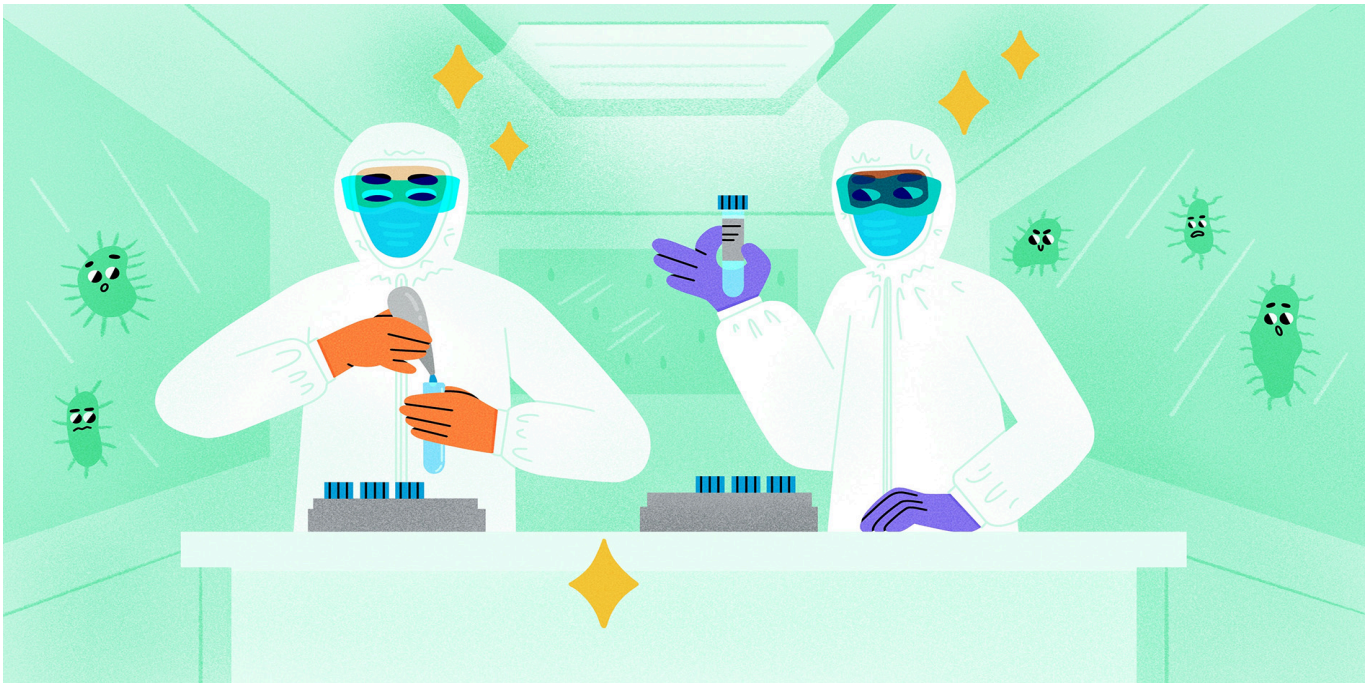
frontiers | Frontiers for Young Minds

HUMAN HEALTH
Published: 12 January 2023
doi: 10.3389/frym.2022.894320



PRODUCING SAFE MEDICINES: CLEANROOMS CONTROL MICROORGANISMS

Kirstie Alice Goggin[1*], *Mark Thompson*[1] *and Tim Sandle*[2]

[1]*MTL Projects Ltd., Bishop Auckland, United Kingdom*

[2]*Bio Products Laboratory, Elstree, United Kingdom*

YOUNG REVIEWER:

ANJISHNU

AGE: 15

Medicines are chemicals that are used to cure, slow, or prevent disease. Some medicines are injected into the bloodstream, so production facilities must make sure those medicines do not contain microorganisms, toxins, or particles. If they did, the medicines could make people very ill and even cause death, which is the opposite of what medicines are supposed to do! That is why medicine production around the world is strictly monitored, to prevent anything bad like this from happening! In this article, we discuss how to control microorganisms in medicine production, ensuring that medicines are safe for patients.

