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Dipl.-Ing. Thomas Hinrichs

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Safety cabinets for the GMP compliant production of CMR-drugs

Contact
Dipl.-Ing. Thomas Hinrichs
Degree in Bioengineering
Area of expertise - Medical Technology
Hamburg University of Applied Science
Head of Product Management and Marketing
Berner International GmbH
Mühlenkamp 6
D-25337 Elmshorn, Germany
Tel.: +49/4121/4356-0 Fax: +49/4121/4356-20
t.hinrichs@berner-international.de
www.berner-international.eu

When handling dangerous substances such as cytostatics, it is vital to protect the person and their environment by using safety cabinets. However, the aseptic and particle-free production are equally important.
The following specification demonstrates the modes of operation and differences between safety cabinets.

Safety cabinets in laboratories

Corresponding regulations on a European and national level demand the use of safety cabinets [1-8].

The employer is obliged, before the commencement of activities, to carry out a hazard analysis and take the necessary protective measures [9]. A frequent safety measure is the use of safety cabinets (SC), see figure 1.

During the aseptic production of toxic parenteral preparations, the so-called CMR[a] substances, safety cabinets for cytostatics (SCC) need to be in operation [10].

When handling biological substances with a potentially infectious, toxic or allergenic potential the use of class I, II or III microbiological safety cabinets (MSC) is required [11].

The most fundamental properties of a SC are the protective functions such as personal, product and cross contamination protection.

Air flow mechanics: This is what counts!

The correct combination of laminar downflow air in the workspace and the air inflow in the working aperture (see figure 2), together with the filtration of particles, essentially safeguards the protective functions.

From a flow mechanics point of view, a well-designed air flow is of special significance, i.e. laminar downflow with no backflow and an optimal balance between inflow and downflow air.

The aim is the fast and safe removal of contamination, without endangering people, environment or product. For years, 0,4 m/s was regarded to be the optimal air flow velocity to guarantee best possible protective functions [12]. For several years now, the airflow velocities are no longer standardised. The manufacturer of a SC has to determine the optimal airflow conditions, within the lines of the design.

Figure 1: BERNER FlowSafe® Safety Cabinet

Under these requirements the protective functions are to be demonstrated during type testing using the microbiological method (see figure 3).

Every SC has an optimal "operating point". Intensive testing of the protective functions especially within the thresholds is of special significance. The determined target airflow velocities are to be officially recorded in the documentation. These are to be verified regularly, during production by the manufacturer as well as in the laboratory by the user.

An example will serve to illustrate the importance of this interrelationship:

If the kinetic energy of the laminar flow is signifcantly larger than the air inflow, then

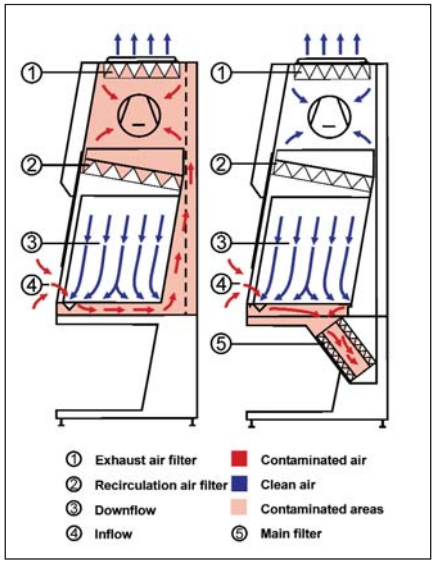

Figure 2: Side view of the design, function 2- and 3-Filter-System

Figure 3: Microbiological testing of the personal protection

personal protection can no longer be guaranteed (see figure 4, left). If, however, the inflow air is dominant, then product protection is questionable. (see figure 4, right).

This interaction is a well-known fact and should receive adequate attention during development [13]. In the USA, this variation in airflow, has been standardised for many years as "Performance Envelope Testing" [14].

Filter technology

Filters in a SC are definitely the most relevant safety component. The built-in HEPA[b] filters must filter contamination safely and comply with at least class H 14 [15]. The filters are to be arranged and dimensioned in such a way, that reliable and continuous functioning can be guaranteed. This applies especially to leakage protection and leak tightness. All filters need to be protected from mechanical damage and unsuitable loads. In particular during cleaning of the workspace or servicing, unintentional damages must be prevented [16].

