Guidance for Aseptic Transfer Processes in the NHS: Addressing Sporicidal Issues

1st Edition

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A report by the
NHS Pharmaceutical Micro Protocols Group

This document has been prepared on behalf of the NHS Pharmaceutical Quality Assurance Committee by the NHS Pharmaceutical Micro Protocols Group. Membership of the Group is shown below.

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Aseptic Transfer Processes in the NHS: Addressing Sporicidal Issues

Executive Summary

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- The presence of viable organisms and in particular bacterial spores in the Grade A environment constitutes a real risk of contamination in aseptically prepared products and potential patient harm.
- The likelihood of product contamination is low but the consequences are severe.
- It is therefore necessary to improve transfer techniques and incorporate additional measures to enhance the sterility assurance of aseptic preparation.
- Consideration should be given to the use of pre-sterilised double or triple wrapped materials to reduce reliance on the operator dependent wipe-spray transfer processes. (Note: a proposed specification for multi-wrapped components has been developed, see Section 5).
- Where this is not possible, the MHRA Guidance (2015) requires changes in practice. In particular, a 2-stage wipe and spray disinfection process and the incorporation of a sporicidal agent in the first stage.
- A survey of suppliers was conducted to inform this guidance document.
- Only sporicidal agents are considered suitable; sporistatic agents are not. The accepted sporicidal agents are Chlorine, Hydrogen Peroxide and a combination of Hydrogen Peroxide and Peracetic Acid.
- **Although spraying is the most effective method of application, evaluation of best practice recommends that the sporicidal agent is applied as an impregnated wipe in order to limit health and safety and corrosion effects.**
- When evaluating sporicidal effectiveness for the in-use conditions – no current EN standards are fully applicable. Some suppliers do offer supportive information, however, caution must be used in the interpretation of the data.

Executive Summary - continued

- In the absence of any official standards for the efficacy of transfer disinfection, the NHS Pharmaceutical Micro Protocols Group has determined the **minimum sporicidal efficacy** *in situ* to be greater than **log 2 kill within 2 minutes.**

- A specification for a sporicidal product has been developed (Section 3). At the time of this review, all commercial products were aqueous based which has significant limitations e.g. evaporation times, spreadability and paper integrity.

- **A review of the transfer disinfection processes for each unit should be undertaken to ensure the best fit transfer disinfection process**. This should include a review of the current methodology and the development of a defined process appropriate for sporicidal agents, in particular, the use of wipes.

- Any changes to the transfer disinfection process should be implemented via a robust change control system that includes an assessment of health and safety issues in addition to those factors that could affect product quality.

Best Practice for Transfer Disinfection (minimum requirement)

Stage	Step	Presentation	Sterile Agent	Minimum Contact Time	Rationale	Risks	Risk Mitigation
Stage 1	**Step 1**	Impregnated Wipe	Sporicidal	2 minutes	• Removal of any dust, dirt or films • Physical removal of spores • Application of layer of sporicide to the product to elicit vegetative and sporicidal cell kill • Prevent microbial transfer into clean room (including spores)	• Dirt layers not removed • Damage of integrity of packaging – in particular paper based system – by soaking with sporicidal based aqueous solutions • Transference of contamination onto other surfaces by multi-use of wipe surface and unorganised wipe patterns e.g. transfer of dirt, residues and microbes	• Storage in clean stores • Process defined and staff trained • The use of fresh wipe surface for each stroke • Use of organised wipe patterns
	Step 2	Spray	Alcohol 70%	2 minutes	• Application of disinfectant to kill vegetative cells • Dilution of sporicidal residues • Aid evaporation and drying of surfaces	• Damage of integrity of packaging by soaking with alcohol solutions • Viable spores still present after Stage 1 • Sporicidal agent retained on packaging. • Risk of penetration through packaging	• Process defined and staff trained • Additional step to remove in Stage 3 • Additional wipe step at Stage 2 Step 4
Stage	**Step**	**Presentation**	**Sterile**	**Minimum**	**Rationale**	**Risks**	**Risk Mitigation**

			Agent	Contact Time			
Stage 2	**Step 3**	Spray	Alcohol 70%	2 minutes	• Application of disinfectant to kill vegetative cells • Dilution of sporicidal residues		• Process defined and staff trained
	Step 4	Impregnated Wipe	Alcohol 70%	2 minutes	• Physical removal of spores • Application of disinfectant to kill vegetative cells • Removal of sporicidal residues • Removal of excess alcohol to facilitate complete evaporation • Facilitate handling	Transference of contamination onto other surfaces by multi-use of wipe surface and unorganised wipe patterns	• The use of fresh surface for each wipe • Use of organised wipe patterns • Process defined and staff trained

Further details in **Section 2.**

Aseptic Transfer Processes in the NHS: Addressing Sporicidal Issues

1 Introduction

Following a series of patient deaths in 2014 linked with *Bacillus cereus* infections (MHRA, 2014) and observations of practice and microbiological monitoring made during audit processes; a reconsideration of aseptic transfer processes became necessary. This guidance aims to review some of the current incremental changes to the standards relating to the transfer disinfection process for aseptic preparation or manufacture. In particular, to address the key issues that relate to the introduction of an addition step and the routine use of sporicidal agents.

The use of operator dependent wipe-spray transfer disinfection techniques has been recognised as one of the weakest links in the aseptic process. In response to this, a number of amendments have been proposed by the MHRA in their Guidance for Specials Manufacturers, January 2015 (commonly referred to as the MHRA Q&As).

The purpose of this document is to provide guidance to the UK licensed Specials Manufacturers and Unlicensed NHS Aseptic Preparation Services and suppliers for effective transfer disinfection in compliance with the MHRA requirements.

This paper considers the options available and makes recommendations.

In particular, the following issues are assessed:

1. **Incorporation of an additional wipe step to the 2-stage transfer disinfection process – that is 2 x wipe/spray process.**
2. **Introduction of a sporicidal agent.**
3. **The use of pre-sterilised multi-wrapped procedure kits as a means to reduce or eliminate the use of disinfectants in the transfer disinfection process.**

Aim

To ensure that all items or equipment to be used within a Grade A critical work zone are either sterile or decontaminated effectively and safely.

1.1 Background

At the time of writing, the majority of NHS aseptic units had adopted a two-stage transfer disinfection process involving a first stage with spray-wipe steps (typically from the preparation room into the isolator cleanroom) followed by a second stage involving a spray step (into the isolator transfer hatch). 70% alcohol (denatured ethanol or propanol) was routinely used. This is in compliance with the Quality Assurance of Aseptic Preparation Services (Beaney, 2006).

A variety of practices have been observed with use of wipes. Impregnated wipes demonstrate a greater reduction in bioburden than dry wipes which are wetted *in situ* and are therefore preferred for aseptic disinfection transfer (Panousi et al, 2009). Evidence indicates that the dry wipes are rarely wetted enough to readily release sufficient alcohol onto the surface. In addition, the undulating and micro-structures of surfaces being disinfected does not facilitate the effective delivery of disinfectant by the wipe process.

Although natural fibre wipes may potentially shed more particulates, they have the advantage of increased wickability over most synthetic materials, holding more liquid and therefore releasing more disinfectant to kill surface-borne organisms. They also entrap particles and absorb residues more readily.

In summary, the roles and uses of wipes are:

1. To physically remove the bioburden from the surface
2. To ensure the presence of sufficient disinfectant for long enough to kill vegetative and where possible, spore forming micro-organisms
3. To facilitate the destruction and removal of contaminants by the application of pressure against microbial cell walls during the wiping process.

A fresh surface of each wipe (achieved by systemically folding the wipe) is required to prevent the transfer of the bioburden from the wipe to other surfaces

It has long been known that bacterial (and to a degree fungal) spores are resistant to alcohol disinfectant (typically up to x1000 more resistant than vegetative bacterial cells). Therefore, a wipe stage was introduced to physically remove the bacterial and fungal spores. The wipe phase also serves to remove grease and protective dirt layers.

There is evidence that although the wipe phase is effective, the majority of organisms (60-70%) isolated on glove prints (finger dabs) in NHS units are spore forming organisms (Personal communication John Rhodes, Stockton QC 2015). It has been a concern that although the level of finger dabs contaminated is usually not more than 3% of all plates dabbed in isolators (typically slightly higher in laminar air flow cabinets), the presence of vegetative (non-sporing) as well as spore forming organisms shows the inefficiencies of current practices. This probably reflects the fact that the processes are very operator dependent; subject to variable levels of consistency and can never guarantee 100% sterility assurance.

Bacterial spores are routinely found in low numbers on the surfaces of medicines and the packaging of containers used in aseptic manipulation. They have also been isolated as

contaminants in untreated sources of alcohol. For this reason all alcohols used in cleanrooms should be sterile, preferably gamma irradiated or sterilised by other chemical methods. Spray bottles should be designed to limit the ingress of bacteria following the development of negative pressure in the bottles after spraying (for example, the bag in the bottle device).

The risks of microbial contamination on transfer are further reduced by the use of no touch techniques to manipulate closed systems. Even though numbers and frequencies may be small, all deviations in a Grade A (and where appropriate, Grade B) environment should be investigated and all parameters trended.

Effective education and training of operative staff will reduce the finger dab contamination levels. Sustained diligence, supervision and monitoring is required to ensure that good practices are maintained, for example, the folds and webs of products and packaging are wiped, fresh wipe surfaces used for each single wipe and complete treatment of **all surfaces** is achieved.

Traditional and rapid gassing methods using vaporised hydrogen peroxide and/or peracetic acid have proved to be very effective at eliminating both vegetative and sporing micro-organisms with repeatable and auditable cycles.

Capacity planning should reflect the time required for effective transfer disinfection, particularly for non-routine working schedules (MHRA Guidance for Specials Manufacturers, 2015).

Risk
In summary, it is recognised that the presence of viable organisms and in particular bacterial spores in the Grade A environment constitutes a real risk of contamination in aseptically prepared products and potential patient harm. **Arguably the likelihood of product contamination is low but the consequences can be severe. Recent incidents have demonstrated that even with diligence and good practice, contamination, particularly under exceptional circumstances, can occur.** **It is therefore necessary to improve surface sanitisation techniques and incorporate additional measures to enhance the sterility assurance of aseptic preparation.**

1.2 MHRA Q&As January 2015

The MHRA introduced formal guidance for the interpretation of GMP in aseptic preparation in September 2013. This was updated and replaced as 'Guidance for Specials Manufacturers' in January 2015 (commonly referred to as the MHRA Q&As) (MHRA, 2015). The alterations and additions were made largely in response to a number of inspection deficiencies and observations, including an incident involving contamination of parenteral nutrition mixtures produced by a commercial specials unit (June 2014) which resulted in the infection of 23 neonates with *Bacillus cereus* and was linked to the death of 3 babies (MHRA, 2014).

The Guidance for Specials Manufacturers 2015 included a number of statements relating to transfer disinfection processes from the storage areas into the critical Grade A work zones. These have been listed separately in Appendix C.

There is also a statement concerning the status of gassing isolators versus the current widely used spray-wipe processes to disinfect materials and components being transferred into either isolators or unidirectional flow cabinets (Section 2.2.2), which highlights the limitations of operator-based processes and encourages the consideration of gassing technology when new units are being planned.

Two main components to achieve effective sporicidal transfer disinfection will need to be considered:

1. An effective sporicidal agent is employed for an appropriate validated contact time.
2. Effective techniques are routinely used by operators for all stages of transfer disinfection.

We need to be cautious in the development of these techniques that we do not replace a microbiological problem with a chemical problem especially in radiopharmacy and tissue culture units. A risk assessment is required.

