Disinfectants in Manufacturing Environments – Use & Abuse

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Overview

- Extracts from chapter “Disinfectants Program” in Microbiology in Pharmaceutical Manufacturing, 2nd Edition, 2008, Ed by Richard Prince, Published by PDA, Bethesda
- Terminology
- Classes of Disinfectants
- Rotation of Disinfectants
- Relative Microbial Susceptibilities
- Qualification of Disinfectants

Introduction

- Disinfectants and sanitizers are used in a multitude of situations where there is a need to control microorganisms.
- In the present context we are concerned with their use in the pharmaceutical industry.
- There are a wide range of chemicals that are used for this purpose and they fall into a number of classes of chemicals.
- Few chemicals are active against all types of microorganisms and this leads to the necessity of selecting the most appropriate chemical biocide for its intended purpose.

Terminology

- Antiseptic
  - These are chemicals that are used on living tissues
  - Their main purpose is to either kill or inhibit microorganisms in a safe manner for the body
  - Cannot be relied upon to provide the same kill factors as disinfectants
  - Sometimes referred to as skin disinfectants – use caution with term!

Terminology (cont)

- Antibacterial
  - Increasingly popular with marketers of consumer products
  - Refers to their ability to reduce/kill bacteria numbers
  - Have lesser performance characteristics than disinfectants
  - May be developed for either inanimate surface use or for hand/body use

Terminology (cont)

- Antimicrobial
  - Literally means “against microbes”
  - Does little to inform about the nature of the activity or the target organism
  - Antimicrobial products may kill or simply inhibit microbial growth
  - Often, but not always, targeted to specific organisms or restricted groups of organisms, e.g. antibiotics and anti-acne treatments

Terminology (cont)

- Cidal
  - Applied as a suffix to a class of organisms to indicate a chemical will kill, e.g. bactericidal, fungicidal, tuberculocidal, virucidal, sporicidal

Terminology (cont)

- Disinfectant
  - Chemical agents that are used on inanimate surfaces
  - Expected to kill high numbers of vegetative bacteria, fungi and some viruses, but not necessarily spores and not necessarily all viruses
  - Expectations are for a 10^6 colony forming unit kill in a specified time although for viruses this may be lessened to 10^3 – 10^4, mainly for practical testing considerations
  - Sometimes be categorized by the stringency of the testing they have undergone, e.g. high, intermediate or low level disinfectants for medical device disinfection

Terminology (cont)

- Germicidal
  - Another generic term used to indicate an ability of a chemical to kill a variety of organism types
  - More commonly used in North America

Terminology (cont)

- Sanitizer
  - Often misused or used inappropriately
  - Compounds that *reduce* but not completely eliminate the numbers of microorganisms on inanimate surfaces
  - Often sanitizers have a lesser efficacy than disinfectants
  - Reference to bringing microorganisms to a sanitary or hygienic level
  - Does not in itself indicate removal or killing of *large* numbers of organisms

Terminology (cont)

- Sterilant
  - Sterility is the condition where all microorganisms are killed
  - Chemical that is able to kill all forms of microbial life including bacteria, bacterial spores, fungi, fungal spores and viruses
  - Not necessarily viroids or prions
  - May be disinfectants that require a longer contact time to achieve the killing of bacterial endospores, e.g. ethylene oxide, glutaraldehyde

Classes of Disinfectants / Sanitizers

- *Quaternary ammonium compounds*
- *Phenolic compounds*
- *Chlorine compounds*
- *Alcohols*
- *Hydrogen peroxide*
- *Peracetic acid*
- *Aldehydes*

Classes of Disinfectants / Sanitizers (cont)

- *Quaternary ammonium compounds*
  - Cationic surface-active agents having both hydrophobic (water-repelling) and hydrophylic (water-attracting) regions in the molecular structure
  - Most active against Gram positive organisms but are also active against many Gram negative organisms
  - Notable exceptions to this are *Pseudomonas aeruginosa* and other pseudomonad-type organisms
  - Formulations can be enhanced to include activity against these microorganisms
  - Exhibit general lack of activity against mycobacteria, spores and non-lipid (hydrophilic) viruses
  - They are severely compromised by organic soils
  - Do not affect a wide variety of work surfaces so that materials compatibility is rarely

Classes of Disinfectants / Sanitizers (cont)

