Selection of Disinfectants for Use in the Pharmaceutical Industry

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Introduction

Cleaning and disinfection of surfaces are essential steps for maintaining the cleanliness of pharmaceutical manufacturing operations. The USP, for example, requires stringent procedures to be followed during the manufacturing of pharmaceutical preparations (as stated in USP Chapter <797>) (1). One step towards achieving microbial control within a clean room is the use of defined cleaning techniques for walls, ceilings, floors and surfaces at working height together with the application of suitable detergents and disinfectants.

One of the more difficult tasks facing pharmaceutical organisations is with the selection of disinfectants, particularly in ensuring that the disinfectants selected are appropriate and that the effectiveness of the disinfectants are periodically assessed (2). The need for a scientific rationale for the selection of disinfectants is outlined in the USP chapter Chapter <1072> ‘Selection of a Disinfectant for Use in a Pharmaceutical Manufacturing Environment’ (3). Disinfectant suppliers like schülke can work with pharmaceutical companies to help them to select the most suitable types of disinfectants. The selection of a disinfectant involves the careful consideration of a number of factors and this article outlines the most important factors which need to be taken into account.

Disinfectants

A disinfectant is one of a diverse group of chemicals which reduces the number of microorganisms present (normally on an inanimate object). There are various 'official' definitions of the process of disinfection and disinfectant agents, one of the most straightforward is from the ISO standard on Aseptic Processing (ISO 13408–11), where a disinfectant is defined as:

"[a] chemical or physical agent that inactivates vegetative micro-organisms but not necessarily highly resistant spores" (4)

Disinfectants vary in their spectrum of activity, modes of action and efficacy. Some are bacteriostatic, where the ability of the bacterial population to grow is halted. Here the disinfectant can cause selective and reversible changes to cells by interacting with nucleic acids, inhibiting enzymes or permeating into the cell wall. Once the disinfectant is removed from contact with bacteria cells, the surviving bacterial population could potentially grow. Other disinfectants are bactericidal in that they destroy bacterial cells through different mechanisms including causing structural damage to the cell; autolysis; cell lysis and the leakage or coagulation of cytoplasm (5). Within these groupings the spectrum of activity varies with some disinfectants being effective against vegetative Gram positive and Gram-negative micro-organisms only while others are effective against fungi. Some disinfectants are sporicidal in that they can cause the destruction of endospore forming bacteria (these are the most difficult forms of microorganisms to eliminate from cleanroom surfaces). However, a chemical agent does not have to be sporicidal in order to be classed as a 'disinfectant' or as a 'biocide'. (6) The bacteristatic, bactericidal and sporicidal properties of a disinfectant are influenced by many variables, not least their active ingredients.

Selection of disinfectants

There are many different types of disinfectants for use within the pharmaceutical industry (7), with different spectrums of activity and modes of action. The mechanisms of action are not always completely known and continue to be investigated. A range of different factors needs to be considered as part of the process of selection including the mode of action, and also efficacy, compatibility, cost and with reference to current health and safety standards (8).

In examining these criteria further, the main points to consider when selecting a disinfectant are:

a) A disinfectant must have a wide spectrum of activity. This refers to the ability of the disinfectant to kill different types of microorganisms and microorganisms which are in different physiological states.

b) Whether there is a requirement that the disinfectant is sporicidal. This requirement influences the type of disinfectant purchased. Sporicidial disinfectants tend to have greater health and safety considerations and some, particularly chlorine based disinfectants, are aggressive to certain types of surfaces and will cause discoloration and abrasion.

c) The disinfectant must be rapid in action with an ideal contact time of less than ten minutes. The contact time is the time taken for the disinfectant to bind to the microorganism, traverse the cell wall and membrane and to reach its specific target site. The longer the contact time, then the longer the surface or article needs to be left for prior to use.

d) The disinfectants selected must have different modes of action. Some different types of disinfectants and their different modes of action are discussed below. The emphasis on different modes of action is also tied to the regulatory expectation that disinfectants are rotated, which is discussed later.