On consideration of the MHRA guidance, the following important changes were identified:

Key Changes to previous practice
1. The introduction of two discrete decontamination stages, with a wipe and spray exercise performed at both stages. 2. The first stage must include use of a sporicidal agent. 3. Increased rigor in the wipe-spray process, for example, wiping with defined wipe patterns; cleaning in folds, particular attention to the rubber septa of vials and the break lines of ampoules. 4. The removal of outer packaging at the earliest stage possible (including the flip-off tops of vials). 5. Reduced and minimised bioburden levels on materials and components before aseptic transfer decontamination. 6. Effective contact time for sanitisation agent. 7. The time between sanitisation and use should be minimised. 8. Quality routine and periodic assessment of manufacturing processes including aseptic transfer. 9. The in-use shelf life for sanitisation agents must be defined and monitored. 10. The usual bioburden or micro-flora on the surface of items to be transferred should be determined and assessed periodically.

1.3 Methodology

In order to evaluate the information available on sporicidal agents in the pharmaceutical sector, a 26-part questionnaire was sent out to all known suppliers of sporicidal disinfectants (12 suppliers asked, 10 replied, one company with an additional product in the development stage and one company with a product being developed for the market). The questionnaire required summary answers with appropriate evidence backing up the claims.

A copy of the questionnaire can be found in Appendix A.

A follow-up questionnaire, particularly around the Phase 3 and 4 efficacy studies, requested additional information.

The responses were carefully reviewed by the NHS Pharmaceutical Micro Protocols Group and the data collated into a number of tables, some of which are to be found in the appendices.

To facilitate an understanding of the material, the sporicidal products reviewed were split into two categories:

1. Products suitable for general cleaning\disinfection (this will be considered in a later publication)
2. Products suitable for transfer disinfection processes (Appendix B).

The considerations in this guidance document were restricted to the latter group. Many products, presented in different formats, were suitable for use in both areas.

2 Best Practice

The aseptic transfer disinfection process incorporating a sporicidal agent is essentially a compromise between the need to apply the agent effectively to all surfaces, protecting the operator and preventing any ingress into the medicinal product.

It is considered advantageous to apply the sporicidal agent as early in the process as possible, primarily to prevent transfer of spores into the cleanrooms, but also to limit the environmental effects of these powerful oxidising agents to areas away from critical equipment and surfaces.

2.1 Goods receipt from non-aseptic areas

Items taken from a general storage area into an aseptic suite should be wiped to remove dust and bioburden using an alcohol dampened wipe. This has been demonstrated to be effective in some units. Care should be taken to not overly wet any paper packaging, for example, syringe, needles and similar products.

The above should be subject to a risk assessment.

An aqueous-based sporicidal wipe is not considered appropriate at this stage as this may damage the integrity of the packaging at an early point in the process.

Important – this decontamination process is not considered to be part of the normal transfer disinfection process and should only be considered as the reduction of gross contamination.

2.2 Transfer disinfection

2.2.1 Isolators

The issues addressed here consider the effectiveness of agent delivery and order of use. The recommendations are to apply the decontaminating agents in the order indicated in the diagrams that follow (pages 14-15).

Some considerations to the advantages and disadvantages of delivery methods follow:

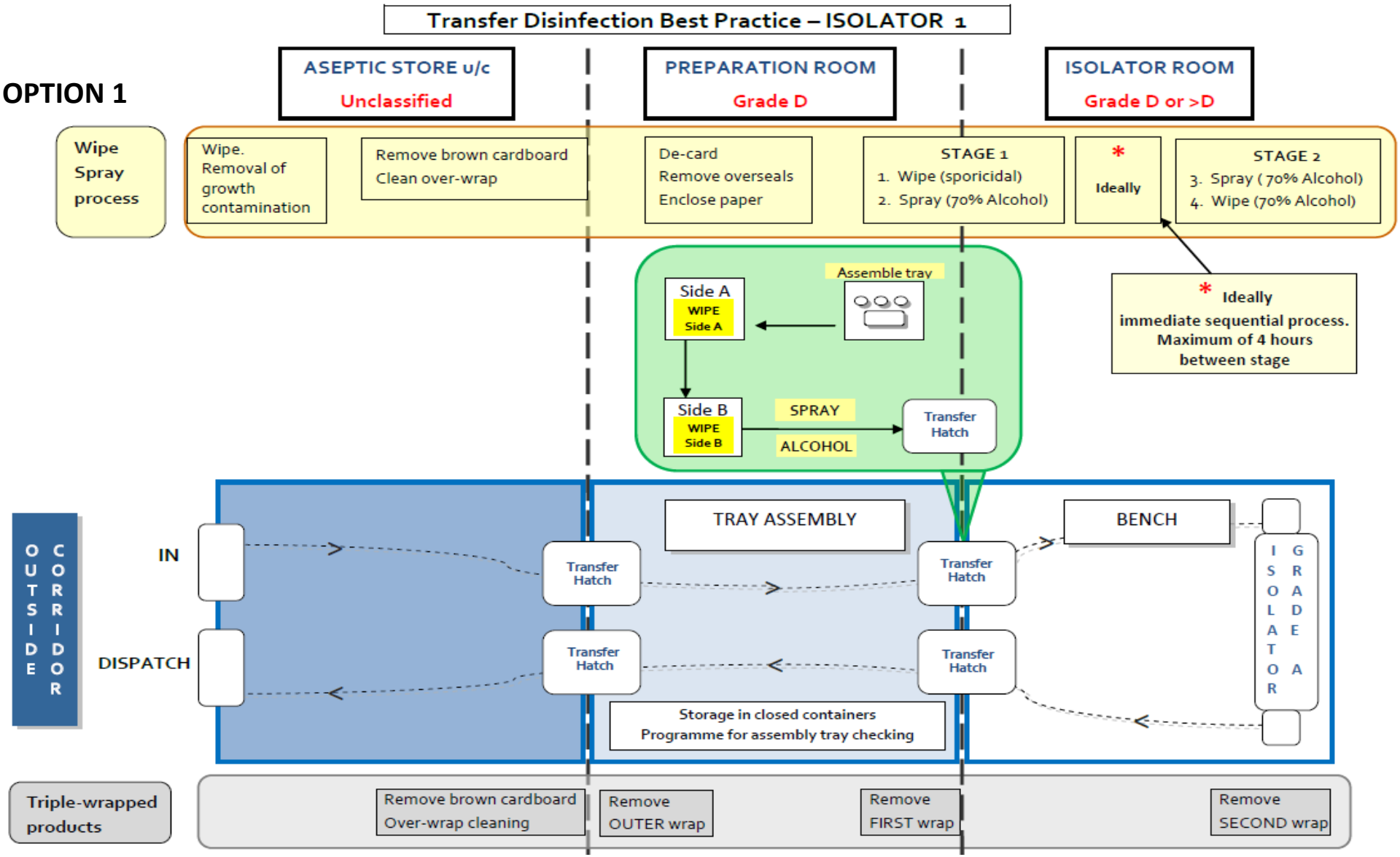
A wiping process allows the opportunity for delivery of decontaminating agent, mechanical removals of, and physical damage to, any micro-organism present. However, it sometimes fails to deliver adequate agent to chemically decontaminate. For example, with the wiping of paper based syringe packaging – it is hard to completely wet the 'paper' component as well as the plastic backing. It is also dependent upon operator technique as well as the nature of the wipe media and the amount of agent present.

A spraying process allows delivery of a sporicide to all surfaces to facilitate the killing of any spores present and is the ideal delivery method. However, all commercial products are currently in an aqueous base and are therefore prone to droplet coalescence on certain surfaces compared with the spreading and wettability of an alcoholic medium.

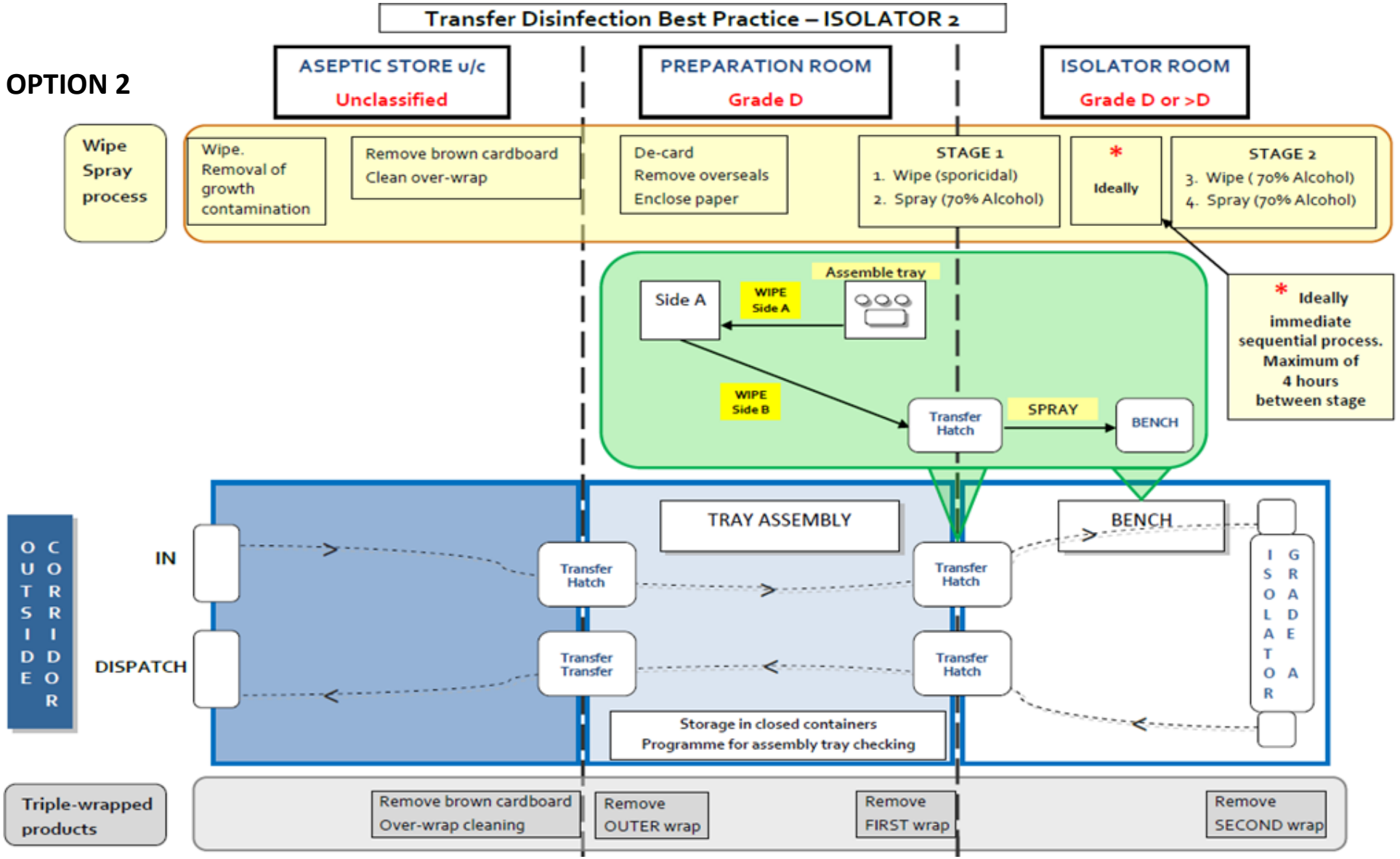
Although spraying may offer greater delivery of a sporicidal agent and therefore be a better solution microbiologically when compared with a wiping application, health and safety issues may restrict the use of such sprays unless local exhaust ventilation is available.

The particular transfer disinfection process selected for use should be designed to meet the specific needs and configuration of the aseptic service concerned, and follow suitable assessment of risk, impact and product and operator safety.