WHY DO MEDICINES NEED TO BE STERILE?

When swallowed, tablet or liquid medicines travel to the stomach and liver where they are broken down and sent to the places in the body where they need to act. The stomach contains strong acids that kill **microorganisms**, so manufacturers do not need to worry much

MICROORGANISMS

Small organisms that cannot be seen with the naked eye, including bacteria, viruses, or fungi.

about controlling microorganisms in medications that are swallowed. However, fungi can be quite problematic, so many precautions must still be taken in the production of non-sterile oral medicines.

Other medicines are injected into the bloodstream, which helps them to act faster than oral medicines. These medicines are called **parenterals**. Parenterals are used if a patient is very sick or unconscious or is unable to swallow. Because these medicines enter the bloodstream, they must be **sterile**, meaning they must be free from bacteria or other living microorganisms. If an injectable medicine contains microorganisms, those microorganisms can travel around the body and multiply, making people very sick. Therefore, production facilities called **cleanrooms** use special technologies to prevent microorganisms from getting into medicines.

PARENTERALS

Medicinal products that are administered into the bloodstream or the eye.

STERILE

Free from microorganisms; totally clean.

CLEANROOM

An engineered space that maintains low concentrations of airborne particles to greatly reduce microorganisms.

WHAT ARE CLEANROOMS?

Cleanrooms are special rooms where things like dust, microorganisms, and particles are filtered out. The air is changed regularly to keep the area as clean as possible. Cleanrooms are classified into various levels (A, B, C, or D) depending on the number of microorganisms and particles allowed in the room [1]. Grade A is the "cleanest" cleanroom, whilst D is the least clean, but still much cleaner than you can imagine! Even though cleanrooms are highly controlled, microorganisms and particles can still sneak in! Figure 1 shows what a cleanroom looks like.

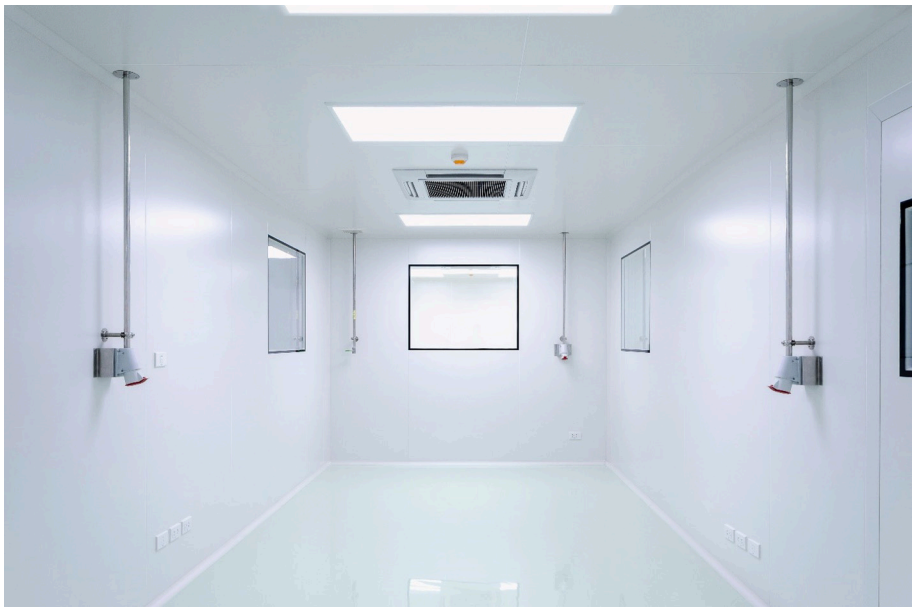


Figure 1

A typical cleanroom. Notice the smooth surfaces, the lack of windowsills, and the vents in the ceiling.

SOURCES OF CLEANROOM CONTAMINATION

Producing injectable medicines is very complex! From beginning to end, injectable medicine production requires highly skilled people and special equipment. Microorganisms can sneak into cleanrooms in several ways, including on people, through water or air, on surfaces, and through the transport of items in and out of cleanrooms.

