Energy Impact of Ventilation and Air Infiltration
14th AIVC Conference, Copenhagen, Denmark
21-23 September 1993

Clean Room Technology

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High quality is a prerequisite for industry to sell its products. To secure an optimized production and at the same time assure a minimum of wastage, it is often required that the production takes place in an environment where control is exerted on the particle concentration in the air and also on thermal conditions.

Medical production is subjected to requirements from the authorities to comply with definite requirements of purity, according to the pharmaceutical in question.

Micro-electronic or mechanical industries indispensably require clean room technology, if rejections of finished products are to be avoided.

Experience shows that the quality of many food products gets an improved durability and less risk of bacterial contamination, when clean room technology is applied in the sections of production where the food products are most vulnerable to contamination from raw materials, air, water and human beings.

1. Background

Clean room technology has its origin in the military exploitation of nuclear energy. However in the 1950 and the 1960 the more peaceful utilization accelerated.

The micro-biologically controlled room – **the clean room** – was accepted and prevailed in the industries where dust and microorganisms were real "poison" to the products – i.a. in the pharmaceutical and the electronics industries. For these industries it was necessary to operate in clean rooms or with elements from the clean room technology to be able to deliver goods of the quality wanted by the market. Within the food industry, the producers started later to implement complete solutions corresponding to those known in the pharmaceutical industry.

Clean room technology is not a universal solution, solving all problems by killing all micro-organisms. The clean room technology is a tool which – by its many elements – succeeds in getting control of both particle concentration, as well as the microbiological contamination of the room.

For pharmaceutical production and food processing, it is primarily a question of avoiding live micro-organisms, while for the electronics industry it is a question of avoiding all types of particles. As dead particles however often act as "carriers" of live (bacteria, spores, fungi) the problem to a certain extent remains the same: full control of the particle content in the rooms.

The purpose of applying clean room technology is the wish to:

- exclude the surroundings affecting the production
- prevent spreading of contamination to the production
- prevent dangerous substances affecting the personnel
- prevent cross-contamination from one product to another

Figure 1 shows which factors that essentially influence the product, for which "protection" is wanted by means of a clean room technology.

2. Definitions

The expression **clean room** leaves many thinking of ultra-clean surroundings, where the personnel work in space suits. In reality the word covers a wide range of cleanliness levels.

There are very many different definitions of a **clean room**. The most precise – and probably also the most frequently used – is the following from FED-STD-209E:

> "A room in which the concentration of airborne particles are controlled and which contains one or more clean zones."

In the definition there is thus not any distinction between live and dead particles.

3. Standards

The standardization work within clean room technology has a tendency both in national and international work to be harmonized.

Thanks to the international standardization work, a uniform language and basis have been established for everybody working with clean room technology – users, designers and producers.

The standards define:
- Production requirements for application of clean room facilities
- Fundamental concepts and structural requirements
- Measuring methods for control of compliance with the requirements
- Requirements for the correct use of the clean rooms.

The word "standard" is used as a general term and covers actually a wide spectrum of:
- Standards
- Technical orders
- Recommended papers
- Recommendations

In this paper the word "standard" covers all areas.

The standard can primarily be divided into two main groups:
- Pharmaceutical standards
- Engineering standards

The pharmaceutical standards comprise both national and international standards. An important example is the EC "Good Manufacturing Practice", (GMP). The requirements indicated in this standard ensures that the quality requirement for the production of pharmaceuticals are uniform in most of Europe, which assures both the producers uniform exporting conditions and the consumers a uniform quality.

As an example, the EC-GMP requirements to cleaniliness are indicated below:

	Max. contents of particles per m^3 = or >		
Class	0.5μ m	5.0 μ m	Max number of micro org per m^3
A laminary airflow	3,500	0	under 1
B	3,500	0	5
C	350,000	2,000	100
D	3,500,000	20,000	500

Table 1: EC-GMP air classification

In the text of the GMP it is indicated which class is required for specific production purposes.