OPTION 1


Transfer Disinfection Best Practice – ISOLATOR 1
ASEPTIC STORE u/c
Unclassified
PREPARATION ROOM
Grade D
ISOLATOR ROOM
Grade D or >D
Wipe
Spray
process
Wipe.
Removal of
growth
contamination
Remove brown cardboard
Clean over-wrap
De-card
Remove overseals
Enclose paper
STAGE 1
1. Wipe (sporicidal)
2. Spray (70% Alcohol)
*
Ideally
STAGE 2
3. Spray (70% Alcohol)
4. Wipe (70% Alcohol)
Assemble tray
Side A
WIPE
Side A
Side B
WIPE
Side B
SPRAY
ALCOHOL
Transfer
Hatch
* Ideally
immediate sequential process.
Maximum of 4 hours
between stage
OUTSIDE CORRIDOR
IN
DISPATCH
TRAY ASSEMBLY
BENCH
Transfer
Hatch
Transfer
Hatch
Transfer
Hatch
Transfer
Hatch
ISOLATOR GRADE A
Storage in closed containers
Programme for assembly tray checking
Triple-wrapped
products
Remove brown cardboard
Over-wrap cleaning
Remove
OUTER wrap
Remove
FIRST wrap
Remove
SECOND wrap

OPTION 2


Transfer Disinfection Best Practice – ISOLATOR 2
ASEPTIC STORE u/c
Unclassified
PREPARATION ROOM
Grade D
ISOLATOR ROOM
Grade D or >D
Wipe Spray process
Wipe. Removal of growth contamination
Remove brown cardboard
Clean over-wrap
De-card
Remove overseals
Enclose paper
STAGE 1
1. Wipe (sporicidal)
2. Spray (70% Alcohol)
*
Ideally
STAGE 2
3. Wipe (70% Alcohol)
4. Spray (70% Alcohol)
* Ideally immediate sequential process. Maximum of 4 hours between stage
Assemble tray
Side A
WIPE Side A
WIPE Side B
Transfer Hatch
SPRAY
BENCH
OUTSIDE CORRIDOR
IN
DISPATCH
TRAY ASSEMBLY
Transfer Hatch
Transfer Transfer
Transfer Hatch
Transfer Hatch
BENCH
ISOLATOR GRADE A
Storage in closed containers
Programme for assembly tray checking
Triple-wrapped products
Remove brown cardboard
Over-wrap cleaning
Remove OUTER wrap
Remove FIRST wrap
Remove SECOND wrap

2.2.2 Laminar Air Flow Cabinets

The processes are essentially similar to that of isolators, however, there may be more risk to the operator and environment from a wider dispersion of aerosols by the airflow from the laminar flow hood. This supports the use of a sporicide at the first stage.

The recommendations are to apply the sanitisation agents in the order indicated in the above diagrams. The process should be very clearly defined to minimise variability between operators. This should be supervised closely to ensure compliance.

As stated in section 2.2.1, the particular transfer disinfection process selected for use should be designed to meet the specific needs and configuration of the aseptic service concerned, and follow suitable assessment of risk, impact and product and operator safety.

2.3 Alternative Approaches – pre-sterilised wrapped packaging

The use of terminal gamma-irradiated (or, potentially, Ethylene Oxide (EtO) sterilised) components (overwrapped in the form of bulk or procedure packs) offer a safer and time efficient alterative to the use of liquid sporicidal agents, albeit at a cost.

Typically, components of this nature are triple wrapped and also enclosed within a dust outer wrap (of a lower grade plastic) surrounding the packs. During assembly these components are all packed in a minimum grade ISO 7 cleanroom and finally placed in a cardboard box for subsequent sterilisation by gamma irradiation (see Appendix D).

In theory, given the maintenance of the integrity of the cardboard box, the dust wrap will be sterile as well as the items within it.

Note: circumstances for items sterilised by EtO gassing are different because there cannot be a polythene overwrap and there must be a penetrable area on every layer of packaging.

On receipt, the cardboard outer of such items should be used for storage in a general pharmacy store. The cardboard should then be removed when the products are transferred into the preparation \ support room.

The outer dust cover may be removed or alternatively the surface of the dust cover might be wiped and disinfected to remove excess dirt and to prepare it for storage and use in the preparation \ support area.

Handling the triple wrapped items:

a) The first wrap is then removed by dropping the contents directly into a suitably sporicidal disinfected tray sitting in the transfer hatch between the preparation room and clean room. Care should be taken not to handle the inner pack.
b) The second wrap is removed in similar manner into the isolator transfer hatch or into the LAF cabinet. Care should be taken not to handle the inner pack.
c) The component(s) \ item(s) are removed from the third and final wrap in the isolator (or laminar flow hood) before processing.

2.3.1 Ideal Specification for pre-sterilised procedure packs

The following ***ideal*** specification should be considered when you are evaluating the use of pre-sterilised procedure packs:

Characteristic	Properties	Criteria
Design	The design of the wraps should have: • no folds or webs to decontaminate • minimum creases on the surfaces to facilitate even and effective wiping	Important
Quality of Components	The primary source and quality of components and any previous sterilisation treatment should be considered Re-sterilisation may affect the quality of the item (for example, a double irradiation dose can cause discolouration and render plastic syringes brittle)	Essential
	The components should be compatible with the packing materials and subsequent treatment processes Functionality tests should be undertaken	Important
	Full traceability of all key constituents and processing	Essential
	Cytotoxicity tested	Important
	Latex free	Essential
	Low binding properties / adsorption / leaching	Desirable
	Low particle loading	Desirable
Quality of Packaging	Effective robust seals (circa 10mm wide) welded either textured or smooth These should have no exposed folds	Essential
	Outer wrap dust packaging (not for EtO unless added after sterilisation)	Important
	The packaging materials should be robust (for example, 100um PAPE, Polyclear or similar material)	Essential
	Dye intrusion testing data should be available	Desirable
	The permeability of the overwraps to moisture and contamination should be assessed	Desirable
Manufacture	Prepared in minimum grade ISO 7 cleanrooms	Essential
	Sealing pressure, temperature and time should be validated and routinely monitored for reproducibility. There should be an agreed tolerance Bags are generally prepared by an initial sealing of 3 sides, the positioning of materials in the bag and then the final seal will need to be assessed	Essential
	The components should be stability tested having been through a typical re-sterilisation process Particular care must be taken over the reprocessing, in particular 're-sterilisation', of components (see proposed MHRA Guidance)	Important
	Packages should be pressure tested using pressure decay and drop tests – these should be a realistic worse case specific to the product presentation	Desirable
	ISO,BSI, CE or equivalent – audit processes applied to suppliers	Essential
	Suppliers audited by NHS auditor	Essential

Characteristic	Properties	Criteria
Sterilisation	If EtO sterilisation used – what is the penetration into inaccessible parts to sterilise and the desorption of the gas?	Essential
	Gamma Irradiation - >25kGy (Typical max 45 kGy) Validation certification available	Essential
Compatibility	Multi packs – the following point should be considered and risk assessed • How long can these be stored after opening if not used immediately? It is advised that packs are not used beyond one session unless this has been validated	Desirable
Use	Easy tear or peel opening (with tear indent or start point)	Essential
	Contained components strategically orientated for clean removal from packaging	Important
	Capped syringes to minimise accidental touch contamination on removal from packaging	Important
Presentation	Pack Size considerations Labelling • Batch Number and expiry date • For single use only • Sterile	Essential
VHP	Hole for hanging on final container for VHP	Desirable

3 Ideal Specification for Transfer Disinfectant

This section is intended to guide the decision making processes when selecting agents for aseptic transfer disinfection. The following ***ideal*** specification should be considered when reviewing options.

Characteristic	Properties	Criteria
Spectrum of activity	The ideal agent will effectively kill the following • Bacteria – Gram-positive and Gram-negative • Fungi including fungal spores, moulds and yeast • Enveloped and naked viruses • Bacterial spores	Essential
Effectiveness	**Agent demonstrates at least > log2 reduction of viable spores within 2 minutes**	Essential
	Rapid Action - effective within 2 minutes	Essential
	Penetration - penetrates biofilms and remains effective with general levels of soiling	Essential
	Stability - Chemically stable throughout its allocated shelf life and effective shelf life once opened	Essential
	Durability – effective for the full period of contact, i.e. remains wet and does not degrade	Essential
Health and Safety	No objectionable odour	Important
	Minimal hazard to operatives (COSHH considerations)	Essential
	No environmental monitoring or detect required	Important
	Easy and safe disposal	Desirable
	Use causes minimum risk of Upper Limb Disorder (RSI)	Desirable
Corrosiveness	Non-corrosive to metals and other vulnerable materials (such as door seal, hinges, filter seals etc.)	Important
	Low particle generation	Important
	No or low residues	Essential
Compatibility	Consumables, packaging, equipment – see corrosiveness	Important
	Gloves – should not penetrate or degrade glove materials	Important
Quality	Manufactured to appropriate EU GMP and ISO standards and evidence by Certificate of Analysis etc.	Essential
	Registered under BPR (Biocide Products Registration)	Important
	Maintains sterility in use (e.g. bag in the bottle or filtration systems)	Essential
Presentation	Sterile	Essential
	Double or Triple wrapped	Important
	Robust packaging	Important
	Value for money	Desirable
	Ready and easy to use - Preactivated (or closed system activation)	Important

If presented as a spray – all the above characteristic apply, special attention is required for the following		
	The dispensing system should minimise the potential for contamination of the supplied contents	Important
	The dispensing system should minimise the risk of RSI related injuries	Desirable
	Adjustable spray patterns	Important

If presented as a wipe - all the above characteristic apply, special attention is required for the following		
	The wipe should have good disinfectant retaining properties	Essential
	The wipe should not shed particles	Important
	The size of the wipes suitable for effectively wiping the surfaces and easy to fold	Essential
	The wipe should deposit enough product to achieve effective disinfection for the full period of contact	Essential
	Packs are effectively and easily re-sealable (particularly multi use presentations e.g. tubs)	Desirable
	Disinfectant does not interact with the wipe\carrier system	Essential

No formal comparisons of commercially available products have been made against this specification.

4 Sporicides

4.1. Classification of Sporicides

The sporicides can be classified according to chemical activity and presentations available.

Chemical Activity	Wipe availability in 2015	Spray availability in 2015
Sporicidal Agents		
Chlorine	√	√
Hydrogen Peroxide		√
Hydrogen Peroxide and Peracetic Acid	√	√
Sporistatic Agents		
Triamines	√	√

A more detailed breakdown of presentations is available in Appendix B.

4.2 Sporicidal Agents

Sporicidal agents render bacterial or fungal spores no longer able to germinate and produce viable, vegetative cells. They are powerful oxidising agents which elicit their kill by the oxidation of proteins and other key cellular components. Sporicidal chemicals include agents such as ethylene oxide, glutaraldehyde, formaldehyde, hydrogen peroxide, peracetic acid, chlorine dioxide, sodium hypochlorite, sodium dichloroisocyanurate, ozone and iodine based products.

The Technical Committee (CEN/TC 216 "Chemical disinfectants and antiseptics") of the European Committee for Standardisation has defined a sporicide as a *product which kills dormant bacterial spores of relevant test organisms under defined conditions.*

Sporistatic agents act via a different mechanism. They mostly act and kill as the spore germinates back to a vegetative cell, and do **not** normally *per se* kill the spore. Examples of these agents include alcohols, biguanides, quaternary ammonium compound (QAC), di- and tri- amines and phenols. They may show some activity against spores depending on the state of the culture (that is, the percentage of organisms in a germination phase). Some sporistatic materials may be sporicidal at high concentrates and prolonged contact times.

The current range of sporistatic agents are not appropriate for the sporicidal step in the transfer disinfection process and have limited use in clean rooms and critical work zones.