- *Phenolic compounds*
  - Have been used since the dawn of the disinfectant era in the seventeenth century
  - Originally obtained by distillation from coal tar, nowadays principally of synthetic origin
  - One of the original disinfectant benchmarks was the phenol coefficient (PC)where activity was compared to phenol itself
  - PC has lost a lot of its relevance today as modern formulations, including phenol derivatives have phenol coefficients of hundreds or even thousands with some organisms
  - Phenol derivatives have a good wide-spectrum of activity against Gram negative, Gram positive bacteria and fungi
  - Not generally effective against spores or the hydrophilic viruses
  - Do not suffer from materials incompatibility
  - Some offer residual disinfectant effects on surfaces; need to consider risks of residues impacting on product quality

Classes of Disinfectants / Sanitizers (cont)

- *Chlorine compounds*
  - Very wide spectrum of activity including vegetative bacteria, fungi, mycobacteria, viruses and spores
  - Activity can be severely affected by various factors such as organic soil, elevated temperatures, uv light and pH
  - Very corrosive towards many materials, including stainless steel

Classes of Disinfectants / Sanitizers (cont)

- *Alcohols*
  - Usually ethyl alcohol (ethanol) or isopropyl alcohol (isopropanol) - widely used in concentrations of 60 - 70% v/v in water
  - Isopropanol is said to have a slightly higher activity
  - Very effective against bacteria but not their endospores, have some fungicidal activity and some virucidal activity to lipid coated viruses such as herpes and influenza viruses but not other viruses
  - Do not suffer from materials incompatibility
  - Do not leave residues on surfaces
  - Commonly used to sanitize hands during aseptic operations

Classes of Disinfectants / Sanitizers (cont)

- *Hydrogen peroxide*
  - Very wide spectrum of activity including vegetative bacteria, fungi, mycobacteria, viruses and spores
  - Breakdown products are water and oxygen so no residual issues
  - No materials compatibility issues
  - Vapor phase hydrogen peroxide (VPHP) technologies have become popular sterilizing systems in the pharmaceutical industry

Classes of Disinfectants / Sanitizers (cont)

- *Peracetic acid*
  - Powerful oxidizing substance, formed from the reaction of hydrogen peroxide with acetic acid
  - Bactericidal, fungicidal, virucidal and sporicidal
  - Materials compatibility issues due to its oxidizing characteristics
  - Very pungent making it unpleasant and hazardous to work with
  - Products have been developed that are a blend of hydrogen peroxide and peracetic acid that have much better use profiles whilst retaining their efficacy

Classes of Disinfectants / Sanitizers (cont)

- *Aldehydes*
  - Used as disinfectants and sterilants: comprise glutaraldehyde and formaldehyde
  - Both chemicals are pungent making them difficult to work with and are also sensitizing agents; in the case of formaldehyde, also a suspected carcinogen
  - Broad spectrum of activity, being bactericidal, fungicidal, virucidal and sporicidal
  - Neither are recommended for use in liquid form in manufacturing situations; formaldehyde continues to have some limited use, mostly in biologicals production facilities and laboratory biohazard cabinets

To Rotate or What to Rotate – Now That is a Question!

- *Regulatory expectation* -
  - Use of a single type of disinfectant could lead to a build up of resistant organisms
  - Thereby render the microbial control program ineffective
  - Appears to be little if any evidence that this occurs in actual practice
  - A rotation plan should be in place for the manufacturing plant
- *The evidence –*
  - There have been examples of disinfectants and antiseptics that have been contaminated during manufacture, usually in quaternary ammonium compound formulations
  - Laboratory-based experiments show evidence of resistance build-up from using a single disinfectant
  - Examples of quaternary ammonium products diluted and stored for too long having bacterial contamination and of 70% alcohols (in clean rooms) similarly contaminated with *Bacillus* spp
- *The counter–evidence*
  - No practical evidence of resistance build-up from using a single disinfectant when stored properly, used at the manufacturers recommended dilutions and used within a validated in-use period once dispensed
  - When a manufacturing environment remains in a state of microbial control (whether in terms of total counts or types of microbes identified), that strongly suggests that the existing disinfection regimen is working and should not be changed

To Rotate or What to Rotate – Now Here is a Compromise!

