A Knight in Shining Armor

(Cleanroom Inhabitant – A Perspective Yesterday, Today & Tomorrow)

Global Cleanroom

Community Meet

Hyatt, Pune, 28th Feb. 2020

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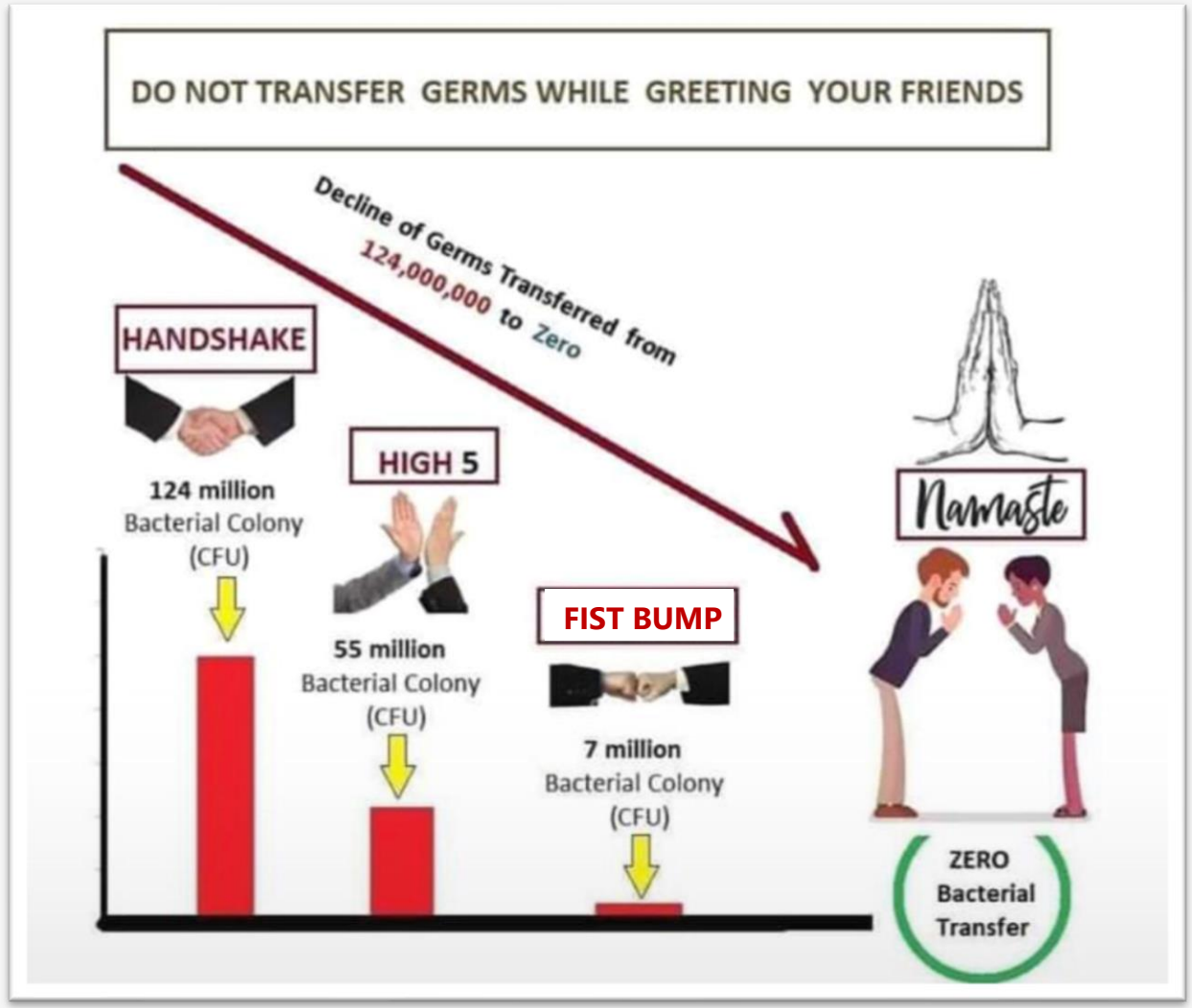
Disclaimer

The views and opinions expressed in the presentation are those of the presenter based on knowledge and best understanding of prevailing regulatory scenario. Should it at any point in time contravene, in which case the guideline and the official status shall prevail

Namaste

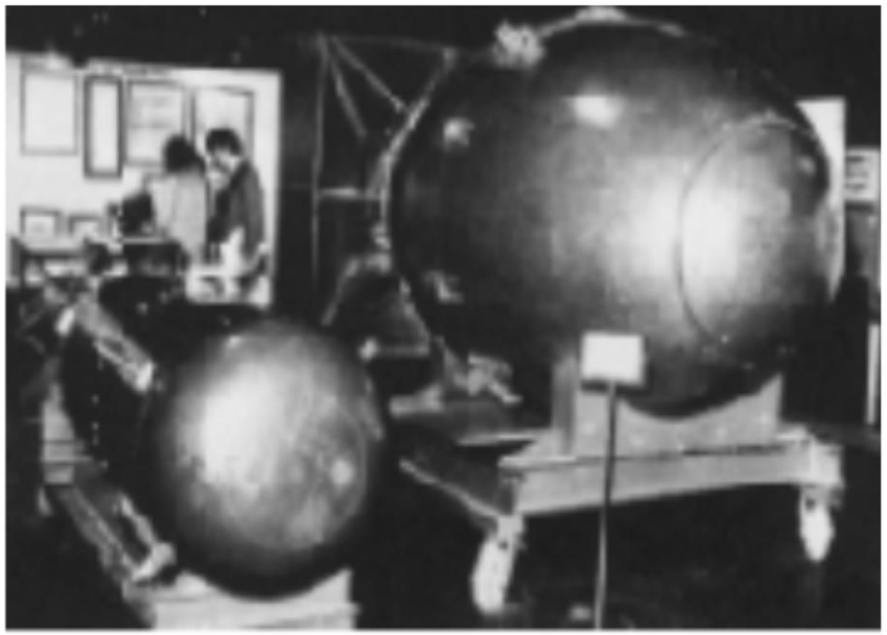

DO NOT TRANSFER GERMS WHILE GREETING YOUR FRIENDS
Decline of Germs Transferred from 124,000,000 to Zero
HANDSHAKE
124 million Bacterial Colony (CFU)
HIGH 5
55 million Bacterial Colony (CFU)
FIST BUMP
7 million Bacterial Colony (CFU)
Namaste
ZERO Bacterial Transfer

Contents

History of Cleanroom

- Increasing complexity and precision of some manufactured products led to the requirement for contamination control techniques

- First HEPA filter designed in the 1940's by R&D firm Arthur D. Little under a classified USA government contract as part of the Manhattan Project, where the first atomic bomb was developed during World War II.



"Little Boy" and "Fat Man"

http://www.c-vac.com/history.html

History of Cleanroom

- HEPA a major advancement in air filtration technology – solved a critical need to control very small particles which had become contaminated by nuclear radioactive sources.

- Next 50 years HEPA filtration gradually evolved – Technological breakthroughs in aerospace, pharmaceutical processing, photographic film manufacturing, data processing and micro-electronics demanded higher and higher levels of air cleanliness.

Some of the biggest achievements of mankind – lunar landing, silicon chip, safe drug products could not have been possible without the HEPA filtration

Cleanroom

- Cleanrooms are typically used in scientific research and manufacturing to provide a controlled environment for handling sensitive components and samples.
- Cleanrooms are constructed in a way to minimize particles from being introduced, generated or retained inside the room.
- The higher the level of cleanliness, the lower the particles inside the room.

Cleanroom

Early types of cleanroom were non-unidirectional airflow (or turbulent airflow) cleanrooms

Early cleanroom manufacturing

The Micronclean Cleanroom Handbook, Neil Clayton Tim Eaton

Cleanroom

Cleanrooms are typically classified as ISO 5 or ISO 6

CLASS	NUMBER OF PARTICLES PER m^3 BY µm SIZE					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO 1	10	2	--	--	--	--
ISO 2	100	24	10	4	--	--
ISO 3	1,000	237	102	35	8	--
ISO 4	10,000	2,370	1,020	352	83	--
ISO 5	100,000	23,700	10,200	3,520	832	29
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7	--	--	--	352,000	83,200	2,930
ISO 8	--	--	--	3,520,000	832,000	29,300
ISO 9	--	--	--	35,200,000	8,320,000	293,000

Cleanroom

- Developments in modern health-care products – led to the global use of closely-controlled and regulated Pharmaceutical and Biomedical cleanroom manufacturing facilities.

- Pharmaceutical cleanrooms not only provide control of environmental particulates and fibres but also have additional emphasis on the monitoring and control of microbiological contamination.

Such facilities also incorporated aseptic techniques & sterilisation processes, developed since the early 1900's within hospital operating theatres & pharmaceutical cleanrooms.

Cleanroom

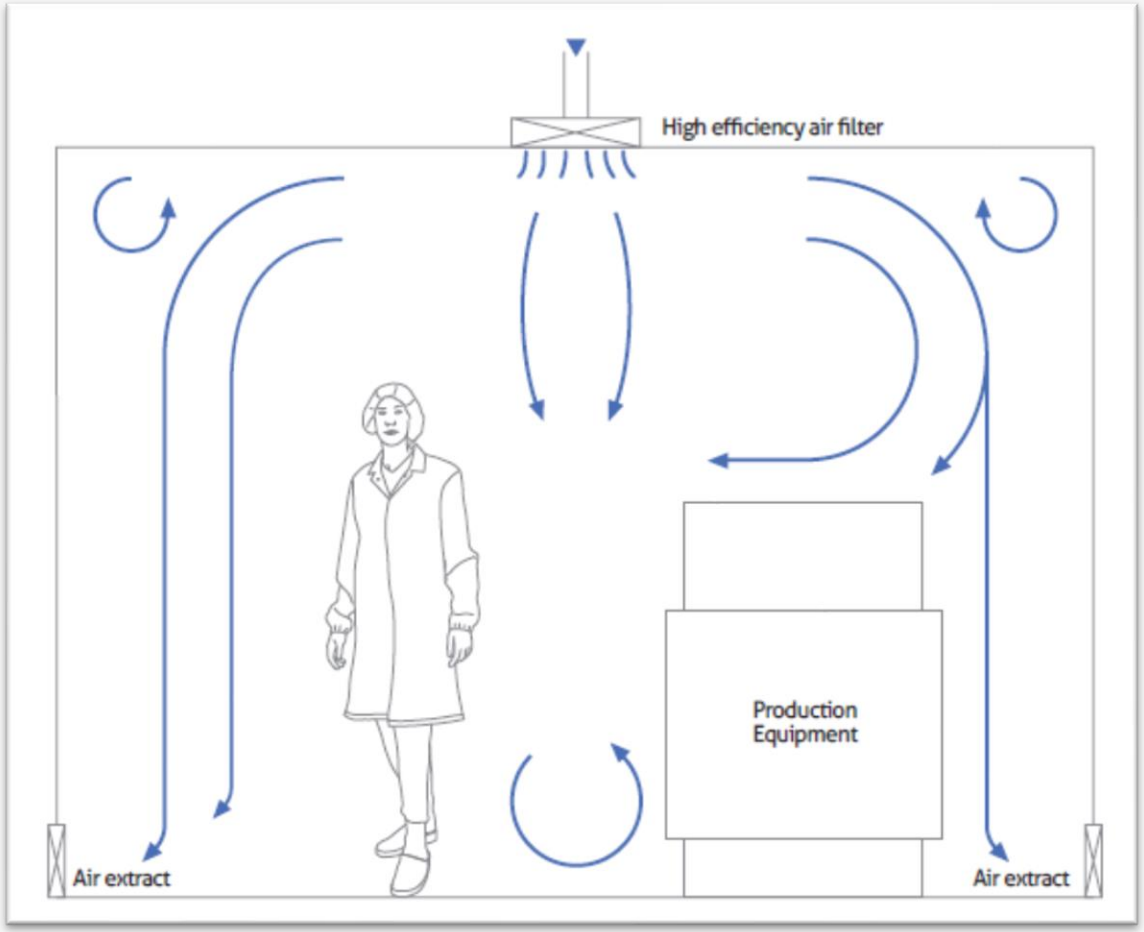
- A cleanroom is designed, constructed and maintained to provide a production environment that minimizes the possibility of product contamination.
- The type of product & the degree of control required to protect the product are the factors in determining cleanroom specifications.
- In general, simple room shapes allow for effective airflow patterns and cleaning thus, usually cleanrooms are box-shaped with no or as less as possible obstructions.