After consultation with experts in the field, it is held that the Triamines are sporistatic agents (personal communications; Sandle and Maillard, 2015) and therefore are not appropriate for aseptic transfer processes.

Note
Purchasers should confirm the agent is sporicidal. Sporistatic agents are not suitable. Caution: Triamines are not considered to be sporicidal but do have sporistatic properties, that is, the sporistatic agent needs to be retained on the surface in order to inhibit the germination of spores.

The current sporicidal products on the market are based on three oxidising active ingredients:

- Chlorine
- Hydrogen peroxide
- Peracetic acid

4.2.1 Chlorine

In use, chlorine based disinfectants (bleaching agents), have various active chemical species.

Hypochlorous acid is a weak acid with the chemical formula HOCl. It forms when chlorine dissolves in water, and it is the HOCl moiety that actually does the disinfection when chlorine is used to disinfect water for human use. It cannot be isolated in pure form due to rapid equilibration with its precursor. HOCl is an oxidiser and is available as a sodium salt sodium hypochlorite (NaOCl). This elicits its bactericidal activity by acting on a wide variety of biomolecules, including DNA, RNA, fatty acid groups, cholesterol and proteins. The formation of hypochlorous acid is dependent on pH conditions (optimum at pH 5.5-6.0).

Sodium dichloroisocyanurate (NaDCC)
NaDCC is a chemical compound widely used as a cleansing agent and disinfectant; this salt is an active ingredient in many bleaches. It is a colourless, water soluble solid. It is an oxidiser that reacts with water to ultimately form hypochlorous acid. Dissolution in water produces a series of complex equilibria among a variety of chlorinated and non-chlorinated isocyanurates and free available chlorine (FAC) in the form of hypochlorous acid (HOCl). The perceived advantage is that in solution the salt acts as a reservoir for chlorine which can be advantageous when subject to high organic loads. The optimum pH for activity is pH 6-7.

Chlorine dioxide is a chemical compound with the formula ClO_2. As one of several oxides of chlorine, it is a potent and useful oxidising agent used in water treatment and in bleaching. It is a neutral chlorine compound and is very different from elemental chlorine, both in its chemical structure and in its behaviour. One of the most important qualities of chlorine dioxide is its high water solubility, especially in cold water. Chlorine dioxide does not hydrolyse when it enters water but remains a dissolved gas in solution. Chlorine dioxide is approximately 10 times more soluble in water than chlorine. It is claimed to be less corrosive than chlorine. The optimum pH for activity is pH 2-10.

Hypochlorite
Hypochlorite is an ion compound of chlorine and oxygen, with a chemical formula ClO^-, which can combine with a number of counter ions such as Na^+ (household bleach) and Ca^+ (used for water treatment) ions, to form the corresponding hypochlorites. In essence, they can be regarded as salts of hypochlorous acid. They are relatively unstable in their pure form and

therefore generally handled as aqueous solutions. A 5% solution has a pH of 11 whereas a concentrated sodium hypochlorite solution has a pH up to 13.

Sodium hypochlorite in its natural state exists in hydrated form but has not been prepared drier than the pentahydrate which is unstable at o°C. Diluted solutions such as domestic bleach possess much better stability. Calcium hypochlorites can be produced on an industrial scale and have good stability.

Acidification of hypochlorites generates hypochlorous acid which exists in equilibrium with chlorine gas, which can bubble out of solution.

$$2H^+ + ClO^- + Cl^- \rightleftharpoons Cl_2 + H_2O$$

The equilibrium is subject to Le Chatelier's principle; thus a high pH drives the reaction to the left by consuming H^+ ions, promoting the disproportionation (simultaneous reduction and oxidation) of chlorine into chloride and hypochlorite, whereas a low pH drives the reaction to the right, promoting the release of chlorine gas.

Hypochlorites are generally unstable and many compounds exist only in solution. Hypochlorite is unstable with respect to disassociation of chlorine. Upon heating, it degrades to a mixture of chloride, oxygen and other chlorates:

$$2ClO^- \longrightarrow 2Cl^- + O_2$$
$$3ClO^- \longrightarrow 2Cl^- + ClO^-_3$$

This reaction is exothermic and in the case of concentrated hypochlorites can lead to a dangerous thermal runaway and potentially explosions. Care must be exercised in the disposal of these products!

Chlorine-based products are very susceptible to the presence of organic material and can be rapidly inactivated.

Chlorine-based disinfectants are corrosive and most leave residues which should be removed before use to minimise the transfer of chlorine species or salts into the products.

4.2.2 Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is a colourless liquid that is the simplest peroxide (a compound with an oxygen-oxygen bond). It is used as a strong oxidiser, bleaching agent and disinfectant, its chemistry being dominated by the nature of its unstable peroxide bond which will readily mediate reactive free radical chain reactions which fragment and interaction with nucleic acids, lipids and proteins, both structural and functional. These free radicals are highly reactive transient species and readily decompose.

It is essentially unstable and decomposes to form water and oxygen, leaving no residues.

$$2H_2O_2 \Rightarrow 2H_2O + O_2$$

It demonstrates broad-spectrum activity against bacteria, yeasts, viruses and bacterial spores. Being highly reactive oxidising agents, they are intrinsically unstable and corrosive by nature. The stability and reliability of the solutions requires validation.

Activity against spores is a function of both concentration and time (stronger and longer are better). For safety reasons hydrogen peroxide is used as a disinfectant in concentrations ranging from 3-6% (available and sustained). (Vapour phase hydrogen peroxide sanitisation works somewhat differently and is generally considered more effective).

4.2.3 Peracetic Acid

Peracetic acid (also referred to as peroxyacetic acid or PAA) is an organic compound with the formula CH_3CO_3H. It is a colourless liquid with a characteristic acrid odour similar to acetic acid (e.g. vinegar). Peracetic acid is often combined with acetic acid or hydrogen peroxide in solution to maintain the stability of the peracid. Peracetic acid has found widespread use in healthcare, food processing, and water treatment because of its broad antimicrobial properties particularly as a surface disinfectant.

A mixture of acetic acid with hydrogen peroxide in solution will form peracetic acid. The equilibrium constant is dependent on the concentrations and conditions (pH) of the reaction:

$$H_2O_2 + CH_3CO_2H \rightleftharpoons CH_3CO_3H + H_2O$$

Peracetic acid is more active around pH7 compared to pH 8-9. It is more effective at raised temperatures, for example, it is five times more active at 35°C than at 15°C.

4.3 Sporistatic Agents

4.3.1 Triamines

Triamine is a general term describing organic compounds with three amine groups. Triamines, including Alkyl Triamines, were developed as general disinfectants. They are usually considered to be sporistatic agents (see 4.2). Amines are thought to act on the cytoplasmic (inner) membrane inducing the loss of amino acids leading to cell inactivation. Commercial products are often combined with quaternary ammonium compounds (QACs) with which they work synergistically. They are ineffective against spores because the agent has limited penetration to the inner membranes of the cell.

5 Practical Considerations with the use of Sporicidals

5.1 Efficacy

5.1.1 Introduction to disinfection standards

A recognised approach to disinfectant efficacy validation is to follow the CEN (European Committee for Normalisation) Technical committee 216 work programmes which provide a systematic approach to the validation of disinfectant efficacy.

A number of BS EN methods have been issued as a result of the CEN work program. The literature defines in detail how disinfectants should be tested against a range of type cultures under controlled conditions. There are clearly defined pass criteria and results are expressed as either pass or fail. All the methods include rigorous validation requirements which are performed in parallel to the test itself. In general, for efficacy testing of disinfectants only quantitative test methods should be used.

A tiered approach for the testing of disinfectants is recommended – these fall into the tiers indicated below (Phase 1 – Phase 3).

Manufacturers of sporicidal agents were surveyed as indicated in Section 1.3. The results for 'efficacy' are assessed in this report. The majority of the agents assessed fell into two broad categories, those containing hydrogen peroxide and those based on chlorine. The results were considered in relation to the BS EN Standards.

5.1.2 Phase 1 tests

These are quantitative laboratory suspension tests to establish the basic activity of the product or active substance (that is bactericidal, fungicidal, virucidal etc. activity) without regard to specific conditions of intended use. These tests may be used during the development of the product, but are not accepted for product authorisation.

Disinfectant Standard	Organism Types	Type	Typical Performance Criteria (Requirements may vary by claim)
EN 1040	**Bacteria** *Staphylococcus aureus*, *Pseudomonas aeruginosa*	Quantitative suspension test for the evaluation of basic bactericidal activity of chemical disinfectants and antiseptics.	5 log reduction in ≤5 minutes
EN 1275	**Fungi** *Candida albicans, Aspergillus brasiliensis*	Quantitative suspension test for the evaluation of basic fungicidal or basic yeasticidal activity of chemical disinfectants and antiseptics.	4 log reduction in ≤15 minutes

5.1.3 Phase 2 comprises two steps:

5.1.3.1 Phase 2 step 1 tests

These are quantitative laboratory suspension tests designed to establish the concentrations at which the product meets specified requirements under "in-use" conditions (that is, bactericidal, fungicidal, virucidal etc. activity). The tests simulate practical conditions appropriate to its intended use, that is, *in vitro* tests for mixtures and solutions. In these tests, in-use conditions (e.g. temperature, contact time, interfering substances) are considered in the test method.

Although these laboratory methods may differ in their design and experimental detail, they are all based on the principle of adding a test inoculum to disinfectant (or vice versa) and taking samples at specified times. The biocide in each sample is then neutralised and the survival of the organisms assessed. In practice, the methods can be classified into two groups, according to how the end-point of the test is determined.

Quantitative tests

Samples of untreated and biocide-treated micro-organisms are plated on nutrient medium after neutralisation. After incubation, the number of colony forming units (cfus) is determined and the log reduction in viable counts determined.

Capacity tests

The biocide is challenged successively with the test organism at defined time intervals, typically of use when the disinfectants are challenged by new bacteria periodically (e.g. swimming pools). Following each inoculation, samples are taken, and after a suitable contact period has elapsed, the biocide is neutralised and the sample incubated in a suitable growth medium to determine the surviving micro-organisms. The result is expressed as the amount of the accumulated inoculum that was required to produce the "failure".

In order to evaluate agents intended for use in transfer disinfection, it is necessary to consider the quantitative tests.

Disinfectant Standard	Organism Types	Type	Typical Performance Criteria (Requirements may vary by claim)
EN 1650	**Fungi** *Candida albicans*, *Aspergillus brasiliensis*	Quantitative suspension test for the evaluation of fungicidal or yeasticidal activity of chemical disinfectants and antiseptics used in food, industrial, domestic and institutional areas.	4 log reduction in ≤15 minutes
EN 13704	**Spores** *Clostridium difficile*	Quantitative suspension test for the evaluation of sporicidal activity of chemical disinfectants used in food, industrial, domestic and institutional areas. Interfering Substances Clean 0.03% w/v bovine albumin Dirty 0.3% w/v bovine albumin + 0.3% w/v washed sheep erythrocytes	3 log reduction in ≤60 minutes

5.1.3.2 Phase 2 step 2 tests

These are quantitative laboratory tests which simulate in-use or practical situations which mimic real-life conditions, for instance by pre-drying the micro-organisms onto surfaces in order to establish that the product has bactericidal, fungicidal, virucidal etc. activity. After measuring the time-concentration relationship of the disinfectant in an in-vitro test (Phase 2 step 1), these practical tests are performed to verify that the proposed in-use dilution is likely to be adequate in real life conditions. Standardised simulated tests are available for several uses (hard surface disinfection, hand wash or rub, instrument disinfection) but there are no standard tests available for many others, including the transfer disinfection process. The best we can do at present is to infer effectiveness from the information presented.

