surfaces are touched by a gloved hand which then touches a product, contamination is transferred to the product. These surfaces can also be sources of contamination if poor quality constructional components are used, which break up and disperse fibres, wood chips,

plaster etc. Cleanroom clothing, gloves and masks have surfaces that are contaminated, either by the people wearing them or as a result of contact with other cleanroom surfaces. The product will be contaminated by direct or indirect contact with any of these surface sources.

Personnel within the cleanroom can disperse contamination from the skin, mouth and clothing. This contamination can be transferred to the product through the air, or by contact with their hands or clothing.

Machines are another source, as they can generate contamination from their moving parts or by other means. Ancillary parts, and tools used to repair or adjust machines, can be sources. Raw materials, containers and packaging that are brought into, or piped into the cleanroom, may be contaminated and should be considered as potential sources.

16.1.2 Airborne and contact routes of transfer

As well as identifying the sources of contamination in a cleanroom, the routes of transfer must be considered. The two main routes are airborne and contact. Contamination can also occur from fluids but this is not discussed.

Contamination can be dispersed into the air and transferred to the product. If the particles are small they may float off to other parts of the cleanroom. However, if they are large, like fibres, chips, cuttings, or spittle from people's mouth, they will remain within a short distance of their sources and fall directly onto the product.

Contact routes allow contamination from the surfaces of machines, tools, containers, packaging, raw materials, gloves, clothes, etc. to come into contact with the product. Contact contamination can occur in several ways. One example is when personnel handle a product and the contamination on their gloves is transferred onto the product, and another is when the product comes into contact with dirty containers or packaging.

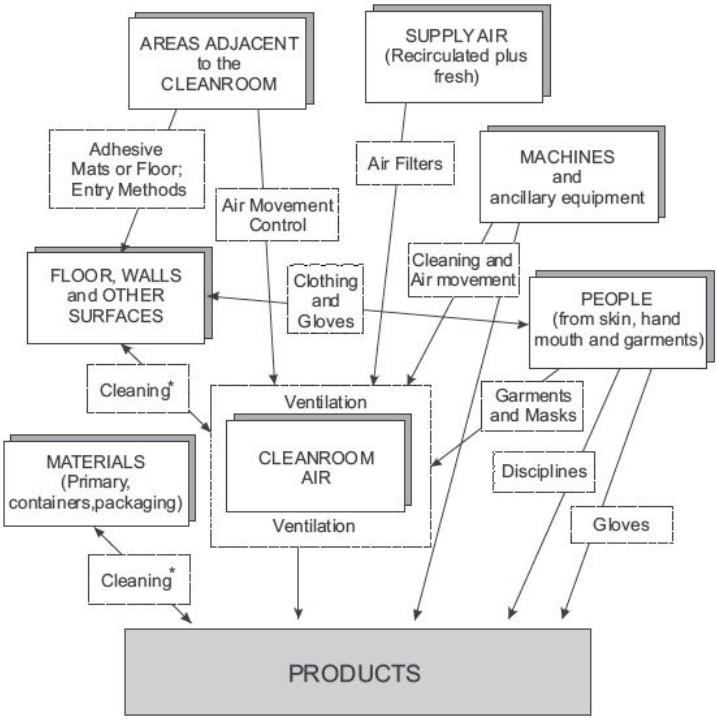
Using information of the type discussed in this and the previous section, the sources and routes of transfer can be ascertained and a 'risk diagram' constructed for any cleanroom.

16.1.3 Construction of a risk diagram

Construction of a risk diagram is a good method of understanding how contamination arises from sources, and the routes by which it reaches the product. The way a product is contaminated is often poorly understood but by constructing a risk diagram a greater understanding will follow. The risk diagram should show potential sources of contamination, the main routes of transfer, and the methods of controlling this transfer. It may be necessary to construct several diagrams where the process is complex, or where it is necessary to control different contaminants, e.g. particles, microbe-carrying particles, and chemical contamination.

Figure 16.1 is an example of a risk diagram showing the main sources of microbial and particle contamination in a typical cleanroom. It also includes the routes of transfer of contamination and means of control.

Figure 16.1 Sources, routes and control measures for particle and microbial contamination in a cleanroom



*Sterilisation and disinfection may be required where microbes are a contaminant

The transfer of contamination around the room can be very complicated, as in theory everything in the cleanroom can be contaminated by everything else. However, in practice, it should only be necessary to consider the major sources and routes of transfer of contamination. It is interesting to note the central role of air, which receives and transports many of the types of contaminant in a cleanroom.

By definition, the greatest risk to the product will be in what is called the 'critical zone'. This is where the product is open and exposed to contamination. It may be desirable to carry out a more detailed risk assessment of the process going on in the critical area, and a risk diagram for that specific area will be useful.

An important and difficult part of risk management is assessing the degree of risk from the various sources of contamination, and then controlling or minimising the risk. This is Step 2 in the RMC method.

16.2 Step 2: Risk Assessment and the Control of the Sources of Contamination

When all sources of contamination in the cleanroom and their routes of transmission have been identified, a risk assessment is carried out. Risk assessment is also called hazard or risk analysis. It ascertains the degree of importance of the various risks in a cleanroom and their potential for contaminating a product or process.

Risk assessment is the most difficult part of risk management. It is especially difficult if the cleanroom is new and not yet operational, as few useful measurements of the concentrations of contamination in the cleanroom environment will have been collected. However, lack of monitoring results should not prevent preliminary risk assessments being made. It will, in any case, be necessary at a later stage (Step 4) to verify and reappraise these tentative conclusions and, if necessary, to make changes. Another difficulty in risk assessment is the correct choice of the model of risk that is used to calculate the degree of

risk from the various sources of risk. This can be a major problem, as the use of a poor risk model will give a poor assessment of the risks. To ensure the best choice of model, it is necessary to understand what 'risk' means in cleanrooms, and base the model of assessing risk on the fundamental equations of contamination transfer.

16.2.1 Fundamental equations of contamination transfer

Equations have been derived that calculate the risk of transfer of contamination by the two main routes of contamination in cleanrooms. The first route is 'contact' where contaminated surfaces such as gloves, clothing, machinery, tools etc. transfer contamination to the product by contact. The second route is 'airborne' where the contamination dispersed into the air by people and machinery deposits onto, or into, the product. The two equations given below are applicable to both inert and microbe-carrying particles.

The variables given in the two equations are the fundamental 'risk factors' that determine the amount of product contamination. If exact numerical values are available, the exact amount of product contamination can be calculated. It therefore follows that the closer the risk assessment model is to the fundamental equations, the more accurate the calculation of risk. The two equations are as follows:

Airborne contamination

The risk to a product from airborne deposition is determined by the following equation:

Equation 16.1

Number of airborne particles deposited onto a product in a given time = deposition rate (no/cm^2.s) ×area of product exposed (cm^2) ×time of exposure (s)

where the deposition rate is the number of particles that will deposit from the air onto a given surface area in a given time.

Surface contact

The risk to a product from surface contact is determined by the following equation:

Equation 16.2

Number of particles transferred by surface contact = concentration of particles on the source surface (no/cm^2) ×transfer coefficient x area of contact (cm^2) ×number of contacts

Where, the transfer coefficient is the proportion of contamination that is transferred from the donating source to the receiving surface.

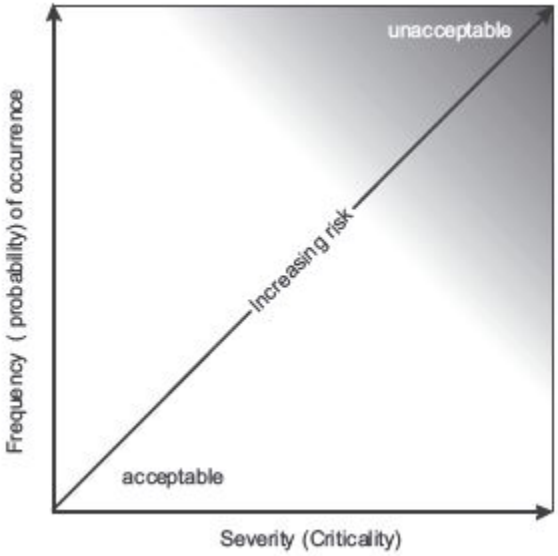
The units in both these equations can be changed to more convenient units if desired e.g. centimetres can be changed to metres, and seconds to minutes, or hours.

16.2.2 What does 'risk' mean in cleanrooms?

The definition of risk is given in ISO 14644-6 as 'the 'combination of the probability of occurrence of harm and

the severity of that harm'. Harm in a cleanroom can be considered as being the amount of contamination transferred to the product from a hazard, where a 'hazard' is a source of contamination.

Figure 16.2 Increase in risk caused by an increase in the frequency (probability)



Risk consists of two components and can be expressed mathematically as follows:

Equation 16.3

$$Risk = criticality\ of\ the\ occurrence \times frequency\ of\ occurrence$$

The first component is the ‘criticality’ or ‘severity’ of the risk, and the second its ‘probability’ or ‘frequency’ of occurrence. This concept is shown graphically in Figure 16.2, where it can be seen that as the ‘criticality’ and ‘frequency’ increase, either separately or in combination, the risk increases.

In cleanrooms ‘criticality’ is the amount of contamination that will be dispersed (released) from the source, transferred and then deposited onto the product, and the ‘frequency’ of the occurrence is the number of surface contacts, or the length of time that the product is open to airborne contamination.

16.2.3 Risk descriptors and scoring methods

Actual numerical values required to solve the fundamental equation of airborne contamination (Equation 16.1) are usually available, and the likely amount of airborne contamination of a product can be calculated. However, in the case of surface contact, the numerical information required from risk factors such as the ‘number of contacts’ or ‘transfer coefficient’, is usually unavailable. To overcome this problem, the degree of risk can be scored using descriptors such as ‘high’, ‘medium’ and ‘low’ and these descriptors are given a score. These scores are applied to the risk factors and multiplied together to obtain what is called the ‘risk rating’. On occasions, information may be so lacking that a variable related to the risk factor has to be used e.g. the number of people in a cleanroom could be used as a descriptor of airborne contamination. Descriptors of risk can be considered as surrogates for the missing information on the degree of risk.

Where descriptors are used, a method of scoring for risk is required. It is easier for a person to describe risk by simple words that denote greater or lesser importance, and then to allocate a score to the word. To obtain the greatest accuracy, the descriptors and scores should span the whole range of contamination risks and be distributed around an average value encountered in the cleanroom, the risk scores being in proportion to the meaning and importance of the words.

A variety of scoring systems are used in risk assessment but the system shown in Table 16.1 works well in assessing risk in cleanrooms and is used in this chapter.

Table 16.1 Risk scoring system

Degree of risk	Score
Extremely low	0.001
Very low	0.01
Low	0.1
Medium	0.5
High	0.7
Very high	0.9
Extremely high	1

As discussed above, the most accurate method of assessing risk is to use the best-available numerical information in the fundamental equations. This works well when assessing the risk in each step of a process, and is discussed in section 16.2.5. However, this approach can be time consuming and such detail may not be necessary. If a broader approach is required e.g. the whole cleanroom

suite is to be assessed for major risks, then a risk model based on the fundamental equations but using descriptors to score risk can be used. An example of this approach is now given.

16.2.4 Overall risk assessment method

The overall risk method considers all of the main hazards or sources of contamination, in a cleanroom suite, and uses a risk model based on the fundamental equations given in Section 16.2. The overall risk model is as follows:

Risk from particle or microbial contamination (risk rating) $= A \times B \times C$

where

A = concentration of particle or microbial contamination on, or in, a source;

B = likelihood of transfer from the source to the product;

C = frequency of transfer of contamination.

The risk rating, which gives the degree of risk of a source, can be determined for each source of contamination by assigning risk scores to the risk factors A to C, as given in Table 16.1, and multiplying them together.

Table 16.2 Allocation of risk scores to risk factors

Risk factor A Concentration of particle or	**Risk factor B Ease of dispersion (release), movement and deposition of**	**Risk factor C Frequency of occurrence – number of surface**

microbes on, or in, a source	contamination from source to product	contacts, or time of exposure of product
extremely low = 0.001	extremely low = 0.001	extremely low = 0.001
very low = 0.01	very low = 0.01	very low = 0.01
low = 0.1	low = 0.1	low = 0.1
medium = 0.5	medium = 0.5	medium = 0.5
high = 0.7	high = 0.7	high = 0.7
very high = 0.9	very high = 0.9	very high = 0.9
extremely high = 1	extremely high = 1	extremely high = 1

Examples of the overall method

The following two examples demonstrate the overall risk assessment method by calculating the degree of risk (risk rating) from both microbecarrying particles and inert particles on the wall of a cleanroom, and from the hands of personnel.

Example 1:*Assessment of the risk associated with cleanroom walls*.

Firstly, for Risk factor A, the concentration of contamination, should be assessed. It is known from sampling that the concentration of microbes and particles on a wall surface is ‘very low’ and a risk score of 0.01 is allocated.

Risk factor B should now be considered. Particles will adhere to the wall and will not be dispersed by air currents. They will be transferred when a person touched the wall and then the product. This transfer can occur relatively

easily and a score of 0.7 is used. Although a transfer can occur easily it seldom does and this frequency is assessed by risk factor C.

People do not go around touching walls in the non-cleanroom situation, and the additional disciplines in a cleanroom should reduce the frequency. Risk factor C is therefore scored as 'extremely low' i.e. 0.001. The risk rating of wall contamination is obtained by multiplying all three risk factors together to obtain a risk rating of 7×10^{-6}.

Example 2:*Assessment of the risk associated with the hands of a person manipulating product*

A maximum score of 1 is given for risk factor A (amount of surface contamination) if ungloved hands are used, as hands have very large amounts of both particle and microbial contamination. This contamination is easily transferred from the hands to the product through contact, and so a 'high' score of 0.7 is allocated to risk factor B. The score allocated to risk factor C depends on how often the product is touched but in this example a risk score of 'medium' i.e. 0.5 is allocated. Thus, an overall risk rating of 0.35 would be allocated if ungloved hands were assessed.

If a single pair of gloves is used, they should maintain a barrier against contamination on the hands, although they will pick up contamination through touching surfaces in the cleanroom. They can occasionally be punctured and allow contamination to escape from the skin to the glove surface. A 'low' score of 0.1 is therefore allocated to risk

factor A (amount of surface contamination on the glove). The risk rating associated with gloved hands, would therefore be reduced by ten fold to 0.035. In a similar manner, the use of double gloves might reduce the risk rating to 0.0035.

It can be seen from the above two examples that hands have a high potential risk of contamination and are very much more important than the hazard presented by the cleanroom walls.

The risk assessment method shown in these two examples should be applied to all of the major sources of contamination identified in the cleanroom. These sources are likely to be similar to those shown in Figure 16.1.

Control and reduction of overall risk

When all the sources of contamination in a cleanroom have been identified and their risk rating obtained, it is necessary to consider if the risk needs to be reduced. This can be done by implementing a control method to reduce the risk score of one or more of risk factors A, B and C. The importance of obtaining an effective control method should be related to risk rating; the higher the risk rating, the more effective the control method should be. If the control method is shown by risk assessment to be insufficiently effective then a more effective control method should be adopted.

Figure 16.1 shows methods that can be used to control the routes of spread of contamination. These are:

1. HEPA or ULPA air filters can be used to prevent any contaminants entering with the supply air. However, unfiltered air can pass through holes in damaged filters, or by-pass the filter owing to poor filter housing construction and this should be regularly checked.

2. Airborne contamination from areas outside the cleanroom, e.g. outside corridors and service plenums, can be prevented from entering the cleanroom by setting room pressures that ensure that the air moves from the cleanroom outwards, i.e. from clean to less-clean. Doors must be kept closed, and the use of air locks will minimise undesirable air movements. The transfer of surface contamination from less-clean to clean areas is controlled by careful changing into suitable cleanroom clothing in a changing room airlock. The use of adhesive cleanroom mats and flooring, as well as the removal, or covering, of dirty outdoor shoes prevents surface contamination being transferred from the floors of these areas into the cleanroom.

3. Although the cleanroom air supplied to a cleanroom is filtered, the dispersion of contamination into the air in the cleanroom from people and machinery makes it as source of contamination. As well as being a source, it is also a route by which other sources transfer their contamination to the product. Airborne transfer of contamination can be reduced by the use of a nonunidirectional ventilation system to dilute the contamination, or a unidirectional ventilation system to sweep it away. A separative device such as an isolator or minienvironment will give a physical barrier and an additional supply of filtered air.

4. The possibility of transfer of surface contamination from floors, walls, ceiling, tables, trolleys etc. in the cleanroom is minimised by cleaning, or in the case of biocleanrooms, sterilisation or disinfection, and any contamination that becomes airborne is controlled by ventilation.

5. People disperse contamination from their mouth, hair, clothing and skin. Cleanroom garments and gloves will minimise this dispersion and contamination that cannot be controlled (as well as that produced by their clothing) can be minimised by the ventilation system.

6. Contamination from machines can be minimised by the design of the machine, or by the use of exhaust air systems to draw the contamination away. Cleaning (and sterilisation and disinfection where necessary) can control surface contamination on the machine.

7. Raw materials used to make products, or from which products are assembled, as well as containers and packaging, should be made from materials that do not generate contamination. They should also be manufactured in an environment that ensures the minimum contamination on, or within, them. They should be correctly wrapped to ensure that they are not contaminated during delivery, and when the packaging is removed on entry, contamination does not occur. Materials that are not sufficiently clean will require to be cleaned or, if in fluid form, filtered.

All of these control methods are discussed in more detail in the various chapters of this book.

16.2.5 Risk assessment in critical zones

The method described in the previous section 16.2.4 uses an overall risk assessment to identify major sources of risk in a cleanroom suite. However, it may be necessary to assess the risk of contamination in areas such as the critical zone where the major contamination risks to the product will be found. If this is required, the contamination risks from surface and airborne sources should be analysed separately, as the methods used for assessing the associated risks, and the means of controlling them, are different. The assessment of risk from airborne contamination is generally carried out over the whole duration of the manufacturing process but the assessment of surface contact contamination is generally done for each step of the process. How this can be done is now discussed.

16.2.5.1 Risk from airborne deposition

The airborne contamination during exposure of a product from the deposition of airborne particles and microbe-carrying particles can be calculated by use of the fundamental Equation 16.1. The time units are changed to hours as shown in Equation 16.4.

Equation 16.4

Number of airborne particles (or microbes) deposited onto a product in a given time = deposition rate (no/cm^2.h) × area of product exposed (cm^2) × time of exposure (h)

Numerical values of the variables (risk factors) required to solve Equation 16.4 can be found as follows:

The*deposition rate* of inert particles can be determined by laying out a witness plate, semiconductor wafer, or in the case of microbe-carrying particles a settle plate containing nutrient agar. The number of particles or microbe-carrying particles that deposit onto a known area of plate over a given time is determined, and the deposition rate calculated by use of Equation 16.5.

Equation 16.5

$$\textit{Deposition rate } (no/cm^2.h) = \textit{average count on sample plate} \div [\textit{area of sample plate } (cm^2) \times \textit{time plate exposed } (h)]$$

If, for example, 20 particles were found to deposit in 3 hours onto a surface that was 150 cm^2, then the deposition rate can be calculated as follows:

$$\text{Deposition rate } (no/cm^2/h) = \frac{20}{150 \times 3} = 0.044$$

The sampling plates should be laid out as close as possible to where airborne contamination of the product will occur, and exposed during the manufacturing process for as long as is necessary to obtain an accurate result. Multiple samples would normally be required. Microbial settle plates should be incubated for a suitable time and at a suitable temperature, and the microbial colonies counted to establish the number of microbe-carrying particles that have deposited on the plate. Similarly, the number of

particles that have deposited onto witness plates or wafers should be sized and counted.

If information on the actual deposition rate during manufacture cannot be obtained, the deposition rate can be determined by using reported values of deposition velocity, although this method is unlikely to be as accurate. The following Equation 16.6 is used.

Equation 16.6

$$\textit{Deposition rate } (no/cm^2/h) = \textit{conc. in air } (no/cm^3) \times \textit{deposition velocity } (cm/h)$$

Microbe-carrying particles in the air of an occupied room are dispersed from the people in the room and carried on skin particles that have an average equivalent particle diameter of 12 μm, and a deposition velocity of 0.45 cm/s. Similarly, an average deposition velocity of 0.003 cm/s has been reported in a semiconductor cleanroom for particles ≥0.3 μm. For particles ≥5 μm a deposition velocity of 0.08 cm/s would be a reasonable estimate.

The*surface area* of the product that is exposed to airborne contamination should be determined. This might be the surface area of the neck of a container, or the exposed area of a solid product.

The total*time* that the product is exposed to airborne contamination during manufacture is required, but any time during which the product is protected from airborne deposition should be deducted from the total time. If a batch of product passes through a process, the average

time that a product takes to pass through is taken as 50% of the time that the complete batch takes e.g. if a batch takes 60 minutes to pass through a process the average time that the product is exposed to airborne contamination is 30 minutes.

Practical microbial example Settle plates (surface area 64 cm^2) were exposed for four hours in the zone where containers were filled. The average microbial count over a number of settle plate exposed for four hours was found to be 0.12. Therefore, using Equation 16.5:

$$\textit{Deposition rate } (no/cm^2.h) = \textit{average count on settle plate} \div [\textit{area of settle plate } (cm^2) \times \textit{time plate exposed } (h)]$$
$$= \frac{0.12}{64 \times 4} = 0.00047$$

The container had an inner neck area of 2 cm^2, and was open to airborne contamination for an average of 6 minutes. The number of microbes that would deposit through the neck area of the container is calculated using Equation 16.4.

$$\textit{Number of airborne microbes deposited into a product} = \textit{deposition rate } (no/cm^2.hr) \times \textit{area of product exposed } (cm^2) \times \textit{time of exposure } (hr)$$
$$= 0.00047 \times 2 \times [6 \div 60] = 0.000094$$

It is reasonable to assume that the episodes of airborne deposition of particles are spread randomly through production and therefore approximately 1 in 10 000 products will be contaminated.

Practical particle example A product with a surface area of 200 cm^2 was exposed to airborne particle contamination during manufacture for one hour. There was no information available from witness plates, or wafers, as to the actual deposition rate during production, and a deposition velocity for particles ≥ 0.3 μm of 0.003 cm/s (10.8 cm/h) was assumed. The airborne count of particles ≥ 0.3 μm at the point where the product was exposed was close to the class limit of an ISO Class 4 clean zone, which is 1020/m^3 (0.001/cm^3).

The deposition rate can therefore be calculated from Equation 16.6 as follows:

$$\textit{Deposition rate } (no/cm^2/h) = \textit{concentration in air } (no/cm^3) \times \textit{deposition velocity } (cm/h)$$
$$= 0.001 \times 10.8 = 0.011$$

The total number of particles ≥ 0.3 μm that might deposit on the product from the air can now be calculated using Equation 16.4, as follows:

$$\textit{Number of particles} \geq 0.3\ \mu m \textit{ deposited} = \textit{deposition rate } (no/cm^2/h) \times \textit{area } (cm^2) \times \textit{time } (h)$$
$$= 0.011 \times 200 \times 1$$
$$= 2.2$$

Controlling airborne risk The risk to a product from airborne contamination is dependent on the particle deposition rate, the area of product exposed, and time of exposure to airborne contamination. It may be possible, especially when the manufacturing process is being designed, to reduce the exposure time and deposition area of the product. This might be done by increasing the line

speed, reducing the area of the product exposed, or employing protection to prevent contaminated air getting to the product e.g. a lid on top of a hopper. These methods will give a reduction in airborne risk that is in direct proportion to the reduction of area, or time. However, the introduction of such improvements into an established manufacturing process may require substantial effort and capital expenditure. Other methods that can be implanted without major effort or cost are as follows:

1) reducing the number of people in the area next to the exposed product;

2) improving the cleanroom clothing;

3) using a separative device, or increasing the effectiveness of the existing separative device;

4) if a unidirectional device is used, placing the operator further from the area of contamination by providing a tool such as a long forceps;

5) improving the reliability of the machinery to reduce the number of interventions of personnel to get it working correctly.

After steps have been taken to control airborne contamination, the reduction of airborne deposition into the product should be recalculated.

16.2.5.2 Risk from surface contact

Surface contact occurs when gloves and clothing worn by personnel, or inanimate surfaces such as stoppers, tools, machine parts, and various ancillary items, touch the product and transfer their surface contamination to it. The fundamental equation that determines the amount of surface contamination transferred from a contaminated surface to a product is Equation 16.2.

Number of particles (or microbes) transferred by surface contact
= concentration of particles (or microbes) on source surface (no/cm^2) ×
transfer coefficient × area of contact (cm^2) × number of contacts

Manufacturing carried out in a cleanroom is rarely carried out in one step but requires many steps. The amount of surface contamination transferred to a product during a manufacturing process must therefore be determined by totalling the risk rating of each step. Also, the steps with the most risk can be investigated to reduce risk.

Manufacturing processes can be very complex and only a simple example is used here as an illustration of this risk assessment method. In this example, the product is a cube with the surface area of each side 4 cm^2. The production steps are as follows:

1. The cube is lifted out of a box using an*un*-gloved hand.

2. The cube is placed on the bench of a cleanroom workstation.

3. The cube is lifted with a tool, adjusted and laid back down on the bench. This is done 3 times, the cube and tool being returned to the bench surface after each adjustment.

4. Finally, a container lid is lifted by hand, the cube lifted from the bench using the tool and placed in a container, and the lid replaced.

The amount of contamination transferred to the cube surface is calculated. This is done by using Equation 16.2 to calculate the risk rating of the above four steps, as shown in Table 16.3. It should be noted that to increase the accuracy of the calculation, numerical values are used, and not descriptors as used in the 'overall' risk assessment method. The correct values of the 'area of contact' and the 'frequency' of contact are known, but numerical values of 'transfer coefficients' and 'surface contamination' are uncertain, and 'best estimates' are used. The use of 'best estimates' will give a more accurate result than employing a risk scoring method with descriptors, but if there is no knowledge of the numerical values then a descriptor and score of the type given in Table 16.1 can be used.

Table 16.3 Initial risk ratings of production steps

Step	Conc. [1] on surface/cm^2	Transfer coefficient [2]	Area of contact [3] (cm^2)	Frequency [4]	Risk rating[5]
1 Cube lifted with hand *	1000	0.1	3.5	1	350
2 Cube laid on bench surface*	10	0.1	4	1	4
3 Cube lifted with tool*, ×3	10	0.1	0.5	3	1.5
4 Cube laid on bench*, ×3	10	0.1	4	3	12
5 Container lid lifted by hand* and replaced	1000	0.01	0.1	1	1
6 Cube lifted with tool* and placed into container	10	0.1	0.5	1	0.5
All steps				Total risk rating	= 369

* donating surface

Notes:

1. Actual numerical values of surface contamination should be found by sampling or, failing that, 'best estimates' should be used. In this example the counts/cm^2 of the hand, bench and tool surface are assumed to be 1000, 10, and 10, respectively.