e) Some disinfectants require certain temperature and pH ranges in order to function correctly. One type of disinfectant, for example, may not be effective in a coldroom due to the lower temperature. The reason for this is because the validation standards for disinfectants measure the bactericidal activity at 20^{o}C and therefore the disinfectant may not be as effective at higher or lower temperatures.

f) Prior to the use of disinfectants it is essential that as much dirt and soil is removed as possible. This requires the application of a detergent. Some disinfectants are not compatible with certain detergents. In such circumstances detergent residues could neutralise the active ingredient in the disinfectant. Any disinfectant purchased should be compatible with the detergent used.

g) Other disinfectants leave residues on surfaces. Whilst this can mean a continuation of an antimicrobial activity, residues can also lead to sticky surfaces and or the inactivation of other disinfectants.

h) Different disinfectants are not compatible with all types of surfaces. The disinfectants must not damage the material to which they are applied to (although it is recognised that repeated applications over several years may cause some corrosion). For more aggressive disinfectants a wipe down using water or a less aggressive disinfectant like an alcohol is sometimes necessary in order to remove the residues. In addition to some disinfectants having a corrosive affect, others may be absorbed by fabrics, rubber and so on, which lessens their bactericidal properties (9).

i) The disinfectants must meet the requirements of the validation standards to measure bactericidal, fungicidal and, if appropriate, sporicidal and viriucidal activity. There are detailed standards which describe how disinfectants should be validated, parts of which are undertaken by the manufacturer and some by the pharmaceutical organisation which purchases the disinfectants against a range of different surfaces.

j) The presentation of the disinfectant is an important choice, whether as a pre-diluted preparation in a trigger spray, or as a ready to use concentrate or an impregnated wipe. Disinfectant suppliers like schülke provide a wide range of different presentations of disinfectants.

k) The disinfectants must be relatively safe to use, in terms of health and safety standards. Here the main concern is with operator welfare. A related concern is the impact upon the environment.

l) The cost of the disinfectant is also a factor to consider, especially it is to be used over a large surface area.

m) If the disinfectant is required for use in an aseptic filling area then it will need to be sterile filtered or supplied sterile in a suitably wrapped container. Many disinfectant manufacturers like schülke supply disinfectants which have been sterile filtered (through a 0.2µm filter) and are provided in gamma irradiated containers with outer wrapping.

Carrying out such a review, based on the above factors prior to purchasing a disinfectant, does not guard against the incorrect use of the disinfectant within the pharmaceutical manufacturing facility. Any disinfectant will only be effective if it is used at the correct concentration, applied to relatively clean surfaces using appropriate cleanroom grade mops or cloths and left for the correct contact time.

In addition to surface disinfectants, hand sanitisers are also required (for cleanroom staff to apply either to skin or to gloved hands) as part of a comprehensive disinfection programme.

Types of disinfectants

Disinfectants have varying modes of action against microbial cells due to their chemical diversity. Different disinfectants and target different sites within the microbial cell. These include the cell wall, the cytoplasmic membrane (where the matrix of phospholipids and enzymes provide various targets) and the cytoplasm. Some disinfectants, on entering the cell either by disruption of the membrane or through diffusion, then proceed to act on intracellular components. There are different approaches to the categorisation and sub-division of disinfectants, including grouping by chemical nature, mode of activity or by bacteristatic and bactericidal effects on micro-organisms (10). Some different types of disinfectant are:

Non-oxidising disinfectants

The majority of this group of disinfectants have specific modes of action against micro-organisms, but generally they have a narrower spectrum of activity compared to oxidising disinfectants. This group includes: alcohols like schülke's perform® Alcohol EP (which disrupt the bacterial cell membrane and has a one minute contact time), aldehydes (which have a non-specific effect in the denaturing of bacterial cell proteins and can cause coagulation of cellular protein), amphoterics (which have both anionic and cationic character and possess a relative wide spectrum of activity), phenolics (some phenols cause bacterial cell damage through disruption of proton motive force, while others attack the cell wall and cause leakage of cellular components and protein denaturation) and quaternary ammonium compounds (QAC), which are among the most commonly used disinfectants in the pharmaceutical industry and include preparations like schülke's perform® Concentrate QB (available in convenient single-use bottles which reduces the preparation time)**.** The mode of action of QAC's is on the cell membrane leading to cytoplasm leakage and cytoplasm coagulation through interaction with phospholipids (11).