Residual activity has been claimed for some products. It is presumed that when these products are applied to surfaces, they will not be completely removed or rinsed off after application. This may lead to persistent activity of the biocide on the surface, which can be determined by modified efficacy tests.

Disinfectant Standard	Organism Types	Type	Typical Performance Criteria (Requirements may vary by claim)
EN13697	**Quantitative non porous surface test method** *Staphylococcus aureus* *Enterococcus hirae* *Escherichia coli* *Pseudomonas aeruginosa*	Quantitative non-porous surface test for the evaluation of bactericidal and/or fungicidal activity of chemical disinfectants used in food, industrial, domestic and institutional areas.	4 log reduction in ≤5 minutes

5.1.4 Phase 3 tests (In-use tests)

These are field tests under practical conditions, that is, 'in use' tests and rely on performance qualification protocols to determine the effectiveness of the agent and operator technique. This usually involves the antimicrobial evaluation of the product under actual conditions of use on specified surfaces or materials in a specified environment. As with standard and non-standard laboratory methods, representative organisms or actual organisms of concern may be used. Validated methodologies for these types of tests are not currently available because the practical use conditions under which a product can be used can be very variable and are therefore difficult to standardise.

Note: field tests, although not standardised, can give valuable additional information on the efficacy of the product, provided that the studies are scientifically robust, well reported and provide a clear answer to the question. A negative control without the biocide should be included, or the efficacy should be judged on a comparison of the situation before and after the application.

The use of the 'total immersion method' or the use of contact plates before and after the transfer disinfection process would constitute a simple Phase 3 test.

5.1.5 Phase 4 test

Although there are no official Phase 4 tests, a further evaluation was considered important. The tests suggested here are in essence, Phase 2/3 tests are conducted under the following conditions:

1. At the end of the shelf life of the product
    1. Either as the solution *per se*
    2. or a solution in contact with either the synthetic or natural fibre wipe

2. When a product is reconstituted
    1. just before use
    2. and at the end of its in-use shelf life.

Ideally these should be conducted in a controlled manner to ascertain the microbiological effects of in-use incompatibilities or lack of stability. If no microbiological efficacy testing is available, chemical stability and incompatibility studies must be undertaken to verify efficacy under these conditions.

The rationale for the Phase 4 tests are that the sporicides are generally reactive oxidising species which are essentially unstable or reactive towards packaging or wipe media.

There was no microbiological efficacy data presented in the survey reports to indicate that any Phase 3 and, in particular, Phase 4 tests have been done. However, chemical stability data has been presented for certain storage conditions.

5.1.6 Phase 5 test

Phase 5 tests are indirect but very useful indicators of disinfectant efficacy. Examples include continuous environmental monitoring processes such as operator glove prints (finger dabs). These give not only an indication of the efficacy of the disinfectant but also of the all-important operator technique.

The proportion of vegetative micro-organisms versus the more resistant spore-forming organisms will provide suitable markers in the 'before and after' evaluation of Wipe-Spray; Spray-Wipe process as well as the introduction of the sporicidal disinfectant.

The 'before and after' evaluation might include glove prints, broth immersion method and contact plate methods.

Note: Independent studies by the NHS Pharmaceutical Micro Protocols Group, indicate that approximately a third of the organisms isolated on glove prints are vegetative in nature. Such organisms should be susceptible to the routine alcohol disinfection processes, if this had been undertaken properly. These results indicate an ongoing issue with poor technique particularly around critical awkward to reach areas, such as folds etc..

5.1.7 Contact Times

The time the disinfectant is in contact with the contaminating organism is vital. This is to allow penetration into the microbial cell and for subsequent chemical reactions to take place. In practice, a 2 minute contact time has been established as suitable for alcohol disinfection. A similar contact time is desirable for sporicidal agents. Ordinarily the agent will effect a kill within this period (for example, alcohol will kill in seconds when in direct contact with microbes) but the two minute hold period is required to allow time for the penetration of organic material and waste that can surround the organism.

All the sporicidal products surveyed for this report were aqueous based and appeared to elicit a slower kill rate (although at present this may be an artefact of the fact that these products have been tested to established efficacy protocols which are designed to monitor longer contact times).

It is clear that the majority of aseptic units would find it impractical to operate with two consecutive contact times of greater than 2 minutes.

Contact Times
In the absence any official standards for transfer disinfection, the NHS Pharmaceutical Micro Protocols Group has determined the **minimum sporicidal efficacy** to be: **>log 2 kill within 2 minutes** **ideally >log 3 kill in 2 minutes**

NOTE: Generally the disinfectants do not have

1. to deal with high levels of microbial contamination. Studies have indicated that the bioburdens on consumables and medicines are low (Typically less than 100cfu per item).
2. to deal with high levels of organic contamination.

5.1.8 Information Available

The responses to survey question 19 concerning the efficacy of the sporicidals are assessed in this report. The efficacy of the disinfectants against vegetative bacteria, bacteria spores, fungal spores, moulds and yeasts were expressed as a log kill for defined organism strains using a standard method. The data for efficacy against viruses have not been included.

The results are summarised in Appendix E. Refer to specific data on the supplier's products in this table.

Summary

There are a number of European sporicidal testing standards which are used to validate the claims of commercial sporicides. However, the extent to which these standards reflect the practical application of sporicides in the pharmaceutical transfer disinfection scenario is limited since they do not involve surface contamination and employ contact times in excess of 15-30 minutes.

This situation is further exacerbated by the lack of any regulatory requirements on disinfection efficacy within the UK.

A standard relating to the testing of wipes in in-use conditions (ASTM E2967: May 2015) is currently being released. This may provide further evidence of the effectiveness of these products against spores in transfer disinfection processes. The expectation is that companies will consider providing evidence against this standard.

In addition, the United States Pharmacopoeia has a useful section on disinfection including a theoretical discussion of disinfectant activity (Section 1072 USP, 2015).

The adaptation of such tests as EN 13697 to enable the development of field tests has also been suggested.

5.2 Health and Safety – see Appendix G

The impact of handling these products on the health and safety of the operatives is of prime importance. Chlorine, hydrogen peroxide and peracetic acid products (that is, oxidising agents) are all potentially hazardous; the method of application appearing to be the main risk determinant (that is, spraying presents a higher risk to the operative compared to wiping as a result of a higher exposure to the operative).

These products are generally irritant, in particular to mucous membranes. They are irritant to the eyes, respiratory tract and skin; having differing effects depending on concentration and accessibility.

Short term exposure limits (15 minute reference period) (EH40, 2005)
Chlorine dioxide 0.3ppm
Hydrogen Peroxide 2ppm

Spraying is considered to be the best method of applying a disinfectant to a surface, in particular to pharmaceutical components which have uneven surfaces with many creases many of which are not easily accessible. However, the generation of aerosols in the environment can result in increased access to both the eyes and the respiratory tract, hence limiting the use of this method of application. The risks of exposure should be determined locally by COSHH assessments and environmental monitoring. Exposure should be minimised by the sensible use of Local Exhaust Ventilation (LEV), Personal Protective Equipment (PPE), and high air change rates within the clean room.

Application of disinfectants by wiping is a viable alternative which minimises exposure to these oxidising agents while facilitating the removal of dirt films and the application of disinfectants i.e. two distinct processes:

1. the application of the agents to the surfaces – effecting dislodgement, dissolution and chemical action
2. as well as wiping dirt films from the surfaces – including wicking actions

The wipes should be pre-impregnated with disinfectant as this has been shown to deliver greater amounts of disinfectant to the surface. This will depend not only on the nature of the wipes and the volume of disinfectant available, but also on operator technique. It should be noted that application should be validated and verified. Therefore, suitable training and education is imperative.

5.3 Corrosiveness – see Appendix F

All of the oxidising actives used as sporicidal agents are potentially corrosive. The degree of corrosion will vary depending on the metal present and its quality. There are no recognised standards for the measurement of corrosion in this context.

The corrosiveness of a number of the products has been assessed. However, the lack of a recognised standard has made comparison difficult. Individual assessment should be made wherever possible.

Note:

1. Particular care should be taken when these agents are used with lower grade stainless steel (for example, 304) or mild steel. This should be discussed with your suppliers when purchasing new clean room equipment (for example isolators, pumps etc.).

2. Diligence should be taken with epoxy coated metals. If the epoxy coating is damaged in any way, this may give these oxidising agents access the underlying metal surfaces; permitting extended exposure and speeding up the degradation process.

5.4 Compatibility – see Appendix F

Chlorine and peracetic acid-based products can leave residues on the surfaces. The nature and effect of such residues will vary depending on the product and should be assessed when selecting the disinfectant.

If the residues are not effectively removed in a timely manner, this may

1. facilitate corrosion e.g. rusting, degradation of rubber seals or the interaction with vision panels on isolators leading to fogging or crazing of the plastic, in particular radiopharmaceutical leaded vision panels.
2. allow ingress into the medicinal products and chemically interact with the active drugs.

The latter effect has been observed with radiopharmaceutical agents and may potentially oxidise complex, and therefore susceptible, biologically derived drugs. Although the latter has not been formally observed, the risk should be considered.

The removal of any residues should be effective and where possible should be validated.

Hydrogen peroxide products degrade to water and oxygen and leave no residues when **dry**. (The speed of drying is affected by many factors, e.g., air change rate, air speed/flow, temperature and surface area)

5.5 Quality – see Appendix F

The quality parameters of the various products have been reviewed and are summarised in Appendix F. These include the following factors:

- particulates
- sterility tested
- endotoxins
- residue levels
- presentation (degree of wrapping)
- batch testing and availability of Certificates of Analysis.

The stability of the disinfectants has been assessed chemically for certain products. There are a number of factors that might affect the stability of these oxidising agents including the sterilisation process (gamma irradiation). The stability of products in-use, i.e. effectiveness over the period of exposure or contact time had not been represented in any of the data surveyed in this study.

Some products were available ready to use but others required activation before use.

There is a limited amount of data available for stability both at the end of the shelf life and in-use expiries.

5.6 Manufacture – see Appendix F

With the exception of one product, all the products considered were subjected to sterilisation by filtration followed by aseptic fill. Terms such as 'self-sterilising' are generally not considered valid unless they are supported by evidence.

Diluents for the active ingredient(s) were either Water for Injection or Purified Water. This may result in surfaces retaining a fluid layer for a longer period (due to slow evaporation rates) and the potential to compromise the integrity of paper wraps when compared to alcohol based products.

6 Change Control Processes

Introduction

GMP requires that any change to processes, materials or equivalents is accompanied by a carefully designed change control procedure and concomitant documentation.

In order to facilitate this, the following guidance is offered.

Initial Risk Analysis

Is there an alternative to the sporicidal step?

- Review pre-sterilised triple or double wrapped products available on the market
- If nothing commercially available, commission a design of triple or double wrapped packs suitable for your needs

Processes \ Procedures to be reviewed

- Review current aseptic transfer processes
- Determine the precise transfer process for each type of product – for example ampoule versus 3L PN bag
- Write / define a procedure or process for each type of product
- Suitably define and protect an area for the wiping and spraying of items

Transfer disinfection validation \ bioburden evaluation: options to be considered

1. Total immersion bioburden evaluation method (Process validation)
2. Contact plating (Process\Operator validation)
3. Review of isolates (% sporing vs. non-sporing organisms) and glove print \ finger dabs results of the current practice with 70% Alcohol (**Spray-Wipe; Spray**)
4. Review of isolates (% sporing vs. non-sporing organisms) and glove print \ finger dabs results **post introduction of 4 step process e.g. Wipe-Spray; Spray-Wipe with Alcohol**
5. Review of isolates (% sporing vs. non-sporing organisms) and glove print \ finger dabs results **post introduction of 4 step process e.g. Wipe-Spray; Spray-Wipe with Sporicide**
6. Compare the introduction of the two stages (items 4 and 5)
7. Review long term trend and environmental deviations.