2. The transfer coefficient, which gives the portion of contamination transferred from fingers, bench or forceps to the cube, is given a value of 0.1, i.e. 10% of the contamination is transferred. The chance of transferring contamination from fingers to the inside of the container when lifting and replacing the lid, is assumed to be low and the transfer coefficient is taken as 0.01.

3. The area of contact should not be taken as the surface area of the cube, the tool, or fingers, but the area where contact is made. One side of the cube is 4 cm^2. The surface area of two finger tips contacting a surface is assumed to be 3.5 cm^2, and the tool 0.5 cm^2. In the final step, where the lid is taken off, and replaced, the area of contact between the finger and the inside of the container (if it occurs) is unknown but likely to be small, and assumed to be 0.1 cm^2.

4. The frequency of contact is the number of times the cube or container lid, is lifted, or laid down.

If the information used in Table 16.2 is numerical and accurate, then the risk rating calculated for each step would give the exact number of contaminants deposited on the product. However, a number of 'best estimates' have been used and hence the risk ratings must also be considered as 'best estimates'. The 'best estimate' of the total number of contaminants deposited on the product is therefore 369.

A reduction in the risk to the product from contamination can be brought about by a reduction in any of the four risk factors given in Equation 16.2. In this example, it can be achieved as follows:

1) the operator wears particle-free (sterile when used with microbes) gloves, which reduce the surface contamination of the hands to 1/cm^2.

2) the bench surface is cleaned using a cleanroom wiper (or disinfectant wiper), which reduces the surface contamination to 0.1/cm^2.

3) the tool is hung up when not used and occasionally cleaned (or disinfected).

4) the cube was inspected and laid on the bench surface 3 times. The inspection method is reduced to 2 times.

5) the area of contact is reduced by introducing a new tool, which adequately grips the cube, but is 0.2 cm^2 in surface area.

The new risk ratings are calculated and shown in Table 16.4. It can be seen that the total contamination risk has been reduced from 369 to 0.48, i.e. the proportion of product contamination is 0.48, or about 5 out of 10 products.

Table 16.4 Risk rating after the introduction of control methods

Step	Conc. on surface/cm^2	Transfer coefficient	Area of contact (cm^2)	Frequency	Risk rating
1 Cube lifted with gloved hand	1	0.1	3.5	1	0.35
2 Cube laid on bench surface	0.1	0.1	4	1	0.04
3 Cube lifted with tool × 2	0.1	0.1	0.2	2	0.004
4 Cube laid on bench × 2	0.1	0.1	4	2	0.08
5 Container lid lifted by gloved hand and replaced.	1	0.01	0.1	1	0.001
6 Cube lifted with tool and placed into container	0.1	0.1	0.2	1	0.002
All steps				Total risk	= 0.48

It is possible to introduce further methods to reduce contamination. If double gloves are used, the chance of a puncture is minimised and the surface concentration in step 1 might be reduced to 0.1, and the risk rating of that step to 0.035. If the cube is placed on a precision-cleaned dish (or in the case of microbes, a sterile surface) the risk rating in step 2 might be reduced to 0.004. The total contamination risk is now reduced to 0.126 i.e. the proportion of product contamination is 0.126, or about 1 in 8 of the products may be contaminated.

16.3 Step 3: Establish an Effective Monitoring Programme

The third step of the RMC system is to set up a programme to monitor the sources of contamination, or their control methods, or both.

The programme of monitoring is established by:

1. deciding which contamination sources and transfer routes have to be monitored,

2. deciding on the frequency of sampling,

3. using valid sampling methods,

4. setting appropriate sampling limits that should be seldom or rarely exceeded, and agreeing the actions to be taken when the limits are exceeded.

16.3.1 The sources and routes to be monitored

It is necessary to decide which routes and sources need to be monitored to ensure that contamination of the product is kept under control. The choice should be related to the risk rating. Sources that have higher risk ratings should be monitored, whereas inconsequential ones might be ignored. Thus, sampling should always be carried out in the critical zone, but as the risk becomes less in the background areas of the production cleanroom, and even less in corridors and other support areas within the cleanroom suite, there is less necessity for sampling. Inconsequential risk areas such as the cleanroom ceiling will be rarely sampled. As well as considering the risk rating of the hazard, the concentration of contamination on the hazard and the efficiency of its control method need to

be considered, as a source that has a high concentration of contamination but appears to be well controlled may need to be well monitored in case the control method fails.

It will also be necessary to consider the type of product manufactured in the cleanroom. Products with a low risk from contamination, as reflected by consequences that can be measured in financial, reliability, effectiveness, safety or other terms, or products that present a low risk to the patient, will not require as much sampling as those that carry a high risk.

Given in Table 16.5 are some well-known cleanroom hazards, their routes of transfer and control, and how they might be monitored. Also given are the sections of this book where further information may be found.

Table 16.5 Sources, routes of transfer, and control and monitoring methods used in cleanrooms.

Hazard	Route	Control method	Monitoring methods	Chapter reference
Supply air	airborne	air filters	filter integrity test	13
Areas adjacent to the clean-room	airborne	overpressure; air movement control	room pressure differential	11.2; 5.1.5
	contact	cleanroom mats	mat inspection	18.2.1
Various airborne dispersions	airborne	ventilation	air supply rate or velocity	11.1
			counts of airborne particles	14
			counts of airborne micro-organisms	15.1
			control of airflow	12.2
Floors, walls and other surfaces	contact	cleaning (and, where required, disinfection)	surface counting of particles, and micro-organisms	22.7; 15.3

People	airborne	cleanroom garments	surface counts; inspection for tears; particle penetration testing	20.6
	contact	gloves	inspection for punctures;	21.2.4
			surface contamination counts;	21.2.4
			disciplines.	
Machines	airborne	ventilation	air extract rates and airflow patterns	11.1, 12.2.1
	contact	design of machine; cleaning or disinfection	—	—
			surface contamination	22.6
Raw materials	mainly contact	control of manufacturing of raw materials	particle and bacterial counts within, or on, the materials.	19.2
		cleaning if solid, or filtration if fluids	filtration systems	not discussed
		sterilisation	sterilisation system	not discussed
Containers and packaging	mainly contact	control of their composition and manufacturing environment	particle and microbial counts on surface	19.3 and 22.6
		sterilisation	sterilisation system	not discussed

16.3.2 Frequency of sampling

The frequency of sampling should be established for each defined hazard. This decision will have to be made for each cleanroom and process, as the design of the cleanroom suite and the consequences of a contaminated product will strongly influence the decision.

The frequency of sampling should be related to the degree of risk. The higher the risk, the more frequent the

sampling. For example, the air in the critical zone will require more frequent monitoring than the air in the rest of the cleanroom, and this will require more sampling than the rest of the cleanroom suite. Similarly, the surfaces away from the critical area will require less frequent sampling than surfaces in the critical area. Transfer areas may be an exception and require proportionally more sampling because of the higher risk associated with the materials and personnel that will move into the critical area.

In some cleanrooms, continuous sampling of airborne particles and microbe-carrying particles is carried out at the critical zone, and other hazards may be sampled weekly or monthly. In other cleanrooms, where the risk of contamination has less consequence to the product or patient, the monitoring intervals may be set in months, or years. However, the sampling intervals should not exceed those given in ISO 14644-2 (see Table 10.2 in Chapter 10).

16.3.3 Sampling methods

The RCM system requires a '*valid* sampling method' to be used to monitor hazards. The term 'valid sampling method' is defined here as 'a method that is fit for the purpose, or works well in the situation in which it is being used'. In terms of monitoring, the following require to be demonstrated:

- that the sampling instruments are regularly calibrated;
- that the collection efficiency of the sampling instruments is known and preferably high, and that the variability of the results should be low i.e. the precision should be high. Sampling microbes can be difficult. As well as ensuring that

the media and incubation conditions are correct for the types of microbe sought in the cleanroom, it is necessary to ascertain that there is no loss of growth caused by disinfectant residue left on the surface, or dehydration of the microbial growth medium during air sampling.

- that the hazard has a high enough risk for it to be required to be monitored;
- that the sampling method used is the best available for*directly* measuring the contamination risk of the hazard, or its control method.

The last three requirements are not always easy to determine but, if correctly done, they will ensure that monitoring effort is not wasted.

16.3.4 Setting sampling limits

It is necessary to show that a hazard is under control. A useful approach is to set 'alert' and 'action' limits for the sampling results. An 'alert' level indicates that the contamination concentration is higher than might be expected, and may give an early warning of a potential drift from design conditions. It indicates that the conditions are still under control and that no corrective actions will normally need to be initiated. However, if several 'alerts' are obtained in a relatively short time, or an unusual pattern of results is recorded, then this might suggest that action is required.

An 'action' level is set at a higher concentration of contamination than the 'alert' level and is a level which, when exceeded, requires immediate investigation to identify the cause. The investigation should assess whether the excursion has been caused by sampling error, or it is a genuine excursion. For every excursion considered to be

genuine, the corrective action required to regain control of unacceptable levels of contamination should be established and implemented immediately.

Analysing the monitoring results and setting ‘alert’ and ‘action’ levels is a complicated subject if a statistical approach is used. However, common sense can be used to designate appropriate alert and action levels through inspection of the available sampling data. Advice from the suppliers of the instruments used to monitor the contamination will often assist. However, the use of statistical techniques is the preferred option, especially in cleanrooms where the product is sensitive to contamination. Knowledge of statistical techniques, especially the use of calculation of averages and standard deviations of statistical distributions other than Normal, trend analysis and Shewhart and CUSUM charts may be required. A discussion of these is outwith the scope of this book and, if more information is needed, a statistician should be consulted.

16.4 Step 4: Verification and Reappraisal of the System

The RMC system should be regularly verified to ensure that it is effectively controlling contamination. Monitoring the results from testing (or inspection) of all or part of the finished product will be necessary, as this reflects the most important effect of contamination. If possible, measuring the contamination in, or on, the final product should be carried out. If this cannot be easily done then simulation of the process, such as carried out in pharmaceutical aseptic production, where containers are filled with microbiological medium so as to ascertain the amount of

microbial contamination, is a good alternative. In addition, the following should be carried out:

1. Reassessment of the risk assessment models and risk scoring. The accuracy of the information obtained from risk assessment is dependent on the choice of the risk model and the risk scoring method, and these should be reassessed to see if improvements can be made.

2. Reassessment of the risk ratings of the hazards. These should be reviewed to see if there is any increase or decrease in the degree of risk. Any additional information that is available since the previous verification e.g. new control methods, or additional test results, should be included in this reassessment.

3. The effectiveness of the control methods. If there is any increase or decrease in the risk ratings then consideration should be given to whether a hazard requires increased or reduced control.

4. A review of the sampling programme. Any new information on the degree of risk of the sources of contamination should be used to review the environmental sampling programme with regards to a decrease or increase in the number and placement of sampling points, or the frequency of sampling. The sampling methods should be reviewed to ensure the validity of the method, as should the ‘alert’ and ‘action’ limits with respect to whether they should be increased or decreased.

16.5 Step 5: Documentation

The RMC system requires that to be effective, a contamination control system has an efficient documentation system. This will ensure that there are documents covering (1) the RMC methods described in the preceding sections of this chapter, (2) the monitoring and sampling procedures, and (3) results from the monitoring and sampling. These should be regularly updated to incorporate changes and fresh data.

Regular reports should be issued to all interested people. These should contain an analysis of the monitoring results and any deviations from the expected results. When 'action' levels are exceeded these should be reported. The actions taken to correct the deviations, or the explanations as to why no action was necessary, should also be documented. 'Alert' levels may be reported, particularly those that are repeated or otherwise unusual. A report of the verification of the RMC system is also required on a regular basis, perhaps yearly.

16.6 Step 6: Staff Training

Training in the principles of risk management is a clear requirement for those in the 'Risk Assessment Team'. However, all efforts to control contamination through risk management will fail if the personnel working in the cleanroom areas are not properly trained. They should be trained to understand how the room functions, and how to behave to minimise contamination. This training should be completed prior to first entry into a cleanroom, and at defined intervals thereafter. Suitable items for course content can be selected from this book.

17

Cleanroom Disciplines

Cleanroom personnel are an important source of cleanroom contamination. Almost all micro-organisms found in a cleanroom come from personnel, and personnel are a major source of particles and fibres. They can also contribute to airborne chemical contamination. It is therefore necessary to ensure that contamination generated and transferred to the product by personnel activities is minimised. This is done through cleanroom disciplines that all personnel (including maintenance and service technicians) should adhere to. However, it should be noted that products manufactured in a cleanroom vary in their sensitivity to contamination, and cleanroom disciplines should reflect this. This chapter sets out methods from which the users can choose those that best reflect the degree of risk associated with their cleanroom. Also, when a cleanroom is about to be opened, management is faced with the tasks of recruiting, training and supervising people to work in the room, It is hoped that this chapter will assist management in these tasks.

17.1 People Allowed into Cleanrooms

People, when walking, produce about 1 000 000 particles ≥ 0.5 μm and several thousand microbe-carrying particles per minute. The more people there are within the cleanroom, the greater the concentration of contamination. It is therefore important that the minimum number of

people, i.e. only essential personnel, are allowed into cleanrooms and management should ensure that this is so.

Because many contamination problems are caused by lack of knowledge, only people trained to work in a cleanroom should be allowed in, and all those personnel who are allowed in should have been formally trained in the various aspects of contamination control. Visitors should be discouraged and only allowed in under the control of a supervisor. If a cleanroom is designed with viewing windows, this will usually eliminate the need for visitors to enter. Special care should be taken with service and maintenance technicians, and their tools and materials. This is discussed at the end of this chapter.

People who enter the cleanroom should not disperse significantly greater amounts of contamination than the normal population. Given below are examples of conditions that can cause more contamination than normal, and may therefore be unacceptable. Acceptability will depend on the degree of susceptibility of the product to the potential contamination and it is up to management to decide what is acceptable in their cleanroom.

The following suggestions contain criteria that can discriminate against some personnel. It should be ensured that any discrimination is neither illegal nor unfair. The list also contains a number of temporary conditions that may be a reason for temporarily assigning personnel to a job outside the cleanroom.

- Skin conditions where unusually large amounts of skin cells are dispersed, such as dermatitis, sunburn or bad dandruff.

- Respiratory conditions such as coughing or sneezing caused by colds, flu or chronic lung disease.
- In a biocleanroom, it may be necessary to screen personnel for the carriage of micro-organisms that could grow in the product and cause spoilage or disease. The suitability of personnel for work in a cleanroom should be considered with respect to the susceptibility of the product to specific types of microbial growth.
- People with allergic conditions, which cause sneezing, itching, scratching, or a running nose, may not be suitable for employment in a cleanroom. Sufferers from hay fever are likely to find relief in a cleanroom because the air filtration system will filter out the allergens responsible.

Such people might therefore be allowed to work in the cleanroom. Some Other people may be allergic to materials used in the cleanroom, such as (a) garments made from polyester, (b) plastic or latex gloves, (c) chemicals used in the cleanroom such as acids, solvents, cleaning agents and disinfectants, and (d) products manufactured in the room, e.g. antibiotics.

Depending on the contamination risk within the cleanroom, some or all of the following suggestions should be brought to the attention of the cleanroom staff so that contamination within the room may be minimised:

- Personnel should have a good level of personal hygiene. They should shower regularly and keep dandruff at bay. They should wash their hair after a haircut to prevent hair landing on the product. In the case of dry skin, they should use skin lotion or moisturiser to replace skin oil that is lacking. This should reduce skin dispersion.
- Materials such as cosmetics, talcum powder, hair sprays, nail polish, or similar materials are not normally allowed in a cleanrooms. Anything added on to the body should generally be considered a contaminant. Cosmetics are a particular

problem in semiconductor manufacturing as they contain a large amount of inorganic ions such as titanium, iron, aluminium, calcium, barium, sodium and magnesium. In the photographic industry, iron and iodine ions may give problems. Other industries, which do not have a problem with specific chemicals, may still experience problems as each application of cosmetics will deposit a large number of particles on the skin (up to 10^9 for particles ≥ 0.5 μm). Some of these will detach in the cleanroom.

- In cleanrooms where airborne chemical contamination is considered to be a problem, personnel should not use personal products, such as perfumes, which give off volatile compounds. Some superficially applied medications that give off volatile compounds may be a problem, as may the prior consumption of certain foods.
- Watches and jewellery are normally not allowed in a cleanroom. If jewellery is allowed, it must be under clothing or gloves. Rings can puncture gloves and harbour contamination. Personnel may be reluctant, for sentimental reasons, to remove their wedding or engagement rings. They may be allowed to keep them on if the skin under the rings and the rings themselves are washed. If the rings are liable to puncture the glove they should be taped over.
- Smokers have been reported to produce more particles from their mouth than the normal population. It may be necessary to ensure that they have not smoked for several hours before entering the cleanroom. It has been reported that taking a drink of water before entering the cleanroom reduces the number of particles given off from the mouth. As can be observed by the smell from smokers, they give off volatile compounds after smoking and this may not be acceptable in cleanrooms where chemical contamination is a problem.

17.2 Personal Items Not Allowed into the Cleanroom

As a general rule, nothing should be allowed into the cleanroom that is not required to support the activities within the room. However, it is up to the management of

the cleanroom to decide what items may cause contamination of the product. Items that should be considered for inclusion in a list of prohibited items are:

- food, drink, sweets and chewing gum;
- cans or bottles;
- smoking materials;
- radios, personnel audio equipment, mobile phones, pagers, etc.;
- newspapers, magazines, books, paper handkerchiefs, paper towels and any other paper products;
- pencils and erasers;
- wallets, purses and other similar items;
- items in pockets, especially when the items are accessible through the cleanroom gown or smock.

Given in Section 19.2 of this book is a list of materials that may be required for manufacturing, but may also be a source of contamination. Some items from that list may be added to the above list.

17.3 Disciplines within the Cleanroom

Within a cleanroom, many rules of conduct must be followed to ensure that products are not contaminated. Management must produce a set of written procedures suitable for their room. It may be useful to have these 'dos and don'ts' posted in the change or production area. Commonly used procedures that may be adopted are given below. Please note that the procedures in the following lists do not cover the choice of cleanroom garments, masks, gloves as these are discussed in Chapter 20.

17.3.1 Air transfer

To ensure that air is not transferred from an area of high contamination to one of lower contamination e.g. the outside corridor to the production room, the following disciplines should be adhered to:

1. Personnel must always come in and out of the cleanroom through change areas. The change area is used not only to change clothing, but also to act as a buffer zone between the outer dirty corridor and the inner clean production area. Personnel should not enter through any other entrance, such as an emergency exit that leads directly from the production area to the corridor, as this will allow contamination to enter directly into the cleanroom, and garments may also become contaminated before entry.

2. Doors should not be left open (Figure 17.1). If they are, air will be transferred between adjoining areas because of general air turbulence. Any difference in temperature, and hence air density, between the adjoining areas will also cause a transfer of air.

3. Doors should not be opened or closed quickly, or air will be pumped from the less clean area to the clean area. Door closing devices may help to prevent this by ensuring that the doors close slowly.

Figure 17.1 Doors should not be left open

4. Doors usually open inwards into the production room and are held shut by the higher pressure. However, to aid the movement of personnel who are carrying materials, some doors are hung to open outwards. Such doors should be fitted with door-closing devices to ensure that the doors are held closed against the pressure (Figure 17.2).

5. Doors without handles will assist in preventing the transfer of contamination on gloves.

Figure 17.2 Door closing device may be used

5. When passing through the doors in an airlock, personnel should ensure that the first door is closed before they go through the next one. Electrical interlocks between entry and exit doors achieve this, but care must be taken to ensure that there is no danger of people becoming trapped in the case of fire or electrical power failure. Indicator lights, which show if the doors are shut, are also used. Pass-through hatches used to pass small items into a cleanroom should be used in a similar way.

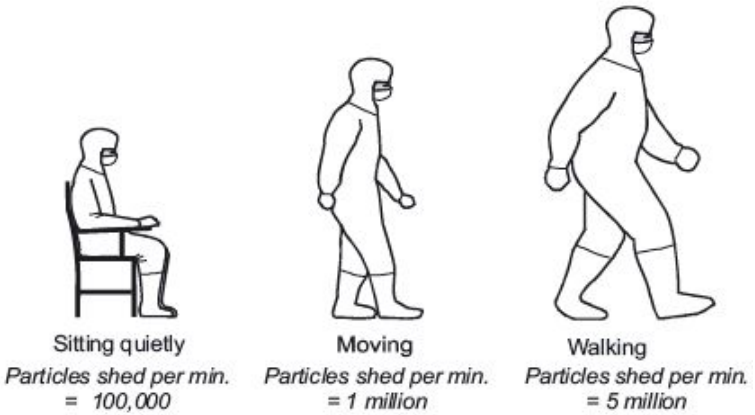
17.3.2 Personnel behaviour

The following suggestions should be considered to ensure that personnel do not contribute to the contamination within the room:

1. Silly behaviour should not be allowed. The generation of contamination is proportional to activity (Figure 17.3). A motionless person can generate about 100 000 particles

≥ 0.5 µm/min. A person with head, arms and body moving can generate about 1 000 000 particles ≥ 0.5 µm/min. A person who is walking can generate about 5 000 000 particles ≥ 0.5 µm/min. Quick movements of personnel can disrupt the unidirectional airflow in a cleanroom and cause higher levels of contamination in the disrupted flow. If people walk close to the open front of a horizontal unidirectional airflow bench, their walking velocity will be higher than the velocity of the air exiting the workstation. They are therefore likely to disrupt the airflow and allow a transfer of contaminated air from the cleanroom into the bench.

Figure 17.3 Particle dispersion in relation to movement



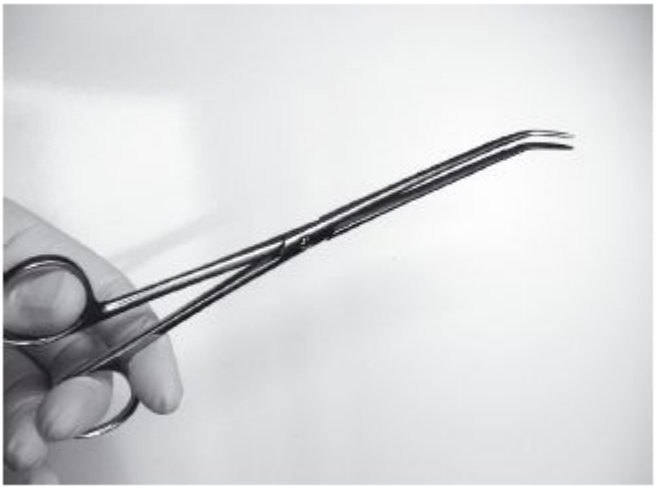
2. Personnel should position themselves correctly with respect to the product, so that contamination does not land on it (Figure 17.4). They should not lean over the product in such a way that particles, fibres or microbe-carrying particles, can fall from them onto the product. If personnel

are working in a flow of unidirectional air, they should make sure that they are not between the product and the source of the clean air, i.e. the air filter. If they are, a shower of particles could deposit onto the product. Methods of working should be arranged to minimise this type of contamination.

3. Consideration must be given as to how products are moved or manipulated. Wherever possible, 'no-touch' techniques should be devised to prevent contamination getting from the hand onto the product. Although gloves are worn in cleanrooms to prevent gross contamination from the skin, they are still likely to be a source of contamination as they may pick up contamination from the wearer's clothing or the cleanroom environment An example of this 'no touch' technique is the use of long forceps to manipulate materials (Figure 17.5). The use of long forceps also enables personnel to position themselves further way from the product so that they are less likely to contaminate the product by airborne transfer.

Figure 17.4 Do not lean over and contaminate the product

Figure 17.5 Forceps reduce contact contamination



Each cleanroom should have its own ‘no-touch’ rules to ensure that the product is not contaminated. Shown in Figures 17.6 to 17.9 are examples of how silicon wafers can be handled in semiconductor areas. These photographs were staged, as it would not be normal practice in a microfabrication facility to handle a silicon wafer except by a vacuum wand, or by robotic means. Figure 17.6 shows the wafer being held by the ungloved hand with the thumb touching the surface.

Oil, chemical and skin particles would contaminate the wafer with catastrophic results. If the wafer is held around the edge of the wafer (Figure 17.7) then contamination is reduced, but can still get onto the surface.

Figure 17.6 Handling with no gloves (very bad technique)

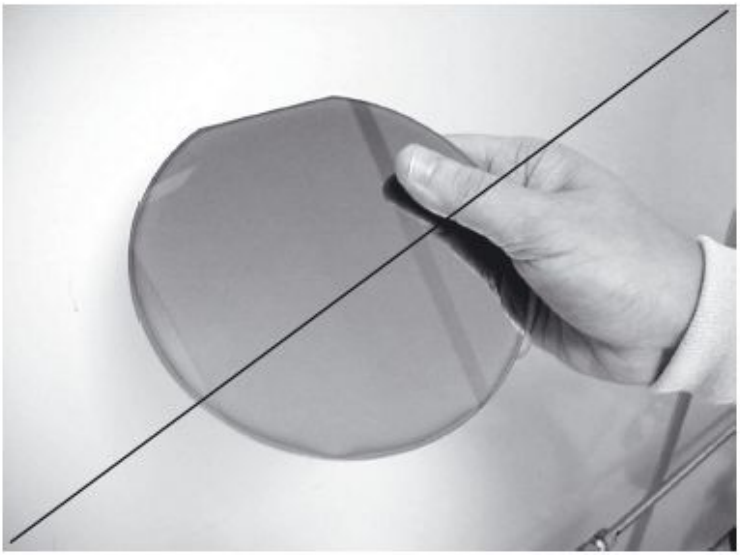
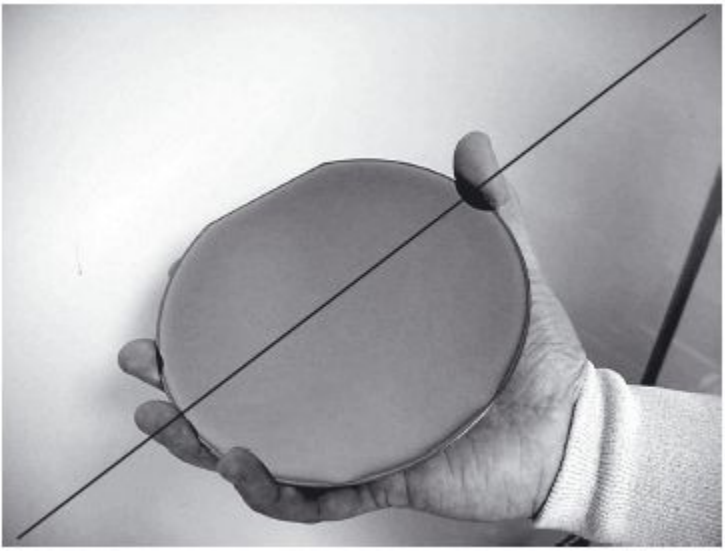


Figure 17.7 Handling at edge without gloves (bad technique)



Use of a glove (Figure 17.8) will reduce contamination yet further, and although this technique is a poor one it is still used where the line widths of a device are large and a low yield acceptable.

