

Is a change of disinfectants necessary?

1. **Guidelines to the Manufacture of Sterile Medicinal Products (Annex 1) supplementing the EU GMP Guideline (revision of March 2009):**

The chapter "Industrial Hygiene", Clause 37¹, states: "The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains."

2. **Development of resistance:**

In this context the issue of the "development of resistance" in connection with the use of disinfectants should be addressed briefly. As in the EU Guidelines the term "resistance" is put up for discussion too quickly and erroneously in the field of disinfection whenever the efficacy of the disinfectant supposedly declines or is deficient.

What does the term "resistance" really mean? "Resistance" could be translated as the ability to withstand or overcome, i.e. the ability of a micro-organism to make a stand against harmful influences and to continue to survive. There are different types of resistance:

- intrinsic resistance:
an organism possesses by nature a different level of resistance against different harmful influences. Thus, different micro-organisms can be killed more or less easily by different disinfectants. This is reflected in the fact that certain test germs are tested for various applications so as to facilitate the selection of the appropriate disinfectant.
- acquired resistance:
resistance may be acquired by spontaneous mutations of genetic material or by transfer of genetic material from other cells.
- adaptation:
The temporary habituation of a micro-organism to harmful influences must be clearly distinguished from a resistance. This only occurs under certain conditions of growth, e.g. lack of nutrients, and cannot be inherited. Such adaptations are generally promoted by misuse of disinfectants, e.g. too weak concentrations.

¹ As from 01 March 2009 (coming into operation of the revised guidelines): chapter on "Sanitation", Clause 61.

As may be inferred from specialist literature, the active ingredients in disinfectants attack the cells of micro-organisms very non-specifically, whereby all structures and functions may be attacked. This differentiates them from antibiotics and chemotherapeutics which attack cells at quite specific target sites so that a development of resistance is easily possible, e.g. by slight changes of the target site.

It is impossible for cells to form a defence against the attack on many fronts made by a formulated disinfectant. If, in practice, some micro-organisms survive after the use of disinfectants, we can only speak here of selection due to adaptation. As different disinfectant concentrations are necessary for growth inhibition (microbistatic effect = reversible damage) and the killing of organisms (microbicidal effect = irreversible damage), in the event of the concentration used falling below the prescribed limits individual cells which were not irreversibly damaged by the existing concentration may survive. As the majority of the other micro-organisms are killed, the selected germs find scope for development.

3. **Avoiding the development of selected germs:**

Thanks to appropriate formulations the spectrum of action of formulated disinfectants is adjusted in such a way that they display a balanced spectrum of action against the micro-organisms which are relevant in practice. Only the use of pure "non-complex" chemicals for disinfection purposes can cause germ selections as a result of gaps in their range of action. A typical practical example in this context is the selection of different mould fungi in under-glass crop production where chlorine bleach liquor is used.

Lower concentration levels than those tested and specified by the manufacturer may not be used. In selecting disinfectants those with a broad spectrum of action should be used, e.g. those listed by the German Society of Hygiene and Microbiology (DGHM) or the German Veterinary Medical Society (DVG).

If sporogenic bacteria are also to be included in the disinfection process, products must be used in their sporicidal application concentrations. Products based on active oxygen, e.g. Perform, are preferable for this purpose.

Summary:

When formulated listed disinfectants are used, the combination of various active ingredients and excipients has already been undertaken during formulation of the disinfectant so that the demands of the EU GMP Guideline to Sterile Medicinal Products can be considered already fulfilled. Correct selection and avoidance of underdosing of disinfectants means that a change of disinfectants is not necessary, particularly when regular microbiological checks reveal no indications of the development of a more frequently encountered germ type.

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