People

Most microorganisms in cleanrooms come from the humans working in those areas. The use of robots can help reduce the number of people needed in the cleanroom, but humans are often still required. Studies in contaminated cleanrooms show that most of the microorganisms are those usually found on human skin [2]. When working in cleanrooms, people must wear specially designed clothing to control contamination. This process is called **aseptic gowning** (Figure 2). This clothing usually includes gloves, masks, shoe covers, hoods and a suit that looks like pajamas. Humans produce high numbers of skin cells (5 billion per day), so even with all this protection, microorganisms can hitch a ride on those shed skin cells, contaminating the cleanroom. Aseptic gowning cannot capture every single one!

ASEPTIC GOWNING

Protective clothing used in very clean environments; provided for one-time use.

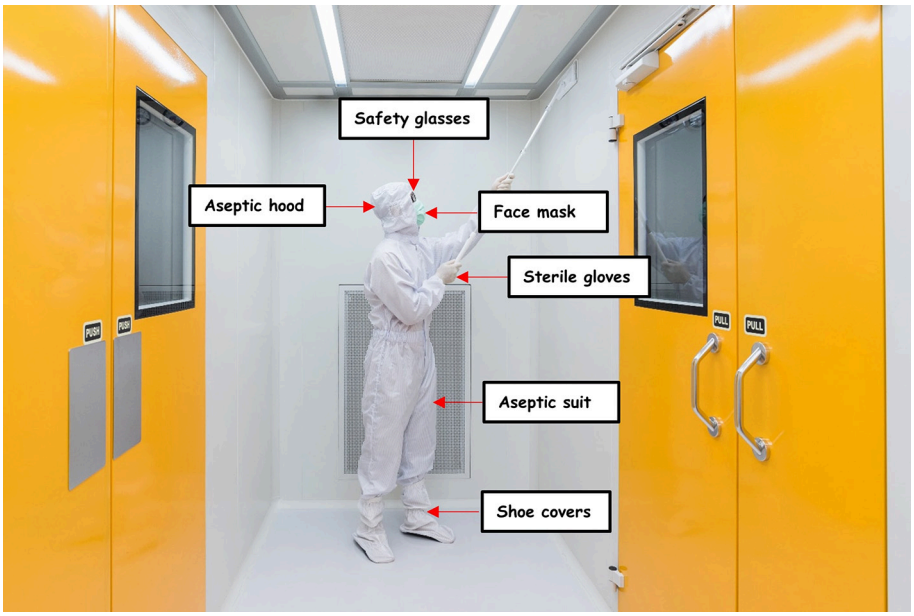


Figure 2

Aseptic gowning usually includes safety glasses, a hood to cover the hair and forehead, a facemask to prevent microorganisms from escaping through the breath, sterile gloves to prevent the shedding of skin cells or spreading of bacteria, an aseptic suit, and shoe covers. Very little skin is exposed in the cleanroom!

Before working in cleanrooms, people must have special training to help reduce contamination. For example, they must move very slowly and try not to touch surfaces. Studies have shown that the more a person moves, the more contamination is generated. For example, a person walking generates around 5 million particles per minute. A person who is standing still only generates 100,000 particles per minute [3]. This is why people who work in cleanrooms should

only move when essential, and they should minimize talking, singing, whistling, and coughing! People are also not allowed to enter the cleanroom if they feel unwell.

Water

Bacteria can sometimes grow in water. So, when producing sterile medicines, a specific type of water called **water for injection** (WFI) is used. In microbiology, the number of microorganisms that can grow is estimated using a measure called **colony forming units** (CFU). In drinking water, for example, up to 500 CFU are allowed per milliliter of water [4]. This means that, in a typical glass of drinking water, there could be up to 118,000 microorganisms! WFI, however, must be essentially free from bacteria, with < 1 CFU per milliliter of solution. So, in a glass of WFI, there could only be up to 50 microorganisms, demonstrating how clean water for injectable medicines must be! If the wrong type of water is used, then the microorganisms could grow and affect the quality of the medicine, potentially making people sick.