Figure 17.8 Handling with gloved hand (poor technique)

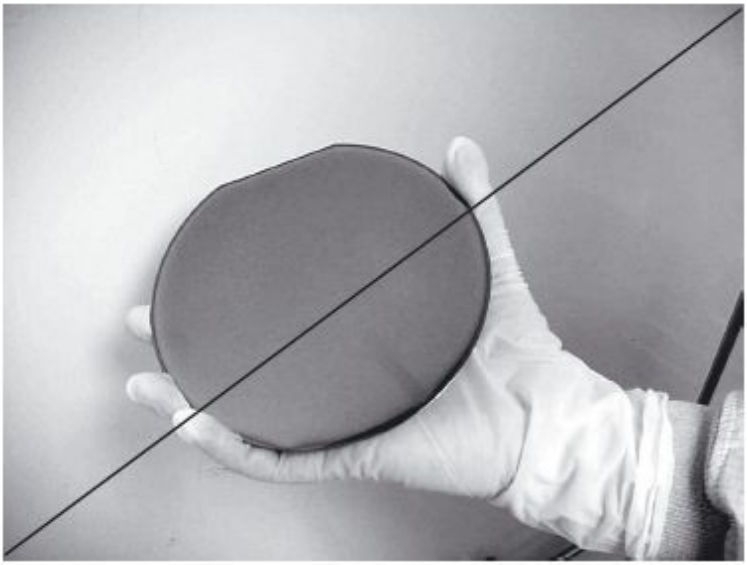


Figure 17.9 Handling with vacuum wand (good technique)

In semiconductor facilities, wafers are handled with a vacuum wand which attaches itself to the back of the wafer (Figure 17.9). Robotic manipulation can also minimise contamination.

Figure 17.10 Do not carry materials next to the body

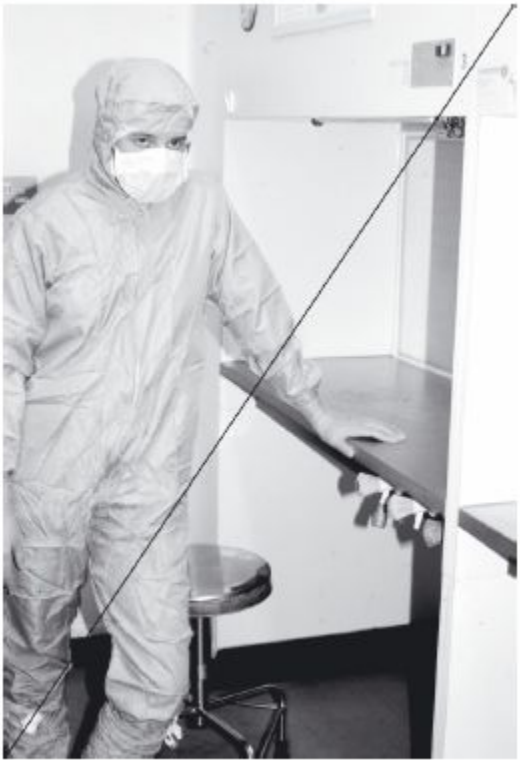
4. Personnel should not carry material against their bodies (Figure 17.10). Although they will be wearing cleanroom clothing, which is much cleaner than indoor or factory clothing, it is not contamination free. Particles, fibres and micro-organisms can be transferred onto the items carried.

5. If gowns or smocks are used as cleanroom clothing, hands should not be placed in trousers pockets and items removed. It is best that there is nothing in the pockets.

6. Personnel should not talk when working over the product, or spittle from the mouth may pass round the imperfect seal between the mask and the skin and contaminate the product Talking, coughing or sneezing can also flex the mask and release contamination from the mask surface. If personnel cough or sneeze, they must turn their head away from the product. Masks are often replaced after sneezing. Masks must be worn over the nose as large particles can be released from the nose when snorting outwards (Figure 17.11).

Figure 17.11 Care should be taken to ensure that the mask covers the nose

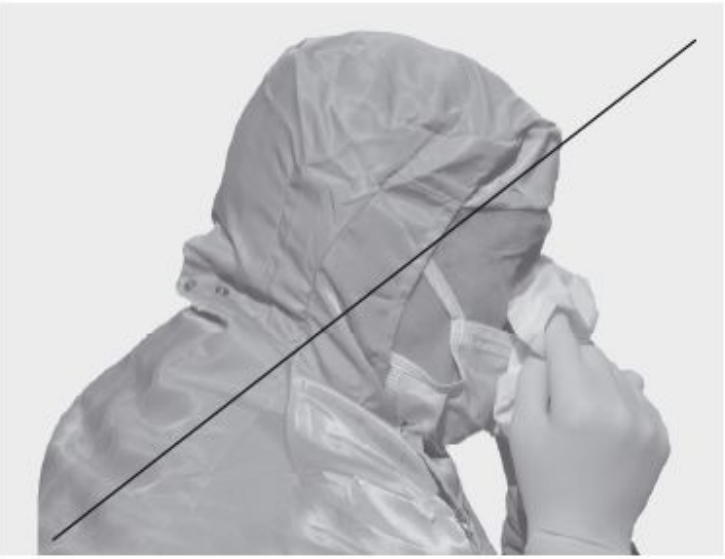
Figure 17.12 Do not touch work surfaces



7. It is generally not good practice for personnel to touch cleanroom surfaces. Although cleanrooms are very much cleaner than areas outside the cleanroom, its surfaces, and those of the machinery and equipment in the room, will have particles, fibres and bacteria on them. Also, if personnel touch their garments or mask, they will pick up contamination on their gloves. This contamination may be transferred to the product. Hands grasped together in front of the body, in the style of a hospital surgeon, will help to ensure that they do not inadvertently touch surfaces.

8. Personal handkerchiefs, whether paper or fabric, should not be brought into cleanrooms (Figure 17.13). These are clearly a major source of contamination and will transfer particles and microbe-carrying particles into the air and onto gloves. Noses should not be blown inside a cleanroom. The change area may be an acceptable alternative area.

Figure 17.13 Do not use a handkerchief



9. Going out of the cleanroom for a drink of water etc. may require a total or partial change of cleanroom apparel.

10. Washing (or disinfection when required) of gloves during use should be considered. Glove washing can be used in cleanrooms where products are handled and there are particular difficulties in keeping gloves clean. In

aseptic pharmaceutical production areas, gloved hands are ‘rinsed' or rubbed with a suitable disinfectant (70% ethanol or iso-propanol) at regular intervals and, always, prior to starting a critical operation. Alcohols are particularly useful in disinfection, as they do not leave a residue on the glove.

11. Do not touch exposed skin on the face.

12. Do not shake hands.

17.3.3 Handling materials

The following suggestions, which refer to the materials used in the cleanroom, should be considered:

- Cleanroom wipers that have low concentration of contamination should be used. The exact type of wiper that is selected will depend on the financial budget and the sensitivity of the product to contamination. It will also be necessary to decide how a wiper should be used. Some additional information is given in Section 22.3.3.
- The movement of materials between the inside and the outside of a cleanroom should be minimised. Every time a product moves out of the cleanroom there is a high possibility of it being contaminated in the lessclean area, and contamination being brought back when it re-enters. It is best to store products in a suitable area within the cleanroom, or in an adjoining clean area which is at the same level of cleanliness.
- It is normal to find that great care has been taken to ensure that a product is not contaminated during its manipulation stages. However, after that, it can often be forgotten and left out in the cleanroom to gather particles. Products that are susceptible to contamination should therefore be kept in closed cabinets, containers, unidirectional airflow benches,

or isolators when they are not being worked on. If the airflow in the cleanroom is unidirectional, storage racks of the type that allow air to flow through are a good choice. Materials should not be left standing on the floor.

- Waste material should be collected immediately into easily identified containers and removed frequently from the cleanroom.
- The cleanroom must be kept neat and tidy. If it is not tidy, it cannot be kept clean.
- Cleanrooms should be correctly cleaned (and disinfected if required). This major topic is discussed in Chapter 22.

17.4 Maintenance and Service Personnel

Through lack of training or supervision, people who enter a cleanroom to maintain or service the machinery can be a considerable hazard. Unless otherwise instructed, maintenance technicians, will apply the same techniques inside the cleanroom as they use outside the cleanroom. Service personnel from outside firms may be completely untrained in cleanroom contamination control techniques. The following is a list of procedures that should be considered for maintenance and service personnel:

- Maintenance and service technicians should only enter a cleanroom with permission.
- Maintenance and service technicians should be trained in cleanroom techniques but, if not, they must be closely supervised when they are within the cleanroom.
- Technicians must wear the same, or equally effective, cleanroom clothing as cleanroom personnel, and use the same techniques to change into cleanroom clothing when entering and exiting cleanrooms. They should never enter the cleanrooms (especially at weekends, or when no one else is around) without changing into cleanroom clothing, although if manufacturing has stopped, the effectiveness of cleanroom clothing could be downgraded a little.

- Technicians should ensure they remove dirty boiler suits (coveralls), etc. and wash their hands before changing into cleanroom clothing.
- Tools that are used routinely for maintaining the cleanroom should be cleaned (and sterilised, if required) and, if possible, kept stored for sole use within the cleanroom. Tools should be made from materials that do not corrode or break up. For example, stainless steel is much preferred to mild steel tools, which may rust.
- If a service engineer brings tools into the cleanroom the tools must be cleaned. A wipe-down with a cleanroom wiper moistened with isopropyl alcohol (often 70%, in water) is a suitable method. Only those tools or instruments that will be needed within the room should be selected, decontaminated, and put into a cleanroom compatible bag or container. This ensures that cases or briefcases, with their associated scraps of paper, fluff etc., which are potential sources of contamination, are not taken into the room.
- Spare parts or items like fluorescent light tubes, which have wrappings, should have the wrappings removed outside the cleanroom and the parts wiped down. Information on the general topic of bringing materials into cleanrooms is given in Chapter 19.
- Written method statements should be kept for each maintenance or testing activity, so that contamination control techniques can be incorporated. These method statements should be adhered to.
- Any instructions or drawings on non-cleanroom paper must not be taken into the cleanroom. They can be photocopied onto cleanroom paper, laminated within plastic sheets, or placed in sealed plastic bags.
- Particle generating operations such as drilling holes, or repairing ceilings and floors should be isolated from the rest of the area. A localised extract or vacuum can also be used to remove any dust generated.
- Technicians should not bring any materials into a cleanroom that are given on the list of prohibited materials in Section 19.1 of this book.

- Technicians must tidy up when they are finished and ensure that the area is then ‘cleanroom cleaned’ by a person with suitable knowledge. Only cleaning agents, materials and equipment that have been approved for use in the cleanroom should be used.

Acknowledgement

I would like to thank Lynn Morrison for posing for the photographs contained within this chapter.

18

Entry and Exit of Personnel

People can disperse millions of particles and thousands of microbe-carrying particles from their skin and clothing. It is therefore necessary for personnel working in a cleanroom to change into clothing that minimises this dispersion.

Cleanroom clothing is made from fabrics that do not break up and therefore disperse the minimum of fibres and particles. Cleanroom clothing also acts as a filter against particles dispersed from peoples' skin and their street or factory clothing.

The type of cleanroom clothing used varies according to the type of cleanroom. In cleanrooms where contamination control is very important, personnel wear clothing that completely envelops them to prevent their contamination being dispersed, i.e. a coverall, hood, facemask, knee-length boots and gloves. In cleanrooms where contamination is not as important, less enveloping clothing such as a smock, cap and shoe covers may be quite sufficient. Information about cleanroom clothing is given in Chapter 20.

Whatever the choice of clothing, garments will have to be donned prior to entering the cleanroom, and in such a way that the outside of the clothing is not contaminated. This chapter describes typical methods.

Some types of cleanroom garment are worn once before being thrown away and others are sent for cleaning and processing, including sterilisation, after being used once. However, in the average cleanroom, garments are normally used more than once. In this case, it is necessary to devise a storage method to minimise the amount of contamination that can be deposited onto them during storage. Possible storage methods are discussed at the end of this chapter.

18.1 Prior to Arriving at the Cleanroom

Poor personal cleanliness is not acceptable in a cleanroom. However, it is not clear how often personnel should bathe or shower, there being little in the way of scientific investigation into this topic. Clearly a shower would be necessary if someone had just had a haircut and was likely to shed hair clippings. It is also known that washing can remove the natural skin oils and, in some individuals, the dispersion of skin and skin bacteria can increase. People with dry skin may wish to use a skin lotion or moisturiser to replace lost skin oils.

Consideration should be given to what clothing is best worn underneath cleanroom garments. Clothing made from artificial fibres, such as polyester, is a better choice than that made from wool and cotton, because synthetic fabrics break up less and disperse far fewer particles and fibres. Close-woven fabrics are also an advantage, as these are more effective in filtering and controlling the particles and microbe-carrying particles dispersed from the skin. Problems from garments under cleanroom clothing will be overcome if personnel are issued with cleanroom undergarments. These should be made from a fabric that is

a) non-linting and b) effective in filtering particles dispersed from personnel.

Personnel should consider whether applying cosmetics, hair spray, nail varnish, etc. at home is necessary, as these may need to be removed prior to entering the cleanroom. They should also consider what rings, watches and valuables they bring to work, as they are likely to be removed and stored. These and other suggestions with regard to staff entering a cleanroom are discussed in Section 17.1.

18.2 Changing into Cleanroom Garments

The best method of changing into cleanroom garments is one that minimises contamination getting onto the outside of the garments. One such method is described below. Some of these procedures may be unnecessary in lower standard cleanrooms, and additional procedures can be introduced in cleanrooms that manufacture products very susceptible to contamination. Alternatives to the proposed method can be used in existing cleanrooms, and are acceptable as long as they give the level of contamination control that is appropriate to the standard of the cleanroom.

The design of clothing change areas is discussed in Chapter 5, where it is explained that the change area is usually divided into zones. These may be separate rooms, or one room divided by crossover benches. Change areas vary in design, but it is common to find them divided into three zones:

(1) pre-change zone,

(2) changing zone,

(3) cleanroom entrance zone.

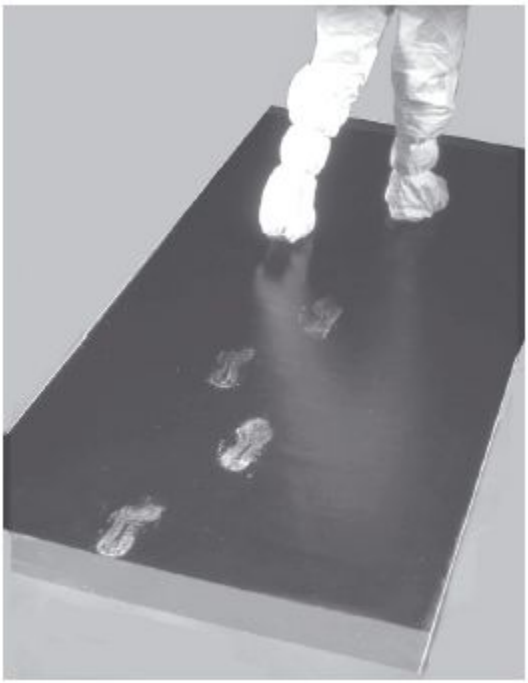
Personnel may move through the zones in the following manner.

18.2.1 Approaching the pre-change zone

Before starting to change into cleanroom clothing, it is best that personnel consider whether they might need to blow their nose. This is not allowed in cleanroom, and if this is done before changing it may save an unnecessary trip out of the cleanroom. Personnel should also consider whether they should go the toilet.

Figure 18.1 Cleanroom shoe cleaner

Figure 18.2 Dycem cleanroom mat



In cleanrooms where outdoor shoes are neither removed, nor effectively covered, shoe cleaners should be used. Cleanroom shoe cleaners are specially made to retain contamination dispersed from the shoe being cleaned and one such type is shown in Figure 18.1.

Sticky cleanroom mats or floorings are often used in the approach to the change room, and sometimes between the change room and the production room. These are specially manufactured for use in cleanrooms. There are two general types. One type is laminated from layers of thin adhesive plastic film and the other from a thick resilient plastic material with sticky properties. Both work by removing

dirt from the soles of footwear as personnel walk over them (see Figure 18.2). After a while they become soiled. In the case of the plastic film version, the topmost layer is peeled off to expose a fresh layer. In the case of the resilient plastic type the surface is washed.

If a laminated mat is used, shoes should be applied to a mat three times to ensure the removal of practically all of the footwear contamination. If the resilient type cleanroom flooring is used, it can cover a floor surface area that is large enough to for a sufficient number of carefully placed footsteps to be taken to ensure effective dirt removal. This is a minimum of three per foot, i.e. six in all.

18.2.2 Pre-change zone

Within the pre-change zone the following tasks may be carried out:

1. Personnel should remove sufficient street or factory clothes to allow them to feel comfortable in cleanroom clothing. If the company provides dedicated clothing to wear under the cleanroom garments, then all street clothing should be removed and replaced with factory garments. Depending on company policy, outdoor boots and outdoor shoes should be removed and cleanroom dedicated shoes put on. The contents of pockets may need to be removed, particularly if gowns (smocks) are worn.

2. Watches, rings and jewellery should be removed. They can harbour dirt, produce chemical and particle contamination, and are liable to tear gloves. Wedding rings that are smooth may be kept on if the ring (and the skin under the ring) is kept clean. Rings that are not smooth can be taped over. Items such as cigarettes and lighters, wallets and other valuables should be securely stored.

3. Remove cosmetics and, if required, apply a suitable skin moisturiser. The moisturiser should not contain chemicals that can cause contamination problems.

4. Don a disposable bouffant hat (mop cap), or hairnet. This ensures that hair will not stick out from under the cleanroom hood.

5. Put on a beard cover, or beard mask, if appropriate.

6. Put on a pair of disposable footwear coverings, or change into dedicated cleanroom shoes.

7. If a hand washing system is located in this area then wash the hands, dry them and, if necessary, apply a suitable hand lotion. However, it is probably best if hands are washed within the change area just before the clean garments are put on (see below). If gloves are used to put on cleanroom clothing, then hand washing can be done here. In areas that have to be microbiologically clean, it will be necessary to wash the hands using a suitable skin disinfectant. Hands can be dried with a nonlinting towel or a hand drier. If a hand drier is used, the best type is one that does not disturb the dirt on the floor. Cleanroom hot-air hand dryers are available, as the type found in ordinary toilets can emit greater than 100,000 particles ≥ 0.5 μm/min.

8. Cross over from the pre-entry area into the change zone. The demarcation between these two zones may be a door or a sit-on crossover bench, or both. A crossover bench ensures that personnel cannot walk between the two zones and enables footwear to be attended to as the bench is crossed. Either dedicated cleanroom shoes can be put on, or disposable plastic overshoes used to cover outdoor shoes. If a bench is not used, then a cleanroom mat or flooring should be used. Personnel should stop at the mat and put their footwear three times to the mat so the minimum of contamination is tracked into the next zone.

18.2.3 Changing zone

Cleanroom garments are put on in this area. Several methods can be used but the following is suggested. This method assumes that a facemask, hood, coverall and overboots are used, but it can be adapted for use with a cap, gown and overshoes. It requires that the garments are put on from the top down.

1. The garments to be worn are selected. If a fresh garment is used, then it should be checked for size and that the packaging is free from tears and faulty heat seals. The packaging is then opened.

2. A facemask and hood (or cap) is put on. It appears to make little difference whether the mask is put under, or over, the hood. Choose which method is the most comfortable. If a hood is put on, the hair must be tucked in and the studs (snaps) or ties at the back of the hood adjusted for comfort.

3. If a hand washing system is installed in this area then the hands should now be thoroughly washed (and disinfected if required). This is possibly the best time for personnel to wash their hands as clean garments will now be handled and contaminated parts of the body, such as hair, face and outdoor clothing, should not be touched again.

4. Gloves, often known as ‘donning gloves’, are sometimes used to prevent the outside of the cleanroom garment being contaminated. Use of these gloves is confined to the higher standard of cleanroom. These should, if required, be put on.

5. The coverall (or gown) should be removed from its packaging and unfolded without touching the floor. It is sometimes possible to get the cleanroom laundry to fold the garment in a way that will minimise both the chance of the garment touching the floor and of the outside surface being contaminated by the personnel’s hands. If this is not done, then the following can be considered.

If a coverall is used, it should be removed from its packing and allowed to unfold without touching the floor. It should be unzipped and turned so that the zip is on the side away from the person.

There are several methods of putting on the garment to ensure that it does not touch the floor. Two examples are as follows:

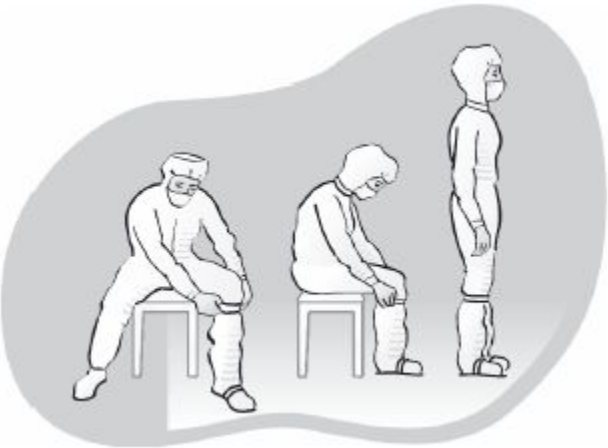
a) One wrist and ankle, along with the zip of the open garment, should be held in one hand and the other side of the garment held in the other hand. One leg, and then the other, is put into the garment without the legs or arms touching the floor. The person's arms can then be inserted and the top of the coverall slipped over the shoulders.

b) The left cuff and left zipper can be taken in the left hand and the right zipper and right cuff taken in the right hand. The coverall legs can then be gathered up by the waist and one leg placed into the garment, and then the other. By releasing one cuff at a time, first one arm and then the other can be placed into the garment.

These methods will work better if the trouser legs have been folded back on themselves during processing in the cleanroom laundry so they are shorter and less likely to touch the floor. The garment should then be zipped to the top, ensuring that the hood (if used) is tucked under the collar. A mirror is useful at this stage. If the garment has press studs (snaps) at the ankles and wrists, then these should be snapped shut.

18.2.4 Cleanroom entrance zone

1. If a crossover bench is available, it should now be crossed over. This bench is used to demarcate the slightly soiled changing-zone from the cleaner entrance zone, and allows cleanroom footwear (overshoes or overboots) to be correctly put on.



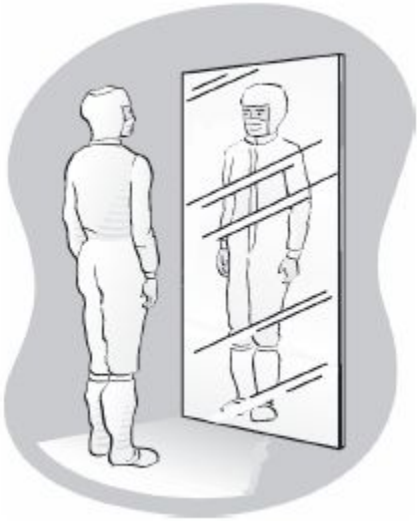
2. Personnel should sit on the bench. One leg should be raised, the cleanroom footwear put on, the leg transferred over the bench and placed on the floor of the entrance zone. Then the other leg should be raised, the cleanroom footwear put on and the leg taken over the bench. While still sitting on the bench, personnel should adjust the legs of the cleanroom garment and the footwear for comfort and security. Personnel should now stand up.

3. If required, protective goggles of the type shown in Figure 18.3 can be put on. These are used not only for safety reasons but to prevent eyelashes and eyebrow hair falling onto the product.

Figure 18.3 Protective goggles

4. The garments should be checked in a full-length mirror to see that they are worn correctly. Check that the hood is tucked in and there are no gaps between it and the coverall (or gown). Check that no hair can be seen

5. If donning gloves have been used, they can now be dispensed with. They can, however, be kept on and a pair of clean gloves put on top. Two pairs of gloves can be used as a precaution against punctures, although sensitivity of touch is lost.



6. If deemed necessary, the hands can again be washed or gloves can also be washed. In a cleanroom that has to be microbiologically clean, it is beneficial to decontaminate the hands by applying an alcohol solution containing a skin disinfectant. Apart from being more efficient, the use of an alcohol solution overcomes the problem of having a washhand basin in the room, with its attendant risk of microbial growth in the drain.

7. Low particle (and if required, sterile) working gloves should now be put on, without the outside of them becoming contaminated. In some cleanrooms this task is left until the person is inside the cleanroom itself. Some gloves may be wrapped in pairs with the cuffs rolled back (in the style used by surgeons); the gloves can then be put on without being contaminated. In this case, the first glove is taken out of the exposed package by gripping the fold of the rolled-over cuff with the one hand and inserting the

other hand into the glove. Two fingers of the gloved hand are then passed under the rolled-over cuff of the second glove and it is lifted from the package. The hand is then put into the second glove, the fingers being slotted into the correct fingers of the glove, and the cuff lifted over the cuff of the cleanroom garment. It is now possible to pull back the cuff of the first glove, making sure that it is completely over the garment's cuff.

8. Many cleanroom gloves are not packed in a way that will allow gloves to be put on without contaminating the glove surface. These gloves must be gripped at the edge of the cuff and put on in a way that is as close as possible to that described above. Gloves packed in pairs will be contaminated less than those packed in 50s or 100s, as it is difficult to remove a glove from a large pack without contaminating those that are left. If considered necessary, the gloves can now be washed or disinfected.

9. Personnel may now proceed into the cleanroom. This may be over a cleanroom mat.

18.3 Exit Changing Procedures

When leaving a cleanroom, personnel will either (i) discard all their garments and on re-entry use a new set of garments (this is the method employed in aseptic pharmaceutical cleanrooms), or (ii) discard their disposable items, such as masks and gloves, and reuse their coverall, smock, etc. on re-entry.

If a complete change of clothing is required on re-entry, then the disposable items such as bouffant hats, gloves, facemask and disposable overshoes are placed in a

container for disposal. If the remainder of the garments are not disposable then they should be placed in a separate container for dispatch to the cleanroom laundry for processing.

If the same garments are to be used again on re-entry, they should be removed so that the outside of the garment is contaminated as little as possible. Cleanroom footwear should be removed, one at a time, at the crossover bench, as each leg is taken over the bench. The coverall should then be unzipped and removed using the hands within the garment to remove it over the shoulder and down to the waist. In a sitting position, one leg is now removed from the garment. The empty arm and leg of the garment should be held so that they do not touch the floor. The other leg can now be removed and the garment stored. The facemask and hood can also be removed.

Garments to be used again on re-entry should be stored to prevent contamination. This can be done in several ways, as follows:

- Each item of clothing can be rolled up. In the case of cleanroom footwear this should be done so that the dirty soles are to the outside. The footwear can now be placed in one pigeon hole, and the hood (or cap) along with the coverall (or gown) into a second one. If considered necessary, the items of clothing can be placed into bags before being put into the pigeon holes.
- The hood (or cap) can be attached to the outside of the coverall (or gown) by means of a snap (stud) and hung up, preferably in a cabinet. The cleanroom footwear can be placed at the bottom of the cabinet. It is best that garments should not touch the wall, or each other. In higher grade cleanrooms, clothing is often hung up in unidirectional

airflow cabinets (see Figure 5.10 in Chapter 5), that are specifically designed to ensure that garments are not contaminated.