Cleanroom

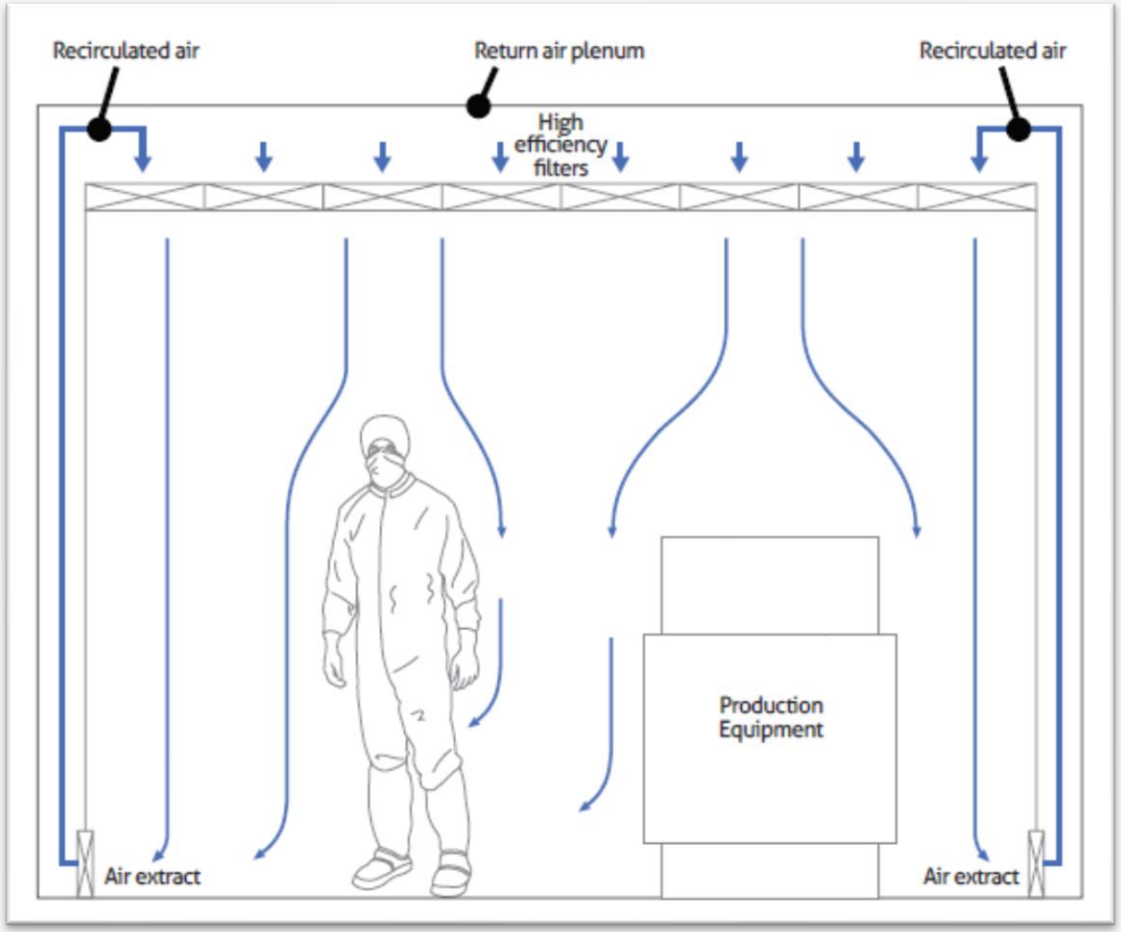
- A cleanroom primarily controls: (a) the introduction and entry of particles, and (b) the generation and retention/ removal of particles within the room.
- High volumes of filtered air supplied to the cleanroom that helps: (a) dilute & remove contamination, and (b) pressurizing it to prevent the entry of less clean air from adjacent areas.