The food processing sector has only to a limited extent its own standards. In France, however, there are special standards for packing of finished food products. Nevertheless, many experiences have shown that the food processing industry to a wide extent may use exactly the same cleanliness requirements as indicated for the pharmaceutical industry. In the actual case, it must be assessed to which cleanliness class the individual product should be produced.

The engineering standards primarily have the purpose of defining the classes, measuring and control procedures, as well as filter classifications. Many major industrial nations have their own standards with definitions of purity class. Nonetheless all have their inspiration from FED STD 209, which was first published in 1963. Edition E which has been in force since autumn 1992 for the first time in metric units. The 209, now has an even bigger

chance of becoming a worldwide standard. FS 209 indicates in addition to the classes of clean rooms, requirements for measuring equipment and procedures.

In 209 a clean room is classified as a figure **M** in accordance with the following equation:

$$\text{Number of particles/m}^3 = 10^M (0.5/d)^{2.7}$$

d is the diameter of the particle in μm.

For particles of 0.5 μm or larger, the following table is ruling:

Particles ≥ 0.5 μm/m³	FS 209 E
10	Class M 1
100	Class M 2
1,000	Class M 3
10,000	Class M 4
100,000	Class M 5
1,000,000	Class M 6
10,000,000	Class M 7

Table 2, Room categories in accordance with FS 209 E

4. Design of Clean Room Facilities

Many parameters influence the quality of the finished product. For the client/user it is essential to find the point with the highest profit in relation to the investment without "going beyond the target", when the requirements have to be converted into results.

Assistance cannot be found in cooking book recipes. Therefore it is necessary to apply standards and previously gained experience as a basis. If the quality should be assured, it requires a careful interaction between a long series of factors, which in the concrete case may have much or little significance.

User Training. To exploit the technology to a maximum it is necessary that the users/personnel understand the background of applying clean room technology, that they know where the contaminating sources are and know exactly which requirements are made for the product in question.

Unambiguous output requirement. The users must be involved right from the beginning of the planning of the facilities: room classification, compressed air purity, water quality, etc. The requirements must be determined in collaboration with the consultants and if necessary be adjusted in the process. It is decisive that the requirements are well argumented. Do not require class M2, if class M4 is sufficient.

Building Layout. It is important that the processing and person flow of the building is designed in a rational way. An inventory must be established of raw materials, finished goods, package materials, and personnel. Avoid crossings of raw materials and finished goods. Cross-contamination from one product to another must be prevented. The personnel's communication lines must also be established.

Ventilation. The ventilation is one of the instruments, we may use to prevent infiltration of contamination and remove a possible contamination in the room. The ventilation must be adapted to the requirements put forward, it shall be designed with the filtration required and shall be carried out with the correct airflow pattern. Ventilation is dealt with later on in this paper. Can **clean zones** be designed as a limited area in order to reduce the ventilation need for the area outside of the clean zone?

Utilities. It is important to be aware of the requirements to the supply media, for example, sterile vapour for humidification, sterile compressed air for processing purposes and sterile water for injection. Which requirements will be made to the piping, supply reliability and control?

Equipment. Production equipment, machinery, etc must comply with the requirements. Has the machinery been designed in such a way that it can be serviced from a non-clean area – or shall the whole production be put to a standstill for servicing? It is also essential that the machinery is accessible for cleaning.

Measuring and control equipment. It must be emphasized that for continual assurance of compliance with the output requirements, it is necessary to establish consistent measuring procedures for cleanliness. The measuring equipment must be constantly available. The operators must be completely confident with the usage of the apparatuses.

Cleaning technique. Right from the first design phase it is necessary to plan meticulously the cleaning methods and needs.

Both **quantifiable** as well as **non-quantifiable** parameters should be applied for the evaluation of the success of a clean room.
Whether the cleanliness requirement has been fulfilled or not is easily observed. But whether the processing flow could be optimised or not, is rather more difficult to verify. However the fulfilment of the expectations of the user to the **non-quantifiable** parameters is of imperative importance to the economic result.

Ventilation

A reasonably designed ventilation system is one of the most important accessories to keep out contamination and remove contamination, which anyway will find its way to the clean area. The selection of the ventilation principle must be decided on a careful evaluation of requirements and needs.