- Select the most appropriate disinfectant available for your plant
- For *non-sterile* product plants select a second disinfectant from a different class of compound or different formulation / supplier
  - This enables some security of supply
  - Use the second product on a reduced frequency, provided environmental monitoring supports effective microbial control
  - Comments are aimed at product-contact surfaces; some plants use multiple products for different surfaces.
- For *sterile* product plants select a second disinfectant from a different class of compound but ensure at least one is sporicidal
  - A second supplier is still a good survival strategy, although getting harder to implement
  - Rotate regularly if only one product is sporicidal or supplement with sporicidal product frequently to avoid build-up of spore-forming organisms

Disinfectant programmes are an integral part of the overall plant hygiene programme and the ultimate success or failure of the program will be reflected in the microbiological environmental monitoring results

Relative Microbial Susceptibilities

Microbial Susceptibility Group (most to least sensitive)	Microorganisms[a]
A	Lipid enveloped viruses (Corona viruses, Hepatitis B Virus, Herpes viruses, Human Immunodeficiency Virus, Influenza viruses, Vaccinia virus[b])
B	Most vegetative bacteria
C	*Staphylococcus aureus*, some gram-negative rods (*Pseudomonas* spp, *Providencia* spp, some diphasic & filamentous fungi (*Trichophyton mentagrophytes*, yeasts (*Candida albicans*), algae
D	Large non-enveloped viruses (Adenoviruses, Rotaviruses, Reoviruses)
E	Some mould ascospores (*Aspergillus niger*)
F	Trophozoites (*Acanthamoeba* spp)
G	Small non-enveloped viruses (Polioviruses, Rhinoviruses, Parvoviruses, Hepatitis A Virus)
H	Cysts (*Giardia* spp)
I	Mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium*)
J	Bacterial endospores (*Bacillus* spp, *Clostridium* spp), viroids
K	Coccidia (*Cryptosporidium* spp)
L	Prions (Transmissible Spongiform Encephalopathies)

Reproduced from Priscott & Dai, Microbiology in Pharmaceutical Manufacturing, 2nd edition, 2008

a Some exceptions may be found to this general scheme due to differing susceptibilities to different chemical agents.

b Blood-borne viruses may be more resistant depending on the organic matrix they are suspended in, for example cell-associated compared with cell free virus.

A Plan For Qualifying Disinfectants In Your Non-sterile Product Manufacturing Plant

- Select suitable disinfectant for intended application
- In parallel with cleaning validation, perform some microbiological sampling of product critical areas
- Products can be introduced to the plant with little further qualification
- Ongoing suitability is checked through environmental monitoring programme of product critical contact sites

A Plan For Qualifying Disinfectants In Your Sterile Product Manufacturing Plant

1. Overview. Includes basic description of facility and the basis for performing the qualification program, including an abbreviated outline of the various parts to the program.
2. Scope. Specifies the scope of the intended works.
3. Abbreviations (sometimes included as an appendix). Self explanatory.
4. Rationale. This is often quite detailed in providing the logic behind the proposed plan, nature of tests to be employed, description of disinfectants to be evaluated, organisms to be used, surfaces to be tested and any other issues and how they will be handled.
5. Roles and responsibilities. This sets out the various roles and designated responsibilities for the various personnel involved in the program.
6. Procedure(s) to be employed. This may describe the time sequence for testing and specific matrices for test format, organism to be used, disinfectant to be used.
7. Acceptance criteria. Lists the acceptance criteria for the proposed work to be deemed successful.
8. Deviations handling procedure. An acknowledgement of how any deviations will be handled and documented.
9. Reporting process. Any specific report format requirements that will be required.
10. Program evaluation and handover. The agreed manner in which the program will be signed off as accepted and the validated products and methods of use handed over to the production personnel.
11. Appendices. These may include lists of cross-referenced documents, test method documents, checklists for necessary actions that form part of the program, results sheets for raw data recording, MSDS sheets for the products to be evaluated, etc.

A Suggested Testing Programme

- There is no single correct way!
- Time-Kill study approach (ASTM, 2003) using the selected disinfectant and contact times bracketing the manufacturers recommended time
- The use-dilution may also be bracketed to demonstrate robustness in use
- Use several organism types comprising both reference strains and plant isolates
  - Environmental isolates can be hard to find in a clean room so it may be necessary to use isolates from surrounding areas
- Progress to a carrier test such as the *AOAC Hard Surface Carrier Test* (HSCT) and confirm the selected contact time with a carrier test system
  - Carriers are glass with inoculum of 10^6 cfu
- Demonstrate efficacy under the proposed use conditions using representative surfaces within the plant
  - Typically done using test coupons of the various surfaces to be evaluated
  - Reductions sought are typically 10^3 for bacteria and 10^2 for spores

In Summary

- Be familiar with correct terminology
- Be familiar with pros & cons of different types of products
- Review your disinfection needs – depending on your operation, you may need to do more or less work
- Bear in mind regulatory expectations but interpret them in a scientifically defendable way
- Don’t panic, be systematic!