Cleanroom

Turbulent airflow cleanroom

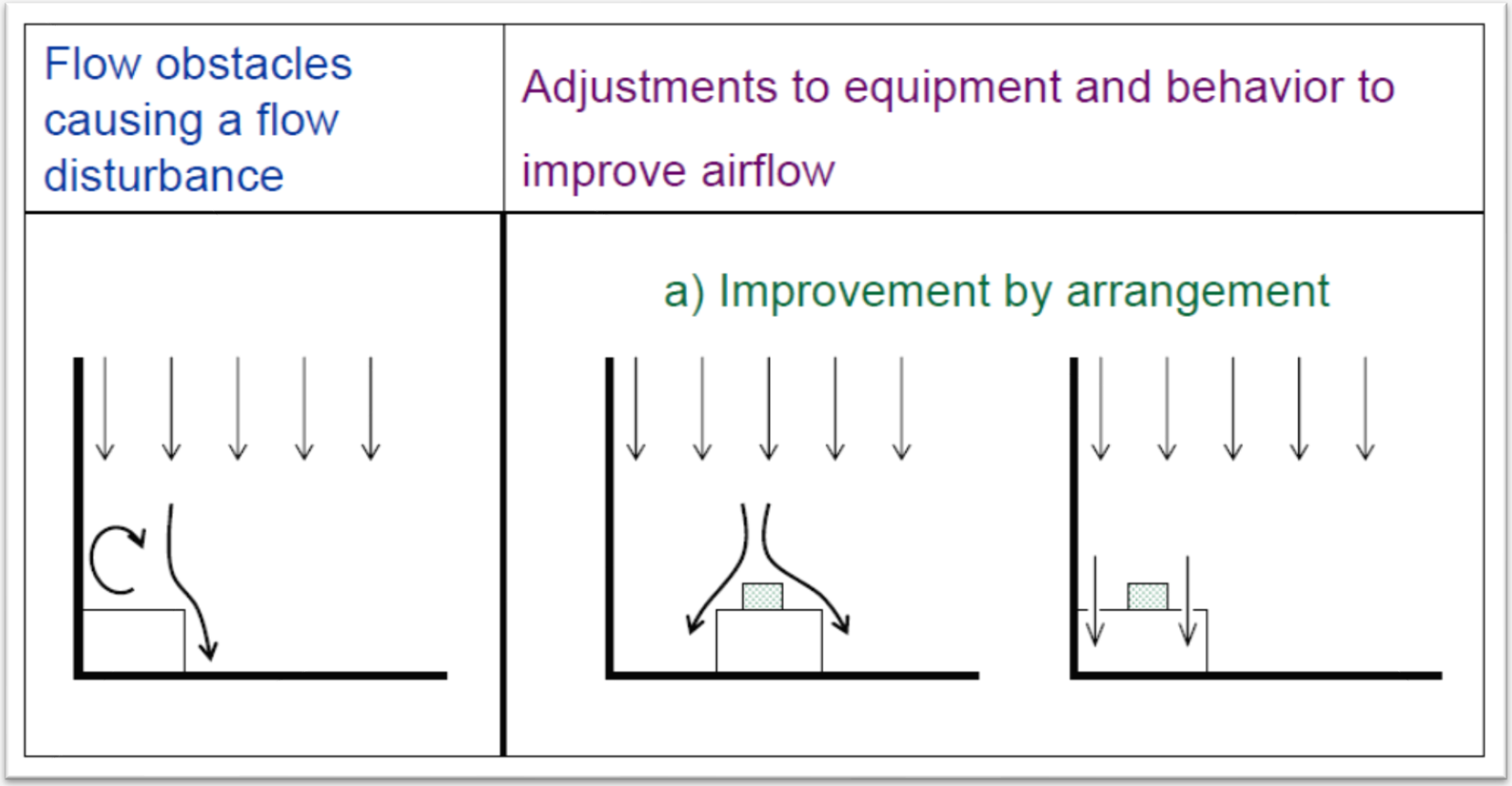


Unidirectional airflow cleanroom

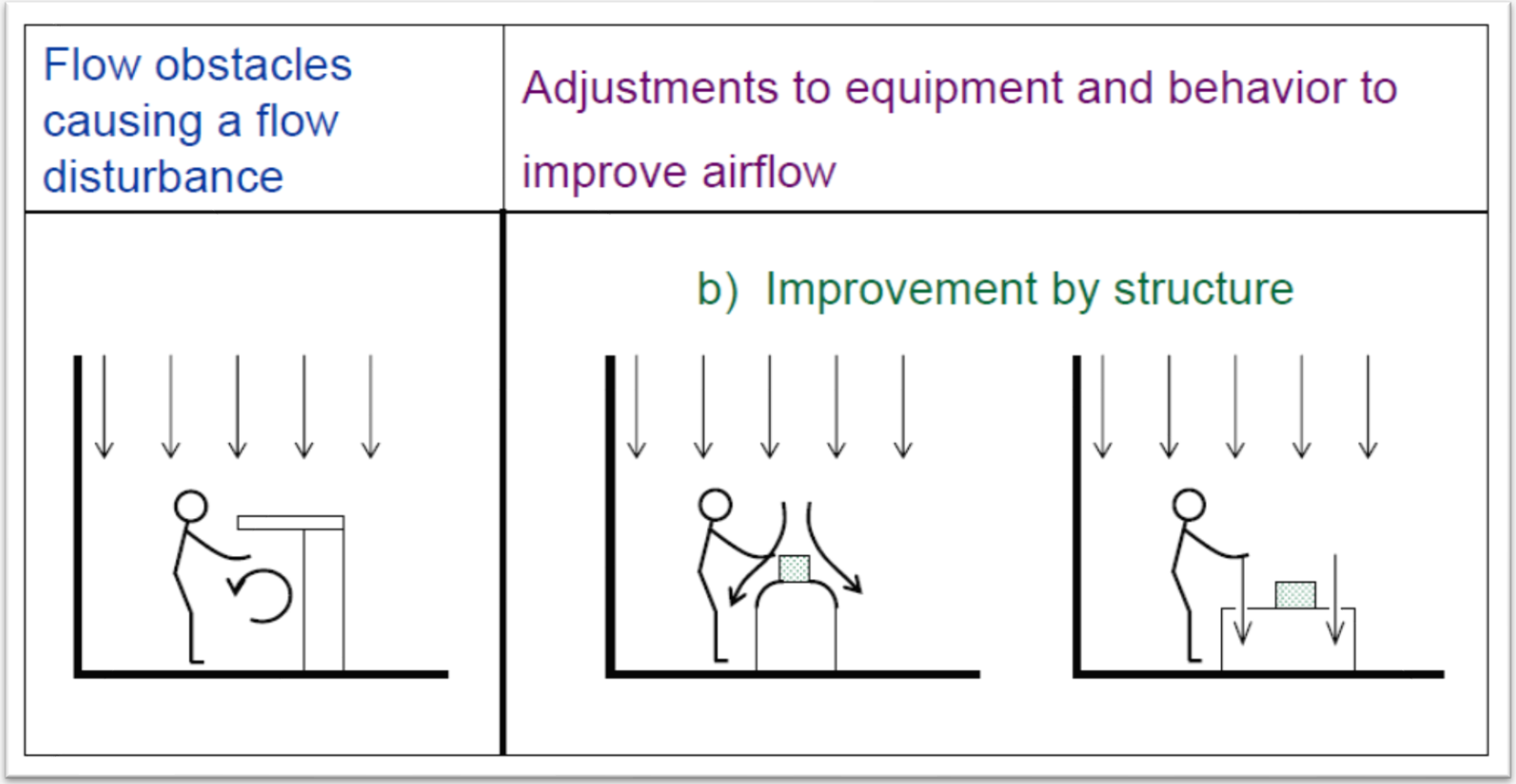


The Microncleaan Cleanroom Handbook, Neil Clayton Tim Eaton

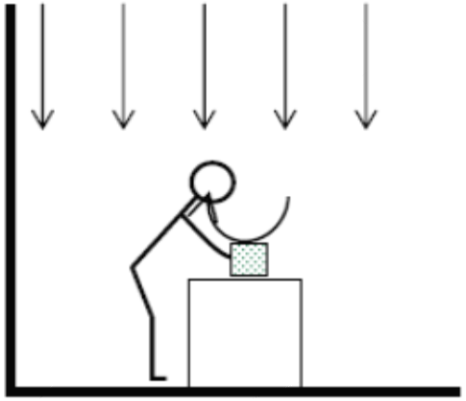
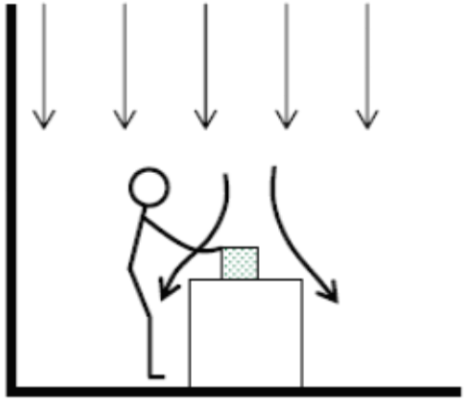
Cleanroom


Flow obstacles causing a flow disturbance
Adjustments to equipment and behavior to improve airflow
a) Improvement by arrangement

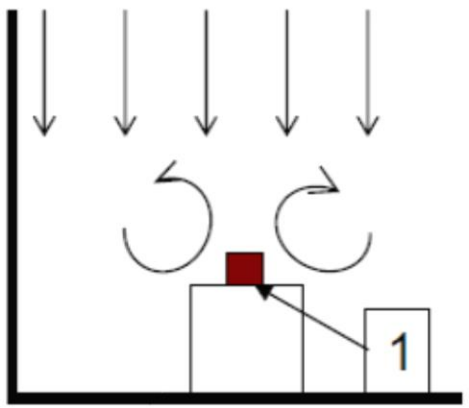
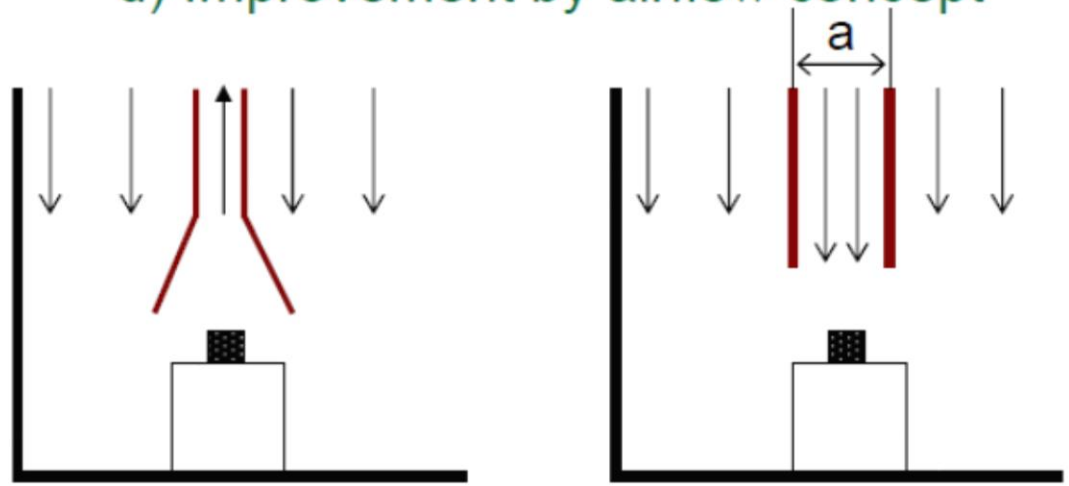
Cleanroom


Flow obstacles causing a flow disturbance
Adjustments to equipment and behavior to improve airflow
b) Improvement by structure

Cleanroom

Flow obstacles causing a flow disturbance	Adjustments to equipment and behavior to improve airflow
	c) Improvement by personnel behaviour 

Cleanroom

Flow obstacles causing a flow disturbance	Adjustments to equipment and behavior to improve airflow
	d) Improvement by airflow concept 

1 = Heat source

a = Local increase in air velocity

Cleanroom

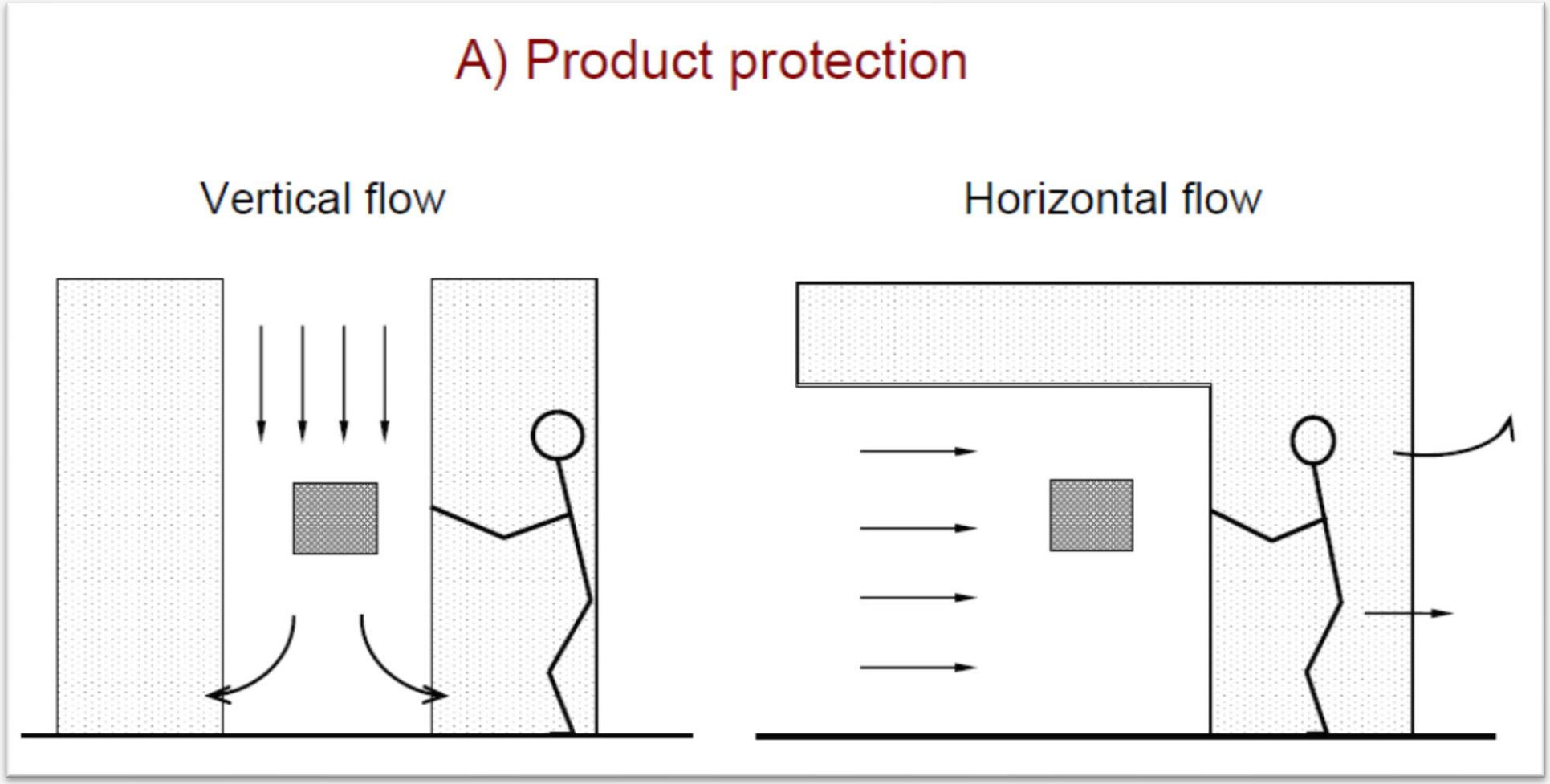
- The transfer of contaminants into a zone protecting a process and/or personnel prevented by using:

  (a) Aerodynamic Measures - Arrangement & Flow Direction

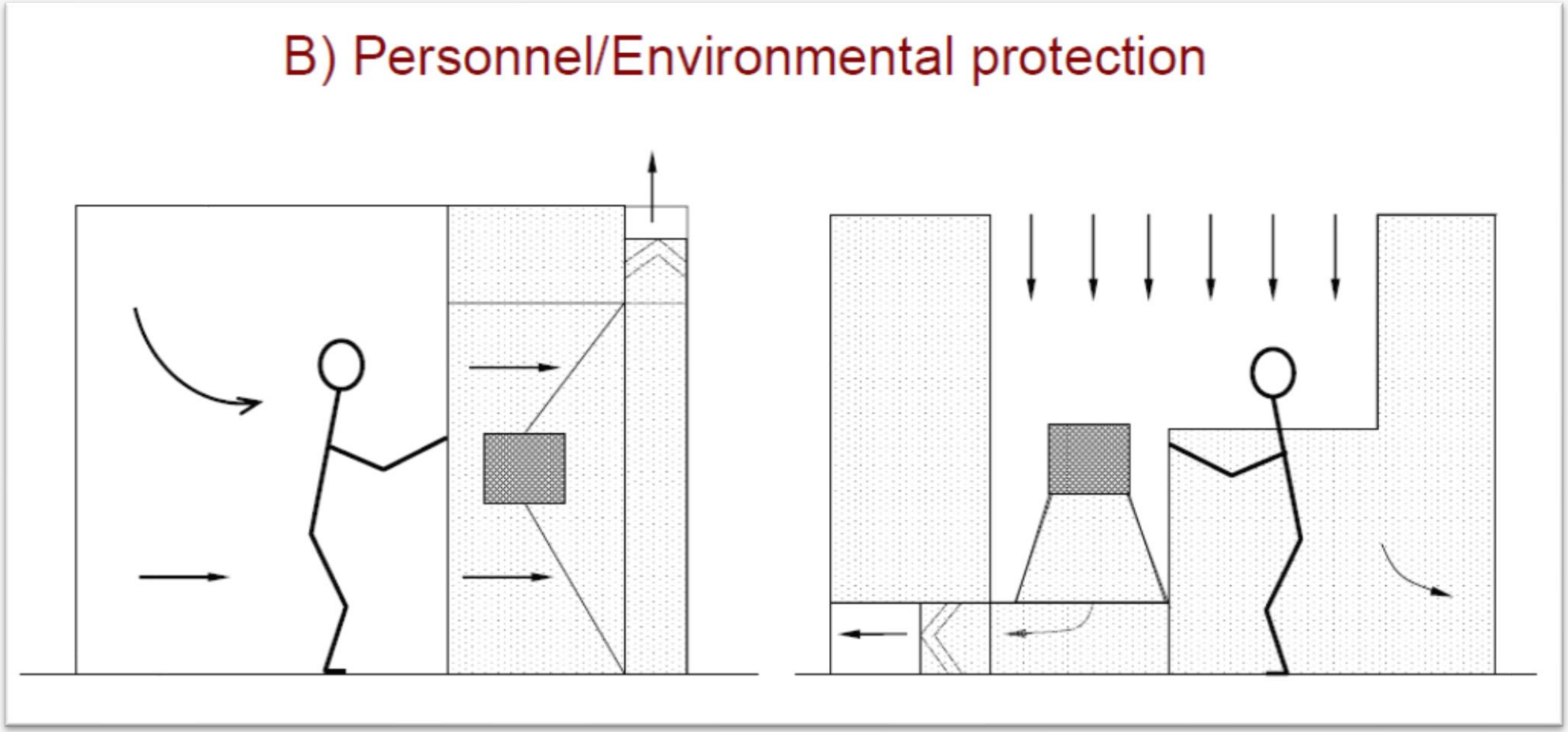
  (b) Physical Barriers – Active and Passive Isolation (if any contact between product and operator/ environment is to be prevented)

- Where required, process exhaust treated to prevent contamination of outdoor environment.