Items 4 and 5 may be combined

8. The evaluation period should not be less than 3 months.
9. The acceptance criteria should be defined before the evaluation process is started , for example, the absence of vegetative cells or spores on any item post wiping.

Impact assessment

These benefits and disadvantages may be useful in undertaking the impact assessment locally.

Benefits

- Reduction in spore bearing organisms in Grade A\B\C\D environments
- Decrease in QA workload on the investigation of OOS
- Improved assurance regarding environment
- Improved patient safety

Disadvantages

- Contact time
- Aqueous product – therefore does not readily dry
- Health and Safety – staff exposure (particularly with sprays) to sporicidals (use of gloves is essential)
- Adverse effects on facilities and equipment - corrosion
- Adverse effect of compounding capacity
- Could the sporicidals hide poor transfer disinfection
- Compatibility with components and packaging.

6.1 Other considerations

Which sporicide will suit the needs of the particular aseptic unit best?
Quality of Product
Natural versus synthetic fibre wipes

- Consider amount of agent held and released by wipe / moisture of wipe
- Wickability / removal power
- Texture of wipe, ability for effective contact with surfaces, closeness/tightness of weave
- Fragility of weave, tear potential, particulate release

Stability of sporicide with the wipe material
Stability of sporicide throughout its shelf life; and\or on preparation in situ and in use
Potential effects on radiopharmaceuticals and other medicines (in particular, biologically derived molecules)
Resources

- Additional costs
- Additional processing time
- Validation costs with new process, agents and operators
- Time for initial evaluation
- Time for Training
- Effects on environment / corrosion – equipment cleaning, treatment or replacement

Packaging design
Fold patterns
Manufacturing methods and conditions
Storage conditions
Presence of protective layers of dirt, soiling etc.
Residues, degraded chemicals, staining, cleaning resistance.

7. References

'EH40/2005 Workplace exposure limits' 2nd Edition Ed. HSE 2011 ISBN 978 0 7176 6446 7.

Panousi MN, Williams GJ, Girdlestone S, Hiom S, Maillard JY (2009). Evaluation of alcohol wipes used during aseptic manufacturing. Letters in Allied Microbiology 48 (2009) 648-651.

Maillard J-Y, Professor of Microbiology CSPPS, Personal communication, 16th June 2015.

MHRA, 2014, 'Bacillus cereus infections: 1 July 2014' (from Public Health England): Online, Available from http//mhra.gov.uk/ [accessed 18 June 2015].

MHRA, 2015 'Guidance for Specials Manufacturers' Online, Available from http//mhra.gov.uk/ [accessed 1st February, 2015].

"Quality Assurance of Aseptic Preparation Services" 4th Edition Ed. A. M. Beaney, Pharmaceutical Press 2006 ISBN 0 85369 615 2.

Rhodes J, Head of Microbiology, Stockton QC, Personal communication 17th June 2015.

Sandle T, e-mail correspondence with Mark Oldcorne, 28th May 2015.

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Appendices

Appendix A	Product Survey Questionnaire 2015

The following questionnaire was developed by members of the NHS Pharmaceutical Micro Protocols Group and circulated to known suppliers of sporicidal agents over the period November 2014 – March 2015

NHS Pharmaceutical Micro Protocols Group
Sporicidal Disinfectant Survey 2015

The use of sporicidal agents within the NHS is currently being considered. Please could you answer the following questions about any suitable sporicidal agents you market, in particular those suitable for transfer sanitisation of components into critical clean areas. Please support with evidence stating source (this may be attached as a file). Please use one form per **sporicidal disinfectant** and **type of presentation\delivery system**.

	Question	Answer	Evidence
1	**Company**		
1.1	Prime contact details		
1.2	Describe the quality systems employed		
1.2.1	ISO 9001		
1.2.2	EU GMP		
1.2.3	Other		
1.3	Describe the manufacturing process. Identify the classification of the blending and filling		
1.4	Where are the manufacturing sites?		
1.5	Please state your progress with respect to registration under BPR		
2	**Trade Name**		
3	Name of Active ingredient		
4	What is the final strength of the active ingredient?		
5	Describe the mode of action		
6	Is the active ingredient provided activated or is it generated by an onsite process?		
7	Q6 If the product is generated on site; describe the chemical process		
8	Identify the diluent? Is the diluent an aqueous base or alcohol base?		

	Question	Answer	Evidence
9	Describe the quality of water used to prepare diluents		
10	What is the final strength of the alcohol if solute is an alcohol base?		
11	Are there any stabilisers (or other components) present? Describe their chemical function.		
12	Is the product pH adjusted? If so explain the buffering system		
13	What presentations are the disinfectant provided in?	☐ Spray ☐ Wipe ☐ Impregnated Mop wipe ☐ Other - specify	
14	If the presentation is a spray…		
14.1	Has the bottle been adapted in any way (e.g. bag in the bottle or filter in spray) to prevent suck back? If so describe the process present		
14.2	What spray bottle sizes are available?		
14.3	Has the spray been sterilized? (state method and dose/conditions)		
15	If the presentation is a wipe (impregnated)…		
15.1	What is the material of the wipes?		
15.2	If the wipes have been supplied impregnated with the disinfectant, state the volume of disinfectant used		
15.3	What is the size of the wipe and describe the fold pattern?		
15.4	Are the wipes individually wrapped or in multipacks?		
15.5	Has the wipe been sterilized? (state method and dose/conditions)		
16	If the presentation is a mop wipe…		
16.1	State size and volume of impregnated disinfectant		
16.2	What systems can the wipes be used on?		
16.3	Are the mops disposable or reused?		
16.4	Are the wipes individually wrapped or in multipacks?		
16.5	Has the mop wipe been sterilized? (state method and dose/conditions)		

	Question	Answer	Evidence
17	If the presentation is in another format…		
17.1	Describe the presentation in full		
17.2	Has the disinfectant been sterilized? (state method and sterilizing dose/conditions)		
18	Disinfectant stability		
18.1	What is the shelf life unopened?		
18.2	What is the shelf life once the pack has been opened?		
18.3	If the disinfectant is activated on site, state the stability of the activated product?		
18.4	Is there any interaction between the disinfectant and wipes/carrier system? If so, identify the effect on the disinfectant and wipe/carrier system.		
19	Efficacy – state the effectiveness against the following classes of organisms stating test utilised and minimum contact time to achieve set log kill. *Ensure you state the EN standard number as well as organism, challenge size and reduction after 2 minutes exposure (a typical contact time for transfer sanitisation) if this is available*		
19.1	Vegetative bacteria		
19.2	Bacterial Spores		
19.3	Fungi \ Moulds		
19.4	Yeasts		
19.5	Viruses		
20	Does the disinfectant leave any residues and at what level? Identify the source, or describe chemical processes involved in the formation, of any residuals present		
21	What are the particulate levels in the product? To what degree are the products filtered in production or *in situ*?		
22	What are the endotoxin levels in the product?		
23	Are the products double or triple bagged? Describe the tear methodology		

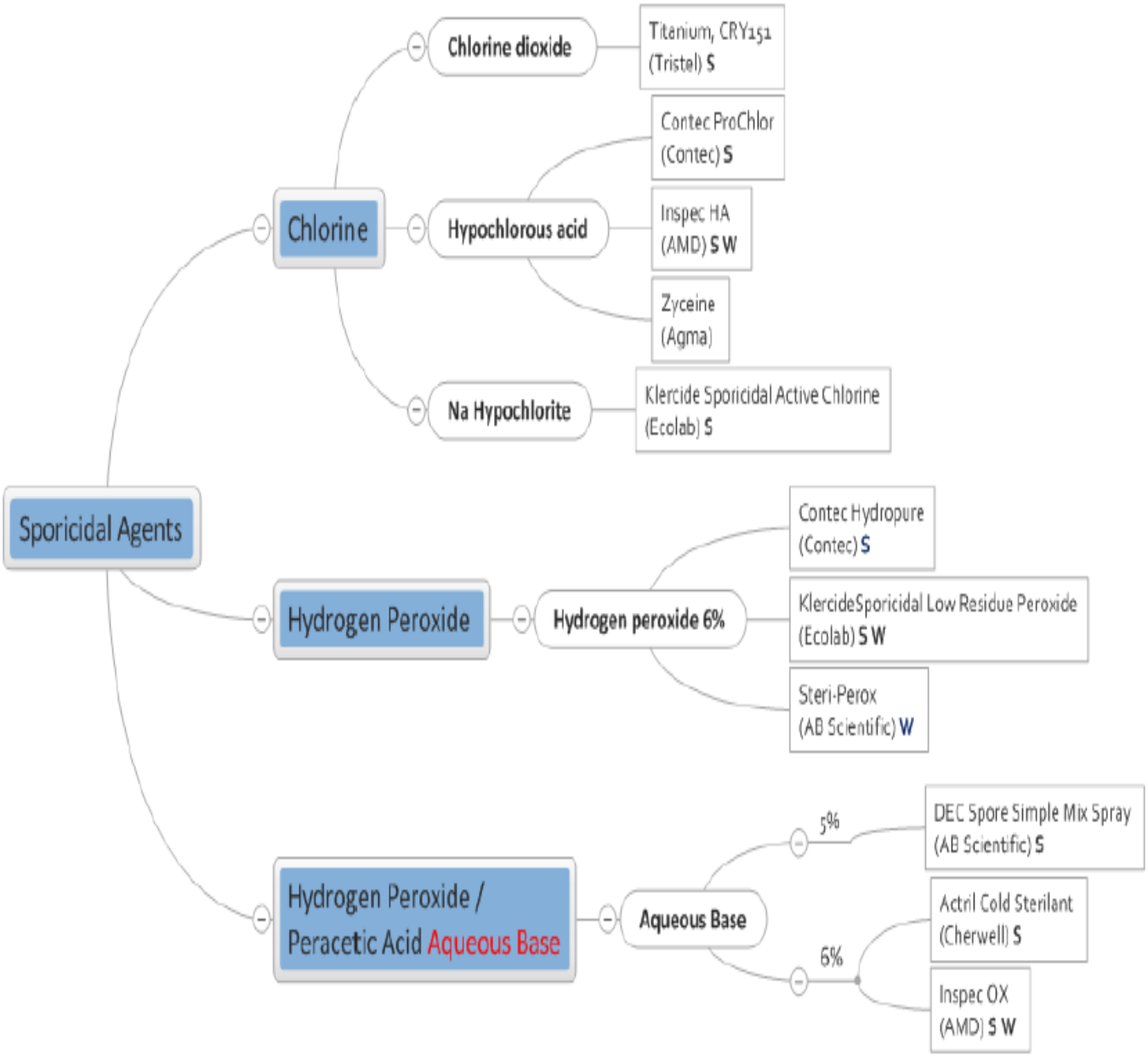
	Question	Answer	Evidence
24	Health and Safety		
24.1	Please supply SDS for the delivery system		
24.2	What are the COSHH warnings?		
24.3	Please state any EH40WEL values for each component present. Is there any other evidence of adverse effects on health?		
24.4	In typical use, is the product likely to exceed EH40 WEL values?		
25	Corrosiveness		
25.1	How aggressive is the product to metals and other surfaces?		
25.2	What testing have you undertaken?		
25.3	State the compatibility with cleanroom components		
26	Presentation		
26.1	What is the container material? Are there any issues with disposal?		
26.2	Is the trigger spray adjustable or a fixed pattern. Have you undertaken any studies to indicate spray patterns?		
26.3	Is the presentation ready to use? Or has it to be prepared\assembled on site?		
26.4	What is the wipe pouch material?		
26.5	Can the wipes be resealed?		
27	Quality Control		
27.1	Are certificates of analysis available? Give an example of the Certificate of Analysis		
27.2	Identify the tests (with their respective limits) undertaken to verify the product. Is each batch tested?		
28	Is a neutraliser required for surface environmental monitoring		

Thank you for taking part in this survey, your cooperation is valued.