- Garment bags can be used. These will have separate pockets for the various clothing items and the bags should be regularly laundered.

Acknowledgements

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19

Materials, Equipment and Machinery

Cleanrooms are built, at great expense, to standards laid down in ISO 14644-1. This ensures that there will be an appropriately low concentration of airborne contamination in the cleanroom to minimise airborne contamination of the product. However, building a cleanroom to the right standard of airborne cleanliness will have little or no effect on items taken into the cleanroom. These items have the potential to contaminate the product through surface contact and the transfer of surface contamination. It is therefore necessary to control the selection, transfer into the cleanroom and use of items such as:

- manufacturing materials, components and packaging;
- machinery and equipment used to manufacture or pack the product;
- tools used for the maintenance, calibration and repair of machinery and equipment;
- clothing for personnel, such as suits, gloves and masks;
- materials for cleaning (and disinfecting where appropriate) the product and cleanroom environment such as wipers, mops, buckets and vacuum cleaners;
- swabs used for cleaning and testing cleanroom surfaces;
- materials used to receive waste and by-products;
- safety apparel and equipment;
- materials used for documentation and record keeping including paper, pens and labels;
- furniture used in the cleanroom such as trolleys (carts), chairs etc.

19.1 Choice of Materials for use in a Cleanroom

Materials and items used during traditional manufacturing in factories without cleanrooms are selected without regard to their potential for causing contamination. If used in a cleanroom, many of these items can cause unacceptable contamination of the product and must be avoided.

Materials used in cleanrooms should not contaminate a product, or the cleanroom environment, the potential contaminants being as follows:

- particles,
- microbe-carrying particles,
- chemicals,
- electrostatic charge.

The type of contaminant that causes problems will vary from cleanroom to cleanroom, and the steps taken to avoid contamination must be tailored to the actual cleanroom; for example some products are only susceptible to microbial contamination, whereas others are vulnerable to particles, chemicals and electrostatic charge. The need to avoid contamination is also related to the quality of the cleanroom, and cleanrooms where products are particularly susceptible to contamination need more stringent control measures than cleanrooms that manufacture less susceptible products.

19.1.1 Materials for production

Depending on the susceptibility of the product to contamination, some or all of the following should be prohibited from a cleanroom:

(1) Items made from wood, rubber, paper, wool, cotton, leather, and other naturally-occurring materials. These should be avoided in most cleanrooms as they will break up during use and shed fibres and particles. Some may leave contaminating chemical residues.

(2) Some metallic surfaces can corrode, and the powdery oxide particles that are produced can spread throughout the cleanroom. Therefore, untreated steel and untreated aluminium should be avoided in most cleanrooms. The use of stainless steel and anodised and hard-anodised aluminium minimises these problems.

(3) Materials that smoke or break up when machined or processed.

(4) The use of powders or abrasives should be minimised. Operations using powders or abrasives may need to be isolated using separative devices such as isolators, fume hoods or mini-environments, and a special clean-up should be carried out each time the operation is performed;

(5) Oils, cleaning fluids and other liquids, if atomised, can travel throughout the cleanroom in the airflow and contaminate products. Aerosolproducing cans are best avoided, as a spray of a few seconds will produce millions of particles ≥ 0.5 μm. Liquids should be dispensed directly onto cleanroom wipers or swabs by using laboratory-squeeze or pump-dispense bottles.

(6) In cleanrooms where products are susceptible to chemical contamination, items that outgas chemicals or have chemicals on their surface should be avoided. In the

semiconductor, disk-drive and nanotechnology industries, uncontrolled exposure to surface chemicals on materials that come into contact with the product, or to chemicals that are outgassed from materials into the cleanroom air and then deposited onto the surface of the product, may cause problems.

(7) In some cleanrooms, products are susceptible to electrostatic discharges. Materials that are unable to continually conduct away an electrostatic charge may cause a problem if the static charge builds up and discharges to an electrically -sensitive product. A static charge may also attract particles to the material, and these particles may cause contamination problems, such as defects in the finished products.

(8) In biocleanrooms, materials that are contaminated with microbes.

The surfaces of some items used in cleanrooms must have an especially low concentration of particle contamination. If they are not supplied free of particles, special cleaning techniques such as ultrasonic baths, or CO_2 icespray methods may be used, depending on the level of cleanliness desired. Rough surfaces should be avoided as they are difficult to clean. For this reason, smooth or polished surfaces are desirable.

Where materials, which would normally be the first choice for manufacture, are identified as contamination sources, substitutes should be found if possible. If substitutes cannot be found, the first choice material may be used, but only in a manner that minimises its potential for

contamination. The associated contamination risks must be identified, and steps taken to control contamination to an acceptable level.

Materials that give rise to unacceptable contamination should be closely controlled within appropriate enclosures, mini-environments or isolators to prevent migration of these contaminants into the surrounding cleanroom.

19.1.2 Cleanroom documentation and labels

Paper and notebooks used in offices and the home should not be used in cleanrooms. Cleanroom-compatible documentation products should be used, including cleanroom paper and notebooks made from plastic-fibre materials. Hard and soft-tipped office pens, as well as pencils and erasers, should also not be used and pens containing cleanroom-grade inks may be necessary in cleanroom where normal inks are a problem. Similarly, labels made from cleanroom-grade substrates will minimise particle dispersion. Tapes that minimise particle deposition, and are manufactured with adhesives that leave a minimum of surface residues, should also be chosen.

19.1.3 Cleanroom equipment and furniture

Equipment and furniture should not be made from fibreboard and similar materials that will break up and disperse fibres and particles, in use or when being cleaned. Such items are best made from electro-polished stainless steel, powder-coated steel or solid plastic. Where cleanroom chairs have soft cushions, these should be of non-shedding impervious flexible plastic and be fitted with

HEPA-filters to prevent the release of particles from inside the cushion into the cleanroom environment.

The choice and location of electronic equipment within cleanrooms should be considered. Many types have cooling fans and the exhaust should pass through a HEPA filter to avoid contaminating the cleanroom. Whenever possible, the air discharge should be below the product work surface to prevent undesirable airflow.

Tool boxes and tools, and other items brought into the cleanroom to maintain the machinery and equipment, should be selected prior to entry, cleaned to minimise contamination, and then kept clean. This is discussed further in Chapter 17.

Provision of storage locations for the clean storage and dispensing of materials used in the cleanroom is important. Certain quantities of materials are needed during production. However, people involved in the operation may be tempted to stockpile excessive quantities in the cleanroom to avoid trips to stockrooms or central supply locations. This includes not only production ingredients and components, but also safety supplies, aprons, gloves and other disposables. This practice should be avoided, whenever possible, to ensure that the storage locations do not become collection points for contamination, or areas that cannot be easily accessed for cleaning.

19.1.4 Cleaning materials

Cleaning materials used in the home, such as paper towels and tissues, should never be used in cleanrooms because of

huge amount of particles and fibres they disperse. Similarly, domestic mops, dusters, and cleaning solutions etc. should not be used. Cleanroom versions of these products are available and discussed in Chapter 22. Cotton-tipped swabs should also never be used in a cleanroom but special cleanroom swabs should be substituted.

19.2 Items Supplied from Outside Manufacturing Sources

Badly contaminated items can arrive in a cleanroom from outside manufacturers and in some instances they may be the single most important cause of contamination of products. Materials manufactured for cleanroom use are normally produced by firms knowledgeable in cleanroom technology. Their products adhere to industry standards and recommended practices, and are manufactured in a way that is compatible with cleanroom requirements. Ideally, they are manufactured in a cleanroom of equal or better classification than that of the cleanroom where they will eventually be used. When materials are a critical ingredient or component of the finished product, it is recommended that the user performs an audit of the supplier. This should be done to ensure that a thorough contamination control program is in place and to set up a useful user-supplier relationship. Sample testing of incoming materials should be done to ensure compliance with specified contamination limits. A proven track record of established manufacturers may reduce or eliminate the need for compliance testing by the user, but this may not be possible for certain items in certain industries, such as the biomedical or pharmaceutical industries.

Materials and items required for cleanroom manufacturing may not have been produced specifically for cleanroom use, and not manufactured in a cleanroom or by people knowledgeable about cleanroom technology. However, some simple suggestions and changes to the manufacturing process may produce useful dividends in minimising contamination. Even if the manufacturer has no cleanroom, a higher level of housekeeping and the use of cleanroom gloves, wipers and non-linting clothing may make a considerable difference to the quality of the product. Attention should also be given to storage and packaging. If the product can be taken from the production machine, and immediately cleaned (if required) and wrapped in suitable clean packaging, the exposure to poor manufacturing conditions is minimised, and this may be sufficient for the purpose required.

The ability to convince a manufacturer to produce a cleanroomcompatible item may not be possible unless sufficient usage can be guaranteed by the user, or group of users. Barring that option, the user may need to choose another product, or be prepared to carefully assess and then minimise the contamination risks when the item is used in the cleanroom. However, many items can be made cleanroom-compatible through special cleaning and packaging techniques. These can be carried out by the user but, where the user is unwilling or unable to do this, cleanroom-product supply companies can provide this service at an additional cost.

Supplies used in the cleanroom, such as cleanroom clothing, cleaning materials and safety supplies, must be monitored to ensure that the correct standard of

contamination control is maintained and no inferior products introduced. Substitutions can be made by the purchasing department in the mistaken idea that they are saving the company money and this should be guarded against. Suppliers of safety supplies are experts in safety equipment but often ignorant of the critical nature of a cleanroom. Any supply changes instigated by the purchasing department should be monitored.

19.3 Wrapping and Transportation of Materials

Proper wrapping of items used in cleanrooms should not only prevent damage during transportation, but minimise product contamination during manufacture in cleanrooms.

If items to be used in a cleanroom are placed in a cardboard box, without any wrapping to protect them against contamination, they will become contaminated with cardboard fibres, as well as polystyrene foam grains, if such protective packaging is used. The surfaces of these contaminated items will then become a contamination source in the cleanroom. Even if the items are put into a clean plastic bag before being placed in a cardboard box, the outside of the plastic bag will be contaminated with fibres and grains. It will then be very difficult to open the bag without getting surface contamination from it onto the inner items. This problem can be overcome by layers of wrapping that are successively cleaned and removed as the items proceed into the cleanroom. This is discussed later.

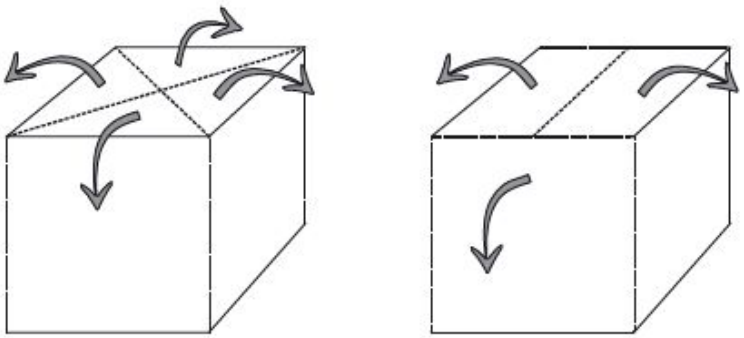
Plastic films and pre-formed containers are the most common materials used for packaging. These are usually lower in particles, fibres and chemical contamination than

many other types of packaging, although they are likely to have some particle, chemical and electrostatic contamination. For example, some plastics can produce an electrostatic charge that may harm the product if discharged to it. Static-dissipative plastic is available. This has the additional advantage of being less likely to attract particles to it, and may therefore be cleaner. Some plastic packaging, such as that made from PVC, which has a high phthalate content to make it pliable, may not be acceptable if outgassing is considered a problem. Consideration should also be given to the way the packaging is applied, or it may trap contamination that may be dispersed when the packaging is removed.

Multiple layers of packaging can help obtain a higher level of cleanliness on the surface of items taken into a cleanroom. Successive layers can be cleaned and removed as the package is taken into the cleanroom and this ensures that the next layer of packaging down is progressively cleaner, and hence the item being taken into the cleanroom arrives much cleaner. Vacuuming and damp wiping of the packaging is a useful method of cleaning the packaging, especially in the initial entry stages. However, as the supplies pass into the cleanroom and the surface of the packaging gets progressively cleaner, it may not be necessary to clean the outside. The number of layers should be considered with respect to the cleanliness level required of the items used in the cleanroom, as well as undue cost and unnecessary waste by-products. The following practical example will illustrate one possible approach.

Small items for use in a cleanroom are manufactured and packed singly in a pre-formed plastic pack. Groups of ten of these single packs are placed into a plastic box with a lid and then vacuum-sealed using plastic film. This box is then sealed into a large plastic film bag that is placed into a cardboard box for delivery. When the cardboard boxes are delivered to the factory where they are to be used, they are stored in an unclassified storage area for eventual cleanroom use. When required, the cardboard box is taken to an area outside the materials transfer airlock and the large plastic bag is taken out, vacuumed with a brush attachment and then wiped with a damp cleanroom wiper. The plastic box is removed from the large plastic bag and passed through the materials airlock using a method described in the next section.

Figure 19.1 Two methods used to correctly remove packaging: ---- edges to be cut



The removal of wrappings should be carried out in such a way as to prevent contamination on the outside of the wrapping getting onto the next layer and finally onto the item for the cleanroom. Two methods are illustrated in

Figure 19.1. These require the carefully cutting of an ‘X or ‘I’ shape across the top to the corners of the package and then down the sides, the peeling of the edges away from the box and the removal of the contents.

The correct method of packaging varies a great deal and depends on the items being packaged, their use, and the design of the materials airlock. It will therefore be necessary for cleanroom management to specify suitable packaging materials and devise a protocol for cleaning and removing the layers of packaging as the required item progresses into the cleanroom.

19.4 Transfer of Items and Small Pieces of Equipment through a Materials Transfer Airlock

A materials transfer airlock is used to transfer materials into a cleanroom. The airlock prevents air entering the cleanroom from less-clean areas outside the cleanroom. A description of an airlock used as a materials transfer area is given in Section 5.2.2. When both sets of airlock doors are shut, the supply air to the airlock dilutes both the contamination that enters when the door from the outside area is open and the contamination that is dispersed by personnel in the airlock. It is common to find that the outer and inner doors of the airlock are interlocked. This is done to ensure that one door cannot be opened until the other one is closed and prevents contamination from the outside uncontrolled area being transferred directly into the cleanroom. Cleanroom mats are often used at the entry to an airlock, and sometimes between the airlock and the cleanroom. These prevent the transfer of contamination on the soles of shoes, and the wheels of trolleys (carts).

The airlock, by itself, does not prevent contamination on the surfaces of materials and equipment from entering the cleanroom. It is the place where the surfaces of items entering a cleanroom are cleaned or decontaminated. Two types of airlocks can be employed to accomplish this, depending on the size of the items being brought in. An airlock with a fixed bench can be conveniently used for transferring small materials and supplies into the cleanroom. However, a bench in the airlock may restrict the entry of larger and heavier items and an airlock without a bench has to be used. Both arrangements are discussed below.

19.4.1 Materials transfer airlock with a bench

Small items can be easily transferred into the cleanroom through a materials transfer airlock containing a bench. The bench divides the airlock into two, with the clean side nearest the cleanroom and the dirtier side nearest the outside area. Items destined for the cleanroom are placed on the bench. The surface of the bench can also be divided into dirty and clean zones, and marked accordingly. To illustrate how such an airlock might work, the same items being transferred into the cleanroom and discussed in the previous section are again considered.

Cardboard boxes, paper and polystyrene foam packaging will cause gross contamination of the airlock and should not be carried into it. The outer bag is removed from the cardboard box, vacuumed, brushed and wiped down with a damp wiper. This is done outside the airlock. It is cut open using a method similar to that illustrated in Figure 19.1 and

the vacuum-sealed box removed. The box is taken into the airlock.

The door between the outer area and the airlock is opened and a person enters by walking over a cleanroom mat. Depending on the classification of the destination cleanroom, an appropriate level of gowning for that person should be considered, such as disposable bootees, hair covering, smock and gloves. The drawings show a person without cleanroom clothing, and this would be appropriate for cleanrooms with higher particle concentrations.

Figure 19.2 Transfer bench is cleaned

The transfer bench is cleaned or, if required, disinfected (Figure 19.2). The vacuum-sealed box is brought into the airlock and placed on the ‘wrapped receiving’ or ‘dirtier’ part of the bench (Figure 19.3).

Figure 19.3 Wrapped items placed on ‘wrapped receiving’ side of bench

The outer plastic wrapping may have had some contamination trans-ferred to it when the outer plastic bag was removed and the plastic vacuum film round the box may be further cleaned and then removed (Figure 19.4).

Figure 19.4 Wrapping removed

The outer plastic wrapping that has been removed is now deposited into a suitable container and the inner item is placed on the ‘wrapping removed’ or ‘clean’ part of the bench (Figure 19.5).

Figure 19.5 Unwrapped item placed on clean side of bench

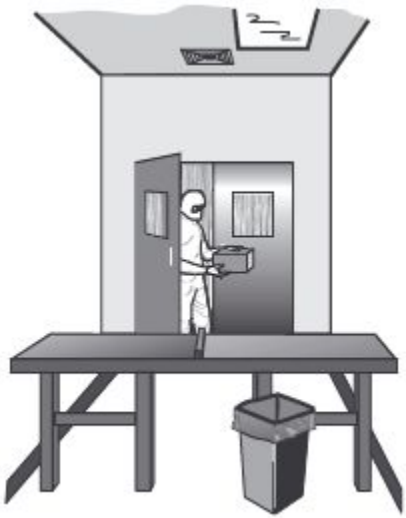
The person who brought in the box from the outside area then leaves and closes the door. The airlock is left for a few minutes to allow the airborne contamination to come down to a concentration that does not significantly affect the cleanroom when the door into it is opened. The time for the airlock to settle down to this concentration can be ascertained by means of tests with a particle counter. This time is then used to set a timer for the door interlocks or the door indicator lights. When the airlock has come down to the required particle concentration, cleanroom personnel can safely enter the airlock and pick up the box to take it into the cleanroom (Figure 19.6).

Figure 19.6 Cleanroom personnel pick up the material

Cleanroom personnel then pass back into the cleanroom (Figure 19.7) and store the plastic box in the cleanroom. When a component is required for manufacture the lid is taken off the plastic box, the component removed, and the lid shut. The preformed packaging containing the component should then be removed.

It should be noted that the passage of personnel through the materials transfer airlock is blocked by the transfer bench, and it is important that signs inside the cleanroom clearly state that this is not an emergency exit and that all personnel fully understand this.

Figure 19.7 Material taken into cleanroom



19.4.2 Materials transfer airlock without a bench

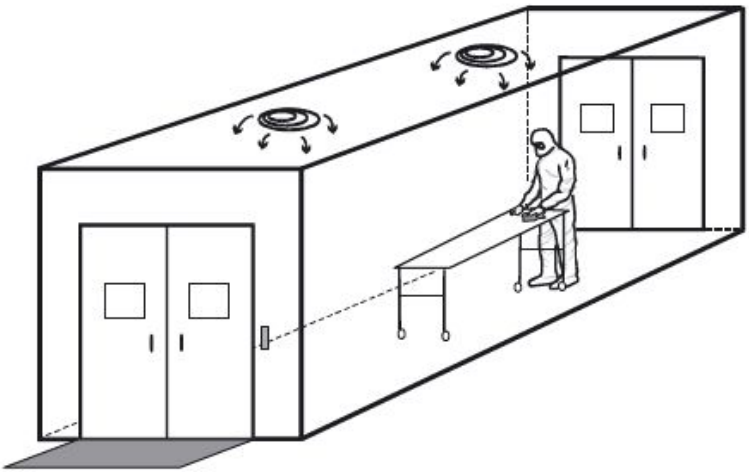
An airlock without a bench is often used when bulky and heavier materials must enter the cleanroom but cannot be carried by personnel. Such items are carried in on a wheeled trolley (cart) that is substituted for a bench. The airlock is likely to be similar to that shown in Figure 19.8.

Wooden crates and cardboard packaging are removed in the outer lessclean area and, where possible, the protective plastic wrap is left intact. The surface of the plastic wrap, or equipment surface, should now be vacuumed, or damp wiped, or both. These larger items are then loaded onto the trolley and taken into the airlock over a contamination control mat. The outer wrapping is again wiped clean and removed by personnel dressed in the acceptable level of cleanroom clothing. After this is done, they withdraw and

the airborne contamination in the airlock is allowed to drop to a suitable concentration.

Personnel from the cleanroom then enter the transfer area to get the supplies. The final layer of wrapping is now removed and final cleaning performed. If the supplies are heavy and cannot be lifted, the trolley will have to enter the cleanroom and it will therefore have to be cleaned in the airlock before this occurs. If the supplies are not individually heavy, they can be transferred to a cleanroom-designated trolley that has been brought from the cleanroom for this purpose. It may be considered necessary to use a cleanroom mat or flooring to remove the contamination from the wheels of either trolley (cart), as it is pushed into the cleanroom.

Figure 19.8 Materials transfer airlock suitable for a trolley



19.5 Entry of Heavy Machinery and Bulky Items

It is sometimes necessary to take large machines, and other heavy and bulky items, in or out of a cleanroom. A method to do this should be established when the cleanroom is designed and a number of possible methods exist. These are as follows:

1. ensure that the materials transfer airlock is sufficiently large,

2. provide a doorway direct from an outside corridor into the cleanroom,

3. provide a removable panel between the outside corridor and the cleanroom.

4. where the cleanroom has not been designed and constructed using one of the above entry methods, it will be necessary to break through a wall into the cleanroom.

The possible methods that can be used are now explained in detail.

19.5.1 Large materials transfer airlock

A sufficiently-large materials airlock is the best solution for transferring large, bulky items in and out of the cleanroom. It should be designed to be large enough to accommodate every piece of equipment that could possibly be taken into the cleanroom. As discussed in section 19.4, the airlock may be divided into two areas by a bench. If it is anticipated that the entry of a large item is likely to be very infrequent, then a bench system that can be removed and replaced can be used. However, if the bench is

attached to the floor, it should be attached in such a way that it can be easily removed to leave a level surface that will not be an obstacle to the wheels of any carrying equipment. For the same reason, raised doorway thresholds should be avoided. If it is anticipated that a machine or piece of equipment that will be brought into the cleanroom could be taller than the doorway, then a removable panel above the doorway should be provided. Such a panel may also be required in any of the further solutions described in the next three sections of this chapter.

19.5.2 Doorway direct into the cleanroom

A convenient solution for getting machinery and other large items in and out of a cleanroom is to provide a set of double doors to serve as a passageway in the cleanroom wall. The doorway will normally lead directly from the cleanroom to an outside non-cleanroom area and should therefore be secured against casual use. However, locking these doors may present a danger to employees and a legal liability to management in the case of an emergency. Employees must be strongly warned against opening the doors for any reason other than emergency evacuations and alarms should be installed to prevent unauthorized use.

19.5.3 Removable panels

Another method is to use a modular wall system with panels that can be removed from the stud support system to create an entrance. Designed and constructed properly, the panels can be removed and replaced with minimal disruption and contamination risk to the cleanroom. However, the method is less convenient to use, and more

likely to generate contamination than a set of double doors. However, it eliminates the emergency exit problem discussed in the previous paragraph.

19.5.4 Demolition of a cleanroom wall

It is quite common in an established cleanroom to find there is no method provided for the entry of large items such as machines. Sometimes it is possible to get a machine through the changing rooms, but if the materials transfer airlock is too small, it is likely that the changing area will also be too small. In this situation, the cleanroom wall has to be breached. If this must be done, it is best to reinstate the cleanroom wall to incorporate a permanent doorway, or removal panel as the need for a large entry point is unlikely to be a one-time event. The scenario described below makes that assumption.

The demolition of a wall must not be carried out using normal building methods. Instead a discipline must be imposed on the workers to ensure that the method they use minimises contamination.

If cleanroom personnel pass through the demolition area on their way to a cleanroom they are likely to pick up dirt on their feet and clothing and take it into the cleanroom. The closer the demolition area is to cleanroom entry area the more likely this is to occur. The area round the wall to be breached must therefore be isolated and sealed so that no dust escapes. The construction of a dirty corridor to this isolation area, from an area away from the cleanroom, is the best solution. The use of cleanroom mats is helpful in minimizing foot-borne contamination.

Inside the cleanroom, an isolated area must be constructed using cleanroom compatible panels, e.g. plastic films with studding. This structure should be airtight and all seams should be sealed to prevent migration of contamination into the cleanroom. The ceiling air filters within the isolated area should be shut off, or covered, to prevent pressurisation of this area. Air returns should also be covered to prevent contamination entering the air recirculation system. Demolition of the existing wall can now proceed.

Whether the entry of a bulky item requires a full shutdown of manufacturing, or brief periods of stoppage during normal operation of the cleanroom, will be determined by a thorough risk assessment. The demolition of a wall is a very contaminating activity, especially when drywall or other traditional construction materials have been used, and it is advisable to shut down manufacturing operations. However, when this is not possible, demolition and construction activities can coexist with cleanroom operation activities provided proper precautions are observed.

The wall opening is cut and reconfigured for a doorway, or removable panel system. Dismantled wall board, construction blocks, and other particle-generating materials should be put into covered rubbish carts before being taken out of the area. Thorough and frequent cleaning is needed to prevent dirt being tracked into the cleanroom. On completion of the demolition, the floors and walls (permanent and temporary) on the cleanroom side are cleaned and the doors or panel systems for the new entrance point are installed. After installation, the floor and

temporary walls in the cleanroom are thoroughly cleaned again and the air supply terminals and return grilles uncovered. The air is allowed to circulate and the temporary wall system is removed from the cleanroom. The new entrance point is now complete but other steps need to be considered before the machinery can enter the cleanroom and be set to work.

19.5.5 Further considerations for the entry of machinery and bulky materials

The equipment used to lift heavy items into a cleanroom is unlikely to be compatible with cleanroom cleanliness. It must therefore be cleaned, but as this is likely to be difficult, it may be considered better to cover the lifting equipment with clean plastic film that is taped in place.

If a doorway, or removable panel system method, is used in lower quality cleanrooms, it may be acceptable to clean the machines outside the cleanroom, bring them into the cleanroom, shut the opening, thoroughly clean the machinery and the cleanroom, and test the cleanliness of the cleanroom environment. This complete operation is likely to take several days and it is almost impossible to carry out without some contamination of the cleanroom. However, this may be acceptable.

An alternative and more secure method is to erect temporary walls round the doors or panels between the cleanroom and the outside to simulate the characteristics of a permanent airlock. A temporary, airtight airlock that is large enough to enclose the machinery is constructed in the non-cleanroom area outside the entrance point, to act as a

cleaning chamber and airlock. If the entrance point is a removable panel rather than a doorway, a temporary airlock may be built on the inside of the cleanroom to protect the cleanroom when the panel is taken down from the outside.