Cleanroom

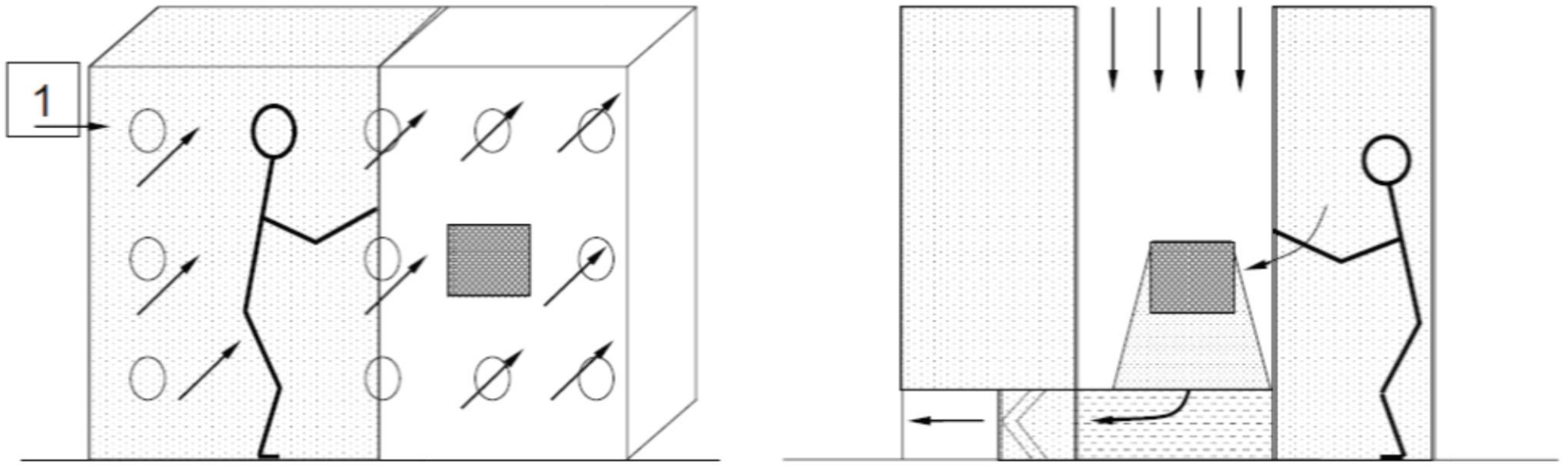


Cleanroom



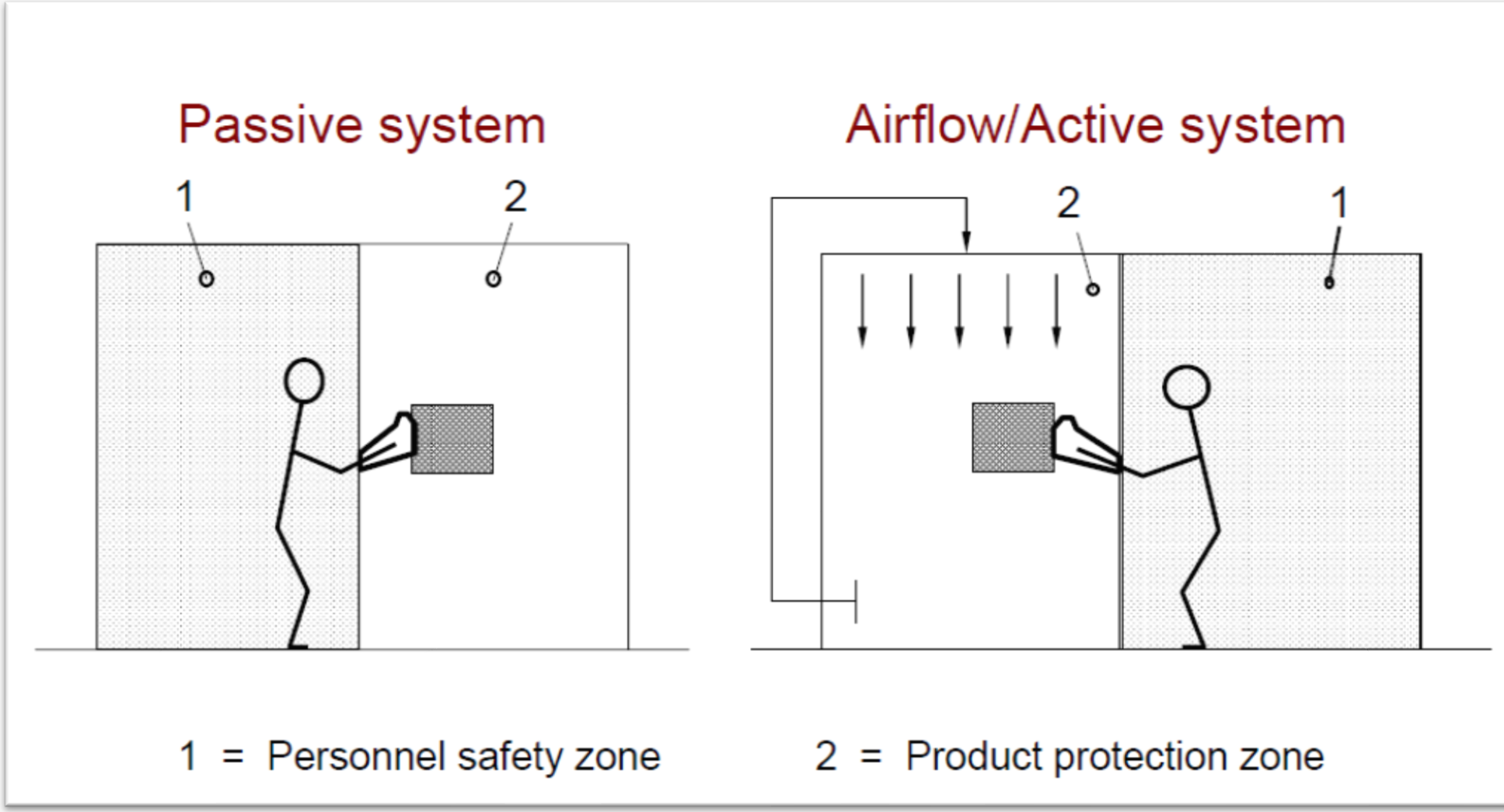
Cleanroom

C) Personnel/Product/Environmental protection



1 = Flow direction perpendicular to graphic plane

Cleanroom


Passive system
1
2
Airflow/Active system
2
1
1 = Personnel safety zone
2 = Product protection zone

Cleanroom

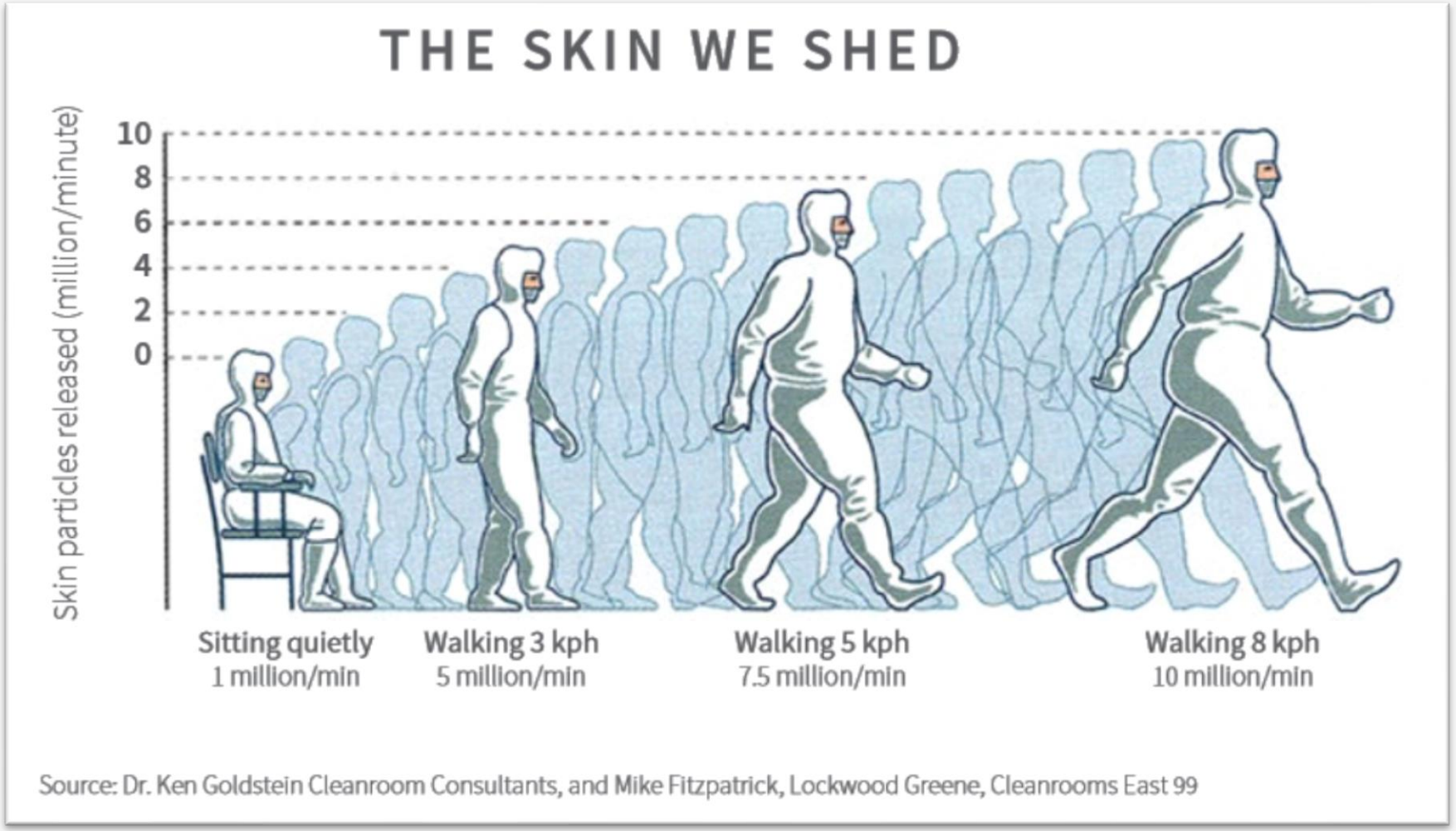
- The cleanroom constructed with materials that:

  (a) do not generate particles
  (b) can be effectively cleaned to remove deposited contamination.

- Personnel entering & working in cleanroom are the biggest source of particulate contamination and are required to wear appropriate cleanroom clothing to minimise this risk.

- Even the cleanest of people are naturally contaminated. Our bodies are natural host to unwanted bacteria, along with the shedding of skin cells, hair and exhale of bio-organisms.