Appendix B	Classification of Sporicidal agents and their presentations

The sporicidal agents are classified according to their active ingredients, the presentations available and their suitability for transfer disinfection.

Sporicidal Agents suitable for Transfer Disinfection



Key:
Transfer Disinfection
S – Spray
W – Wipe

Other sporicidal agents are available, but it has been agreed by the MPG and suppliers that these are more suitable for 'cleaning' and not appropriate for transfer disinfection

Appendix C	MHRA Guidance for Specials Manufacturers 2015

The following are the relevant extracts from the MHRA Guidance for Specials Manufacturers published in January 2015 relating to the minimum expectations for aseptic transfer disinfection processes

3.5.20 What is the minimum expectation for the sanitisation of components and equipment being transferred into the grade A working zone?

In this section it is assumed that components used for aseptic manufacture such as licensed products, needles, luer connections etc. are transferred into a preparation room, stored, with subsequent transfer through airlocks into the manufacturing room and then into a cabinet or isolator.

The storage of paper and cardboard in the preparation room should also be minimised whilst at the same time ensuring that the product is protected, secure and information is still available to use the product correctly

Before transfer to the manufacturing room, a sanitisation step using a spray and wipe technique including a sporicidal agent designed to inactivate bacterial and fungal spores must be carried out. (Step 1)

Before transfer to the working zone a second sanitisation step using a spray and wipe technique including a disinfectant must be carried out. (Step 2)

- The minimum expectation is therefore two discrete decontamination steps, with a spray and wipe performed at **both** steps and the first decontamination steps must use a sporicidal agent.
- The only exemption from using a sporicidal agent in step 1, at the current time, is for the manufacture of radiopharmaceuticals and biologicals only where evidence is available that the product performance may be affected by sporicidal residues. Justification may be possible for other medicines however documentation to support the approach taken should be available
- During sanitisation, particular attention should be paid to the rubber septa of vials and break lines of ampoules, which should be subjected to all stages of the sanitisation treatment. Over-seals should therefore be removed at the first sanitisation stage.
- An effective contact time for the sanitising agent should be used. Third party supplier data may be used, provided that this is reviewed to demonstrate its relevance to the intended use. Where contact time differs from the manufacturers recommendations, this should be supported by scientifically valid microbiological studies.
- Consideration should also be given to the air classification of the Preparation room and a risk assessment should be performed where the preparation room is unclassified to consider if any additional controls are required.

3.5.21 What factors should be considered in developing a surface sanitisation strategy?

- The bioburden challenge presented by the type of item being sanitised. i.e. number of surfaces, ease of cleaning.
- Minimum residence period post sanitisation (2 minutes are usually applied as a guidance value for a disinfectant effect with longer times required for a sporicidal effect)
- Periodic verification of sanitisation effectiveness should be carried out with frequency based on a risk assessment.
- Extended storage time of sanitised components is considered to be a risk factor, and subsequent sanitisation steps prior to use should address this risk.
- Steps should be taken to minimise the exposure of items supplied as sterile prior to entering the Grade A work zone.
- Cleaning of any folds where sealed packages are required to be sanitised.

3.5.22 What agents should be used to achieve the above sanitisation?

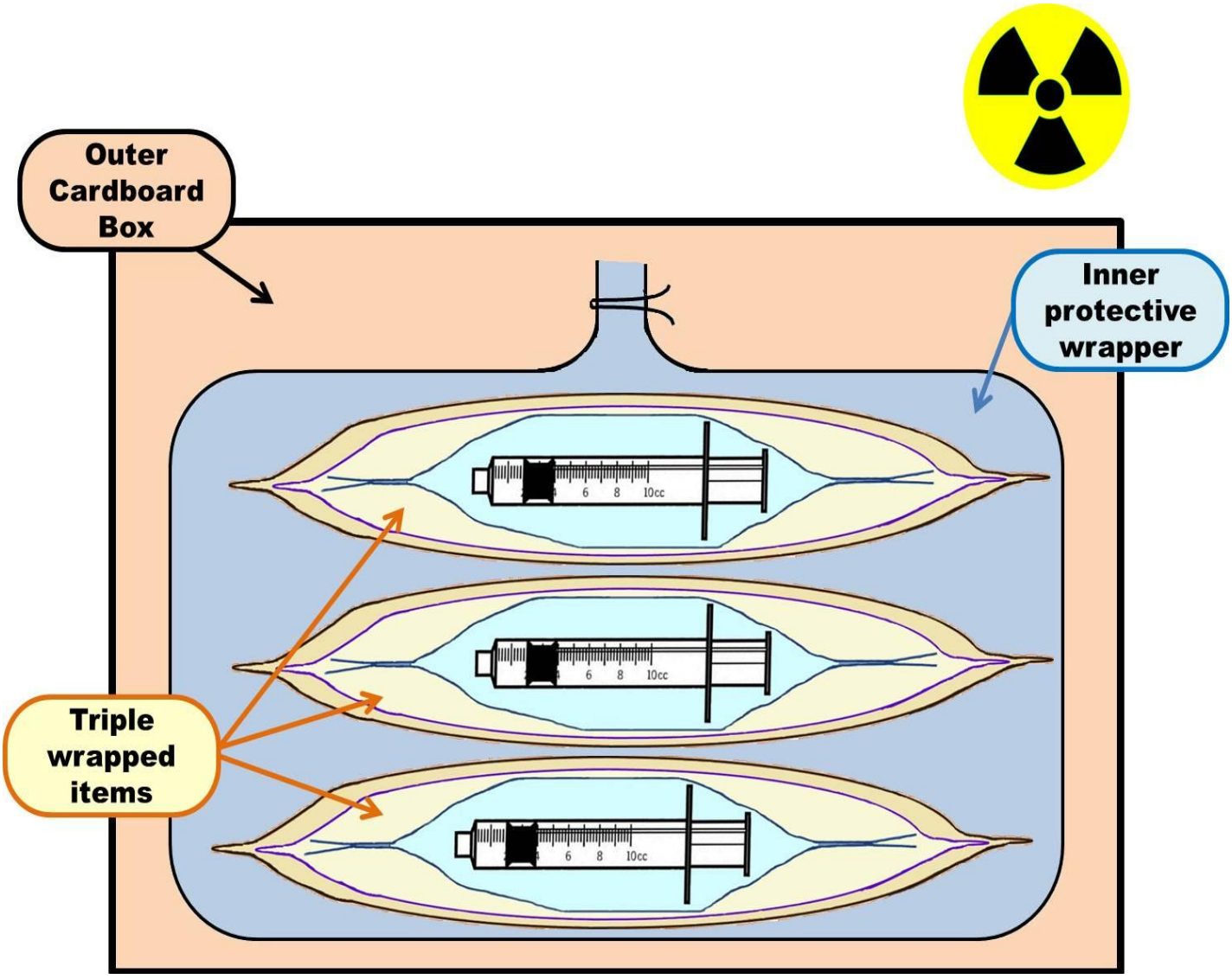
- Agents used typically consist of 70% ethanol or IPA and include a sporicidal agent such as Hydrogen Peroxide.
- Solutions should be sterile if used for aseptic processing at the last sanitisation step.
- Wipes used should not shed particles and be sterile when used at the last stage of transfer for aseptic products.

3.5.23 What controls are expected for sanitisation agents?

- For purchased items there should be an assurance from the manufacturer regarding the quality of the supplied item and confirmation that the product is sterile if specified. For items sterilised by irradiation there should evidence that this process has been completed satisfactorily.
- The dispensing system should minimise the potential for contamination of the supplied contents, typically this could involve a bag in bottle or some other mechanism which reduces the potential for contamination ingress as the contents are used.
- The in-use shelf life should be justified and documented for such sanitisation agents and information from manufacturers can be accepted. There should be an indication on the spray bottle as to the date of opening and processes in place should ensure that units are not used beyond the specified shelf life.
- During use steps should be in place to ensure that external surfaces of the spray unit are sanitised such that bottles do not present a risk of cross contamination.

Appendix D	Sterile Triple Wrapped Product

Diagram of sterile triple-wrapped product



Appendix E	Efficacy Product Comparison Tables

Chlorine Based						
Product	**Active Ingredient**	**EN Test Specification**			**Company Tests**	
		EN Test	**Test Organisms – pass criteria**	**C**	**Test Organisms >log 2 kill in 2 minutes**	**C**
Titanium (Cry -151)	Chlorine Dioxide 160 – 200ppm	EN13704	*B subtilis* at least log 3 reduction in 60 minutes	C	1 min *Bacillus subtilis* >3.10 *Bacillus pumilis* >3.48 *Clostridium difficile* 3.81	C C C
		EN1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	1 min *Aspergillus brasiliensis* >4.23 Candida albicans >4.21	C C
		EN 13697	*A brasilensis* at least log 3 reduction in 15 minutes *C albicans* at least log 3 reduction in 15 minutes	C	1 min Candida albicans >3.90,	C
Contec ProChlor	hypochlorous acid >1000ppm available chlorine	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	1min *B subtilis* > Log3.5	C
		EN1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	1 min *C albicans* >log 5 reduction *1 min A brasiliensis* >Log 3 reduction	C C
		EN13697	*A brasilensis* at least log 3 reduction in 15 minutes *C albicans* at least log 3 reduction in 15 minutes	C	1 min *C albicans* >log 5 reduction *1 min A brasiliensis* >Log 3 reduction	C C
		EN 1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	15 mins for >log 4 reduction of *A brasilensis* 15 mins for >log 4 reduction of *C albicans*	NC NC
		Phase 3 Field Test	Stainless steel Surface Paper packaging of syringe Plastic packaging of syringe Control - B. subtilis 6.2 x 10^7 spores (SS and plastic) Control - B. subtilis 4.1 x 10^7 spores (paper) 1 minute exposure		Stainless steel Surface – No viable spores recovered Paper packaging of syringe – 5.75 log reduction Plastic packaging of syringe– No viable spores recovered	C C C
Inspec HA	hypochlorous acid 200ppm	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	2 mins against spores	C
		EN 13697	*A brasilensis* at least log 3 reduction in 15 minutes *C albicans* at least log 3 reduction in 15 minutes	C	20 mins for *A brasilensis* 15 mins for *C albicans*	NC NC

Chlorine Based						
Product	**Active Ingredient**	**EN Test Specification**			**Company Tests**	
		EN Test	**Test Organisms – pass criteria**	**C**	**Test Organisms >log 2 kill in 2 minutes**	**C**
Zyceine	Hypochlorous acid 2500ppm as free chlorine	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	5 mins for >log 3 reduction of *B subtilis*	NC
		EN 1650	*C albicans* at least log 4 reduction in 15 minutes	C	15 mins for >log 4 reduction of *C albicans*	NC
		EN 13697	*A brasilensis* at least log 3 reduction in 15 minutes *C albicans* at least log 3 reduction in 15 minutes	C	15 mins for >log 4 reduction of *A brasilensis* 15 mins for >log 4 reduction of *C albicans*	NC
Klercide (WFI) Sporicidal Active Chlorine	Na Hypochorite	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	10 mins for log 3 reduction of *B subtilis*	NC
		EN 1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	5 mins for a >log 4 reduction of *A brasilensis* 5 mins for >log 4 reduction of *C albicans*	NC
		EN 13697	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	15 mins for >log 4 reduction of *A brasilensis* 5 mins for >log 4 reduction of *C albicans*	NC