Appropriately gowned personnel clean the inside of the temporary airlock and the equipment to be brought into the cleanroom. The doors between the airlock and the cleanroom are then opened (or the panel removed) and the machinery or equipment transferred. This is done by appropriately gowned personnel who come from the cleanroom and move the machinery to the required location in the cleanroom. The doors are then closed, or the panels reinserted, and the temporary airlock removed. The machinery and the cleanroom are then thoroughly cleaned and the cleanliness of the cleanroom tested.

19.6 Transfer of Materials through Hatches and Sterilisers

Items for use in a cleanroom can be transferred into cleanrooms by methods other than a materials transfer airlock.

A popular means of transferring small items in or out of a cleanroom is by the use of a pass-through hatch. The actual size of the hatch will depend on the size of the materials that have to be transferred, but the pass-through hatch shown in Figure 19.9 has doors approximately 90 cm by 90 cm and a depth of about 40 cm. The hatch is normally placed at a height that is convenient for personnel of all statures to reach, although in the case of the transfer of heavy items it may be convenient to have it at floor level.

Figure 19.9 Pass-through hatch

Some pass-through hatches are not ventilated but rather rely on the pressure difference between the cleanroom and the supporting area to ensure a small flow of air past the doors in the right direction, i.e. from the cleanroom, through the pass-through hatch and into the support area. The passthrough hatch is used in a similar way to the materials airlock. If an item is passed into a cleanroom, the following transfer method may be used:

- the person outside the cleanroom opens the pass-through hatch door and cleans the hatch;
- a layer of packaging is taken off and the item placed into the passthrough hatch;

- the door is shut;
- the person on the other side of the hatch opens the inner door and removes the item. The item may be cleaned, or another layer of packaging removed if a higher degree of contamination control is required.

It is common to find that the pass-through hatch has an electrical or physical interlock that prevents the two doors being open at the same time, thus preventing an undesirable exchange of air into the cleanroom.

Sterilisers, such as autoclaves and hot air ovens, are used to transfer materials in and out of biocleanrooms. To do this efficiently, double-door sterilisers are used. The door outside the cleanroom is opened and the nonsterile material is loaded into the steriliser. The steriliser then proceeds through its sterilising cycle. After that is complete, the steriliser door into the cleanroom is opened and the sterilised materials removed. Sterilising tunnels are often used where containers are sterilised, usually by dry heat, as they pass slowly from the outside to the inside of the cleanroom.

Acknowledgement

Figure 19.9 is reproduced by permission of Thermal Transfer.

20

Cleanroom Clothing

Large numbers of particles and bacteria are dispersed from the people in a cleanroom. Special clothing is worn to control this dispersion and hence the contamination within the cleanroom.

Figure 20.1 Old operating room clothing

The use of clothing to reduce the dispersion of particle and bacteria originated in hospitals. At the end of the 19th century it was realised that surgeons who inspected patients' infected wounds in hospital wards transferred bacteria-containing pus and blood onto their own clothing. When they moved to the operating room they infected wounds.

To protect the patient's wound during surgery, sterile gowns were used. Figure 20.1 shows an old operating room where the surgeon in the forefront of the picture can be seen wearing a sterile gown over his normal clothes. The addition of a sterile gown was an improvement, but cleanroom clothing has evolved to further reduce contamination. Cleanroom clothing works as follows:

- by being clean (and where necessary sterile) it minimises the transfer of contamination by touch from the surface of personnel's clothing to product,
- by reducing airborne dispersion from personnel and the surface of their cleanroom clothing.

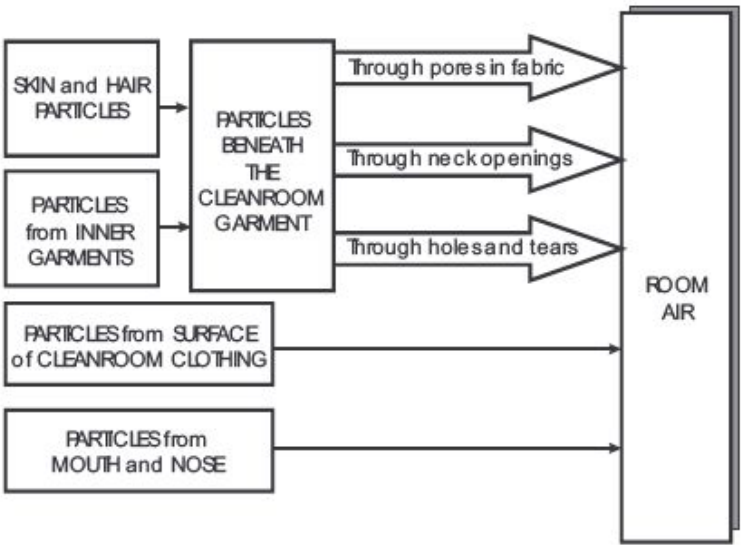
Contamination that is transferred by contact of clothing with the product is minimised by the regular cleaning and processing of cleanroom clothing in special cleanroom laundries. The use of synthetic fabrics, such as polyester, that are inherently 'cleaner' and do not break up like natural materials such as cotton, also helps to reduce the amount of surface transfer of fibres and particles. These topics are discussed later in this chapter. The reduction of airborne dispersion is now discussed, this topic being conveniently considered in two parts, i.e. inert particles and microbecarrying particles.

20.1 Sources and Routes of Inert Airborne Particle Dispersion

The airborne dispersion rate of inert particles, i.e. these not carrying microbes, varies from person to person, and in one person it varies from day to day. Also, the greater the person's activity, the greater the number of particles that are dispersed. Dispersion is dependent on the clothing

worn, but can be in the range of 10^6 to 10^7 particles per minute for particles ≥ 0.5 µm, i.e. up to 10^{10} per day. These particles are dispersed into the cleanroom air and may be deposited onto the product, or onto other surfaces in the cleanroom, from where they can be further transferred onto the product.

Figure 20.2 Sources and routes of airborne particles and microbe-carrying particles dispersed from people



People may disperse particles from the following sources:

- skin,
- hair,
- mouth and nose,
- clothing worn under cleanroom garments,
- cleanroom clothing.

The routes of dispersion of particles are through the following parts of cleanroom clothing:

- pores in the fabric;
- poorly sealed closures at the body (e.g. zips), neck, ankles and wrists
- damage to the fabric, i.e. holes and tears.

The routes and sources of airborne dispersion shown in Figure 20.2 are those that occur when coveralls are worn. However, when coats or smocks are worn, there is no barrier between a person's legs and the bottom edge of the coat and hence contamination is freely dispersed from underneath the garment.

20.1.1 Sources of inert airborne particles and mechanisms of release

The sources of particles dispersed into cleanroom air are listed in the previous section and shown in Figure 20.2. These are now discussed in more detail in relation to their importance and their mechanisms of release.

20.1.1.1 Skin

People shed approximately 10^9 skin cells per day. Skin cells are approximately 33µm × 44 µm in surface area, and between about 3µm and 5µm thick. They are found in the cleanroom either as whole cells or as fragments.

Skin cells may be washed away when bathing or showering, or released onto clothing and then laundered away. However, very large numbers are dispersed into the

air. These skin particles are a major source of airborne contamination.

20.1.1.2 Clothing under cleanroom clothing

What people wear under their cleanroom garments has a large effect on their airborne particle dispersion rate. If the clothing under the cleanroom garments is made from natural fabrics, such as a cotton shirt, cotton jeans or woollen jersey, large quantities of particles will be dispersed. The reason for this is that these natural materials are manufactured from fibres that are short and break up easily.

Figure 20.3 shows a photograph of the structure of cotton and it is not difficult to envisage fragments of the fibres breaking off. These fragments then combine with dispersed skin particles and pass through the outer layer of the cleanroom garment.

Figure 20.3 Cotton fabric photographed through a microscope. Magnification about 100 times

If the inner clothing is constructed from synthetic fabric, the particle challenge from the inner garments can be reduced by 90%, or more. This can be reduced further if the inner garment has good filtration efficiency against skin particles.

20.1.1.3 Cleanroom clothing

The cleanroom industry has placed considerable emphasis on minimising the particles dispersed from cleanroom clothing, i.e. on the non-linting properties of the fabric and on the cleanliness of the clothing. As will be seen from further reading of this chapter, this is sometimes over emphasised. However, natural fabrics, such as cotton, give off an unacceptably high number of particles, and must never be used in cleanroom clothing.

Cleanroom clothing is made from fabrics manufactured from synthetic plastic materials, such as polyester or,

occasionally, nylon which are unlikely to break up, and have been shown to contribute only about 5% of the total number of particles dispersed by a person; the majority of particles coming from a person's skin or inner clothing.

Figure 20.4 A poor cleanroom fabric with large pores (about 80 μm to 100 μm equivalent diameter) between the threads

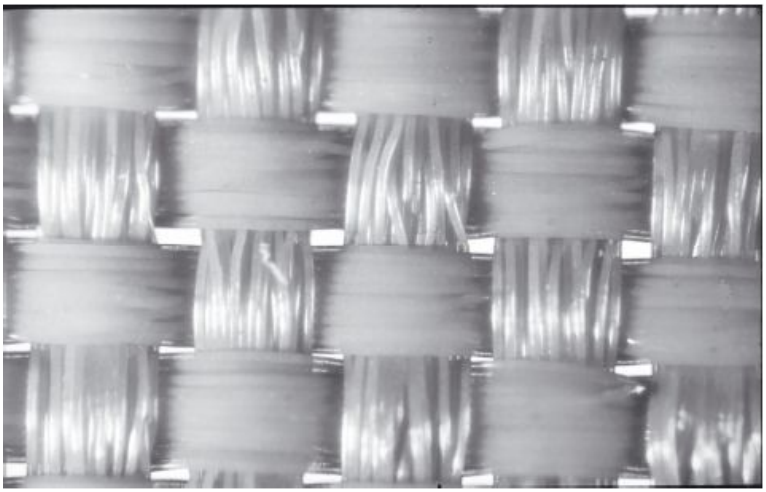


Figure 20.4 shows a photograph of the structure of a synthetic cleanroom fabric. This fabric is relatively ineffective in reducing airborne dispersion because of the large holes or pores between the threads. However, the fabric is woven from threads made from continuous synthetic monofilaments. This ensures that few particles are dispersed from the fabric.

20.1.1.4 The mouth and nose

People disperse particles from their mouth or nose. When people sneeze, cough or talk, they emit particles. Snorting out through the nose also disperses particles. These mechanisms, and the means of preventing them, are discussed in Chapter 21.

20.1.2 Routes of airborne transfer of particles

Although fabrics of the type shown in Figure 20.4 shed few particles by breaking up, they do little to prevent particles passing through them. The pores at the intersection of the threads of the fabric shown in Figure 20.4 are between 80 μm and 100 μm, owing to the monofilaments having a large diameter, and the fabric not being woven tightly. The particles generated from the skin and the inner clothing can therefore pass easily through. It is therefore not a desirable cleanroom clothing fabric. A cleanroom fabric should be manufactured so that it can prevent particles passing through. This is discussed later in Section 20.3.

As people bend, or sit down, or stand up, or move their arms, pressure can build up under their cleanroom clothing. The pressure is greater as the air impermeability of the fabric increases. The particles under the cleanroom clothing may then be pumped out of closures at the neck, ankles and wrists, and other closures such as zips. Secure closures can minimise this, and although they should be tight, they should not be uncomfortable.

20.2 Sources and Routes of Airborne Microbial Dispersion

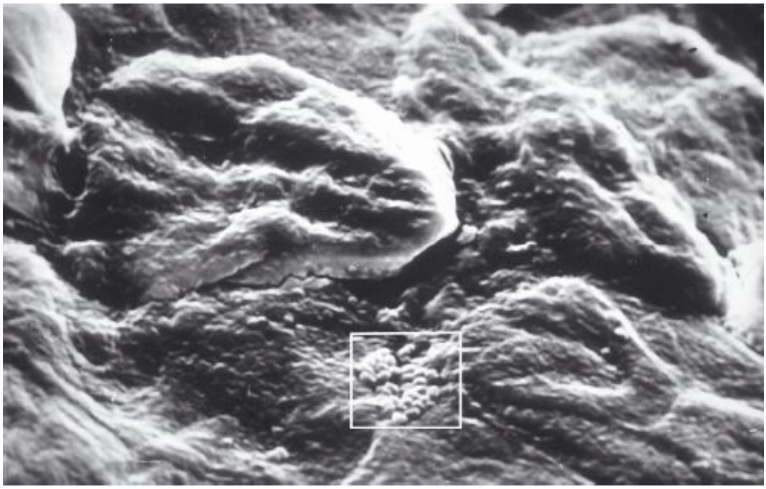
The sources and routes of microbe-carrying particles from people are the same as for inert particles, as shown in Figure 20.2. However, the relative importance of the microbial sources is different.

20.2.1 Sources of micro-organisms

People are normally the only source of micro-organisms in a cleanroom. Almost all of the micro-organisms found in the cleanroom air come from people's skin, although some come from the mouth and nose. Information on dispersion from the mouth and nose is given in Chapter 21.

People shed one outermost layer of epithelial cells every 24 hours. A small but significant proportion of skin cells is dispersed into the cleanroom air with micro-organisms on them. When people wear ordinary indoor clothing, the airborne dispersion rate is about 2500 microbe-carrying particles per minute, this rate being greater in males than in females. Micro-organisms grow and divide on the skin, and can be found as either a small microcolony, or as individual cells. Figure 20.5 shows a microcolony of about 30 bacteria on the skin.

Figure 20.5 Microcolony of bacteria on surface of skin



The majority of skin cells dispersed into the environment do not have micro-organisms on them. On average, about one in ten of the skin cells dispersed have micro-organisms, with an average of about four microorganisms on each of these. The type of micro-organism on airborne skin cells is almost always bacteria, as this is the type of micro-organism found on the skin.

Unlike inert particles, most microbe-carrying particles in cleanroom air come from the skin. Large numbers of inert particles come from the person's inner clothing and small numbers from the break-up of cleanroom clothing but these are not major sources of microbe-carrying particles.

20.2.2 Routes of airborne microbial dispersion

The routes of transfer of microbe-carrying particles through cleanroom clothing are the same as for inert particles as shown in Figure 20.2. These are:

- the pores in the fabric;
- poorly sealed closures at the body (e.g. zips), neck, sleeves and ankles;
- damage to the fabric, i.e. tears and holes.

Microbe-carrying particles are also expelled from the mouth. When a person is breathing, microbial dispersion is too low to be measured, but speaking, coughing and sneezing each produce a significant amount. This is discussed in the next chapter.

Fabrics used for cleanroom garments are more effective in reducing microbial dispersion than reducing inert particle dispersion. The reason for this is that the average size of microbe-carrying skin cells is much larger than that of the majority of inert particles found in the air. Although microbes are small and usually a few micrometres in size, e.g.*Staphylococcus aureus* is about 1 μm, they are rarely found in a unicellular form in cleanroom air. As explained in a previous section, microbes are carried on skin cells that range in size from about 1 μm to over 100 μm, with an average equivalent diameter of about 12 μm. Many of these are nevertheless still small enough to pass through the pores in cleanroom fabrics.

20.3 Types of Cleanroom Clothing

20.3.1 Clothing designs

The most effective type of cleanroom clothing is that which completely envelopes a person. It should also be made from a fabric that has effective filtration properties and secure closures, including those at the waist, wrist, neck and ankle. However, this type of clothing can often be the least comfortable and most expensive.

The choice of clothing will depend on what is being produced in the cleanroom. A poorer standard of cleanroom may use a cap, zip-up coat (smock) and shoe covers (Figure 20.6). In a higher standard of cleanroom, a one-piece zip-up coverall, knee-high overboots and a hood that tucks under the neck of the garment will be typical (see Figure 20.7). A spectrum of designs exists between these two general types of garment. Further information is given in section 20.3.4.

Figure 20.6 Cleanroom garments suitable for a lower standard of cleanroom (note that, depending on the application, gloves and masks may be used)

Although some of the best cleanroom clothing can be 100 times more costly than the most basic, it is important to note that purchasing good clothing can be very cost effective. It is not unusual for an organisation to pay millions of pounds (or euros or dollars) for a new cleanroom that is used by less than ten people. The organisation's buyer may then purchase the cleanroom

clothing in ignorance of its function and refuse to spend a little extra money to buy clothing that will achieve a drop in airborne contamination to match that of the new cleanroom.

Figure 20.7 Cleanroom garments suitable for a higher standard of cleanroom (note that a mask would normally be worn)

20.3.2 Cleanroom fabrics

When choosing a cleanroom garment, the type of fabric used is an important consideration. Useful information about cleanroom fabrics is presented in the IEST-RP CC003. This recommended practice, which is a very informative document on cleanroom clothing, is published by the Institute of Environmental Sciences and Technology and information on where it can be obtained is given in Section 4.

Cleanroom fabrics should be resistant to deterioration through break-up (linting). However, the most important property is their ability to filter the contamination generated from the skin, and from the clothes worn under the cleanroom clothing. The fabric's effectiveness can be assessed by measurement of the air permeability, particle retention, and pore-size. These tests are discussed in Section 20.6.

` Knitted fabrics are considered to be incompatible with cleanroom use, as the instability of the fabric can provide an easy passage for contamination through the pores in the fabric. Cleanroom fabrics are normally woven from nylon and polyester threads, the most common being polyester. This type of clothing is worn, processed in a cleanroom laundry and worn again. The most common weave used to produce cleanroom fabric is a 'plain' weave, as this can be woven more tightly than other weaves in order to provide a more effective barrier. Cleanroom fabrics are often calendered after weaving by being pressed through heated rollers to soften and flatten the filaments; this reduces the

pore size of the fabric, and hence its permeability to particles.

Figure 20.8 shows a fabric made from finer monofilaments of polyester and more tightly woven than the poor fabric shown in Figure 20.4. It is therefore a better particle filter. More tightly woven fabrics made from smaller diameter microfibres are also available. These are even better as long as the closures at the neck, ankles and wrists are able to resist the extra pressure generated by the lower air permeability of these fabrics.

Figure 20.8 Typical construction of a cleanroom fabric

Non-woven fabrics, such as Tyvek, are used as single, or limited reuse, garments. They should be cleaned in a cleanroom laundry prior to use but repeated cleaning is not recommended. They are especially popular for visitors or builders when constructing the room, but are also routinely

used in cleanrooms. Other non-woven fabrics are successfully used in the manufacture of cleanroom garments. Flexible membrane barrier fabrics, such as GoreTex, which uses a breathable membrane laminated onto, or between, synthetic woven fabrics, are very efficient. They are expensive, and hence are normally only used in the higher standard cleanrooms.

The movement of a person generates an air pressure behind the garment fabric, and the tighter the construction the higher the pressure. This results in unfiltered air being pumped out of the closures and therefore closures at the neck, cuffs and bottom of trousers must be secure.

The number of holes and tears in garments must be kept to a minimum or contamination from under the garments will flow through unhindered. Garments should be inspected, both at the laundry and before being put on. Any garments with holes or tears should not be used. Care must also be taken to minimise holes in the garment by means of good construction.

20.3.3 Garment construction

A cleanroom garment should be constructed to ensure that contamination is not generated as a result of the method of garment manufacture. Consideration should be given to the following:

- prevention of the raw edges of the fabric from fraying;
- construction of the edge, jointing and finishing seams to prevent (a) loose threads from frayed edges from being liberated, (b) seam separation, and (c) passage of unfiltered air through needle holes;

- minimisation of contamination, by selecting sewing threads that are made of synthetic, continuous multifilaments and compatible with the fabric cleaning and sterilisation processes to be used;
- minimisation of shedding from zippers, fasteners, shoe soles, and other items used to manufacture garments, which should not chip, break up or corrode. They should be able to stand up to multiple laundering and, where necessary, sterilisation;
- prevention of dirt collecting, there should be no pockets, belts, pleats, darts, hook-and-pile fasteners (Velcro) and other similar dirt collectors;
- minimisation of the collection and shedding of particles by avoiding folded-over collars, folded cuffs, sewn-on emblems, pen tables etc.;
- reduction of contamination from loose cuffs. Elasticised or knitted cuffs are comfortable, and assist donning but are not an effective filtration barrier, and will lose their elasticity and may be a source of contamination.

20.3.4 Choice of garments

Table 20.1 Recommended garment configurations given in IEST-RP-CC003.3

Apparel Type	Air Cleanliness Classes of ISO 14644-1						
	ISO Class 7 and 8	ISO Class 6	ISO Class 5	ISO Class 5 for Aseptic	ISO Class 4	ISO Class 3	ISO Class 1 and 2
Inner suit	AS	AS	R	AS	R	R	R
Hair cover (bouffant)	R	R	R	R	R	R	AS
Woven gloves	AS	AS	AS	NR	NR	NR	NR
Barrier gloves	AS	AS	AS	R	R	R	R
Facial cover	AS	AS	R	R	R	R	AS
Hood	AS	AS	R	R	R	R	AS
Powered head-gear	AS	AS	AS	AS	AS	AS	R
Frock	R	AS	AS	NR	N	NR	NR
Coverall	AS	R	R	R	R	R	R
Two-piece Suit	AS	AS	AS	NR	NR	NR	NR
Shoe cover	R	AS	AS	NR	NR	NR	NR
Boot	AS	R	R	R	R	R	R
Special foot-wear	AS	AS	AS	AS	AS	AS	AS

R = Recommended, NR = Not Recommended, AS = Application Specific

The type of garment used in cleanrooms can vary. Information on the type of clothing that may be worn in different types of cleanrooms is given in the IEST RP-CC-003.3 and shown in Table 20.1.

Information on clothing for pharmaceutical cleanrooms is also given in Annex 1 of the European Union Guidelines to Good Manufacturing Practice (2008 edition). The type of clothing expected in the various grades of pharmaceutical cleanrooms is as follows:

'Grade D [approximately equivalent to ISO Class 8 at rest]*:*

Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn.

Grade C [approximately equivalent to ISO Class 7 at rest]*:*

Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

Grade A/B [approximately equivalent to ISO Class 5 at rest]*:*

Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.'

The FDA Guidance for Industry (2004) recommends:

'gowns are sterilised and nonshedding, and cover the skin and hair (face-masks, hoods, beard/moustache covers, protective goggles, and elastic gloves are examples of common elements of gowns).'

20.3.5 Comfort

Cleanroom clothing can sometimes be hot and uncomfortable, and therefore some thought may be required to maximise comfort. Clothing should be provided in a selection of sizes. If the clothing is reusable it is quite common to have personnel measured and issued with their own clothing. The design of cleanroom garments should also provide closures at the neck, ankles and wrist that are a tight, yet comfortable.

Shoe coverings can cause problems. Simple, thin-plastic shoecoverings can tear, fall off and stick to cleanroom mats. If more substantial shoe coverings are selected, the sole should not mark flooring, or slip on wet floors. It is also important to use a good system of fastening to ensure that the shoes stay securely on.

The thermal comfort of cleanroom garments can be assessed by comfort indexes, such as water vapour permeability e.g. MVTR, and Clo values. However, although these give an indication of comfort, it is best to get your personnel to try the clothing out in your cleanroom. Inevitably, personnel will prefer garments that give the minimum of protection, as they allow high air exchange and are therefore more comfortable. It will be up to management to ensure that contamination control properties are pre-eminent, but a certain amount of trade-off may be necessary.

20.4 Processing of Cleanroom Garments and Change Frequency

20.4.1 Processing

Cleanroom clothing becomes contaminated during use and has to be exchanged regularly for fresh. If disposable clothing is used, it is simply thrown away, although some types can be processed a few times. If clothing is to be reused, then it is usually cleaned in a cleanroom laundry. Other processes, such as antistatic treatment, disinfection or sterilisation, can also be carried out at the time of cleaning by a suitable cleanroom laundry.

Cleanroom laundries are built solely for processing cleanroom garments. A typical cleanroom laundry will have a design similar to that shown in Figure 20.9. There will be a 'soil area' where the garments are received and sorted out to minimise cross-contamination. Shoe covers will be separated. Garments from different cleanrooms should be kept separate to ensure that chemicals, or other toxic contaminants found in one cleanroom are not transferred to the garments of another. This area is also often used for inspection and repair of the garments.

The garments will then be put into a pass-through washer so dirty clothing can be fed into one side of the washer and clean garments emerge into the folding area. The washer will be fed with water that has been processed to purify it. The types of detergent and additive should be considered. For example, anionic detergents may contain sodium ions that are unlikely to be compatible with semiconductor production, and non-ionic surfactants are best. Dry cleaning machines are occasionally used for cleaning cleanroom garments; these machines may present a problem in cleanrooms where outgassing of chemicals is a problem

Figure 20.9 Diagram of a cleanroom laundry

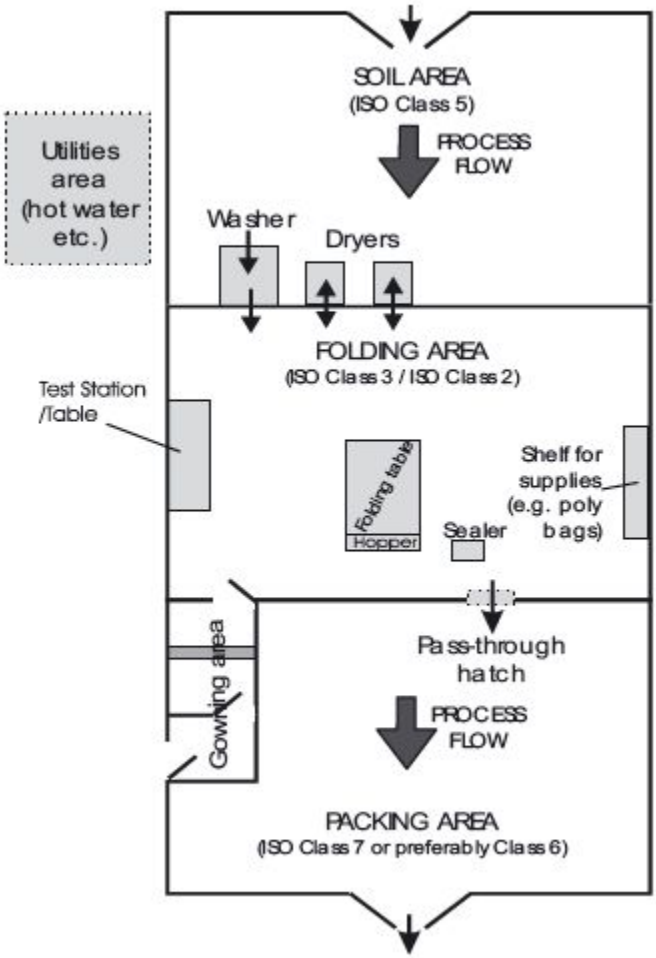


Figure 20.10 Cleanroom laundry showing the washers, tumble dryers and table for folding

When the garments come out of the washing machine they will come into the folding area (see Figure 20.10). They are then loaded into a tumbler dryer that is supplied with filtered air. A tunnel drier may also be used. When dry, the cleanroom garments are inspected for holes or tears, folded and placed in clean bags. These are sealed and passed out of the folding area through a hatch into the packaging area for dispatch.