Cleanroom


THE SKIN WE SHED
Skin particles released (million/minute)
10
8
6
4
2
0
Sitting quietly
1 million/min
Walking 3 kph
5 million/min
Walking 5 kph
7.5 million/min
Walking 8 kph
10 million/min
Source: Dr. Ken Goldstein Cleanroom Consultants, and Mike Fitzpatrick, Lockwood Greene, Cleanrooms East 99

Cleanroom

- Non-filtered air varies greatly from location to location and also varies over the course of time.
- Enormous quantity of particulate matter are generated by natural events and human activity – source & size varies
- Most of these particles are invisible to the unaided eye and as microscopic particles remain suspended in air, or fall slowly under gravity, they can travel great distances.

Cleanroom

Common particles & their relative sizes

PARTICLE CONTENT	PARTICLE SIZE (µm)
Sneeze particles	10 – 300 µm
Hair	50 – 150 µm
Pollen	7 – 100 µm
Dust	<0.1 – >100 µm
Visible	50 µm
Bacteria	1.0 – 10 µm
Flu virus	0.07 µm

Settling distance in air

PARTICLE SIZE (µm)	SETTLING DISTANCE (cm/100s)
100.0	2620.0
10.0	30.6
1.0	0.35
0.1	0.00865
0.01	0.000695
0.0037	---

Particle Measurement System "Beginner guide to particle technology"

Limitation

- Achieving & maintaining particulate free & sterile manufacturing environment is not possible
- In any environment where human operators are present microbial contamination cannot be completely eliminated
- Highest levels of cleanroom design and best aseptic practices is not a guarantee for completely eliminating particulates/ microorganisms shedding into the cleanroom environment by human operators

Limitation

USP <1116>, "an expectation of zero contamination at all locations during every aseptic processing operation is technically not possible and thus is unrealistic"

USP 36 General Information / ⟨1116⟩ Aseptic Processing Environments 785

permitted. [NOTE—A description of terms used in this chapter can be found in the *Appendix* at the end of the chapter.]

The guidance provided in this chapter and the monitoring parameters given for microbiological evaluation should be applied only to clean rooms, restricted-access barrier systems (RABS), and isolators used for aseptic processing. ISO-classified environments used for other purposes are not required to meet the levels of contamination control required for aseptically produced sterile products. The environments used for nonsterile applications require different microbial control strategies.

A large proportion of products labeled as sterile are manufactured by aseptic processing rather than terminal sterilization. Because aseptic processing relies on the exclusion of microorganisms from the process stream and the prevention of microorganisms from entering open containers during processing, product bioburden as well as the bioburden of the manufacturing environment are important factors governing the risk of unacceptable microbial contamination. The terms *aseptic* and *sterile* are not synonymous. *Sterile* means having a complete absence of viable microorganisms or organisms that have the potential to reproduce. In the purest microbiological sense, an *aseptic* process is one that prevents contamination by the exclusion of microorganisms. In contemporary aseptic healthcare-product manufacturing, *aseptic* describes the process for handling sterilized materials in a controlled environment designed to maintain microbial contamination at levels known to present minimal risk.

In any environment where human operators are present, microbial contamination at some level is inevitable. Even the most cautious clean-room environment design and operation will not eliminate the shedding of microorganisms if human operators are present. Thus, an expectation of zero contamination at all locations during every aseptic processing operation is technically not possible and thus is unrealistic. There are no means to demonstrate that an aseptic processing environment and the product-contact surfaces within that environment are sterile. Monitoring locations should be determined based upon a assessment of risk. Although manufacturers should review environmental monitoring results frequently to ensure that the facility operates in a validated state of control, monitoring results can neither prove nor disprove sterility. Because of the limitations of monitoring, manufacturers cannot rely directly on monitoring, statistics, or periodic aseptic-processing simulations to ensure a sterility assurance level.

Environmental monitoring is usually performed by personnel and thus requires operator intervention. As a result, environmental monitoring can both increase the risk of contamination and also give false-positive results. Thus, intensive monitoring is unwarranted, particularly in the ISO 5 environments that are used in the most critical zones of aseptic processing.

A number of sampling methods can be used to assess and control the microbiological status of controlled environments for aseptic processing. At present, nearly all of these methods rely on the growth and recovery of microorganisms, many of which can be in a damaged state caused by environmental stress and therefore may be difficult to recover. The numerical values for air, surface, and personnel monitoring included in this chapter are not interided to represent limits or specifications but are strictly informational. Because of the variety of microbiological sampling equipment and methods, it is not scientifically reasonable to suggest that the attainment of these values guarantees microbial control or that excursions beyond values in this chapter indicate a loss of control. The assessment of risks associated with manufacturing environments must be made over a significant period, and in each case, the contamination recovery rate metric should be established on the basis of a review of actual findings within the facility. The objective of each user should be to use contamination recovery rates to track ongoing performance and to refine the microbiological control program to foster improvements. When optimum operational conditions are achieved within a facility, contamination recovery rate levels typically become relatively stable within a normal range of variability.

There are no standard methods for air sampling, and available literature indicates that air-sampling methods are highly variable. It should not be assumed that similar sample volumes taken by different methods will produce similar rates of recovery. Many factors can affect microbial recovery and survival, and different air sampler suppliers may have designed their systems to meet different requirements. Also, sample-to-sample variation in microbial sampling can be extensive. Limited data are available regarding the accuracy, precision, sensitivity, and limits of detection of monitoring methods used in the aseptic processing of healthcare products.

Surface sampling methods are also not standardized. Different media are employed, and in the case of swabs, different results have been reported for wet and dry swab methods and contact plates. Replicate sample contact plates should be expected to give similar results under identical conditions, but rates of recovery have been reported to be both lower than expected and highly variable. In general, surface monitoring has been found to recover <50%, even when used with relatively high inoculum levels on standardized coupons. In actual production environments where organisms are stressed to varying degrees, recovery rates may be lower.

ADVANCED ASEPTIC TECHNOLOGIES

Advanced aseptic technologies can be defined as those that do not rely on the direct intervention of human operators during processing. At present, technologies such as isolators, blow/fill/seal, and closed RABS (designs that are never opened during setup or operation) may be considered advanced aseptic technologies, provided that direct intervention by gowned personnel is disallowed during processing. In recent years, isolator technology has found a broad acceptance in healthcare manufacturing. Isolators and closed RABS effectively separate the operator from the critical aseptic processing environment. Because these systems substantially reduce contamination risk, their microbiological control levels are higher than those of conventional clean rooms that have comparable particulate air classification level, for example, ISO 5.

CLEAN ROOM CLASSIFICATION FOR ASEPTIC PROCESSING ENVIRONMENTS

The design and construction of clean rooms and controlled environments are covered in ISO 14644 series. This standard defines the performance of a clean environment with respect to the concentration of total particulates per unit volume. ISO 14644-1 stipulates the total particulate counts allowed for a clean environment to meet the defined air quality classifications. The reader is referred to this standard regarding the design characteristics and certification of clean environments.

Pharmaceutical manufacturers are concerned with nonviable particulate contamination in injectable products (see *Particulate Matter in Injections* ⟨788⟩). Unlike microbial contamination in which experimental data suggest that humans are the only significant source, nonviable particulates can arise both from humans and from processing equipment. Studies indicate that gowned humans slough particulate and microbial contamination at a rather consistent rate. However, the relationship between microbial (viable) and nonviable contamination does not hold for particulates shed by processing equipment. Where equipment is the primary source of particulate matter, the resulting particulates are essentially all nonviable.

The argument that if fewer total particulates are present in a clean room, it is less likely that airborne microorganisms will be present is true only if human operators are the

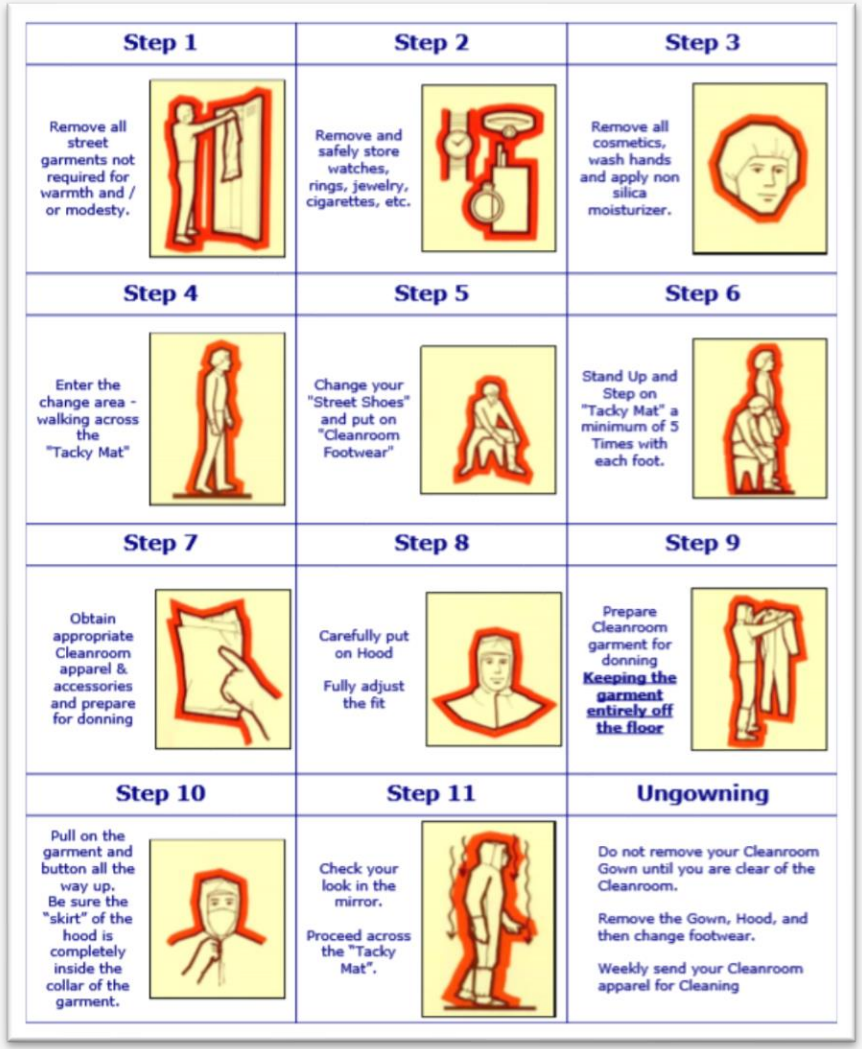
A Knight …

In Europe, knighthood was conferred upon mounted warriors. Knighthood had become associated with the ideals of chivalry, a code of conduct for the perfect courtly Christian warrior. Often, a knight was a vassal who served as an elite fighter, a bodyguard or a mercenary for a lord, with payment in the form of land holdings. The lords trusted the knights, who were skilled in battle on horseback.