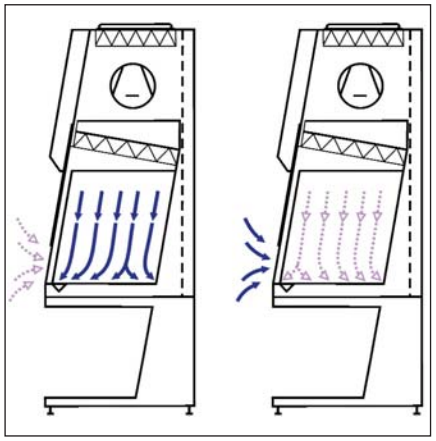

Figure 4: Correlation In- and Downflow

2- and 3-filter-systems (see figure 2) differ in the number of integrated HEPA-filters. The fundamental design and functions are very similar. The essential difference is the additional HEPA-filter, the so-called main filter, which is generally located directly below the work surface. A high risk potential will virtually always necessitate the use of 3-filter-systems [17].

Due to the redundant HEPA-filtration 3-filter-systems provide twice as much protection as a 2-filter-system, in relation to the exhaust air and downflow air of the SC. The very high rate of filtration of 99,999 999 75% in MPPS[c] provides better protection than a single class U17 ULPA[d] filter.

Immediate filtration of contamination

A fundamental argument for the use of a 3-filter-system is the filtration of particulate contamination immediately below the work surface. The most important safety-related part, the HEPA main filter, is located as close as possible to the potential "source of contamination" – the workspace. This means, that the extent of the contaminated area is significantly smaller, than for a 2-filter-system (see figure 2). All potential contaminated areas are easily accessible for cleaning and disinfection. Elaborate and cost-intensive replacement of downflow and exhaust filters will not be necessary [18].

Much service work, such as the exchange of fans or filters after the main filter level (see figure 2), can be carried out much safer, quicker and cost-effective. If a 2-filter-system is contaminated with hazardous substances, which cannot be decontamined in the SC (e. g. CMR-drugs), experience has shown that servicing will prove to be very laborious. The SC has to be hermetically sealed in a negative pressure tent, where a service technician wearing personal protective equipment carries out his work. From a health and safety point of view that is a substantial compromise.

A further advantage is that, as a general rule, the recirculation and exhaust filters will not need to be replaced. The HEPA main filter with the filtration rate of at least 99,995% of all particles means that the subsequent filters effectively operate under particle-free conditions.

Low-contamination filter change and disposal

The main filter location allows for a low-contamination easy filter replacement. A low-contamination filter change is defined as a segmented HEPA filter, which can be replaced during the continuous operation of the SC and thereby ensuring personal protection. An alternative is the Oelmeyer-process [19], established in nuclear technology, better known as the "bag-out-technology". In the end the decisive factor is determined by, in addition to a safe replacement, the overall size of the individual filter components.

Contaminated downflow and exhaust air filters in the SC (see figure 2, left) are entirely unsuitable for safe replacement, transport and subsequent decontamination. Experience has shown that these filters measure up to 1,8 x 0,6 meters. In accordance with the definition of a low-contamination filter replacement, the parts of the filter to be deactivated from a HEPA main filter level must not exceed a certain size. However, no explicit maximum size has been set. There is, however, a regulation which states that filter components should fit into normal waste disposal containers.

Waste disposal containers, which are generally available in most laboratories, have a capacity of 60 and 90 litres. A segmented main filter consists of, for a traditional system, up to 18 wedge filters, or for a more innovative one up to nine compact cartridge filters (see figure 5). Basically: The smaller the filter component, the better. The described HEPA cartridge filters fit into many waste disposal containers for thermal decontamination.

Ultimately, the only option for the safe deactivation of filters contaminated with CMR substances is incineration. Collection, transportation and incineration has to be carried out at a hazardous waste incineration site by a facilities management company.

Figure 5: Conventional wedge filter versus innovative cartridge filter of HEPA main filter systems

EDP assisted systems

Today, modern SCC use EDP supported systems (e.g. Cypro, Cato®), in order to raise the safety level of drug production. The necessary parts such as monitor, interface(s), cable, PC, scale and if applicable keyboard are to be integrated in such a way, to assure the safe operation of the SC. Important information should be easily visible, panel, scale and interfaces need to be within easy reach (see figure 6).

Figure 6: Working with EDP systems

a Cancerogenic, mutagenic, toxic to reproduction: e.g. cytostatics, virusstatics
b High Efficiency Particulate Air
c Most Penetrating Particle Size
d Ultra Low Penetration Air

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Documents and further information

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- German law: http://bundesrecht.juris.de
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Mühlenkamp 6 ▪ 25337 Elmshorn ▪ Germany
☎ +49/(0)4121/4356-0 ▪ 🖷 +49/(0)4121/4356-20
✉ info@berner-international.de ▪ 🌍 www.berner-international.eu