

HYGIENE GOAL ACHIEVED?

P+F Trend Report: Disinfection of cleanrooms

Stringent hygiene standards are required in cleanrooms for the manufacture of pharmaceuticals, pharmaceutical substances and additives, cosmetics and foods. Cleaning alone is not enough; disinfection is needed – at regular intervals. What is new in the area of disinfection? The P+F editorial staff investigated this issue.

"Blast it! When the batch is finished, we have to disinfect again. The same routine every time!" This describes the reaction of many employees in the cleanroom. Because the procedure cannot be carried out "in a flash", since it requires extreme thoroughness. "In the cleanroom, a surface that shines is not automatically considered clean", Frank Duvernell, Managing Director of Profi-Con Contamination Control, confirms. He knows that the usability of a cleanroom depends strongly on proper disinfection.

Regulations that make sense

Although it is an unpleasant activity, disinfection cannot be avoided. It would be pointless to list all the regulations, standards and directives here – the operator knows that disinfection is indispensable and therefore he complies with the regulations, because otherwise the risk of contamination would be too great. Who would want to have to throw away an entire batch? Or even worse, the unconceivable situation in which a contaminated product is put into circulation and sold to a consumer. There is no general rule as to how often disinfection is necessary. What has to be disinfected? What is the cleanroom classification? What are the contamination risks? "Surfaces that come into contact with the product should be disinfected at least daily, and if there is a high risk of contamination, several times daily; floors also daily." That is the recommendation of *Margarete Witt-Mäckel, Account Manager Pharma at Schülke & Mayr*. "Also after switching products or batches and following maintenance and repairs." *Jan Gladig, Market Manager at Bode Chemicals*, explains: "In the end, one has to fulfil the cleanliness requirements for the specific environment." The decisive factor is the product manufactured in the cleanroom, the requirements of the product and the resulting classification of the room. Therefore, the frequency of disinfection can vary from company to company. To assess the effectiveness of a cleaning and disinfection concept, micro-biological monitoring is conducted concurrently. The data is re-assessed on a regular basis and analyzed in a trend analysis.

In addition to monitoring of the environment, an exact analysis of the standard procedures is recommended. This enables the timely creation of a suitable and effective concept in cooperation with the supplier. Effective "trending" is also necessary. Such a risk-based look toward the future can anticipate future challenges to be faced by the disinfection concept.

Micro-biological monitoring takes place at the intervals recommended in the guidelines – EU GMP Guideline, Annex I or FDA Aseptic Guide – once per shift, for example. In non-critical areas, such as the production of oral moulds, quarterly monitoring is sufficient under some circumstances. The testing frequency depends on the cleanroom class, the product being manufactured and the empirical data. Monitoring can be used to determine if the pre-defined conditions are exceeded and to take measures to eliminate the deviations. It also detects the development of adaptive-resistant micro-organisms. "Regardless of that, further monitoring may be conducted when a new disinfection system is introduced, in order to test the effectiveness", *Axel Schroeder, Key Account Manager, Pharmaceuticals and Biotechnology at basan GmbH*, explains.

In-house dilution or ready-to-use product?

The regulations for the manufacture of sterile medications require very high standards for disinfecting agents. The required sterilization can be carried out at the plant after preparing the solution by means of sterile filtration using suitable sterile filters. What seems fast and easy at first glance, however, in practice involves high technical expenditure and risks. Because every sterilization process has to be validated.

Alternatively, it is possible to purchase already sterile-filtrated and sterile-packaged disinfecting agents. They have already been sterile filtrated during manufacture and gamma irradiated after initial packaging. While sterilization at the plant – which is worthwhile with the use of larger quantities – involves higher technical expenditure and risks, sterile disinfectants are available only in small units and cause a high level of waste. On the other hand, the sterile disinfectants are accompanied by reports and certificates, thus reducing the operator's validation costs.

In selecting a suitable cleaning method, two methods are primarily used: wiping and spraying, or a combination of the two. An alcohol-base spray disinfectant is used, for example, on small surfaces or on critical surfaces to be disinfected so that there is little or no residue, because alcohol evaporates, leaving no residue. For reasons of time, operators tend to prefer spraying, but spraying is permitted only in combination with wiping, because this is the only way to ensure that contamination, such as residual dead cell matter, is completely removed from the surface. Other areas, such as inaccessible equipment, can only be sprayed, on the other hand.