… and his Shining Armor

Controls

A well designed gowning room and strict gowning procedure must be followed in order to maintain a cleanliness classification



https://www.e-s-c.com/wp-content/uploads/2018/03/Cleanroom_Gowning_Poster_Class_8.pdf

Controls

Depending on the cleanroom classification and application, the gowning as well as the procedure may vary

0.5 μm Particles / Minute	Street Clothing	Frock & Bouffant	Hood & Coverall
Sitting	302,000	112,000	7,450
Swing Arms	2,980,000	300,000	18,700
Twisting Upper Body	850,000	267,000	14,900
Walking	2,920,000	1,010,000	56,000

https://www.e-s-c.com/wp-content/uploads/2018/03/ESC_Cleanroom_Recommended_Garment_Use.pdf

Controls

ISO Class 4 (10)	ISO Class 5 (100)	ISO Class 6 (1,000)	ISO 7 (10,000)	ISO 8 (100,000)
Full Coverage Hood c/w Face Mask			Hood or Bouffant	Bouffant
Coverall			Coverall or Frock	Frock
Full Coverage Boots		Boots	Dedicated Footwear	
Gloves			Gloves (Optional)	
Recommended Frequency of Change				
Per Entry		Daily		Daily or as Required
Sterile Areas per Entry				

https://www.e-s-c.com/wp-content/uploads/2018/03/ESC_Cleanroom_Recommended_Garment_Use.pdf

Heuristic Perspective

Before the aseptic processing technology evolution;

Horribly contaminated humans, shedding clouds of particles roamed controlled spaces, invading sterile products manufacturing processes

Gowning, booting and hair-netting the contaminated helped tame the beasts and manage the risk;

But their presence could not be denied… that is until now…

Advancement in the last 10 years in aseptic processing equipment;

Has armed the pharmaceutical manufacturers with the defensive systems

Future is creating a true "No Man's Land"

Where human intervention and its risk are banished forever

Heuristic Perspective

- Parenteral products manufacturing requires a controlled and validated clean production environment. If the terminal sterilisation of the final product is not possible, aseptic manufacturing is the only alternative
- In aseptic production, product exposure to the environment during different stages of the manufacturing process cannot be avoided. Aseptic manufacturing of sterile products requires a high level of contamination control
- Biggest risk factor in sterile manufacturing is personnel. People tend to shed like hair, skin cells, saliva, sebaceous matter, sweat, particles from clothing and exogenous particles and substances into the cleanroom

Heuristic Perspective

- Adequate cleanroom garments, as well as undergarments, are critically important to reduce the risk of contaminating the environment or products

Regulatory Perspective

USA, 21 Code of Federal Regulations, Part 210

§ 211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

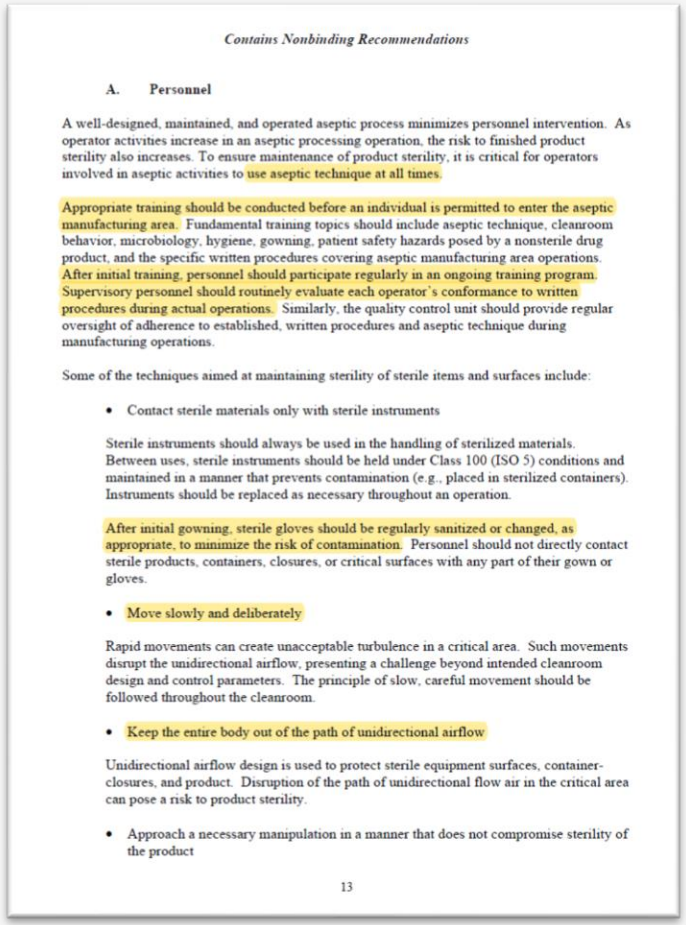
(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

Regulatory Perspective

USFDA, Guidance for Industry Sterile Drug Products
Produced by Aseptic Processing — Current Good Manufacturing Practice



Contains Nonbinding Recommendations

A. Personnel

A well-designed, maintained, and operated aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. To ensure maintenance of product sterility, it is critical for operators involved in aseptic activities to use aseptic technique at all times.

Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a nonsterile drug product, and the specific written procedures covering aseptic manufacturing area operations. After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations.

Some of the techniques aimed at maintaining sterility of sterile items and surfaces include:

- Contact sterile materials only with sterile instruments

Sterile instruments should always be used in the handling of sterilized materials. Between uses, sterile instruments should be held under Class 100 (ISO 5) conditions and maintained in a manner that prevents contamination (e.g., placed in sterilized containers). Instruments should be replaced as necessary throughout an operation.

After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces with any part of their gown or gloves.

- Move slowly and deliberately

Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended cleanroom design and control parameters. The principle of slow, careful movement should be followed throughout the cleanroom.

- Keep the entire body out of the path of unidirectional airflow

Unidirectional airflow design is used to protect sterile equipment surfaces, container-closures, and product. Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility.

- Approach a necessary manipulation in a manner that does not compromise sterility of the product

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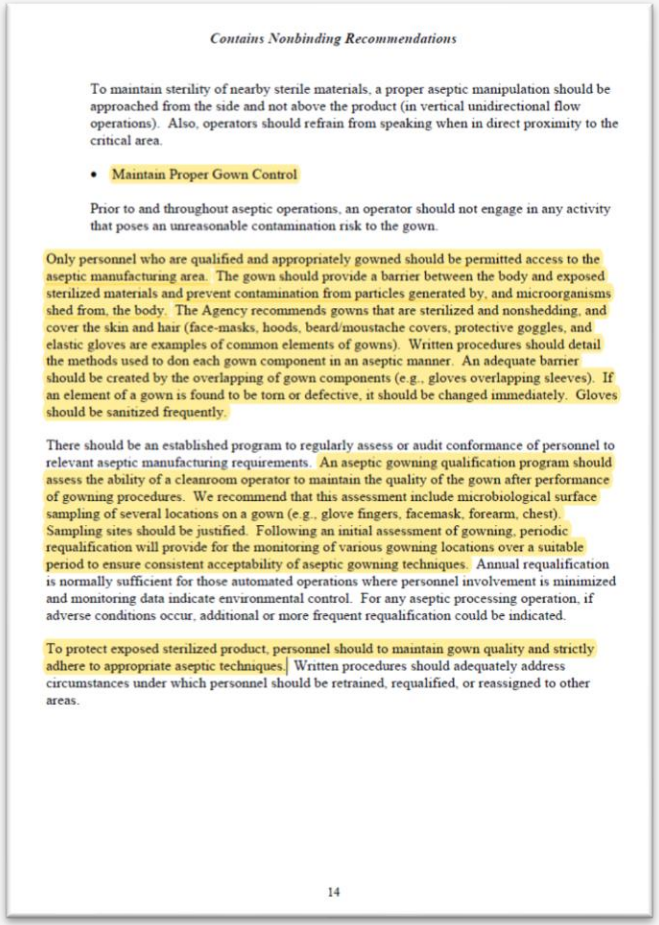

Contains Nonbinding Recommendations

To maintain sterility of nearby sterile materials, a proper aseptic manipulation should be approached from the side and not above the product (in vertical unidirectional flow operations). Also, operators should refrain from speaking when in direct proximity to the critical area.

- Maintain Proper Gown Control

Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown.

Only personnel who are qualified and appropriately gowned should be permitted access to the aseptic manufacturing area. The gown should provide a barrier between the body and exposed sterilized materials and prevent contamination from particles generated by, and microorganisms shed from, the body. The Agency recommends gowns that are sterilized 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). Written procedures should detail the methods used to don each gown component in an aseptic manner. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of a gown is found to be torn or defective, it should be changed immediately. Gloves should be sanitized frequently.

There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a cleanroom operator to maintain the quality of the gown after performance of gowning procedures. We recommend that this assessment include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest). Sampling sites should be justified. Following an initial assessment of gowning, periodic requalification will provide for the monitoring of various gowning locations over a suitable period to ensure consistent acceptability of aseptic gowning techniques. Annual requalification is normally sufficient for those automated operations where personnel involvement is minimized and monitoring data indicate environmental control. For any aseptic processing operation, if adverse conditions occur, additional or more frequent requalification could be indicated.

To protect exposed sterilized product, personnel should to maintain gown quality and strictly adhere to appropriate aseptic techniques. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

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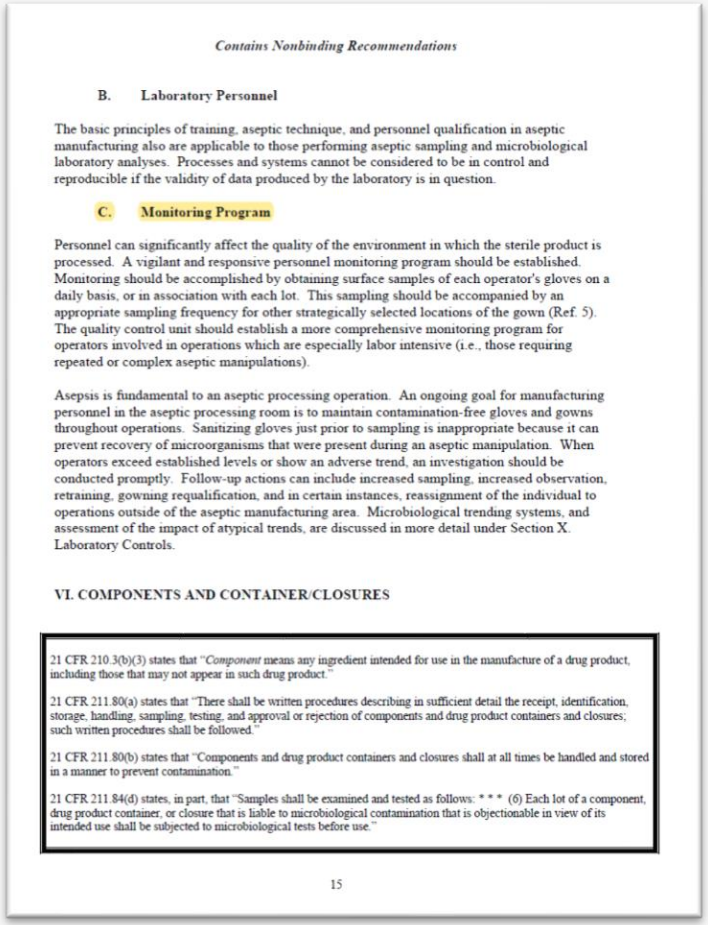


Contains Nonbinding Recommendations

B. Laboratory Personnel

The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing also are applicable to those performing aseptic sampling and microbiological laboratory analyses. Processes and systems cannot be considered to be in control and reproducible if the validity of data produced by the laboratory is in question.

C. Monitoring Program

Personnel can significantly affect the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each operator's gloves on a daily basis, or in association with each lot. This sampling should be accompanied by an appropriate sampling frequency for other strategically selected locations of the gown (Ref. 5). The quality control unit should establish a more comprehensive monitoring program for operators involved in operations which are especially labor intensive (i.e., those requiring repeated or complex aseptic manipulations).

Asepsis is fundamental to an aseptic processing operation. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves and gowns throughout operations. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. When operators exceed established levels or show an adverse trend, an investigation should be conducted promptly. Follow-up actions can include increased sampling, increased observation, retraining, gowning requalificaton, and in certain instances, reassignment of the individual to operations outside of the aseptic manufacturing area. Microbiological trending systems, and assessment of the impact of atypical trends, are discussed in more detail under Section X. Laboratory Controls.

VI. COMPONENTS AND CONTAINER/CLOSURES

21 CFR 210.3(b)(3) states that "*Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."

21 CFR 211.80(a) states that "There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed."

21 CFR 211.80(b) states that "Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."

21 CFR 211.84(d) states, in part, that "Samples shall be examined and tested as follows: * * * (6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."