In figure 2 the most common ventilation principles for clean room facilities are indicated. Traditional ventilation – mixed or by displacement – is applied, where the requirements are not very high. Laminary flow – horizontal or vertical – is applied combined with recir-culation in rooms, where the requirement to purity is very high.

In clean rooms of today it has become quite common that the traditional ventilation is combined with the laminary flow, in such a way that a clean room will be designed with a "controlled background" with mixed ventilation combined with one or more "clean zones" with a laminary flow. Consequently a considerable reduction in the ventilation need is achieved – less investment and less operation costs.

Under all circumstances it is essential that both the inlet and the exhaust fittings are placed so that the physical laws are appraised – movements of air as a consequence of the thermal effect and sedimentation of "heavy" particles. Dead "angles" not being ventilated should be avoided, as the contamination might pile up in such places.

Within the biotechnology, it might be necessary to protect the processing, at the same time as which it is necessary to protect the operator against a contamination risk from the processing. Here the isolator module could be a solution. It is possible to find small glove boxes or large boxes accommodating a person (via access from the bottom through a completely covering protection suit on the upper part of the body) that enables the person to carry out his activities.

As mentioned, the choice of ventilation principle is based on the actual requirements. It is important that already at an early stage of the design phase, it is realized which ventilation principle to apply, as the space required for positioning is very different.

Many factors are controlled by means of the ventilation:

The purity of the room. The change of air is primarily calculated according to the requirement of purity and infiltration of contamination into the room.
Air movement patterns. It should be clarified whether the need is for laminary, non-laminary flow or a combination of them. In general, it should be noted that requirements for a class M4 or better, normally would be carried out as a laminary flow. By sensible positioning of the inlet and exhaust fittings it is secured that the contamination is removed "at source" to the extent possible.
Pressure conditions. To maintain the purity in the room, clean room facilities normally are designed as "a room in the room" with a lower pressure than in the purest area. A

variation pressure of 15 Pa from area to area is normal. If spreading of hazardous substances from the clean room should be prevented, the opposite solution could be considered, that is, the clean room has the negative pressure in relation to the adjacent rooms. Under the circumstances it is important to establish airlocks securing that the variations in pressure are not equalized by opening of doors. If the inlet/exhaust volume flows vary, it is important to implement regulation equipment currently securing that the pressure conditions are correct. The regulation equipment should in addition be prepared for soiled filters and fittings.

Temperature and humidity. The production often specifies exact requirements to temperature and humidity, determining the design of the ventilation systems. If no special requirements, it is the personnel's comfort requirement that determines the ventilation.

A very important factor in the ventilation system is the **filtration.** The main part of the particles damaging the products within the food processing and pharmaceutical industries are larger than 0.3 μm. High-efficient filters (HEPA-filters) have a very high degree of separation of these particles. Therefore it is important that the correct filters are installed and that the ventilation system be prepared making it possible to gain full control of the room condition with regard to the particle content.

In figure 3 a principle is shown of the ventilation of a clean room with laminary flow for all the room. Due to energy cost-efficiency as much air as possible is recirculated through local ventilation units with ventilators and HEPA-filters. A certain amount of fresh air is added through the central ventilation system, in which a portion of the room air is recirculated. This system conditions/adapts the air in order to comply with the requirements to temperature and humidity.

The development is moving rapidly within industry. A clean room system has typically a life time of about 10 years. Therefore it is necessary to secure that the requirements of "today" and "tomorrow" have been fulfilled. On the other hand, there is no need to make more costly or complicated systems by guessing what will be the requirements of "the day after tomorrow".