The wiping method makes use of the classic mop-and-bucket system, consisting of a mop and two or three buckets. Large surfaces are moistened with the disinfectant by means of a mop. Semi-automatic appliances for wiping disinfection are available on the market. Dusko Filipovic, Key Account Manager, Sterile Disinfectants at PMT, comments: "Such appliances ensure that the disinfectant remains on the surface for up to 10 minutes – saving a lot of time during disinfection."

Rotation – to be on the safe side

"The disinfectant is selected based on the utilization, the disinfecting method, compatibility with materials, toxicology, rinseability and safe use for the product. The level of cleanliness of the surface to be disinfected is also important, because the cleaning effectiveness, the protein resistance and possible errors due to addition of soap have to be taken into account", Margarete Witt-Mäckel summarizes. Nevertheless: Even if one is satisfied with the selected disinfectants and the degree of success, rotation is necessary at regular intervals. Just as housewives change their washing powder and car drivers switch to a different brand of fuel, the regulations require the use of at least two types of disinfectants. When changing the required combination of substances, however, care must be taken to prevent reactions between the chemical components, since this could result in reduced effectiveness or discoloration of surfaces. Critics see no danger of resistances, since disinfectants, unlike antibiotics, attack micro-organisms non-specifically. Rotation is supposed to prevent resistances, but there are numerous studies furnishing proof that resistances are not an issue. Jan Gladig confirms this: "With proper disinfection – for example, compliance with the correct dosage – no resistances are to be expected."

However, different micro-organisms differ in their sensitivity to individual anti-microbial substances. While one bacterium already reacts to a concentration of 0.25 %, another one may only react to a concentration of 2% or higher. If a 1% disinfectant solution is used, for example, the less sensitive bacterium will remain on the surface and could multiply and spread unnoticed, in the event of longer monitoring intervals. Rotating the substance prevents such selection.

"The operator can decide how often to rotate; there are no regulations in this regard. The fact is that residue from the previously used disinfectant must be removed thoroughly, which does not happen all that often", Frank Duvernell explains. "In any case: Sterile disinfectants should be used economically, because they are expensive", according to Wolf-Dieter Wanner, who is a pharmacist and Sales Director at Shield Medicare, a division of Ecolab. But adequate disinfection should always be carried out, without trying to save in the wrong place. "Dialogs between the user and the industry

currently show a clear trend in Germany toward safe disinfectants", Peter Koger, Technical Sales Manager for Europe at Veltek, explains. "Peroxide disinfectants and quaternary bonds are becoming more important in daily use." Koger knows that many companies use a sporicidal substance at least once a month, with the rotation principle "one disinfectant – one sporicide".

Just as disinfectants tackle the micro-organisms, surfaces are not always immune to them either. Tensides and salts can leave residue; disinfectants and products with an alkaline pH value can cause corrosion; and alcohol can make surfaces porous if they are not resistant to alcohol. Many users are currently in search of a disinfectant that also has a cleaning effect and leaves no residue. The problem here is that the chemicals used have to be sufficiently effective against bacteria, which means that there will always be some degree of side effects. The problem with effectiveness against spores is the limited number of sporicidal substances, namely chlorine, active oxygen and aldehyde, and the side effects, such as odours, corrosion and residue. Their use is therefore avoided, if possible.

Fumigation: When is it necessary?

Despite their effectiveness, standard disinfectants are not sufficient in many situations; in this case, fumigation is the only choice. Fumigation is used when a new cleanroom is built, when a new assembly machine is installed in the cleanroom or following construction. The ideal substance for fumigation – formaldehyde – is no longer used in the present day; alternatives are available. Some of these can be used in a fogging system. *Dr. Rudolf Hüster, Managing Director of Scienticon Scientific Consulting*, is familiar with this issue: "Fumigation is always called for when a high safety level is desired, or when microbes are detected not only on surfaces, but also on the products." Fumigation reaches every nook and cranny. But it requires shutdown of the cleanroom during fumigation and the application time, which means that it always involves production downtime. Dusko Filipovic comments: "One of the biggest challenges for the industry is the elimination of formaldehyde from the market. Since the use of formaldehyde in cleanrooms should be avoided, alternative methods such as the use of vaporous hydrogen peroxide or other fogging methods are being used instead."