15

Regulatory Perspective

The Rules Governing Medicinal Products in the European Union, Volume 4 – EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Part 1, Chapter 2: Personnel

Personnel Hygiene

2.15 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.16 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

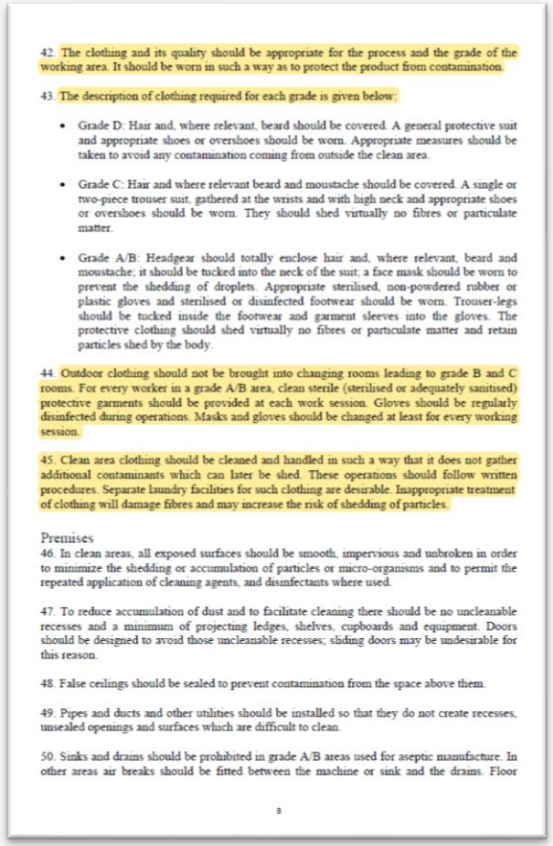
2.17 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.19 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

Regulatory Perspective

EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1 Manufacture of Sterile Medicinal Products



42. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

43. The description of clothing required for each grade is given below:

- Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
- Grade C: 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: 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.

44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

Premises

46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

47. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

48. False ceilings should be sealed to prevent contamination from the space above them.

49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

50. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor

8

Regulatory Perspective

Depending on the jurisdiction, aseptic production of sterile medicines must meet various regulatory requirements, such as those set out in:

- Annex 1 of the EU Guidelines to Good Manufacturing Practice
- US Food and Drug Administration (FDA) Guidance for Industry on sterile drug production
- Japanese Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing

Regulatory Perspective

Current EU-GMP guidelines require:

- The use of sterilised or adequately sanitised garments for grade A/B areas
- A written procedure for changing and washing that is designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas
- Reusable garments are required to be cleaned and handled in a way that the garment does not gather additional contaminants that can be shed later

Regulatory Perspective

The current EU-GMP Annex 13 for the Manufacture of Sterile Medicinal Products includes:

- Little guidance on cleanroom garment qualification, except that it needs to be "appropriate"
- Reusable garments should be replaced based at a set frequency determined by qualification"

Regulatory Perspective

New draft EU-GMP Annex 14, published for consultation in December 2017:

- Explicitly introduces the application of QRM principles
- Provides more details on gowning, including the requirement that gowning is part of a holistic contamination control strategy
- Requires that garments must be sterile and visually checked for cleanliness and integrity
- Requirement that "reusable garments should be replaced based at a set frequency determined by qualification or if the damage is identified"

This compels manufacturers to produce data regarding the effect of reprocessing on the fabric and the overall garments

Regulatory Perspective

c). The operator's forehead was not covered allowing exposed facial skin over the critical ISO 5 laminar flow areas where sterile injectable drug products are processed.

d). We observed the gowning practices of the pharmacist prior to the production of Bevacizumab (0.05 mL) 25 mg/mL Injection (Avastin 25 mg/mL Injection). (b) (6) entered the sterile production area wearing a single pair of non-sterile gloves. Within the clean room (b) (6) donned a second pair of gloves, sterile latex, powder free. When (b) (6) extended (b) (6) arms to ensure that (b) (6) fingers filled the appropriate position, the pharmacist's bare wrist and forearm were exposed to the ISO 7 clean room environment.

Protective apparel is not worn as necessary to protect drug products from contamination.

We observed that the apparel worn by personnel who were producing injectable drug products in the ISO-7 cleanroom did not cover all skin areas on the forehead, around the eyes, and on the necks of the workers. Hoods and goggles were not used. The bairnets, beard covers, face masks, and disposable lab coats that were worn were non-sterile items. The workers were gowned as described in the firm's written procedure P&P No. 7.040, "Gowning."

Regulatory Perspective

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Specifically, your firm uses non-sterile hair covers, mouth covers, and gowns as clothing for personnel who aseptically process drug products in the clean room.

On March 18 and 19, 2013, a technician, (b) was observed aseptically processing drugs in the ISO 5 Hood, within the ISO 7 clean room, with exposed skin on the face and neck and exposed hair not fully covered by the technician's hair cover. Additionally, clothing worn by the personnel outside the clean room in unclassified areas was not completely covered by the gowning around the neck area, below the knee, and around the backside of the operator . The operator observed was aseptically processing prescriptions for the following aseptically processed drug products:

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

a). Sterile drug products are aseptically manipulated by the clean room operators who were observed wearing non-sterile eyeglasses, a non-sterile hair net, and non-sterile under garments that were worn outdoors prior to entry to the clean room.

b). The clean room operator was observed re-using coveralls that were hanging on a hook in the anteroom.

Cleanroom Garments (Risks)

Risk Factors with Cleanroom Garments Include:

- Gowning Procedures & Processes
- Qualification (Garment Design, Gowning Procedures & Processes)
- Laundering
- Packing
- Cleaning & Sanitization/ Sterilisation
- Inspection & Repairs
- Storage
- Handling and Logistics

Cleanroom Garments (Design & Qualification)

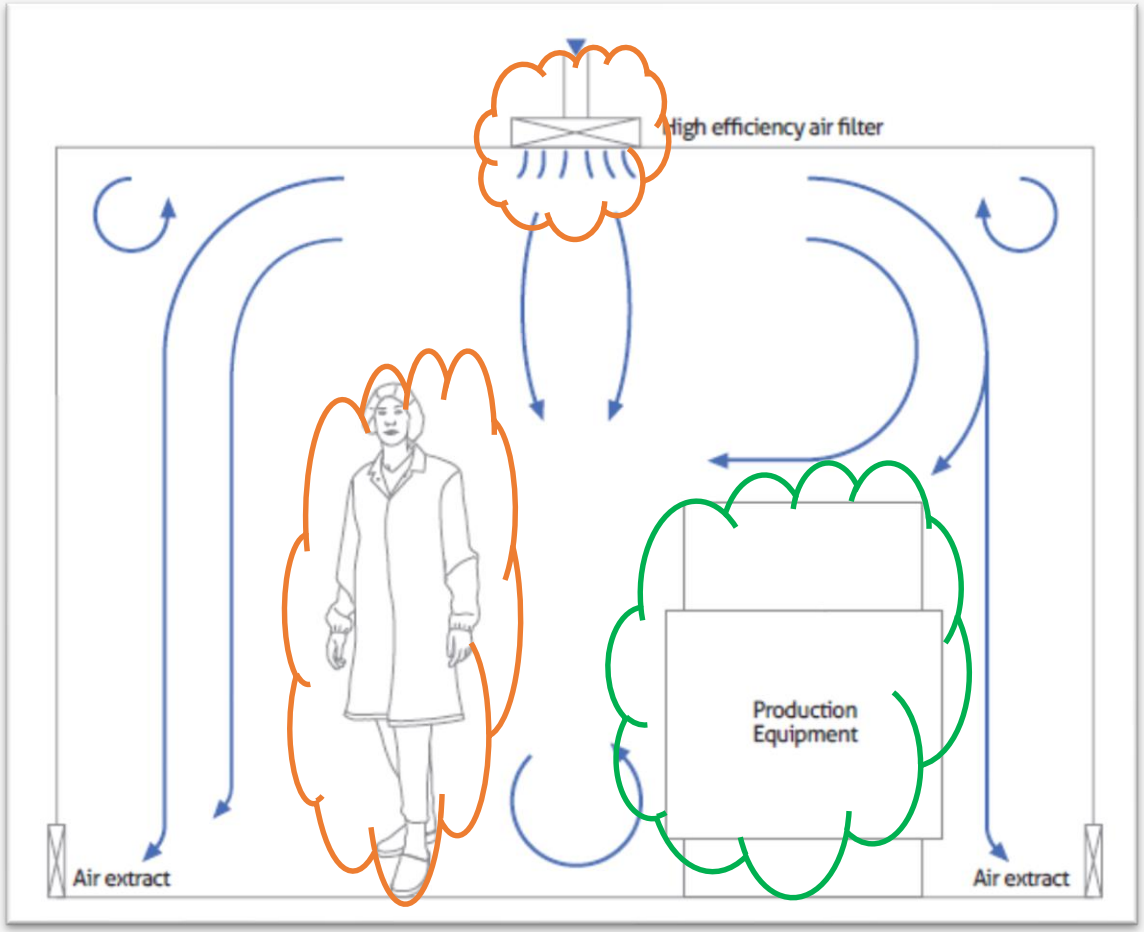
Material qualification	Performance testing	Stability testing	Usability evaluation
Cleanroom garments • Fiber and particle shedding • Sterilization compatibility • Sterility assurance level • Pyrogenicity • Particle filtration efficiency • Bacterial filtration efficiency • Porosity • Surface resistivity	*Cleanroom garments* • Body box testing • Helmke drum test	*Single-Use garments* • Properties and characteristics at the end of shelf life *Reusable garments* • Properties and characteristics after maximum number of laundering and sterilization cycles	*Use scenarios* • Transfer to classified storage area • Readability of label • Easy opening of packaging • Aseptic unfolding of garments • Gowning • Donning additional accessories (e.g., sterile gloves, face mask, goggles) • Work situations
Packaging • Fiber and particle shedding • Bioburden • Penetration of commonly used disinfectants	*Sterile packaging* • Influence of transport on integrity/ sterility (ISO 11607-1)	*Sterile packaging* • Packaging integrity sterility at the end of shelf life (ISO 11607-1)	*Packaging* • Aseptic presentation of garments (multiple layers)