WATER FOR INJECTION

Water of extra high quality without significant contamination.

COLONY FORMING UNITS

A unit which estimates the number of viable microbial cells in a sample.

Air and Ventilation

Cleanrooms use two main types of ventilation systems: unidirectional air flow and turbulent air flow (Figure 3). Unidirectional airflow is used for contained areas and creates a Grade A (cleanest) environment. In unidirectional air flow, devices blow air rapidly in straight lines, either horizontally or downwards (Figure 3B). The ceilings contain special filters, and the floors and walls have vents that suck out any microorganisms in the air. Turbulent airflow (Figure 3A) is used when a room has lots of equipment and hard-to-reach areas that cannot be reached by unidirectional flow. Air flows through the whole room and is sucked out through a filter that removes any microorganisms.

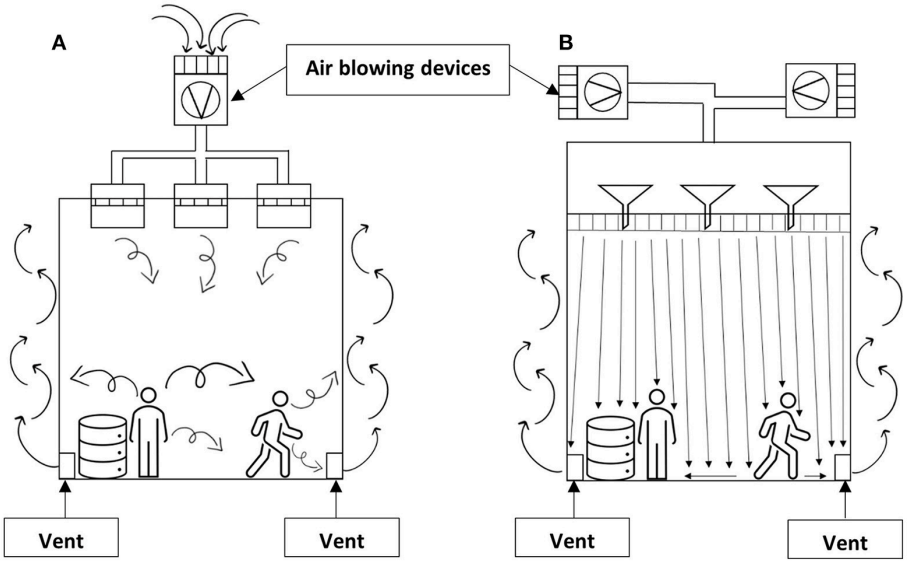


Figure 3

Figure 3

Cleanrooms use two main types of ventilation systems: Unidirectional air flow and turbulent air flow. **(A)** In turbulent air flow, filtered air mixes with airborne contaminants, which are removed through the exhaust system. **(B)** In unidirectional air flow, air is continuously supplied in one direction and sweeps contaminants away from the cleanroom environment.

Surfaces

Cleanrooms are designed to prevent microorganisms from settling and growing. Any equipment is made of hard, smooth materials that microorganisms cannot grow on, like stainless steel. Surfaces are also cleaned and disinfected regularly. Sometimes, **antimicrobial** materials like silver are added into surfaces to stop microorganisms from growing. Most cleanroom surfaces are smooth because microorganisms can settle and grow on rough surfaces. Microorganisms are much less likely to stick to smooth surfaces, so they will be picked up by the ventilation system and sucked out through the filters [5].

ANTIMICROBIAL

Capable of destroying or inhibiting the growth of microorganisms.

Transport of Items In and Out of Cleanrooms

Materials must frequently be moved in and out of cleanrooms, and every time materials are moved in, there is the potential for microorganisms to hitch a ride into the cleanroom! To control this, anything entering a cleanroom must be cleaned first. This includes the use of disinfectant solutions that kill microorganisms and their spores. Spores are released by microorganisms and have the potential to grow into new microorganisms. Materials are also moved into cleanrooms through transport chutes that have unidirectional airflow. This reduces contamination risk by sweeping any microorganisms off the surfaces and into the ventilation systems before the materials are moved into the cleanroom.