Oxidising disinfectants

These disinfectants generally have non-specific modes of action against micro-organisms. They have a wider spectrum of activity than non-oxidising disinfectants, with most types able to damage endospores, but they can pose greater risks to human health and therefore require greater control. This group includes: halogens like iodine and oxidising agents like peracetic acid, such as schülke's sporicidal perform® Concentrate PAA, chemical containing oxygen deposits like perform® Concentrate OXY (available in single-use sachets) and hydrogen peroxide. Concentrate OXY has an excellent material compatibility and does not damage most surfaces.

Hand sanitisers

There are many commercially available hand sanitisers with the most commonly used types being alcohol-based gels or alcoholic hand rubs like desderman® Pure provided by schülke. With hand sanitisers the most important factor is the hand rubbing technique for the sanitisers are most effective through the act of agitation by rubbing the hand sanitiser into the hands (12).

Disinfectant rotation

In selecting disinfectants many pharmaceutical manufacturers will opt to have two 'in-use' disinfectants and sometimes to have a third disinfectant as a reserve in case a major contamination incident arises, such as a bioburden contamination build up, which appears resistant or difficult to eliminate using the routinely used disinfectants. The reserve disinfectant will often be more powerful and sporicidal, such as an oxidising agent, the routine use of which is restricted because of likely damage to the equipment and premises. Typically the two primary disinfectants are rotated. This is a requirement of regulatory bodies and the strongest pressure for it has come from Europe with the EU GMP Guide stating that "where disinfectants are used, more than one type should be employed" (Annex 1). This quotation is normally interpreted as a requirement for two different types of disinfectant to be rotated. The USP (<1072>), in contrast, is less exacting and poses some questions about the scientific need for rotation.

The argument for rotating two disinfectants is to reduce the possibility of resistant strains of micro-organisms developing. Whilst the phenomenon of microbial resistance is an issue of major concern for antibiotics there are few data to support development of resistance to disinfectants (13). This is particularly so when applied to dry environments such as cleanrooms where microbial replication, as a primary process for gaining resistance, is minimal.

Whilst there is limited scientific evidence to support disinfectant resistance (14), there is a need to meet regulatory expectations and many pharmaceutical organisations adopt policies for disinfectant rotation. When using disinfectants with different modes of activity more often one of the selected disinfectants is sporicidal. With regard to the frequency of rotation this tends to based on the environmental monitoring data. Given that environmental monitoring data should be reviewed for trends on a regular basis this allows the frequency of cleaning and disinfection to be based on risk.

Summary

This article has examined some of the key criteria for the selection of disinfectants in the pharmaceutical industry and has examined some of the main types of disinfectants available. Whilst selection is important, it will matter little how careful the selection of disinfectants has been if disinfectants are not applied and used according to Standard Operating Procedures for the efficacy of the disinfectant will decrease. It is also important to emphasise that once a disinfectant is selected its performance should be periodically reviewed. Such a review is in relation to the effect that the disinfectant has on the surface material and in relation to the environmental monitoring data collected. Given that the objective of the disinfectant is to kill microorganisms and to reduce the surface bioburden then the real test of its effectivity is with the numbers of microorganisms recovered through environmental monitoring and the types of microorganisms found (the ‘microflora’). Thus the selection of disinfectants is not a one-off decision; it must remain part of the on-going quality reviews undertaken by pharmaceutical organisations and for this the expertise provided by disinfectant manufacturers like schülke will be of great value.

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