Hydrogen Peroxide						
Product	**Active Ingredient**	**EN Test Specification**			**Company Tests**	
		EN Test	**Test Organisms – pass criteria**	**C**	**Test Organisms >log 2 kill in 2 minutes**	**C**
Contec Hydropure	6% hydrogen peroxide	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	15 mins for >log 3 reduction of *B subtilis*	NC
		EN 1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	15 mins for >log 5 reduction of *A brasilensis* 15 mins for >log 5 reduction of *C albicans*	NC
Klercide (WFI) Sporicidal Low Residue Peroxide	6% hydrogen peroxide	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	5 mins for a log 7 reduction of *B subtilis* At least 15 minutes for sporicidal action	NC
		EN 1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	15 mins for a log 6 reduction of *A brasilensis* 15 mins for a log 8 reduction of *C albicans*	NC
Steri-Perox	6% hydrogen peroxide		No Data presented against EN standards Data presented from USA			
DEC Spore Simple Mix Spray	6% hydrogen peroxide + 0.4% peracetic acid	EN 13704	No Data Presented		10 mins for >log 5 reduction of *B subtilis*	NC
		EN 13697	No Data Presented		10 mins for >log 5 reduction of *B subtilis*	NC

Hydrogen Peroxide						
Product	**Active Ingredient**	**EN Test Specification**			**Company Tests**	
		EN Test	**Test Organisms – pass criteria**	**C**	**Test Organisms >log 2 kill in 2 minutes**	**C**
Actril Cold Sterilant	6% hydrogen peroxide + 0.4% peracetic acid		AOAC Sporicidal Test Protocols data presented 10 mins for log 5 reduction of C. difficile			
			USP <1072> Surface Challenge Test 5 mins for >log 3 reduction of B. subtillis			
Inspec OX	6% hydrogen peroxide + 0.4% peracetic acid	EN 13704	*B subtilis* at least log 3 reduction in 60 minutes	C	2 mins for >log 3 reduction of *B subtilis*	NC
		EN 1650	*A brasilensis* at least log 4 reduction in 15 minutes *C albicans* at least log 4 reduction in 15 minutes	C	15 mins for >log 5 reduction of *A brasilensis* 15 mins for >log 5 reduction of *C albicans*	NC

Appendix F	Quality Product Comparison Tables

Chlorine Based								
Product	**CofA / Batch**	**Particulates**	**Endotoxin limits**	**Sterility Tested**	**Sterilisation**	**Residues**	**Diluent standard**	**Presentation**
Titanium (Cry -151)	Yes Chemical tests	0.2µ filtration	Product Not tested. In-process test on water	Yes	Sterile filtered into pre-irradiated components	Low levels of Sodium chloride, chlorate, chlorite, plus Citric acid and Sodium citrate	WFI - USP	Double bagged
Contec ProChlor	Yes chemical tests	0.2µ filtration	<0.25EU/ml	BP Sterility Test	Sterile filtered into pre-irradiated components	Ca salt from active ingredient	Purified Water (EP)	Double bagged
Inspec HA	Yes chemical tests	0.2µ filtration	Not tested	Not tested	Aseptic fill into sterilised packaging	Not established	Purified Water	Double bagged
Zyceine	No information provided							
Klercide Sporicidal Active Chlorine	Yes Chemical tests	0.2µ filtration	Not tested	USP Sterility Test	Aseptic fill in sterilised packaging Gamma Irradiated	Yes – due to presence of a non-volatile active ingredient	WFI	Spray Double bagged

Hydrogen Peroxide								
Product	**CofA / Batch**	**Particulates**	**Endotoxin limits**	**Sterility Tested**	**Sterilisation**	**Residues**	**Diluent standard**	**Presentation**
Contec Hydropure	Yes Chemical tests	0.2µ filtration	<0.25EU/ml	Yes EP Sterility test	Yes. Gamma Irradiated	None. Product breaks down into oxygen and water	WFI	Triple bagged
Klercide (WFI) Sporicidal Low Residue Peroxide	Yes Chemical tests	0.2µ filtration	Not tested	USP Sterility Test	Aseptic fill in sterilised packaging	None. Product breaks down into oxygen and water	WFI	Spray Wipe Triple bagged
Klercide Sporicidal Low Residue Peroxide	Yes Chemical tests	0.2µ filtration	Not tested	USP Sterility Test	Aseptic fill in sterilised packaging	None. Product breaks down into oxygen and water	Purified Water	Spray Wipe Double bagged
Steri-Perox	Yes Chemical tests	0.2µ filtration	<0.25EU/ml	USP Sterility Test	Yes. Gamma Irradiated	None. Product breaks down into oxygen and water	WFI	Wipe Double bagged
DEC Spore Simple Mix Spray	Yes Chemical tests	0.2µ filtration	<0.25EU/ml	USP Sterility Test	Yes. Gamma Irradiated	None. Product breaks down into oxygen and water	WFI	Closed system mixing Double bagged
Actril Cold Sterilant	Yes Chemical tests	0.2µ filtration	Not tested	Not tested	EO for components. "It is a cold sterilant and is therefore sterile"	No residues on dry surfaces at room temperature	Demineralised water (Reverse Osmosis)	Double bagged
Inspec OX	Yes Chemical tests	0.2µ filtration	Not tested	Not tested	Aseptic fill in sterilised packaging	Yes. From acetic acid	Purified Water	Double bagged

Appendix G	Heath & Safety Product Comparison Tables

IMPORTANT: All Aseptic Preparation Services should complete a local documented COSHH assessment for the products employed.

NOTE: **Full text of abbreviated R phrases used in these tables:**
R5 – Heating may cause an explosion.
R8 – Contact with combustible material may cause fire.
R10 – Flammable.
R20/21/22 – Harmful by inhalation, in contact with skin and if swallowed.
R35 – Causes severe burns.
R36 – Irritating to eyes.

Full text of classifications used in these tables:
O – Oxidising.
C – Corrosive.
Xn – Harmful.
Xi – Irritant.

STEL = Short Time Exposure Limit
TWA = Time Weighted Average

Chlorine Based

Product	SDS Available	Potential Health Effects	Risk Factors	EH 40	Other Hazards
Titanium (Cry -151)	Y MSDS available for the Activator solution, the Base solution and the Working solution	**Skin contact:** There may be mild irritation at the site of contact. **Eye contact:** There may be irritation and redness. **Ingestion:** There may be irritation of the throat. **Inhalation:** There may be irritation of the throat with a feeling of tightness in the chest.	T: R25; C: R34; N: R50	**Chlorine dioxide:** Short term exposure limit = 0.3ppm Time weighted average (8 hour) = 0.1ppm	*Providing user instructions are followed, exposure limits are unlikely to be exceeded. The 'in use' risk of using chlorine dioxide in hospitals has been investigated by the UK Health and Safety Executive (HSE), and risk assessment document EH72/14 produced by the HSE, reports studies carried out using chlorine dioxide as a sterilising agent for hospital surgical equipment, static sampling concentrations taken measured 15 minutes and 12 hours from mixing were below the 15 minute short term exposure limit of 0.3ppm and the 8-hour TWA of 0.1ppm.*
Contec ProChlor	Y USA	**Eyes:** May cause irritation. **Skin:** May cause irritation. **Inhalation:** Prolonged or excessive inhalation may cause respiratory tract irritation. **Ingestion:** Ingestion can cause gastrointestinal irritation, nausea, vomiting and diarrhoea.			
Inspec HA	Y USA	**Inhalation:** Insure proper ventilation of storage tanks if applicable **Skin:** May cause dryness **Eye:** Direct exposure could produce irritation **Ingestion:** Ingestion of large quantities (greater than one litre) may produce gastric discomfort, nausea, vomiting or diarrhoea **Carcinogenicity:** Active ingredients are not listed by OSHA EPA or any other authority as a carcinogen or tumour promoter	None	None	Risk of decomposition in contact with incompatible substances, impurities, metals, alkalis, reducing agents. Danger of decomposition if exposed to heat.

Chlorine Based					
Product	**SDS Available**	**Potential Health Effects**	**Risk Factors**	**EH 40**	**Other Hazards**
Zyceine					
Premier Klercide Sporicidal Active Chlorine	Y	Not classified as dangerous according to EU legislation	Not classified	None known	Spray Wipe

Hydrogen Peroxide					
Product	**SDS Available**	**Potential Health Effects**	**Risk Factors**	**EH 40**	
Contec Hydropure	Y	**Eye:** May cause irritation. **Skin:** May cause irritation. **Inhalation:** Prolonged or excessive inhalation may cause respiratory tract irritation. **Ingestion:** ingestion can cause gastrointestinal irritation, nausea, vomiting and diarrhoea.	H319: Causes serious eye irritation		WARNING! Irritant. Weak oxidizing agent that is stable under normal conditions. Decomposes to yield Oxygen that supports combustion
Premier (WFI) Klercide Sporicidal Low Residue Peroxide	Y	Irritating to eyes.	R5 Xi; R36 O; R8 Xn; R20/22 C; R35	**H_2O_2** STEL 2ppm (15 Min) TWA 1ppm (8 hours)	
Steri-Perox	Y	**Eye contact:** Symptoms can include irritation, redness, scratching of the cornea, and tearing. Irritating to eyes. **Skin:** Prolonged contact may cause dryness of the skin. **Ingestion:** May cause abdominal pain, burning **Inhalation:** Under normal conditions of intended use, this material is not expected to be an inhalation hazard. sensation, nausea.	O;R8, R5, C;R35, Xn;R20/22		

Hydrogen Peroxide					
Product	**SDS Available**	**Potential Health Effects**	**Risk Factors**	**EH 40**	
DEC Spore Simple Mix Spray	Y	Harmful by inhalation, in contact with skin and if swallowed. Causes severe burns. Ingestion causes burns of the upper digestive and respiratory tracts. May cause lung damage. May cause damage to the liver. May cause damage to mucous membranes in nose, throat, lungs and bronchial system. Prolonged contact causes serious eye & tissue damage. May cause serious chemical burns to the skin. May cause burns in mucous membranes, throat, oesophagus and stomach.	**H_2O_2** O;R8, R5, C;R35, Xn; R20/22 **Acetic Acid** O;R7, R10, C;R35, Xn; R20/21/22,	**H_2O_2** STEL 2ppm (15 Min) TWA 1ppm (8 hours) **Acetic Acid** TWA 10ppm (8 hours)	Heating may cause an explosion. Contact with combustible material may cause fire.
Actril Cold Sterilant	Y	Symptoms/injuries after eye contact: May cause eye irritation. Symptoms may include discomfort or pain, excess blinking and tear production, with possible redness and swelling. Symptoms/injuries after skin contact: May cause slight skin irritation in sensitive individuals. Symptoms/injuries after inhalation: May cause respiratory tract irritation. Symptoms/injuries after ingestion: May be harmful if swallowed. May cause stomach distress, nausea or vomiting.	**H2O2** R5 O; R8 Xn; R20/22 C; R35 **Acetic Acid** R10 Xn; R21 C; R35	**H_2O_2** STEL 2ppm (15 Min) TWA 1ppm (8 hours) **Acetic Acid** TWA 10ppm (8 hours)	
Inspec OX	Y	**Eyes:** Irritating to the eyes **Inhalation:** Potential for exposure by inhalation if aerosols or mists are generated.	**Peracetic Acid** R10 O; R 7 Xn; R20/21/22 C; R35 **H_2O_2** R5 O; R8 C; R35 Xn; R20/22 **Acetic Acid** R10 C; R35	**H_2O_2** STEL 2ppm (15 Min) TWA 1ppm (8 hours) **Acetic Acid** TWA 10ppm (8 hours)	Risk of decomposition in contact with incompatible substances, impurities, metals, alkalis, reducing agents. Danger of decomposition if exposed to heat

This document has been prepared on behalf of the NHS Pharmaceutical Quality Assurance Committee by the NHS Pharmaceutical Micro Protocols Group