SUMMARY

When producing injectable medicines, production facilities must ensure that they have a clean environment and everyone must try their best to prevent contamination of cleanrooms. By doing so, facilities can be confident that medicines will be safe for patients and will work the way they are meant to. Strict cleanliness measures during the production of medicines mean that facilities can rapidly trace the source of contamination, if it occurs, and prevent any affected medicines from being distributed to patients, keeping people safe.

REFERENCES

1. Farquharson, G. J., and Goldschmidt, N. A. 2017. *Understanding Cleanliness Classifications for Life Science Facilities*. Pharmaceutical Engineering. Available online at: https://ispe.org/pharmaceutical-engineering/march-april-2017/understanding-cleanliness-classifications-life-science (accessed March 05, 2022).
2. Study into human particle shedding. 2011. *Cleanroom Technology*. Available online at: https://cleanroomtechnology.com/news/article_page/Study_into_human_particle_shedding/62768 (accessed March 05, 2022).

3. Cleanroom Technology. 2011. *Study Into Human Particle Shedding*. Available online at: https://cleanroomtechnology.com/news/article_page/Study_into_human_particle_shedding/62768 (accessed March 11, 2022).
4. Food and Drug Administration. 2016. *Guide to Inspections of High Purity Water Systems*. High Purity Water System (7/93). Available online at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/high-purity-water-system-793 (accessed March 05, 2022).
5. Whyte, W., Agricola, K., Derks, M. 2015. Airborne particle deposition in cleanrooms: deposition mechanisms. *Clean Air Containment Rev*. 24:4–9.

SUBMITTED: 11 March 2022; **ACCEPTED:** 19 December 2022;
PUBLISHED ONLINE: 12 January 2023.

EDITOR: Michelle Juarez, Cold Spring Harbor Laboratory, United States

SCIENCE MENTOR: Anjan Debnath

CITATION: Goggin KA, Thompson M and Sandle T (2023) Producing Safe Medicines: Cleanrooms Control Microorganisms. Front. Young Minds 10:894320. doi: 10.3389/frym.2022.894320

CONFLICT OF INTEREST: KG and MT were employed by MTL Projects Ltd. TS was employed by Bio Production Laboratory.

YOUNG REVIEWER

ANJISHNU, AGE: 15
Hello, my name is Anjishnu and I am in ninth grade. I have a passion for writing, reading, math, and science. I also like reading about cars and other vehicles. I enjoy playing tennis. I want to study biology when I grow older so that I can pursue a career in science.

AUTHORS

KIRSTIE ALICE GOGGIN
I am a lead scientist at MTL Projects Ltd. I travel to pharmaceutical sites and conduct studies related to contamination control in cleanrooms. I also provide advice to pharmaceutical companies around the world about producing safe medicine I thoroughly enjoy increasing people's engagement in STEM areas and I am passionate about helping people. In my spare time, I am a private biology

and chemistry tutor, helping students do better in school. I have a Ph.D. in analytical chemistry/biology and several publications and awards. I am also a chartered scientist. *kirstie@mtlprojects.com

MARK THOMPSON

I am a chartered engineer with over 25 years' experience in the life sciences industry. I have held senior management roles within Eli Lily, Sanofi Aventis, and Smith and Nephew. I am now the managing director of MTL Projects and Mark Thompson Life Sciences. I give advice to pharmaceutical companies around the globe, including advice about parenteral product manufacture and sterilization. I regularly teach training courses to pharmaceutical organizations, including courses for regulatory inspectors.

TIM SANDLE

I am a chartered biologist with over 25 years' experience in pharmaceutical microbiology. I work for a sterile products manufacturer (BPL) and I am a visiting tutor at the University of Manchester and University College London. I write regularly on the topic of microbiology, contamination control, and quality assurance. I have a Ph.D. in microbiology and I am a fellow of the Institute of Science and Technology.