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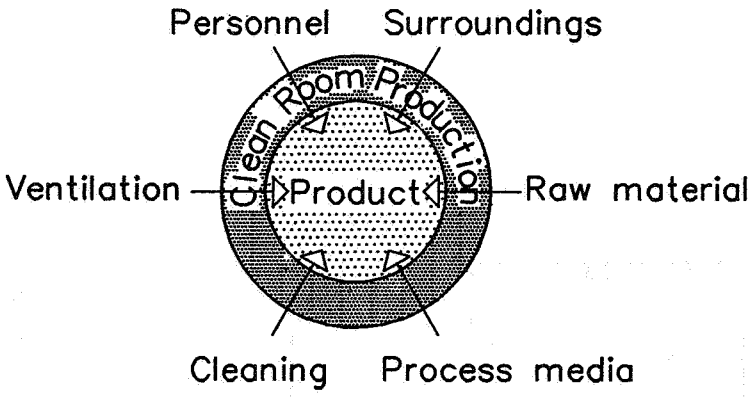

Fig. 1 Clean room production

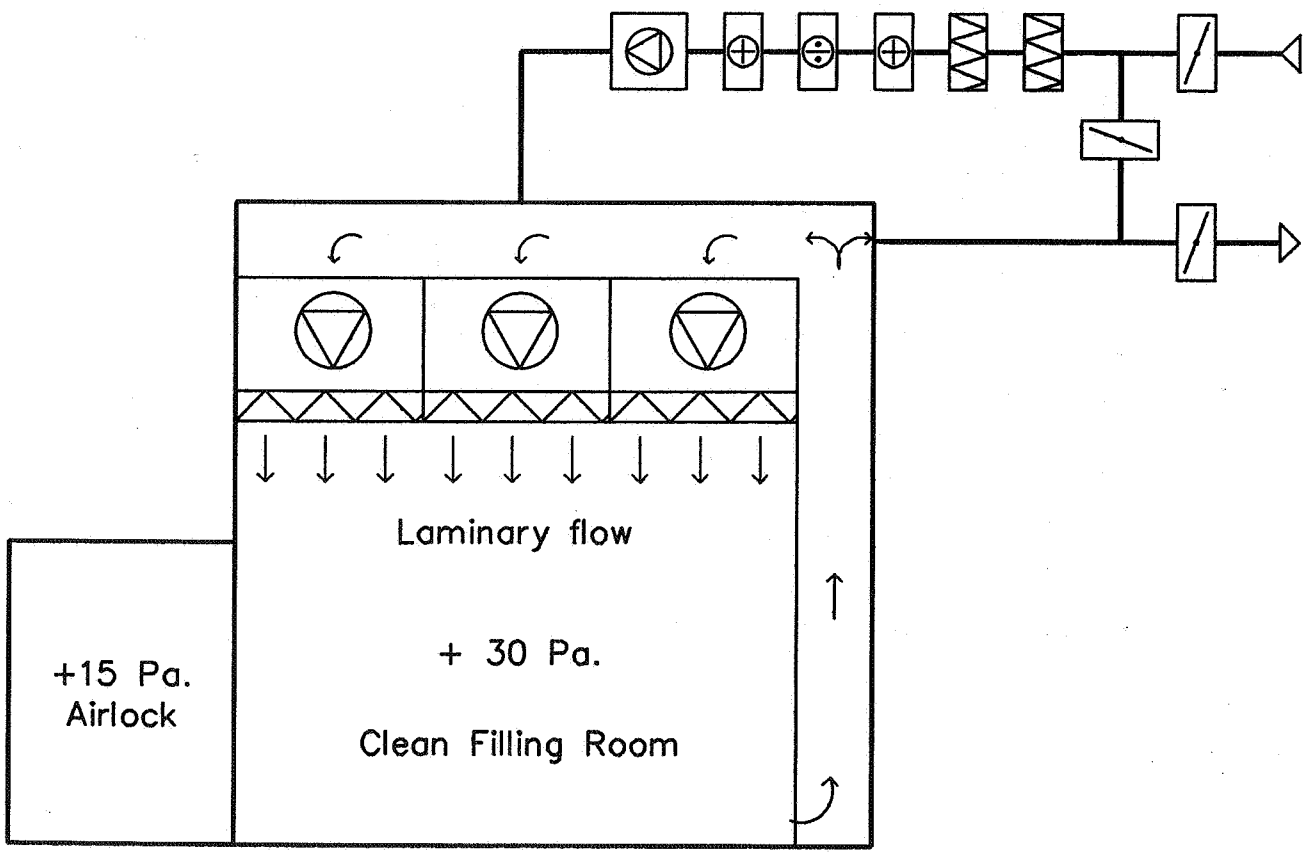

Fig. 3 Room for aseptic filling

cheap

very expensive

future?