Operation successful?

A shiny surface does not necessarily have to be sterile. The success is checked by an air microbe collector or by measuring particles in the air with a particle measuring unit. In addition, surfaces are subjected to a wipe test, for example with Rodac plates or swabs. However, these tests can only be analyzed after 48 hours at the earliest. Production continues meanwhile, with the assumption that the preventive measures for thorough cleaning and disinfection are carried out just to be on the safe side. In aseptic production, the FDA Guideline recommends testing the effectiveness of the disinfectant used against the intruders detected by micro-biological monitoring. There is a trend toward including the building's surfaces in the effectiveness tests of disinfectants. The procedure is facilitated by standardized test methods, for example based on the EuroNorms, in which the disinfectants are tested according to pre-defined standards.

To document the effectiveness of the cleaning process and to ensure that no unwanted contamination can occur due to product residue, cleaning or disinfecting agents or micro-organisms, validation is necessary after each cleaning and disinfection procedure. The validation of disinfectants and processes is extremely time- and cost-intensive. But there is no other choice. "Especially manual tasks are difficult to validate", Margarete Witt-Mäckel explains. "Therefore, work instructions have to be followed strictly." Axel Schroeder adds: "In the cleaning and disinfection of product-contacting surfaces, such as in CIP systems, there has to be a residue validation, which documents that no residue from the substances are transferred to the subsequently manufactured products."

A job for the professional!

Cleanroom disinfection is time-, cost- and personnel-intensive. And it has to be carried out with extreme care, in order to be successful. But who is keen on this unpleasant task, when the larger part of the workday is already over and closing time is near? One should always bear in mind that successful cleanroom disinfection depends largely on the motivation of the employees. No problem, because there are professionals who can do the job. They are building cleaners, ideally also specialized in cleanrooms through intensive in-house training.

The situation is otherwise at Profi-Con Contamination Control: "Cleanroom disinfection has nothing to do with cleaning; it is a technological purging process", cleaning professional Duvernell explains. His staff has the necessary know-how, which the cleanroom personnel would first have to acquire through hard work and at high expense. This is important, because: "If one adds the neutral items that companies tend to forget, it is less expensive to outsource cleaning", Duvernell sums up. He should know, because he has observed that cleanroom operators have been relying more on third-party services for a number of years now. This may be due in part to the economic upswing, but certainly also to the realization that the profitability of a cleanroom is highly dependent on disinfection.

"The regulations and directives reflect the current state of affairs, and the operator complies with them. Amendments are usually useful and elevate the system to ever higher levels of quality", says Duvernell. The directives have been in force for years without any major amendments. "There are committees that discuss these matters and contribute ideas. There have been many recent developments in this area", according to pharmacist Wanner.

Conclusion: There is a trend toward an increased need for safety, which could possibly result in even more frequent cleaning procedures. However, one should always bear in mind the aspect of profitability, just as in the recent trend toward the increased use of disposable systems, such as impregnated wipers, dosing bags or ready-to-use solutions to prevent incorrect dilution. Unnecessary increases in costs should be avoided, especially since good cleaning results can also be achieved with conventional processes. The targeted and effective implementation of cleaning and disinfection measures covers both the increased need for safety and profitability. Each operator must decide for himself whether to use disposable or reusable wipers, or in the present context, conventional or modern processes.

FACTS FOR DECISION-MAKERS

For users

- The type of disinfection is based on the product, the cleanroom class and the risk of contamination.
- The cleaning method must ensure complete removal of all contamination from the surface.
- The FDA requires rotation of the disinfectant at regular intervals.
- In Germany, aldehyde-based disinfectants currently are being used less frequently.
- Fumigation is conducted in newly installed cleanrooms or after construction. This achieves a higher safety level.
- In past years there has been an increase in the use of third-party disinfection services.
- There is a trend toward an increased need for safety, which could result in even more frequent cleaning procedures.
- In the critical control zone A, cleanroom operators use residue-free disinfectants (sterile alcohol/water mixtures) on surfaces that come into contact with the product.