Guidelines

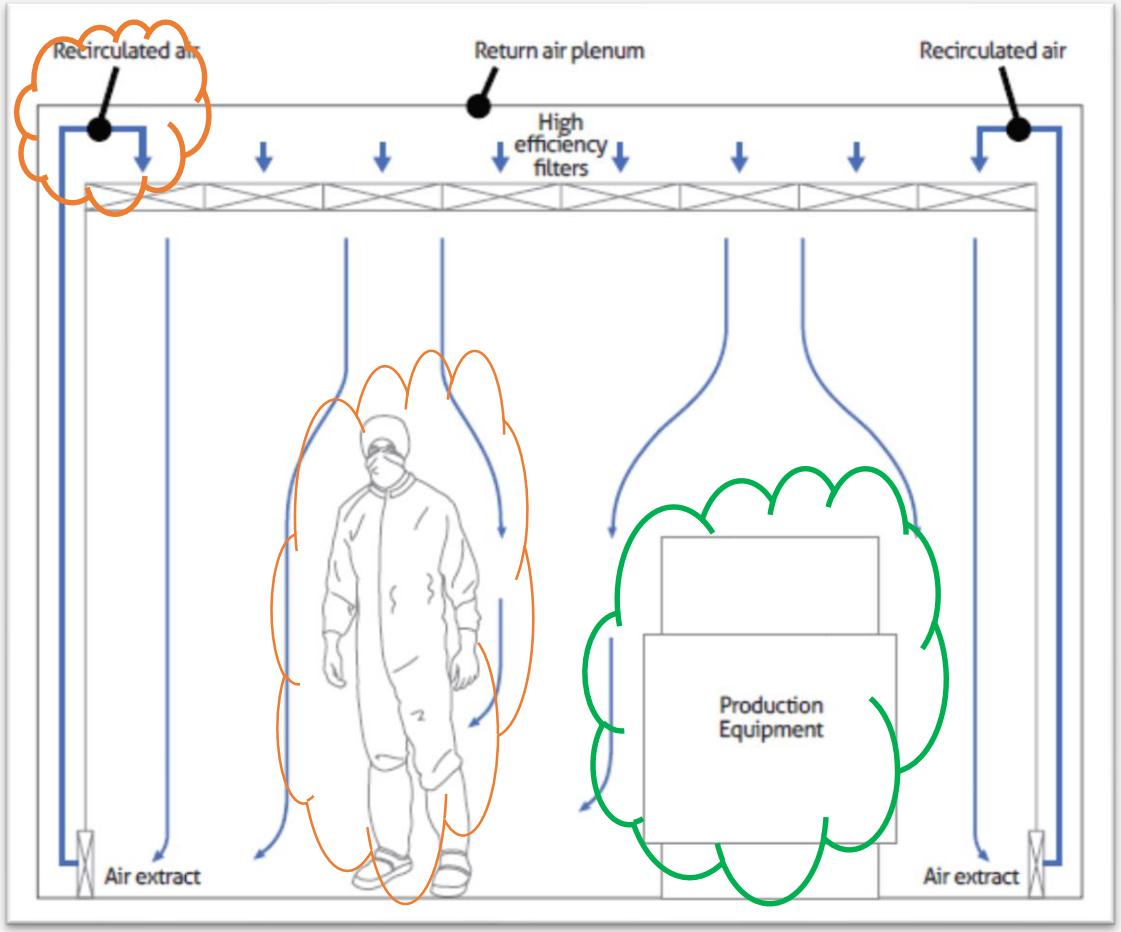
- The ISO 14644-5: 2004 Annex B on cleanroom clothing requirements – can be used to establish the user requirements specification (URS)
- The ISO 13408-1: 2008 includes some general requirements on cleanroom garments for aseptic processing, but does not provide much guidance on cleanroom garment system qualifications
- IEST-RP-CC003.4: 2013 provides guidance on design, selection, specification, maintenance and testing of garment systems.
- IEST-RP-CC003.4: 2013, "Appendix B" proposes tests for assessments of particle penetration and garment cleanliness. It is the most useful document to support the qualifications of cleanroom garment systems.

Advancement & Future

Turbulent airflow cleanroom



Unidirectional airflow cleanroom



The Microclean Cleanroom Handbook, Neil Clayton Tim Eaton

Advancement & Future (Drivers)

STERILITY ASSURANCE

Conventional Cleanroom (Grade A/B)

Contamination Risks – Operator Interventions, Material Transfer

Restricted Access Barrier

Contamination Risks - Operator Interventions, Glove Integrity Failure

Isolator with Gloves

Contamination Risks - Operator Interventions, Glove Integrity Failure

Enhanced Sterility Assurance

- Remove the Operator
- Remove the Gloves

Isolator with No Gloves & No Operator

Conventional

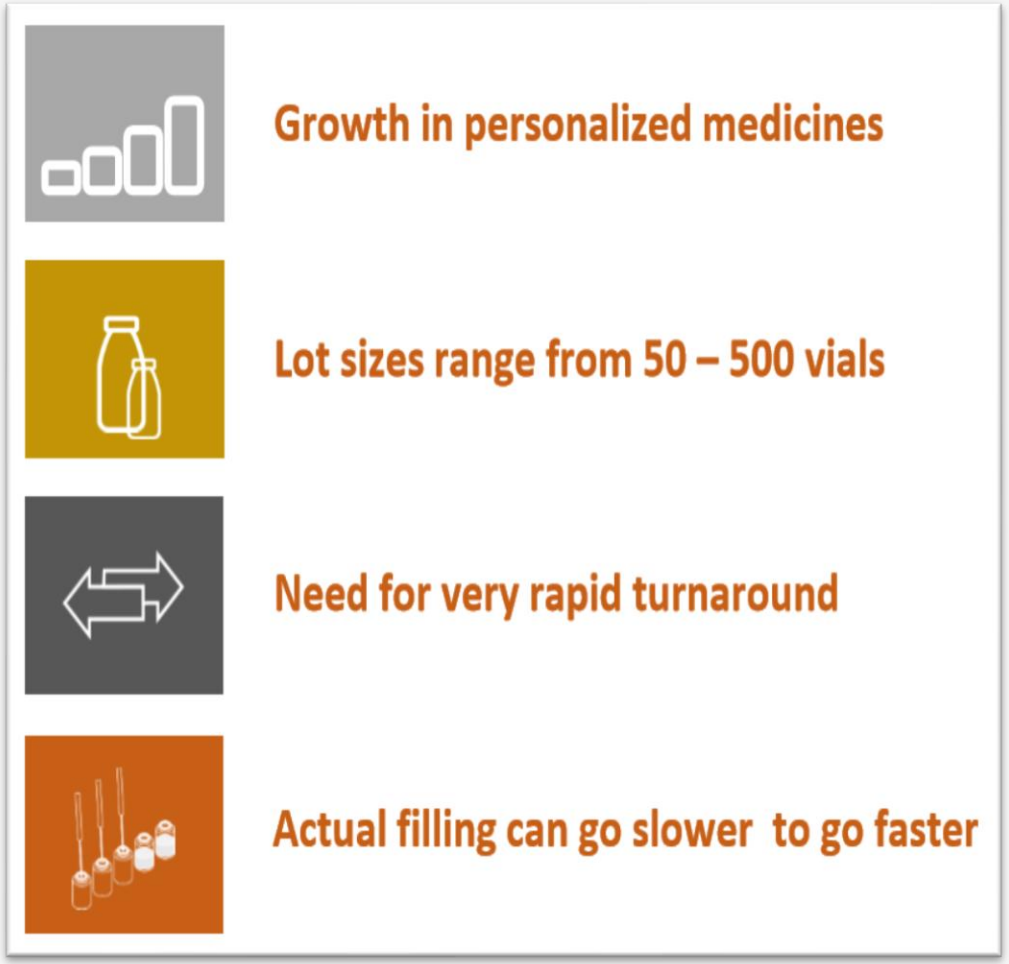
RABS

Isolator

Robotic

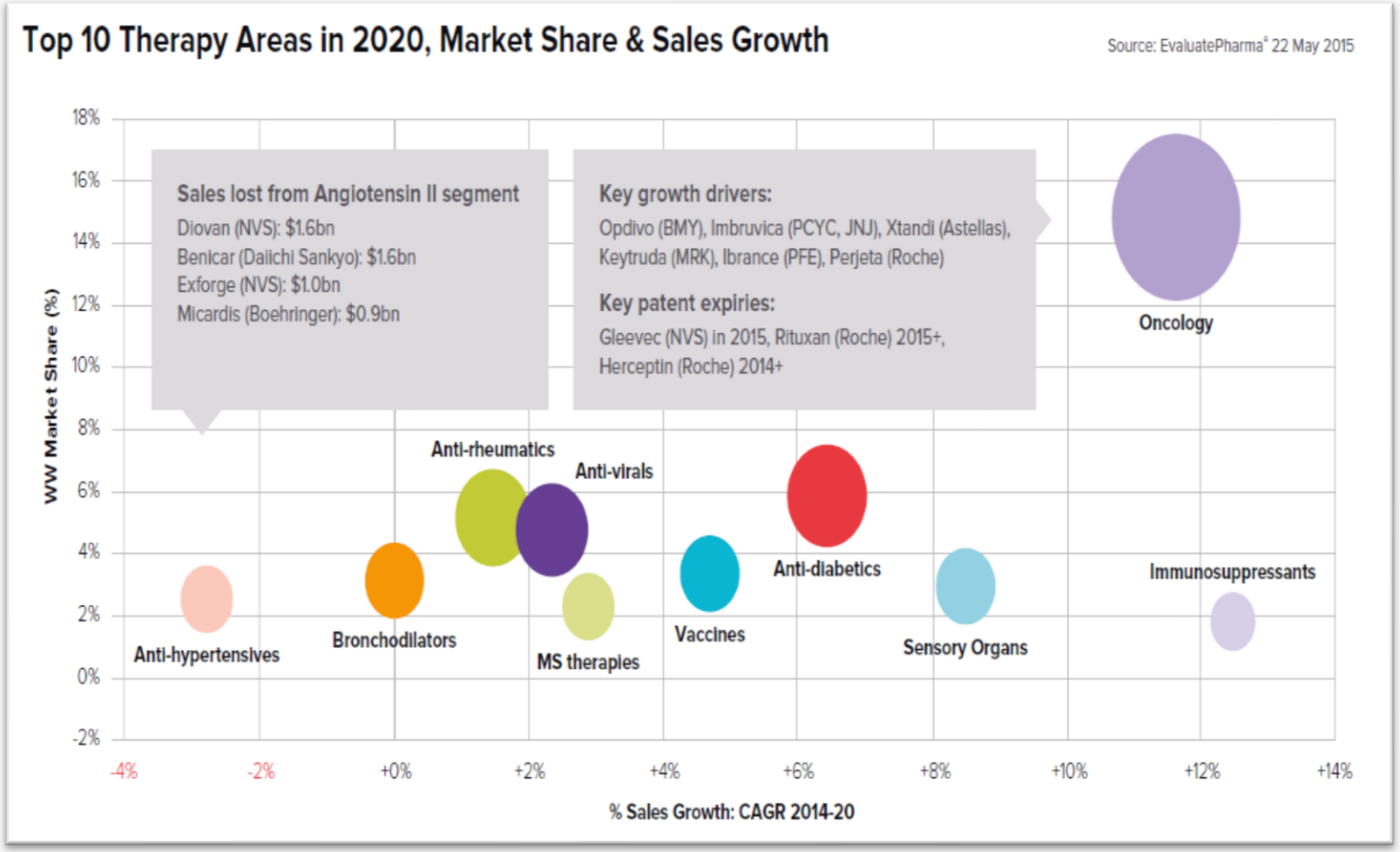
Advancement & Future (Drivers)

We See – Micro Lot Sizes



Advancement & Future (Drivers)

We See – Micro Lot Sizes



Advancement & Future (Drivers)

Business

De-Risk the Supply Chain

Low Volume, High Value Products

Flexible, Agile, Reduced Cycle Times – Vials / Cartridges / Syringes

Advanced Aseptic Technology

Advancement & Future (Challenges)

- Conservatism – Pharmaceutical Industry is Innately Conservative
- Mediocrity – Lack of Process Understanding Industry as well as regulators
- Wrong Benchmarking – Success in past regulatory inspection
- Wrong Perception – Regulatory Hurdle
- Reliability – Robotics, Automation, Components
- High Cost – Technology prohibitively expensive
- Components – Non-standard, not simple to use, variability
- Flexibility – Different components, batch sizes, components sizes
- Environmental Monitoring – Particularly microbiological

Summary & Conclusion

- Contamination Control Technology – cleanroom design, construction, control, management as well as gowning has matured
- Sterile Manufacturing Industry – evolving slowly and deliberately
- Transformation Phase – entering an era where a spate of legacy facilities will be forced to modernize, in say next decade
- High Regulatory Expectation – concern regarding contamination & its impact had never been so high
- Innovative Technology Available – high-end-technology to remove human from the aseptic processing area is now available
- We are almost there…


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
tapadh leat
спасибо
dank je
bedankt
dziękuję
hvala
mauruuru
obrigado
sukriya
kop khun krap
go raibh maith agat
arigatō
takk
dakujem
grazie
terima kasih
merci
mochchakkeram
рахмат
Баярлалаа
faafetai lava
kiitos
dankie
dhanyavad
vinaka
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mahalo
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tanemirt
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enkosi
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gràcie
köszönöm
akun
dankon
aciù
spas
kia ora
chokrane
murakoze