If clothing is to be free of micro-organisms then the garments must be sterilised or disinfected. Sterilisation, i.e. the killing of all microorganisms, can carried out by heat, gas or radiation methods. None of these methods is completely satisfactory. Autoclaving can cause substantial shrinkage, creasing and accelerated deterioration of the fabric. Sterilisation by ethylene oxide gas is gentler on the

fabric, but its toxicity requires outgassing of the fabric at elevated temperatures, and residuals can give unwanted problems. Gamma radiation is a popular method, although this can cause discolouration of clothing and, in time, a breakdown of the materials. Another approach is to use disinfectants in the wash. This method should not damage the fabric and is more economical. However, it is possible that some micro-organisms may be left on the garment, and hence the method may not be acceptable.

The effectiveness of the cleaning process is normally checked by counting the number of particles on the surface on the processed garments. Samples are usually tested in the folding area (at the test station shown in Figure 20.9). Methods used are described in the IEST-RP-CC-003.

20.4.2 Frequency of change

The frequency of changing of cleanroom clothing varies. One might expect that the more sensitive the process is to contamination, the more frequent the changing will be. However, this is not necessarily so. In the semiconductor industry where the cleanrooms are of the highest specification, clothing may be changed once or twice a week, with no apparent adverse effect in the airborne quality of the room. On the other hand, fresh, sterile garments are put on every time personnel move into an aseptic pharmaceutical production area. Guidance on the frequency of the change of garments in a typical cleanroom is given in the IEST-RP-CC-003.3 and this is shown in Table 20.2.

Table 20.2 Recommended frequency of change of garment according to the IEST-RP-CC-003.3

Class of Room	ISO 7 and 8	ISO 6	ISO 5	ISO 5 for Aseptic	ISO 4	ISO Class 3	ISO Class 1 and 2
Suggested Frequency of Change	2 per week	3 per week	Daily	Per entry	Per entry	Per entry	Per entry

Note: Consideration should be given to the effects of seasonal conditions in some geographical areas. Note that the suggestions made are not based on scientific data but instead reflect collective experience of the Working Group that wrote IEST-RP- CC003.3. Individual requirements for change frequency should be determined on a case-by-case basis.

20.5 The Effect of Laundering and Wear

In terms of particle removal efficiency, a garment is usually at its best when new. As it gets older, the fabric will open up and allow more particles to be pumped through. This will occur in both calendered and uncalendered garments but fabrics that are more heavily calendered are more likely to relax through washing and use, and therefore open up more.

One of my investigations concerned the pore size and particle penetration of two garments when new and after being washed 40 times. One garment was made from a heavily calendered fabric and its pore size increased from 17.2 μm to 25.5 μm but the other identically woven fabric, which was less heavily calendered, only increased from

21.7 μm to 24.6 μm. A similar change in particle penetration was also observed. Clothing from one cleanroom user that was said to have been washed 'hundreds of times' had a pore diameter that increased from 18 μm, when new, to 29 μm. It is clear that the contamination control properties of garments can deteriorate with use and that some fabrics will be worse than others.

There is also a problem with holes and tears in the garments caused by accidents or wear. Garments should be checked at the cleanroom laundry.

20.6 Testing of Cleanroom Clothing

Laboratory testing can assess the contamination properties of different types of clothing. The first type of testing is that of the*fabric.* These tests will ascertain its likely filtration properties and are discussed in the next section. The second type of test is concerned with the performance of the*whole clothing system.* This is usually carried out in a dispersion chamber or body box; further information on this method is given in 20.6.2 and in the IEST-RP-CC-003.

20.6.1 Fabric tests

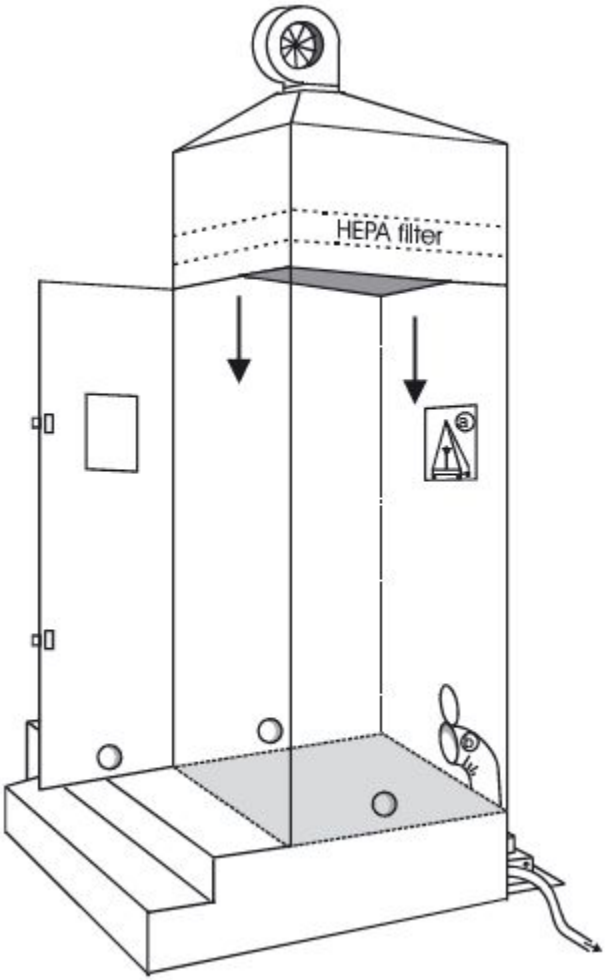
My studies of the contamination control properties of cleanroom fabrics have shown a wide variation in their properties. The equivalent pore diameter varied from 17 μm to 129 μm, the air permeability from 0.02 to 25 ml/s/ cm^2, the efficiency of removal of particles ≥ 0.5 μm from 5% to 99.99%, and particles ≥ 5.0 μm from <1% to 99.99%. This wide variation in the contamination control

properties shows that care should be taken in choosing fabrics.

These laboratory tests identify fabrics that are likely to perform well when made into clothing. However, to compare complete garments, a method that comes close to the real situation in a cleanroom is the body box test.

20.6.2 Dispersal of airborne bacteria and particles

Figure 20.11 Body box: (a) metronome, (b) bacterial and particle sampler



The body box, which I first designed in 1968, is shown in Figure 20.11. Bacteria and particle-free air is supplied through a HEPA filter in the top of the box. A volunteer enters the box wearing the clothing to be studied. After the contamination in the box has been blown out, the volunteer starts to exercise to the beat of a metronome. The number

of particles and bacteria dispersed per minute are then counted. The usefulness of the body box is illustrated by some results.

20.6.2.1 Effect of the garment design on dispersion

Garments should be designed to envelop personnel and prevent the dispersion of contamination. The average number of the bacteria dispersed per minute from a male volunteer in a body box is given in Table 20.3. The person wore normal indoor clothing and then put on different designs of cleanroom clothing made from the same good quality synthetic fabric.

It is clear from these results that the more the clothing envelops the wearer, the better the result. A surgical-type gown worn over a person's everyday clothing will reduce dispersion, but cannot stop the dispersion coming out from underneath it. A shirt and trouser system is more effective, but air will spill out the open neck and trouser legs. The best results are obtained when a coverall with a tuck-in hood and knee-high boots are worn.

Table 20.3 Effect of design on bacterial dispersal rate (counts per minute)

Own clothes	Gown over own clothes	Open-necked shirt and trousers of good fabric	Cleanroom coverall
610	180	113.9	7.5

20.6.2.2 Comparison of clothing made from different fabrics

A comparison was made of a male volunteer wearing his normal indoor clothing and cleanroom clothing. The volunteer wore (a) his underpants only, (b) his normal underpants, shirt, trousers, socks and shoes and (c) different types of cleanroom suits with hood, full-length overboots and latex gloves. The different types of cleanroom suits were made from three fabrics. These were:

1. the poor open fabric shown in Figure 20.5 with a pore diameter of about 100 μm,

2. the tighter fabric shown in Figure 20.9 with a pore diameter of about 50 μm,

3. GoreTex fabric made from a membrane sandwiched between layers of polyester fabric and impermeable to the sizes of particle measured.

A GoreTex suit was also tested with special elasticised closures designed to make an escape of air less likely.

Shown in Table 20.4 is the average number of bacteria dispersed per minute from the male volunteer when he wore different sets of clothing. The greatest dispersion of bacteria occurred when only underpants were worn, but the addition of another filtration layer, i.e. his shirt and trousers, reduced the rate. However, this would not be paralleled for inert particles, unless the clothing was low linting and had good filtration properties. It can also be seen that the poor fabric with large pores reduced bacterial dispersion, but a tight fabric performed even better.

Table 20.4 Bacterial dispersion (counts/min) in relation to fabrics

Underpants	Underpants + shirt + trousers	Open-fabric	Tight fabric	Gore-Tex	GoreTex 'elasticated closures'
1108	487	103	11	27	0.6

As the air permeability decreases, the amount of air pumped out of the garments' closures, i.e. cuffs, neck etc. increases. The difference in pressure inside a Gore-Tex suit with respect to the outside is many times greater than a garment made of a woven fabric. This is reflected in the fact that a higher dispersion rate than expected was found. However, when a Gore-Tex garment with elasticated closures (to minimise air escape) was tested, a further large reduction in bacterial dispersion was achieved. This gave a dispersion rate 170 times less than the open fabric.

The above tests were also carried out to measure dust particles. Shown in Table 20.5 is the particle dispersion per minute.

Table 20.5 Particle dispersion rate per minute in relation to fabric

	Own clothes	Open fabric	Tighter fabric	Gor-Tex	Gor-Tex 'elasticated closures'
Particles ≥0.5 µm	4.5×10^6	8.5×10^5	5.0×10^5	8.2×10^5	3.5×10^4
Particles ≥5.0 µm	1.2×10^4	3550	3810	2260	74

It is interesting to note the general ineffectiveness of cleanroom clothing in preventing the dispersion of small particles (≥ 0.5 μm). If the 'elasticated closures' GoreTex clothing are excluded, it is seen that cleanroom clothing gave only a small reduction in the dispersion of particles ≥ 0.5 μ m (from 10^6/min to 10^5/min). However, these cleanroom garments were much more effective in removing larger (≥ 5.0 μm) particles.

20.7 Static-Dissipative Properties of Clothing

The static-dissipative property of clothing is important in some parts of the cleanroom industry, e.g. in the microelectronics industry where electrostatic charges may destroy micro-circuits. As people move around the cleanroom, the rubbing of their cleanroom clothing against seats and benches, as well as against inner clothing and skin, generates electrostatic charges within the garment's fabric. This static electricity can then discharge to a product such as a microcircuit and destroy it. Cleanroom fabrics are therefore manufactured with continuous threads of conducting material built into the fabric. The following tests can be used to choose clothing that minimises electrostatic discharge:

- the measurement of the resistivity, or conductivity;
- the measurement of the voltage decay;
- the measurement of the voltage produced by a moving person when wearing a garment.

Several methods exist for determining the electrical surface resistance of fabrics. The lower the resistance the better the fabric, as it is assumed that static electricity is more easily conducted away.

The antistatic properties of a fabric may be measured by finding the time it takes for a given static charge to decay from the fabric. This is a better test than measuring electrical resistance or conductivity as it is closer to the practical situation. A known charge is generated on the fabric, and the time for this to reduce to $^{1}/_{2}$ (or $^{1}/_{10}$) of its voltage is determined. Times quoted can vary from less than 0.1 second to over 10 minutes, the shorter time indicating a better fabric.

Shown in Table 20.6 are results published by the British Textile Technology Group, comparing the static charge generated by people wearing garments made of two fabrics. The fabrics were identical except that one had antistatic strips (fabric surface resistivity of 10^{6} ohms/square) and the other fabric was without strips (fabric surface resistivity of 10^{13} ohms/square).

Table 20.6 Body voltage with and without antistatic strips

	Antistatic strips	**No strips**
Resistivity (ohms/square)	10^{6}	10^{13}
Maximum body voltage - person and chair insulated	2500V	3210V
Maximum body voltage - chair earthed and conductive footwear worn	160V	760V

A person wearing a garment made from one of these fabrics got up from a chair and their body voltage was measured when they touched a voltmeter. When the person and chair were insulated from earth, a maximum voltage of

3210 volts was obtained from the standard fabric, and 2500 volts from the fabric with the conductive strips. This is not a very large benefit. However, if the chair was earthed and conductive footwear worn, substantially better results were obtained (see Table 20.6). These results emphasise the need to earth the chair, the person and the clothing. They also show the limitations of conductive strips in fabrics.

Not investigated was the effect of electrically connecting the various items of fabric in a garment. If the various parts of the garment are electrically connected, the conduction of electrostatic charge will be noticeably improved over garments that are conventionally stitched together.

It should be noted that although electricity should be conducted away to minimise static charges on clothing, it should not be conducted to ground so quickly that a large electrical charge might electrocute a person. Conductive materials are those having a surface resistivity of less than 10^5 ohms/square, or a volume resistivity of less than 10^4 ohm-cm, and such materials would allow a dangerous change to go quickly to ground. Insulative materials are those that have a surface resistivity of at least 10^{12} ohms/ square, or 10^{11} ohm-cm volume resistivity, and these materials would be unsatisfactory as they would not allow the static charge on clothing to dissipate. Static-dissipative materials are those having a surface resistivity between 10^5 and 10^{12} ohms/square, or between 10^4 and 10^{11} ohmcm volume resistivity; this resistance should ensure that electrical charges are dissipated but not so quickly that a person could be electrocuted. Materials used in

cleanrooms, including clothing materials, should have a resistivity in this range. It is generally accepted that the surface resistance of a garment system should be about 10^8 to 10^{10} ohms/square to minimise static electricity. Useful information on the problems and solution of static electricity in cleanrooms is given in the IEST-RP-CC022 'Electric charge in cleanrooms and other controlled environments'. Details on how to obtain this document are given in Section 4 of this book.

Acknowledgements

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21

Cleanroom Masks and Gloves

21.1 Cleanroom Masks

People expel large numbers of saliva droplets from their mouth when sneezing, coughing and talking. They may also eject material from their nose when they outwardly snort. These droplets contain oil, salts and microbes, and it is necessary to prevent them causing contamination in the cleanroom. A facemask over the nose and mouth normally does this.

The dispersion of droplets, and the means of controlling them are discussed below.

21.1.1 Dispersion from the mouth

Shown in Table 21.1 are typical numbers of particles and microbecarrying particles that are dispersed by sneezing, coughing and speaking loudly. The number of particles produced by breathing is not reported but is so low that it is difficult to ascertain accurately.

Table 21.1 Number of inert and microbe-carrying particles emitted by a person

	Inert particles	**Microbe-carrying particles**
One sneeze	1 000 000	39 000
One cough	5000	700
Loud speaking (100 words)	250	40

Figure 21.1 shows droplets produced by a sneeze in mid-air frozen in time by high-speed photography. Figure 21.2 shows a lower number of droplets produced by pronouncing the letter 'f'.

Saliva particles dispersed from the mouth vary in diameter from about 1 μm to about 2000 μm. 95% of them are between 2 and 100 μm, with an average size of about 50 μm. Although the count of bacteria in saliva is normally over 10^7 bacteria per ml, not all of the emitted particles will contain bacteria.

Figure 21.1 Particles emitted during a sneeze

Figure 21.2 Particles emitted when pronouncing the letter 'f'

What happens to these expelled droplets and particles depends on their size and hence their rate of drying and settling in the air. If the particles are large, their rate of settling caused by gravitational forces is high, they will fall quickly and they will not have time to dry. Small particles will not fall quickly, but will dry and pass into the air circulation of the cleanroom.

Because of the small amount of dissolved material in saliva, the evaporation of water from the drops of expelled saliva reduces the droplets to about one-quarter to one-seventh of their size. These dried particles, known as droplet nuclei, pass into the air circulation in the room.

The time it takes for particles of water to deposit by gravity can be calculated. A 100 μm particle will drop 1 metre in about 3 seconds, a 50 μm particle will take about 12 seconds, and a 10 μm particle about 5 minutes. It is also possible to calculate the drying time. When the room

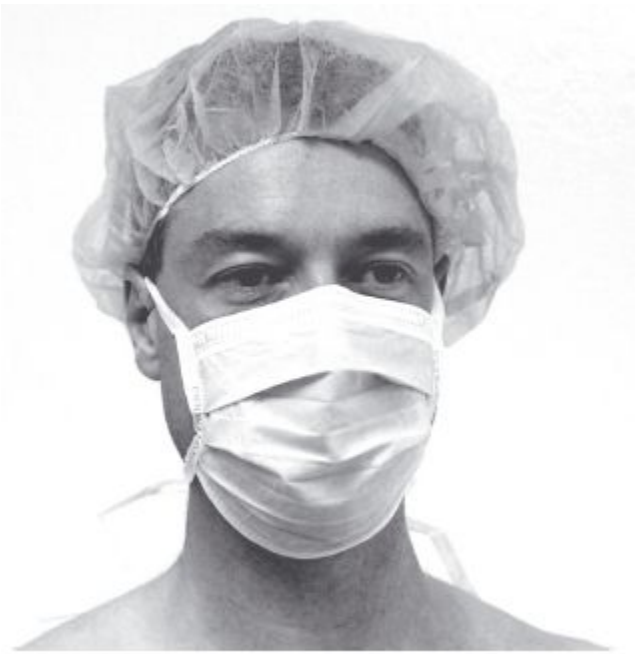
temperature is about 20 °C, particles of water 100 μm in diameter will take about 10 seconds to evaporate, and a 10 μm particle about 0.1 seconds. It can therefore be seen that particles expelled from the mouth must be less than about 100 μm if the water in the particle is to evaporate before they drop onto a product one metre below. It follows that some large droplets of saliva can drop onto products if a facemask is not used.

Many of the particles expelled from the mouth are of sufficient size and inertia to be projected onto the inner surface of a face mask, where they will be easily stopped and retained by a layer of fabric. Efficiencies of over 95% for particles expelled from the mouth are usually obtained by most masks. A loss in efficiency is caused by particles passing round the side of the mask, and much of this is due to small particles (reported to be < 3 μm in the dry state).

21.1.2 Face masks

Masks vary in design, but all are made of some type of material placed in front of the mouth and nose so that when a person is talking, coughing, sneezing, or outwardly snorting, the particles expelled are impacted against it, or removed from the air by filtration.

Figure 21.3 Disposable surgical-style face mask



A common form of mask is the surgical-style with straps and loops, a typical example being shown in Figure 21.3. This one is a disposable type, made from a non-woven fabric, and is thrown away when exiting the cleanroom.

The pressure drop across the mask fabric should be considered. Manufacturers can produce masks that have a very high filtration efficiency against small particles. However, this high filtration efficiency may be unnecessary because (a) the expelled droplets are relatively large and (b) the higher pressure drop across the mask causes the generated particles to be forced round the outside of the mask. The higher pressure drop can be reduced if the masks have a larger surface area of material.

Another type of mask is the ‘veil’ or ‘yashmak’ type, an example of this type being shown in Figure 21.4. Veils can be snapped into hoods, or permanently sewn into the hood at manufacture. Care should be taken to select a material and style that not only controls emissions from the mouth, but is acceptable to personnel.

Figure 21.4 Veil or yashmak type mask as normally worn

Glasses or goggles can provide an additional barrier to skin flakes, eyebrow hair and eyelashes, and prevent them from falling onto critical surfaces (see Figure 18.3 in Chapter 18).

21.1.3 Powered exhaust headgear

Powered exhaust headgear is available that not only provides a barrier to mouth contamination but prevent contamination from the head being dispersed into the cleanroom. Contamination pumped out of the neck closure of the garment will also be controlled. The helmet and face-shield is provided with a filtered exhaust system that draws contamination from the helmet so that contamination does not escape into the cleanroom. An example of such a type of headgear is shown in Figure 21.5.

Figure 21.5 Powered exhaust helmet

21.2 Cleanroom Gloves

21.2.1 Hand contamination control

People's hands have millions of skin particles and bacteria on them, as well as surface oils and salts. To prevent this contamination being transferred to contamination-sensitive products, hand coverings that provide a barrier should be worn.

There are a number of types of hand coverings associated with cleanrooms. Knitted or woven gloves are used in less stringent classes of cleanrooms, i.e. ISO Class 7 and less-clean areas, and are also used as undergloves under other forms of glove to prevent irritation. The knit or weave should be tight and the number of loose threads minimised. This type of glove is not discussed further. Finger cots, which are made from latex or synthetic rubber material, are placed on the tip of a finger and rolled about half way along the finger. They are usually only put on the fingers that touch a surface that should not be contaminated and are generally used in less-critical cleanrooms. These are also not discussed further in this chapter. Barrier gloves, which have a continuous thin membrane covering the whole hand are used in the majority of cleanrooms. This type will be considered in the remainder of the chapter.

21.2.2 Reactions to gloves

Personnel can react unfavourably to cleanroom gloves as they can cause an allergic reaction and contact dermatitis. Latex gloves are a particular problem.

Latex gloves are made from the natural rubber latex collected from rubber trees. The latex contains proteins and some individuals can develop an allergy to latex protein i.e. their body becomes sensitised to latex protein and reacts when it next comes into contact with it. About 5% of the general population is considered to be sensitised to latex but the percentage is much higher in people who regularly come into contact with latex. However, not all

people who are sensitised to latex will develop allergy symptoms.

There are two latex allergies, called Type 1 and Type 4. The Type 1 allergy is the more severe. It will develop as the person becomes more sensitised to the latex protein and the reaction will also become more severe. Itchy red swollen rash, hay fever-like symptoms, and asthma are typical symptoms but anaphylactic shock can occur and even death, although this is extremely rare. The other type of allergic reaction to latex gloves is known as Type 4 allergy and is mainly caused by accelerators used to quicken the formation of latex gloves during the manufacturing process. This type of allergy can also occur in synthetic rubber gloves, such as nitrile and neoprene, when accelerators are used in the manufacturing process. However, rubber gloves are available that are manufactured without the need of accelerators. In the Type 4 allergy the symptoms are a red itchy scaly rash usually found round the wrists and forearms but this may spread. The final type of skin reaction that can occur is 'irritant contact dermatitis'. This is not a true allergy and can occur in other gloves such as vinyl.

Users of cleanrooms should be aware of the possible allergic reaction to latex gloves. Some of the points that need to be considered are as follows:

- are latex gloves necessary for the process because of their higher tactile properties and strength levels, or is an alternative possible?
- latex gloves should be used with low levels of protein and powder (powder can transmit latex protein though the air),

- personnel should be made aware of protein allergy and non-latex gloves made available as an alternative to any staff with a problem.

Avoiding latex allergies may not be the complete solution to hand irritation. Type 4 allergies can still occur when using synthetic rubber gloves such as nitrile, and contact dermatitis can occur through using rubber gloves and other gloves such as vinyl. The use of undergloves may prevent this.

21.2.3 Glove manufacturing process

A number of types of glove are manufactured by dipping a 'former', which has the shape of a hand, into an emulsion or a solution of glove material. Glove formulations used in the manufacture of non-cleanroom gloves can contain about 15 additives that can cause contamination in cleanrooms. Cleanroom gloves should differ from those used domestically by minimising, or not using, some of these chemicals.

Formers are usually made of porcelain, glass or stainless steel. The former is dipped into and removed from the emulsion or solution, and a layer of material allowed to set to form a glove. The glove is then stripped from the former. To allow the gloves to be removed from the former without damage, a release agent is normally employed on the surface of the former. When gloves are removed, they are 'inside out' and the release agent will remain on the outside of the glove unless removed by washing. Release agents may be a problem in cleanrooms, and hence cleanroom gloves differ from domestic ones in that the release agent is kept to a minimum, or an alternative

method used that will minimise undesirable contamination. Such an alternative method can involve washing the gloves to remove the release agent and other additives in the dipping medium. An example of this is the use of magnesium silicate as a release agent in latex gloves made for domestic use. If the magnesium silicate is replaced with calcium carbonate, this powder can be removed from the surface by a mild acid wash. Another way of dealing with the release agent is during stripping. After the gloves have been stripped from the former they may then be turned back 'outside-out' so that the release agent is on the hand side and not on the cleanroom side.

When stripped from the formers, latex gloves are 'sticky'. To correct this, powder is often used but an alternative is the use of a chlorine bath. This is often used with gloves used in the cleanroom. The free chlorine combines chemically with the chemical bonds of the latex and leads to a 'case-hardening' of the surface of the glove. This 'case-hardening' prevents gloves sticking to each other and the washing also helps to clean the gloves.

21.2.4 Glove selection

There are a number of contamination control problems that must be considered when selecting gloves. These are as follows:

1. The gloves may not be sufficiently free of surface contamination, as they may not have been manufactured in a cleanroom, and, even if they have been manufactured in a cleanroom, the manufacturing process is likely to have left contamination. They may therefore require cleaning

before use. Cleanroom gloves should always be selected with regard to their surface contamination and, depending on their use, should be as free as possible of particles, oils, chemicals, and micro-organisms.

2. Gloves can be punctured during use, and this allows contamination to pass through. For example, it has been shown that the number of bacteria coming through a glove when punctured with a 1 mm hole was 7000 from an unwashed hand, and 2000 from a washed hand. Gloves should therefore be sufficiently robust for the purpose for which they will be used.

3. Gloves may be required in some cleanrooms to prevent dangerous chemicals, usually acids or solvents, attacking the operator's hands. An example of this problem is the use of acids in the wet-etch step in semiconductor manufacturing. This should be borne in mind when the glove material is chosen so that materials are chosen that are impervious to the chemicals to be used. Longer, thicker and stronger gloves may also be required to better protect the wearer.

4. Other glove properties that may need to be considered in some cleanrooms are electrostatic discharge properties, surface chemical contamination, heat resistance and outgassing.

It is important to match the potential use of the glove to its material and thickness. You should check with the manufacturer to make sure that the glove fully protects the wearer as well as the product.

21.2.4.1 Polyvinyl chloride (PVC) gloves

These plastic gloves are also known as ‘vinyl’ gloves and are popular in electronic cleanrooms. They give good protection against strong acids and bases, salts, alcohols, amines, peroxides, and water solutions, but are poor for most organics. This type of glove cannot be satisfactorily sterilised, and they are therefore not used in biocleanrooms. They are available in normal and long sleeve-length, and should preferably be long enough to cover the cuff of the garment sleeve. Consideration should be taken of the fact that plasticisers make up almost 50% of a vinyl glove. Plasticisers come from the same group of chemicals that are used to test the integrity of air filters, i.e. phthalates. This material is necessary to make the glove pliable, and has the advantage of giving the gloves antistatic properties. However, it can also causes contamination problems from outgassing and from contact transfer of phthalates onto surfaces.

21.2.4.2 Natural and synthetic rubber gloves

This is the type of glove used by surgeons, and they are traditionally made from naturally occurring latex from the rubber tree. However they are now also manufactured from synthetic rubber, e.g. neoprene and nitrile, which is chemically manufactured. Synthetic rubber gloves are similar to latex gloves and have the advantages of being less likely to produce an allergic reaction and of having a generally better resistance to solvents. They are slightly more expensive than latex.