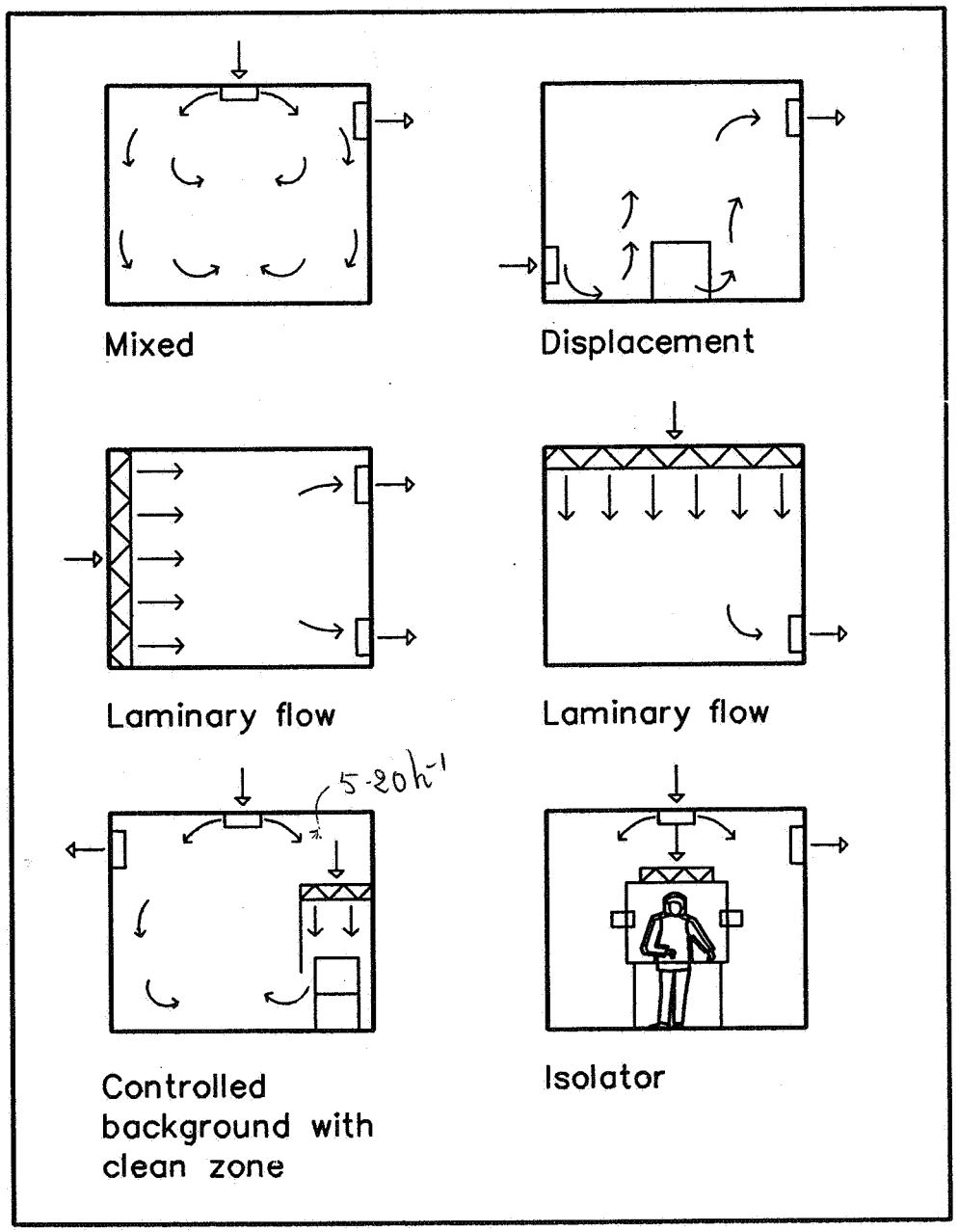

Fig.2 Ventilation principles