Surgeon's and domestic gloves are available either powdered or powder-free, but the powder-free is the type used in cleanrooms. These gloves can are washed further by use of filtered, deionised water and used in ISO Class 4 or ISO Class 3 cleanrooms.

Rubber gloves have good chemical resistance, giving protection against most weak acids and bases, and alcohols, as well as having a fairly good resistance against aldehydes and ketones. They are slightly more expensive to buy than the PVC type, but cheaper than many of the other type of polymer gloves. They can be sterilised. Because of their elasticity, they can be securely stretched over the cuff of a garment.

21.2.4.3 Other types of gloves

Polythene gloves are used in cleanrooms and have the advantages of being free of oils and additives, and of being resistant to puncturing. They are not resistant to aliphatic solvents. The main drawback of this type of glove is that they are constructed from float sheets and the seams are welded. Manual dexterity is reduced with these gloves.

Special gloves for heat resistance or insulation from hot surfaces are generally not made for cleanroom use and therefore, when used in cleanrooms, they should be cleaned thoroughly and their contact with contamination-sensitive material minimised.

Other gloves are made from a variety of polymers and have a variety of useful properties. However, inevitably, they may also have some other undesirable properties, one

of which may be expense. Careful evaluation of the cleanliness and the other properties of these gloves must be done before accepting them for use.

21.2.5 Testing of gloves

Information on the properties of gloves and methods used to test gloves is given in the Institute of Environmental Sciences Recommended Practice, RP-CC005. Tests for surface cleanliness include the measurement of releasable particles and extractables. Other tests include chemical compatibility, tensile properties, protection against cuts, abrasion resistance, barrier integrity and resistance to heat, aging, outgassing, static charge, and micro-organisms. These are detailed in IEST -RP-CC005.3

It may be necessary to ensure that gloves are not punctured after use. There are simple methods available for checking for pinholes in gloves. The used glove can be filled with water and checked for leaks. The glove can also be blown up with air (by mouth is sufficient), closed at the cuff, and squeezed; any leaks can be found by passing the glove close to the face.

Acknowledgements

Figures 21.1 and 21.2 are reproduced by permission of the American Association for the Advancement of Science. I should like to thank Douglas Fraser of the Protein Fractionation Clinic for posing for the photograph for Figure 21.3 and Michael Perry of Analog Devices for posing for the photographs in Figures 21.4. Figure 21.5 is reproduced by permission of Pentagon Technologies.

22

Cleaning a Cleanroom

22.1 Why a Cleanroom must be Cleaned

Cleanrooms are used to protect the products of many industries from contamination. Millions of pounds, euros or dollars, as well as years of effort, can be put into designing and constructing a cleanroom, but little thought and effort may go into keeping the room clean.

It may be asked, 'Why does a cleanroom need to be cleaned? Is it not supplied with large quantities of particle and bacteria-free air, and do not workers wear special cleanroom clothing to prevent dispersion of contamination?' In fact, cleanroom clothing, as has been discussed in Chapter 20, does not stop dispersion and a person can disperse, when wearing cleanroom clothing, over 100 000 particles ≥ 0.5 μm and over 10 000 particles ≥ 5.0 μm per minute. Some machines can also disperse millions of particles per minute. Many of the larger particles will easily settle, by gravity, onto horizontal surfaces. Other smaller particles are thrown from the air stream, or deposited by Brownian motion, onto the various surfaces in a cleanroom. Dirt can also be brought into a cleanroom by means of foot-borne transfer, and on materials required for manufacturing.

Cleanrooms surfaces get dirty and must be cleaned. If they are not, contamination may be transmitted to the product when it comes into contact with the dirty surfaces. It can

also be transferred by secondary transfer when personnel touch a cleanroom surface and then the product. Cleanrooms can appear to be clean but can, in terms of cleanroom requirements, be very dirty. In normal light, the human eye will not see a particle much smaller than 50 μm. Small particles will eventually be seen when their concentration builds up and agglomeration occurs. When this happens in a cleanroom, it is long past being acceptably clean.

Within the total number of particles dispersed by people per minute are hundreds, or thousands, of microbe-carrying particles. These are microorganisms carried on skin cells, or fragments of skin cells, and their average equivalent diameter is about 12 μm. They easily settle, by gravity, onto surfaces in the room. In cleanrooms, such as those used by the healthcare industry, the surfaces of the room must be disinfected to kill the micro-organisms.

22.2 Cleaning Methods and the Physics of Cleaning Surfaces

The main force that holds particles to cleanroom surfaces is the Londonvan der Waals force, this being an inter-molecular force. Electrostatic forces can also attract particles to a surface, although the importance of electrostatic forces depends on the type of material used within the cleanroom i.e. whether or not they conduct static electricity. A third force can arise after wet cleaning. Particles that are left on a surface may adhere to it through a bridge of material left when the liquid dries.

If aqueous solutions are used for cleaning, then particles that are watersoluble are dissolved. If solvents such as alcohols are used, then some organic materials may be dissolved. Particles that are soluble are removed in solution. However, the majority of particles found in a cleanroom cannot be dissolved, and the adhesive force that holds particles to a surface must be overcome. Immersing the particle in a liquid, as occurs in wet pick-up vacuuming, damp wiping and mopping, may disperse the particle bridge left after drying. If an aqueous-based detergent is used then the Londonvan der Waals force can be reduced or eliminated. The particle can then be removed from a surface by wiping or mopping.

It is difficult to remove small particles from a surface and the cleanroom industry uses special techniques such as ultrasonic baths and CO_2 ice-spray methods to remove small particles from manufacturing components. However these techniques are not applicable to cleanroom cleaning and cleanroom cleaning techniques described in this chapter are unlikely to remove particles much smaller than 5 μm.

The methods that are generally used for cleaning a cleanroom, are as follows:

- Vacuuming (wet or dry),
- Wet wiping (damp mopping or wiping),
- Picking-up with a tacky roller.

The efficiency of these cleaning methods depends on the surface being wiped. If the surface finish is rough or pitted then it is more difficult to remove particles situated within

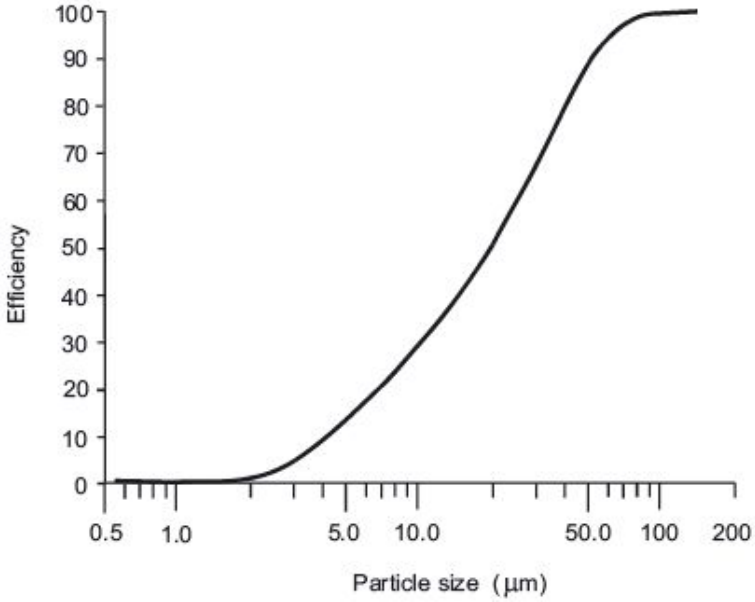
the surface blemishes. Thus, it is necessary for surfaces in a cleanroom to be smooth.

22.2.1 Vacuuming

There are two types of vacuuming method used to clean cleanrooms: dry and wet. Dry vacuuming depends on a high velocity of air moving towards the vacuum nozzle and the force of this air overcoming the adhesion forces of particles to the surface, thus detaching them. However, a vacuum cleaner cannot generate an air velocity that is sufficient to remove small particles.

Figure 22.1 is a graph of results I obtained for the removal efficiency of dry vacuuming of different sizes of sand particle from a glass surface.

Figure 22.1 Efficiency of dry vacuuming



A nozzle of an industrial vacuum was pushed along a surface covered with particles. It may be seen that most of the particles over 100 µm are removed, but smaller particles are inefficiently removed, and at a size of 10 µm only about 25% are removed. This experiment shows that the majority of particles on surfaces are not removed by dry vacuuming, and domestic experience confirms this. How many people would be content to vacuum a vinyl floor and do nothing more? A light-coloured kitchen floor would, in a very short time, be seen to be in an unacceptable condition.

Water and solvents have much higher viscosity than air, so that the drag forces exerted by liquids on a surface particle are very much greater. Therefore, if a wet pick-up vacuum

system is used, the additional drag forces on the particles will substantially increase the collection efficiency.

22.2.2 Damp wiping

Damp wiping, with wipers or mops, can efficiently clean cleanroom surfaces. The liquid used allows some of the particle-to-surface bonds to be broken and particles to float off. This is especially true if a surfactant is used. However, many particles will still adhere to the surface, and the mop or wiper's fibres are needed to push and detach these particles. The particles are then retained in the wiper or mop. A damp wiper is more efficient than a dry one, as the drag forces in the aqueous solution or solvent are much greater and will more efficiently drag particles off the surface. Experience at home with a dry duster and damp cloth confirms this.

Some wipers and mops are more efficient than others. As they work by pushing and dragging particles, the more efficient ones are those that make good contact with particles; for example a wiper made from a fine fibrous material of the right structural density will be more effective than one made from large fibres and either a too dense or too open a structure.

22.2.3 Tacky rolling

Tacky rolling works by rolling a tacky surface over a surface to be cleaned. The particle removal efficiency of tacky rollers is dependent on the strength of the adhesive force of the roller's surface. The greater this force, the more the number of particles that are removed. Other

factors, such as the surface softness of the roller, which allows better contact with the particle's surface, will also influence the removal efficiency.

22.3 Implements Used to Clean Cleanrooms

The implements used in cleanrooms have a similarity to those used for cleaning the home. However, there are important differences. For example, a dry brush should never be used to sweep a cleanroom. I found that these can produce over 50 million particles ≥ 0.5 μm per minute. String mops are not much better, as they can produce almost 20 million particles ≥ 0.5 μm per minute.

Implements used to clean a cleanroom should be made from materials that do not corrode or break-up. Materials commonly used for handles and other solid parts are various types of plastic, stainless steel, and anodised or hard-coated aluminium. Materials used for the cleaning surfaces are usually polyester, PVA, or open-celled polyurethane. If sterilised, the materials must be able to withstand the sterilisation method.

22.3.1 Dry and wet vacuum systems

Dry vacuuming is a popular method of cleaning because it is relatively inexpensive and, because no cleaning liquids are needed, no contaminants are introduced into the cleanroom. However, unfiltered exhaust-air must not pass into the cleanroom. This is achieved by using either a central vacuum source outside the cleanroom, with pipes distributed to the inside of the cleanroom, or by using a portable vacuum with a HEPA or ULPA filter fitted to the

air exhaust. The filter must be placed after the motor to ensure that no particles from the motor are dispersed into the room.

As already explained, a wet vacuum or ‘pick-up’ system is more efficient than a dry vacuum system because of the additional drag forces from the liquid used. It is also generally more efficient than a mopping method, as there is less liquid left to dry on the floor, and hence to contaminate it. Less liquid also means that the floor will dry quicker.

Figure 22.2 Vacuum system being used in its wet pick-up mode

Figure 22.2 shows a cleanroom vacuum system being used in its wet pick-up mode to clean a cleanroom floor. Wet pick-up systems are used on non-unidirectional cleanroom floors, but the use of liquids may not be suitable for the perforated type of floor used in vertical unidirectional airflow systems.

22.3.2 Mopping systems

Cleanrooms are often cleaned with a mop and bucket. Household string mops should never be used as they

contribute a huge amount of contamination. Squeezy-type sponge and other synthetic mops of the type that is bought for use in the home will contribute less contamination when new, but break up through use.

Figure 22.3 Cleanroom sponge-type mop suitable for cleaning surfaces such as walls

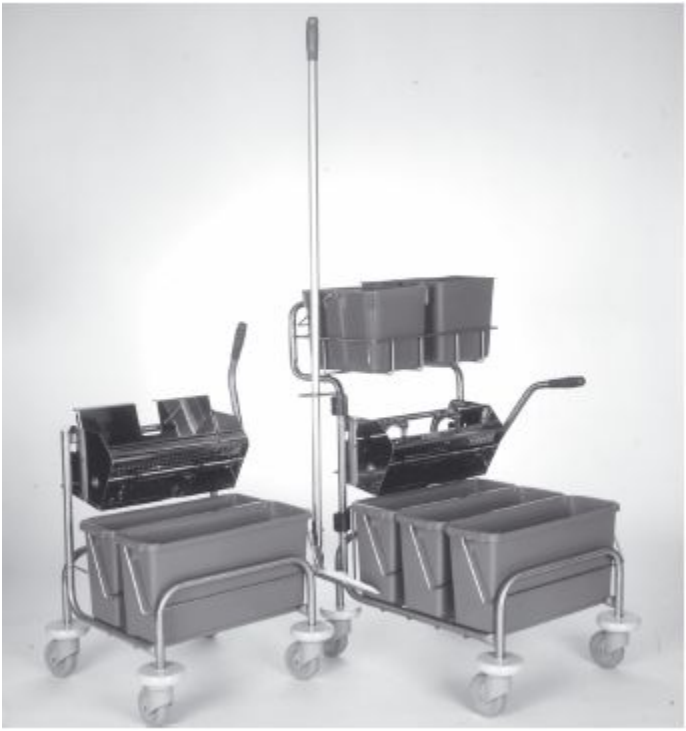
Figure 22.4 Cleanroom mop suitable for floors

Two types of cleanroom mop are shown in Figures 22.3 and 22.4. The cleaning surfaces of these mops are made from materials that do not easily break up. The material can be polyvinyl acetate (PVA), polyurethane open-pore foam, or a fabric such as polyester. The compatibility of the material to sterilisation, disinfectants and solvents should be checked, as some materials are not suitable. Buckets should be made from plastic or stainless steel, the stainless steel type being suitable for sterilisation.

A cleanroom can be cleaned and disinfected by the use of a mop and a single bucket containing water with detergent, or disinfectant. However, the level of cleanliness achieved by this system may not be sufficient for some cleanrooms,

as the dirt taken from the floor is rinsed out into the bucket and reapplied to the floor. Experience in the home tells us that it does not take long before the detergent solution is dirty and the floor is not being cleaned properly. When disinfectants are used, especially chlorinebased ones, the soil contamination may neutralise the disinfectant's effectiveness. Continual changing of the solution goes some way to overcoming this problem, but a greater improvement can be made by using a '2bucket or 3-bucket' system as shown in Figure 22.5.

Figure 22.5 Two and three bucket systems

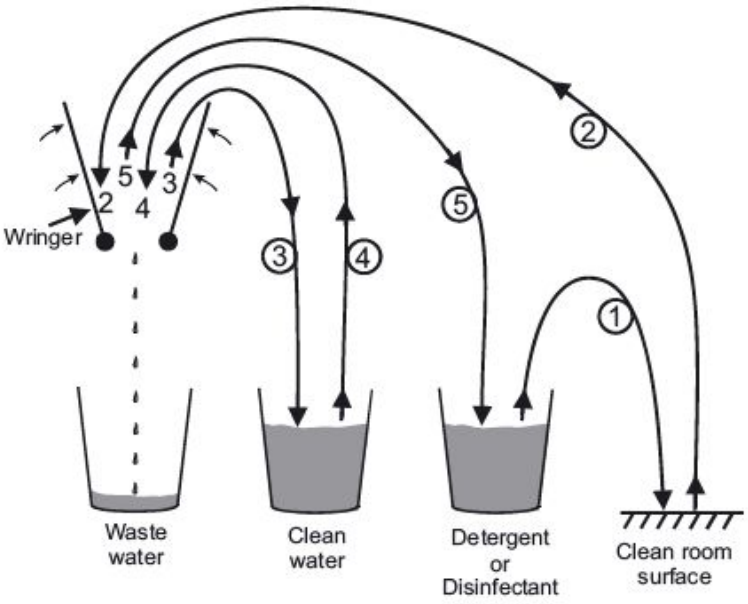


Mop heads, pre-loaded with detergents or disinfectants are another alternative. These are used to clean a predetermined area of surface in the cleanroom. The soiled mop head is then exchanged for a clean one and the soiled one returned to a cleanroom laundry for processing.

Figure 22.6 shows a diagram of a method I suggest for the 2- or 3bucket system. As can be seen, the cleaning or disinfection starts with the mop being dipped into the active solution. The mop can be lightly squeezed to remove excess liquid. The liquid is then spread onto the floor and the floor wiped, or disinfected (stage 1). The mop is then wrung free of most of the dirty water collected in the mop (stage 2), dipped, and rinsed in the clean water (stage 3). The mop is again wrung free of liquid (stage 4) dipped into the active solution (stage 5), and is then ready to carry out the same cycle again (stage 1).

If a 2-bucket system is used, one bucket is filled with active solution and the other with clean water, although an alternative is to use the second bucket for collecting waste liquid. However, the 2-bucket system is not as efficient as the 3-bucket system.

Figure 22.6 How to use a three-bucket mopping system



22.3.3 Wipers

Wipers are dampened (not saturated) with a detergent or disinfectant solution and used in cleanrooms to wipe surfaces and remove contamination. They are also used to wipe contamination from products produced in the room and, when, dry to mop up liquids that may have been spilled. Normal household wipers are not acceptable in cleanrooms as they have a very high concentration of particle, fibre and chemical contamination that is left on the surfaces they clean.

The choice of wiper depends on the contamination problems in the cleanroom. There is no perfect wiper and the selection of a wiper is a compromise. Knowing the use that the wiper has to be put to, the importance attached to

its properties, and the cash available, the best wiper can be selected for the job. The properties of wipers that should be considered are as follows.

22.3.3.1 Sorbency

Sorbency is an important property of wipers, especially when they are used for mopping up spillages and for other similar tasks. The sorbency is the wiper's capacity (the amount of liquid it can absorb in relation to its own weight) and its rate (how fast it can absorb liquid). Sorbency is also important in terms of contamination control, as a wiper with good sorbency will ensure that less liquid is left behind on the surface, and therefore less surface contamination.

22.3.3.2 Wiper contamination

Cleanroom wipers are one of the dirtiest items in a cleanroom. Compared to wipers used in the home they are clean, but a single wiper can contain many times more particles than all the air in the room. It is therefore necessary to choose a wiper that is low in particles. Attention should also be paid to the edges of the wiper, as raw edges can contribute to fibre and particle contamination.

When a wiper is wetted, any material within the wiper that is soluble will dissolve. This may then be transferred onto the surface being wiped. Materials that can be extracted by water, or solvents, are known as 'extractables'. Extractables are particularly undesirable in the semiconductor and similar types of industry. When a low

level of extractables is important, the best wiper for the job should be determined accordingly.

22.3.3.3 Other properties of wipers

Other properties that should be considered are:

- textile strength,
- abrasion resistance,
- static (or antistatic) properties,
- sterility,
- chemical compatibility.

All of the above properties of wipers can be evaluated by the tests suggested in the IEST Recommended Practice RP CC004.

22.3.4 Tacky rollers

Tacky rollers are similar in size and shape to paint rollers used in the home, but they have a tacky material around the outside of the roller. An example of a tacky roller is shown in Figure 22.7.

Figure 22.7 Tacky roller

The roller is rolled over a cleanroom surface in the same way as a paint roller using overlapping passes. The tacky surface of the roller will remove all particles that might otherwise become detached by accidental contact.

22.3.5 Floor scrubbing systems

Floor scrubbing machines that use rotary brushes are available for cleanroom use. The machine has a skirt around the outside of the rotating brushes and an exhaust system to remove particles that are produced by brushing the floor. A high efficiency filter then filters this exhaust along with particles produced by the motor.

22.3.6 Squeegees

Squeegees are used in cleanrooms for cleaning windows and tacky cleanroom flooring.

22.4 Liquids Used in Cleaning Cleanrooms

22.4.1 Cleaning liquids

The ideal cleaning solution for a cleanroom is one that has the following properties:

- non-toxic to people,
- non-corrosive,
- non-flammable, or low flash point,
- fast drying, but not excessively so,
- not harmful to cleanroom surfaces,
- leaves no contamination that is harmful to the product,
- effective in removing undesirable contamination,
- reasonably priced.

No product is satisfactory in all of the above aspects. For example, ultraclean water has many of the listed properties but can promote corrosion on certain surfaces and, without the addition of a surfactant, it is relatively ineffective in cleaning. Some organic solvents also come close to the ideal, but can be flammable, toxic and expensive (consider the toxicity, fire danger and cost of cleaning a whole room with a solvent such as ethanol). The choice of a cleaning agent will be a balanced compromise, the choice of properties being dependent on its required use.

Water used for cleaning should contain a minimal amount of contamination. Many cleanrooms use contamination-free water in manufacturing and this can be

used. Where this option is not available, water as pure as possible should be used e.g. filtered and deionised.

The toxicity, flammability and boiling point properties of various solvents are available from the suppliers, and these will assist in the choice of a suitable solvent. Also available is information on the effect solvents have on materials. Important in the context of cleaning cleanrooms is its effect on plastics, some of which are very vulnerable to solvents. The 'flash point' of the solvent should be considered. This is the temperature at which the solvent will ignite and is often determined by an ignition source 1 cm from the solvent. For example, the flash point of ethanol is 20°C when 20% of the solution is water. Because of their toxicity and flammability, it is difficult to find a good choice of solvent. Alcohols such ethanol and iso-propanol are often used, especially when combined with water to reduce the flammability and increase their disinfecting properties.

Cleaning is often carried out by water containing a surfactant. However, cleaning agents in their household form are often combined with chemicals such as perfumes, sodium chloride, sodium carbonate, sodium metasilicate, tetra-potassium pyro-phosphate, formaldehyde, etc., and such surfactants should not be used. Cleaning agents that are chemically inactive are best.

Most surfactants have a chemical structure of the type shown in Figure 22.8. The molecule has a water-repellent (hydrophobic) part and a waterattracting (hydrophilic) part, and are categorised by the molecular charge on the hydrophobic part of the molecule. On this basis,

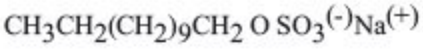
surfactants are known as anionic, cationic, amphoteric and non-ionic types. These four types are shown in Figure 22.8.

The surfactant of choice for cleaning a cleanroom is usually non-ionic, as this is the least reactive of the four types of surfactant and does not contain metallic ions. Anionic surfactants normally contain metallic ions (usually sodium), but it is possible to manufacture them with organic bases and hence avoid the problem of metallic ions. These anionic compounds will still be chemically active and react with chemicals in the wash water or cleanroom environment to produce insoluble chemicals i.e. particles.

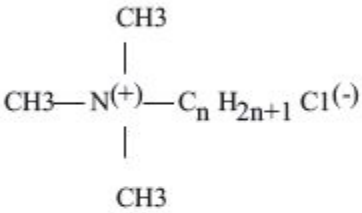
Finally, some thought must be given to particle contamination. When the detergent solution or organic solvent dries, unacceptable particle contamination must not result. The solutions must be therefore free of particles of significant size. This is particularly important in critical areas close to production points, e.g. clean benches, but of less significance in general areas away from the production, e.g. walls, doors and floors.

Figure 22.8 Surfactant compounds

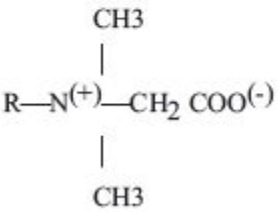
(1) Anionic, e.g. Sodium dodecyl sulphate



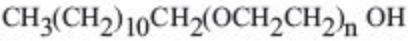
(2) Cationic, e.g. Benzylalkonium chloride



(3) Amphoteric, e.g. Alkyldimethylbetaine



(4) Non-ionic, e.g. Dodecylalcohol ethoxylate



22.4.2 Disinfectants

Disinfectants are used in biocleanrooms to kill micro-organisms on surfaces. Similar problems to those associated with cleaning solutions are experienced. In

addition, disinfectants that are very efficient in killing micro-organisms may not be the best choice in a cleanroom. It is very difficult to produce a disinfectant that is highly toxic to a microbial cell but not to a human cell. It is generally found that these two properties go hand-inhand and the few disinfectants that are effective against microbes, but not toxic, are expensive. It may be best to select the expensive, least-toxic, disinfectants for around the critical area where the product may be contaminated with the disinfectant, but to use less expensive disinfectants in general areas such as floors that are away from the product.

Table 22.1 Properties of disinfectants

	Bactericidal effect				Other properties				
Type of Disinfectant:	Gram +ve	Gram -ve	Spores	Fungi	Corrosive	Stain	Toxic	Active in soil	Cost
Alcohols	+++	+++	—	++	No	No	No	Yes	+++
Proprietary eg chlorhexidine	+++	+++	—	+	No	No	No	Yes	+++
Quats	+++	+	—	++	Yes/No	No	No	Yes	++
Iodophors	+++	+++	+	++	Yes	Yes	No	Yes	++
Chlorine-based	+++	+++	+++	+++	Yes	Yes	Yes	No	+
Phenols	++	+	—	—	No	No	Yes	Yes	+

Quats = Quaternary ammonium compounds. A minus sign shows the disinfectant is likely to be ineffective against the group of microbes given in the table. Effectiveness is indicated by the number of plus signs.

Table 22.1 summarises some of the properties of commonly-used disinfectants. It may be seen from this table that there is no perfect disinfectant. Generally

speaking, phenols, and chlorine-based compounds are less suitable in critical cleanroom areas because of their toxic properties, and iodophors because of their corrosive and staining properties. However, this statement is a general one, as each of the categories in the table has a spectrum of activity that ranges above and below that indicated, and both phenols and chlorine-based compounds are used successfully in cleanrooms. Chlorine-based compounds are a particular problem. They will kill spores, which are generally not killed by other acceptable disinfectants. Therefore, despite being toxic and corrosive, they are used in cleanrooms, although they are not generally used routinely but occasionally e.g. monthly. Quaternary ammonium compounds (Quats), or proprietary disinfectants synthesised to optimise toxicity and disinfection, appear to have fewer problems.

Alcohols are suitable for cleanroom use as they have good bactericidal properties and evaporate to leave practically no residue. The use of 60% or 70% ethanol in water, or 70-100% iso-propanol, is recommended at the point of production, where a minimal carry-over of chemicals is desirable. Incorporation of chlorhexidine, or a similar disinfectant, into the alcohol will increase its effectiveness as a bactericide. The use of a disinfectant such as an alcohol, or an alcohol combined with a proprietary bactericide should be confined, by reasons of expense and fire risk, to the critical area. An aqueous solution of quaternary ammonium compounds, or a phenolic compound, could be used to disinfect the rest of the cleanroom.

Disinfectants are often rotated so that one disinfectant is used for a month, changed to another type for a month, and rotated back to the original one. It is thought that this will prevent microbes becoming resistant to the disinfectant. There appears to be no evidence to support this claim, and it is my opinion that the conditions in a cleanroom make it almost impossible for this to occur. There is a greater chance that a microbe resistant to a disinfectant can be brought into a cleanroom, and hence it is better to choose the best disinfectant that will most effectively kill the widest range of micro-organisms found in a cleanroom, and not rotate it with another disinfectant that must inevitably be less effective. However, microbes that are resistant to the chosen disinfectant may arrive in the cleanroom and this possibility should be monitored.

22.5 How should a Cleanroom be Cleaned?

The method used to clean cleanrooms will vary according to the standard of cleanliness required, and the layout of the room and its ancillary cleanrooms. It is therefore necessary to tailor the cleaning method to the cleanroom. The information in the next few pages should assist in this task. It is also useful to consult IEST RP CC018: 'Cleanroom Housekeeping: Operating and Monitoring Procedures' as well as ISO 14644–5: 'Operations'.

22.5.1 General points

The following general points should be considered when developing a cleaning programme:

1. If you can see any dirt in a cleanroom it is neither a clean room nor a cleanroom and it must be cleaned.

2. It must be understood by those cleaning the room that they are removing particles or micro-organisms that cannot be seen. Although the cleanroom may look clean, it still requires regular and thorough cleaning.

3. To minimise contamination generated by the cleaning process ensure the following:

- the air conditioning is fully functioning and supplying clean air;
- the cleaning staff correctly change into the same standard of cleanroom clothing as the production staff;
- cleaning is not carried out over-actively, as over-activity increases the dispersion of contamination. This coincides with the requirement that cleanroom cleaning has to be more thorough and more efficient than that carried out in the home.

4. Cleaning agents should be diluted in a plastic or stainless steel bucket with distilled, or deionised and filtered water, or with water as clean as can be provided.

5. There is an overlap in the efficiency of cleaning methods but, generally speaking, the cleaning efficiency increases as follows:

Dry vacuuming ⇒ single-bucket mopping ⇒ multiple-bucket mopping ⇒ damp wiping or wet pick-up

6. Cleaning or disinfectant agents should be chosen both for their cleaning efficiency and to minimise the harm to the product. To minimise their contribution to

contamination, they should be used at the lowest concentration that can do the job efficiently.

7. Diluted detergents can support microbial growth, so cleaning agents should be freshly prepared from the concentrated solution immediately before use and never stored in the diluted form. Containers used for handling the diluted agent should not be left about and continually topped up, as there may be bacteria growing in the container. Containers should be thoroughly washed out after each use and left to dry.

8. Bottles with spray nozzles, and aerosol cans, should not be used to apply a cleaning solution or disinfectant to a surface. Tests I have carried out showed that they release several million particles ≥ 0.5 μm with every spray. This may be a danger to the product if the chemical in the spray is a contaminant, and may also temporarily increase the airborne particle counts above the specified concentration. This could cause an alarm condition if the cleanroom is monitored. It is therefore best to use a handpump or squeezy-type of bottle. If a spray must be used, the liquid should be dispensed directly onto a wiper.

9. Where there is 24 hour working, cleaning must be done during production. This is less than satisfactory, but there may be no option. It may be possible to stop production in the surrounding area and cordon it off. This may also remove the risk of people slipping on a wet floor.

22.5.2 Cleaning methods with respect to type of area

Cleaning should be considered in relation to the 'critical', 'general' and 'other' area concept. These areas are as follows:

- The 'critical' zone is the production area where the product is open and exposed to contamination. This is often within an enhanced clean air device.
- The 'general' area of the cleanroom is the area outside the critical zone. Surface contamination in this area cannot directly contaminate the product, but it can be transferred from this area into the 'critical' areas through the air, or by touching surfaces such as walls, tables and floors.
- The 'other' areas are those areas outside the main cleanroom e.g. the materials air lock, changing areas, clean corridors and other ancillary areas.

The critical area should be cleaned the most thoroughly, the general area less thoroughly than the critical area, and the 'other' areas least thoroughly. However, some 'other' areas which produce high concentrations of contaminants, or have a process within the area that is susceptible to contamination may need to be cleaned to a 'general' standard. The time allocated to cleaning a given surface area should also be greatest in 'critical' areas, less in 'general' areas, and least in 'other' areas. It may therefore be useful, especially when cleaning contractors are used, to specify the time that should be spent on cleaning in terms of time per square metre of surface.

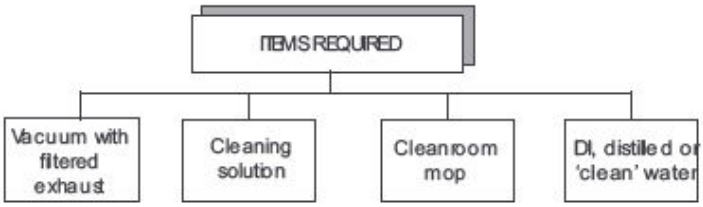
'General' and 'other' areas should be cleaned at a frequency dependent on the standard of the cleanroom but can probably be cleaned prior to, or just after, the work period. This can be done by the staff who normally work in the room, or by cleaning staff, or by contract cleaning staff. Cleaning of the 'critical' areas should be done

frequently. The idea that cleaning should be done only by designated cleaning staff is wrong. Personnel working in the cleanroom are required to clean critical areas at times throughout the day, e.g. prior to the start of producing a fresh batch of product.

22.5.3 Cleaning methods

Shown in Figure 22.9 is a suggested method for cleaning the 'general' and 'other' areas in a cleanroom, and shown in Figure 22.10 is a suggested method for 'critical' areas.

Figure 22.9 Cleaning of 'general' and 'other' areas



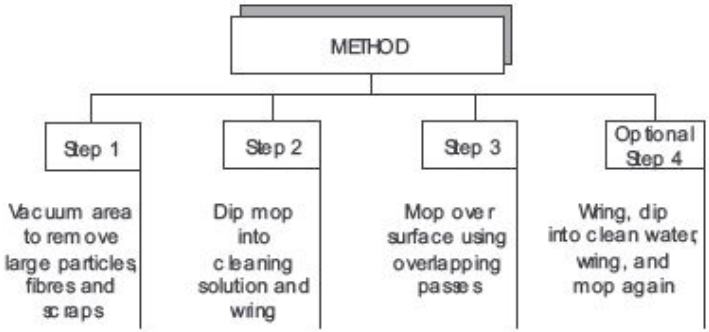
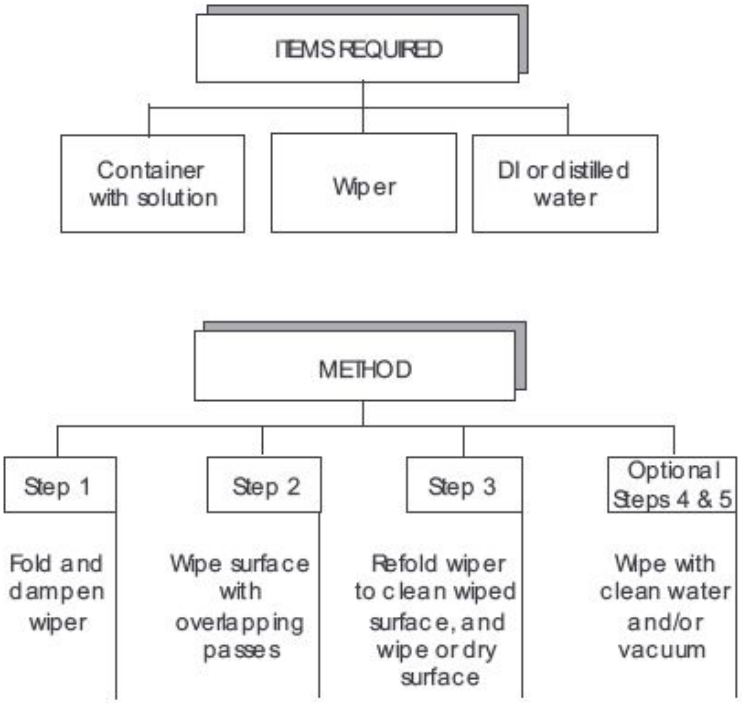


Figure 22.10 Cleaning of critical areas



There are a number of points to be considered with respect to cleaning methods. These are as follows:

1. The cleaning process should start by removing the 'sticks and stones' by means of a dry vacuum. Dry vacuum cleaning in cleanrooms should not be thought of as a cleaning method, but as a pre-requisite to cleaning. Vacuuming is not normally required in 'critical' areas unless the process disperses large numbers of fibres or large particles. Fibres, glass splinters, etc. will be removed by vacuuming but not small particles. Dry vacuuming also removes sufficient dirt to allow a lower concentration of detergent to be used. If the vacuum is not able to lift large

items they should be gathered together with a damp mop and removed.

2. When setting up a method for cleaning a room, consider the fact that because of gravitational settling of particles, horizontal surfaces will become dirtier more quickly than vertical surfaces. Also, surfaces that come into contact with people will become more contaminated than those that do not. This means that ceilings collect only a few particles, and walls a few more. These will therefore require less cleaning than floors or doors where particles will be deposited from the air, or touched.

3. Use overlapping strokes of the wiper or mop. A cleanroom will always appear clean to the eye, and it is therefore not easy to ensure that every area of the surface is cleaned, except by an overlapping pass method. How this might be done is illustrated in IEST-RP-018 and reproduced in Figures 22.11 and 22.12 by permission of the Institute of Environmental Science and Technology. The method used with walls and similar surfaces is illustrated in Figure 22.11. This method can also be used for floors but Figure 22.12 illustrates another method.

4. Cleaning should start at the areas furthest away from the exit to the cleanroom and, when cleaning large items, the furthest point away from the person who cleans it. Where an item to be cleaned varies in its cleanliness, the cleaning should start with the cleanest point first. Using this approach should ensure minimal recontamination of the surfaces.

5. If a damp wiper is used, it should be folded (usually to one quarter size) and as the cleaning proceeds it should be refolded to give a clean surface. After all surfaces of the wiper are used, the wiper should be replaced.

6. Attention should be paid to the cleanliness of the cleaning water. This can be carried out by changing the water when it becomes noticeably discoloured. However, when the water reaches this level it is probably too dirty to be used. The concentration of contaminants on surfaces being cleaned can be measured (using tests described in Section 22.7) in order to calculate the maximum area that can be cleaned before unacceptable levels of contamination are reached in the water. This calculated area can then be used to determine how much of a cleanroom surface can be cleaned before the water must be changed.

7. In ‘critical’, and sometimes ‘general’ cleaning, the process can sometimes be finished by going over the surface with ‘clean’ water so that any residual dirt, surfactant, or disinfectant, is removed. This is especially useful with a single bucket system.

8. If disinfectants are used in an aqueous formulation, it must be remembered that they do not kill microbes instantly. Disinfectants should be applied liberally to ensure that they do not dry off and should be left for at least two minutes, and preferably five minutes, to act. Alcohol will dry quickly; this is permissible, as its method of killing microbes partly depends on the drying of the alcohol.

9. Some wipers can be very efficient in removing particles but shed the occasional fibre. In this situation, the process can be finished by dry vacuuming over the surface.

10. Cleanroom tacky mats and cleanroom tacky flooring will require regular attention. The type of mat made from layers of adhesive plastic film will require the top sheet to be removed when it becomes overloaded with dirt. This should be done by carefully moving the edges of the dirty layer into the centre of the sheet so that the dirt is enclosed before the sheet is removed. Cleanroom tacky flooring should be cleaned using the method specified by the manufacturer. This will normally require mopping, followed by removal of the excess water by a squeegee or wet pick-up vacuum. It should be ensured that no water gets under the flooring, or microbes may multiply there.

11. Rubbish bins should not be too large in comparison to the amount of material that has to be disposed in them. This will ensure that rubbish is not left too long. The bins must be lined with disposable plastic sacks that are of sufficient strength not to be punctured. However, the removal of these liners may generate clouds of contamination and they should not be removed near to any area where the product is exposed. The liner should be removed and tied before it is taken away for disposal.

Figure 22.11 Overlapping method used for walls and similar surfaces

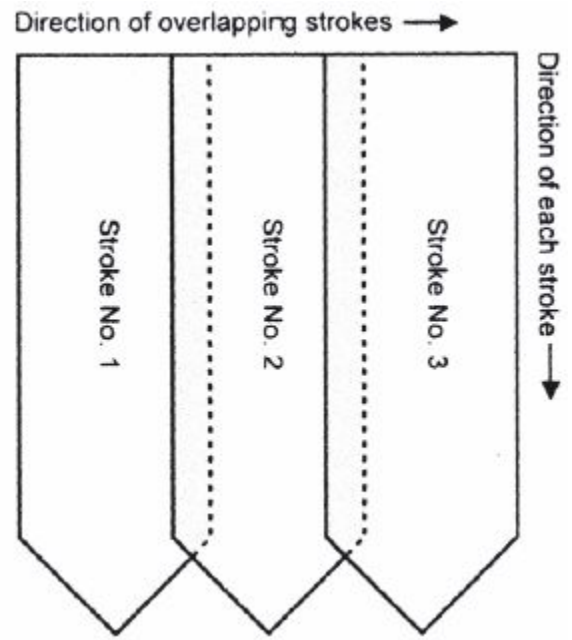
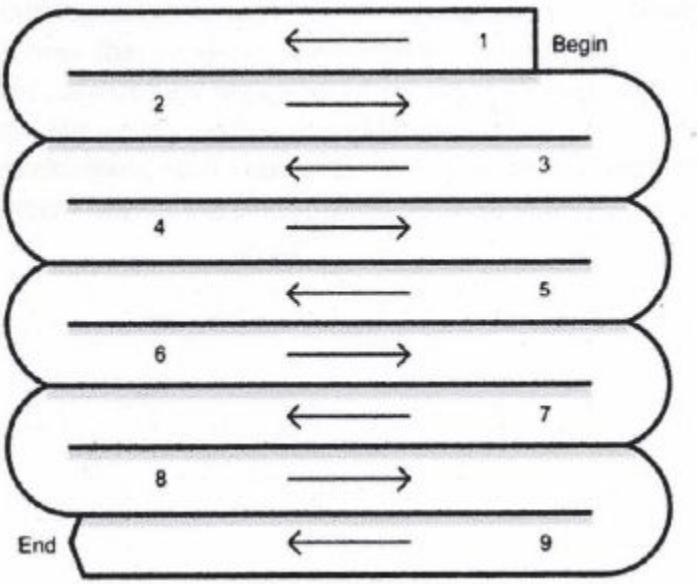


Figure 22.12 Overlapping method used to clean floors



22.6 Cleaning Programme

It is necessary to develop a cleaning programme to ensure that the contamination in the cleanroom is kept at an acceptably low level. The programme will be defined by Standard Operating Procedures (SOPs). These will require consideration of the following points:

1. the classification of the surfaces to be cleaned into ‘critical’, ‘general’ and ‘other’ areas;

2. the allocation of those areas to be cleaned by cleanroom personnel and those to be cleaned by cleaning staff;

3. the frequency of cleaning of the various areas, and the time of day at which cleaning will be carried out;

4. the length of time to be spent cleaning each area;

5. the cleaning equipment, liquids and methods that are to be used to clean the different areas;

6. a determination of how the cleaning is tested to ascertain that surfaces are maintained within the acceptable level of contamination;

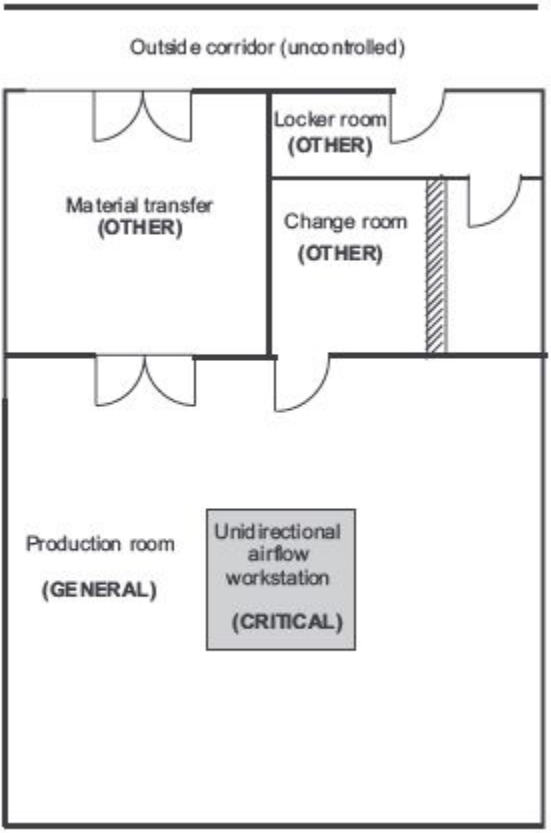
7. the training of personnel involved in cleaning;

8. the documentation of all procedures.

A simple example of how a cleaning programme can be established is now given:

1.Classification of the surfaces to be cleaned into critical, general and other areas

Figure 22.13 Classification of clean areas to be cleaned



The example is of a simple cleanroom suite as previously described in Chapter 5 in which Figures 5.1 and 5.7 show typical layouts. The plan of the cleanroom under consideration is shown in Figure 22.13 along with the clean areas classified into ‘critical’, ‘general’ and ‘other’.

In the centre of the cleanroom is the ‘critical’ area where the product is open to contamination. This area is protected by a unidirectional airflow workstation. The ‘general’ clean area is the rest of the main cleanroom outside the

'critical' area. The 'other' clean areas are the materials transfer airlock and the clothing change area. The corridor outside the cleanroom suite is an uncontrolled area, which is cleaned to the same standard as the rest of the factory.

2. Which areas are cleaned by cleanroom personnel and which are cleaned by cleaning staff?

The cleanroom suite in this example is a small one, so it is more efficient to have cleanroom personnel carry out all the cleanroom cleaning. However, cleaning staff, or personnel from a contract cleaning firm could clean the 'general and 'other' areas but the 'critical' area must be cleaned by cleanroom personnel.

3. Frequency of cleaning in the various zones, and the time at which this will occur

It was decided that the machinery etc. in the critical area will be cleaned in the morning before the start of production. The inner walls in the unidirectional flow workstation will be cleaned every week.

All surfaces in the general area i.e. floor, tables, doors, with the exception of the walls and ceilings, will be cleaned daily.

In the 'other' areas i.e. the change and transfer areas, the floor and cross-over benches will be cleaned daily. All 'other' surfaces, except the walls and ceilings, will be cleaned weekly.

In both the ‘general’ and ‘other’ areas, the walls (including exhaust grilles) will be cleaned every month and the ceilings (including air supply diffusers) will be cleaned every 6 months.

A more exact way of determining the required frequency of cleaning can be ascertained by measuring the surface particle contamination immediately after cleaning and then at intervals afterwards, to see how long it takes for the particle concentration to rise to an unacceptable level. Information on suitable test methods is given in 22.7. This information should be considered, together with an assessment of the degree of risk of contamination being transferred from the surface to be cleaned to the product (see Chapter 16 for advice on risk assessment).

4 Time spent on cleaning

The time spent on cleaning a given type of surface area (time/m^2) will depend on the susceptibility of the product to contamination and the potential of the contamination on the surface to be cleaned being transferred to the product. The time allocated will also depend on the financial resources available and it will be necessary to manipulate these variables to obtain the best answer for each situation.

5 Cleaning equipment, liquids and methods used in the differentzones

The critical area will be cleaned using a cleanroom wiper dampened with 80% iso-propanol alcohol dispensed from a squeezy bottle. Overlapping strokes will be used.

The floor will be cleaned by use of a three-bucket system using a suitable cleanroom mop, although a single bucket system with regular renewal of the cleaning solution after a given area is cleaned, or a preloaded mop-head can be used. The mop (see Figure 22.4) should be a cleanroom type of mop. The walls and ceilings will be cleaned with a cleanroom mop of the sponge-head type (see Figure 22.3). Door surfaces and other small or irregular surfaces (such as exhaust grilles and air supply diffusers) will be cleaned with a damp cleanroom wiper. All surfaces will be cleaned using overlapping passes.

6 Testing cleanroom surfaces to ascertain that cleaning has been carried out to the correct level of contamination

The cleanliness of cleanroom surfaces and the efficiency of cleaning will be determined by a 47 mm membrane filter holder with the membrane support grid removed. This will be attached to a tube connected to a particle counter. The holder is applied to the surface and drawn over a large enough area of surface to give a significant count. Other types of sampling methods available to ascertain the concentration on surfaces and the efficiency of cleaning are discussed in Section 22.7.

An intensive programme of testing will be carried out when the cleaning programme is set up, and the frequency of testing then reduced to a suitable level.

7 and 8 Documentation of procedures and training of all personnel involved in cleaning

All procedures must be documented and all cleaning staff trained. How this is done is outwith the scope of this book and not discussed further.

Further information to assist in the task of producing a cleaning programme is given in both the IEST-RP-018 ‘Cleanroom housekeeping: operating and monitoring procedures’ and in ISO 14644–5 ‘Operations’.

22.7 Test Methods

In the home, it is relatively simple to see if your cleaning has been successful. More often than not, a good look will be sufficient. In a cleanroom, unacceptable levels of dirt are not visible and special testing methods are therefore required. There are two approaches to sampling surfaces in cleanrooms. Firstly, test methods are used to establish how much contamination is on the surface and whether the surface has been cleaned to an acceptable level of contamination. By sampling the surface before and after cleaning the effectiveness of the cleaning can be ascertained. Secondly, methods can be used to establish how quickly cleanroom surfaces will become soiled and this information used to establish how frequently the surface should be cleaned. The test methods available are as follows:

22.7.1 Surface concentration methods

The following methods can be used to establish the concentration of particles on surfaces. They can be used after cleaning to establish that the cleaned surfaces are at an acceptably low concentration, or used before and after

cleaning to check that the cleaning has been carried out efficiently.

1. If a damp black or white wiper is drawn over a given area of cleanroom surface it is sometimes possible to concentrate the soil sufficiently to indicate the amount of dirt on the surface.

2. An ultra-violet light shows up surface particles and fibres that fluoresce. For example, fibres from cleanroom garments will show up.

3. A high-intensity light shone at an acute angle to the surface, in a darkened room, shows up small particles and fibres.

4. Clear sticky tape can be applied to a surface and then removed. The particles stripped from the surface can be counted and sized under a microscope. This method is used to count particles ≥ 5μm. ASTM E 1216–87 outlines such a method. ASTM F25 is useful to consult for information on how to count particles microscopically.

5. Instruments are available for measuring particles on surfaces. A sampling head is pushed over the surface and an optical particle counter measures the particles detached by the instrument.

6. A 47 mm diameter membrane holder, with the membrane support grid removed, can be attached to a particle counter and the particles on a given surface area vacuumed off and counted.

22.7.2 Rate of particle deposition methods

Several methods are available to measure the rate of deposition of particles onto a test surface and used to assist in setting the frequency of cleaning.

Particle-free glass (or clear plastic) slides can be laid out on cleanroom surfaces for a given time that is likely to be measured in hours or days. The number and size of particles that have deposited onto the slides can then be measured microscopically, or determined by the equipment that uses a photometer to measure the light scattered by particles on a test slide. Automatic test equipment used in semiconductor manufacturing areas to count and size particles on silicon wafers can also be used, and the number of particles that have deposition on test wafers laid out on cleanroom surfaces for a given period of time can be determined. Further information about the above test methods is available in IEST-RP-CC018.

22.7.2 Disinfection methods

If information is required about the effectiveness of disinfection methods and the concentration of microbes on surfaces then either a contact plate or swab can be used. Neutralisers against the disinfectant must be incorporated into the microbial media or microbial growth will be inhibited. Such microbiological surface sampling methods are discussed in Chapter 14.

Acknowledgements

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rings

risk

assessment

definition

descriptors

diagrams

management

scoring

Risk Management of Contamination (RMC) system

RMC system*see*Risk Management of Contamination system

robotic manipulation

RODAC dishes*see*replicate organism detection and counting dishes

rubbish bins

Rules Governing Medicinal Products in the European Union, The

safety cabinets

saliva

sampling

air

for cleanroom classification

frequency

impaction

limits

methods

microbial

of personnel

probes

sequential

settle plate

surface

Sandia Corporation

Sandia Laboratories

scanning

scan testing

screening

scrubbing

sealing

self-closers

separative devices

separative enclosures

sequential monitoring system

sequential sampling

service chases

service personnel

services

settle plate sampling

Shell Ondina EL mineral oil

shoe cleaners

shoe coverings

short circuits

sieving*see*screening

silicon wafers

simultaneous monitoring system

skin

SMIF*see*Standard Mechanical Interface Format

smoke alarms

smoke generators

smokers

smoke visualisation tests

soil areas

solvents

SOPs*see*standard operating procedures

sorbency

sound

sound control

sound levels

spare parts

sponges

squeegees

staff*see*personnel

stainless steel

Standard Mechanical Interface Format (SMIF)

standard operating procedures (SOPs)

standards

British

cleanroom classification

clothing

design

history

international

in the USA

monitoring

operating procedures

pharmaceutical

staphylococci

sterile drug products

sterilisation

sterilisers

sterilising tunnels

sticky tape

storage

temporary

straining*see*screening

streamers

streptococci

studless wall systems

substrates

supervision

supplier audits

supply tunnels

supporting clean areas

surface chemical cleanliness

surface concentration tests

surfaces

cleanliness

contamination

surfactants

surgical-style masks

swabbing

synthetic fibres

tacky mats

tacky rolling

technology

temperature

temporary airlocks;*see also*airlocks

temporary storage

temporary transfer areas

terminal filters

terminal sterilisation

terrazzo flooring

testing

additional

cleaning

for leaks

IEST recommended practices

methods

of clean-air devices

of cleanrooms

of clothing

of disinfection

of filters

of gloves

optional

principles

reasons for

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tests

containment leak

filter installation leak tests

filter integrity leakage tests

recovery

smoke

surface concentration

visualisation

thermal aerosol generators

thermal anemometers

three-bucket mopping system

tools

training

transfer areas

transfer-docking device

transfer tunnels

trolleys

two-bucket mopping system

types of cleanrooms

Tyvek

ULPA filters*see*ultra low penetration air filters

ultrafine particles

ultra low penetration air filters (ULPA filters)

compared with HEPA filters

fitting

ultrasonic baths

ultra-violet light

unidirectional airflow cabinets

unidirectional airflow cleanrooms

air movement control

ceilings

filter housings in

filter leaks in

horizontal

measurement of air quantities in

testing

types

vertical

unidirectional airflow devices

unidirectional flow clean-air devices

unidrectional ventilation

vacuuming

vacuum wands

van der Waals forces

vane anemometers

vapour sterilisation

veil-type masks

ventilation

early industrial

for contamination control

in operating rooms

laminar air

methods

plant

unidirectional

vertical unidirectional airflow enclosure

vibration

viewing windows

vinyl sheet flooring

visualisation tests

volumetric air sampling

wall extracts

wall panels

washing

water penetration

water vapour permeability

wear

wet pick-up

wet vacuuming

whistling

Whitfield Ultra-Clean Room

Whitfield, Willis

whole clothing system tests

windows

wipers

wiping materials

wrapping;*see also*packaging

Wrightington Hospital, Manchester

yashmak-type masks*see*vei