正子製藥區
滅菌劑介紹
part II

大綱:

- 潔淨室衛生管理 - 清潔與消毒
- 製藥區消毒劑的選擇
- 消毒劑交替使用
- Biofilm

潔淨室的衛生(Sanitization):

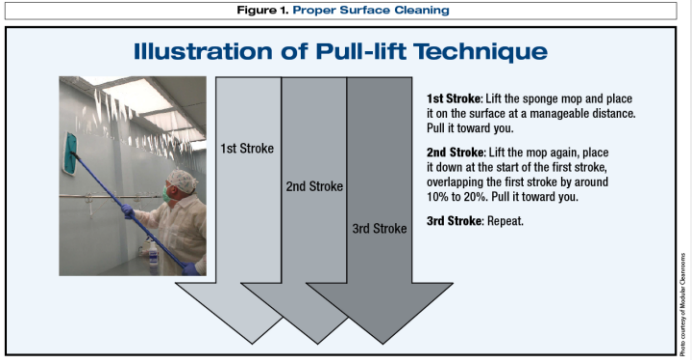
- 製藥場所潔淨室的微生物管控是無菌製劑最基本的要求
- 為達此目的必須對潔淨室的衛生需求制訂清潔與消毒程序
- 選擇及評估適當的清潔劑、消毒劑，交替使用不同消毒劑的時機
- 根據使用消毒劑前後環境監控的情況來決定場所、設備清潔消毒的頻度

潔淨室清潔注意事項–

- 清潔時應針對潔淨室的種類使用適當的清潔工具
- 清潔的效果與清潔劑與物體表面接觸時間，清潔的程度，清潔液的濃度，稀釋用水的水質，清洗等因素有關
- 在確認清潔場所的特性後，選擇適當的清潔劑及清潔工具，操作前清潔劑及清潔程序須經過確效，始能執行潔淨室的清潔工作

清潔劑的種類

- Alkaline Detergents – for removal of organic soil
- Neutral Detergents – used in manual cleaning or with sensitive substrates
- Acidic Detergents – for removal of inorganic residues and salts, and widely used for rouge removal and passivation of stainless steel equipment
- Alcohols – 70 % Isopropyl alcohol used for cleaning Grade A/B



清潔程序

- 由Grade A/B區開始清潔，依序為Grade C，Grade D
- Grade A/B清潔順序：工作檯面，工作臺，桌腳，最後為地板；Grade C/D先清潔天花板，牆壁，地面
- 級 交替

製藥區消毒劑的選擇的參考條件(USP)：

- 需要清除的微生物類型及數量
- 市售消毒劑的作用範圍(機轉及模式)
- 消毒劑供應商的商譽
- 在政府單登記為何種消毒劑：殺菌劑(sterilant)，消毒劑(disinfectant)，或是清潔劑(sanitizer)
- 使用的濃度，方法，與物體表面接觸的時間，被消毒物體表面的特性及選用的消毒劑是否適用
- 物體表面存在有機物質的數量
- 消毒劑使用後是否需要清除殘留的消毒劑
- 是否對物體表面產生腐蝕作用
- 對工作人員是否會造成傷害
- 是否與使用的清潔劑或其他消毒相容
- 是否有消毒劑交替使用的計畫
- 應避免消毒劑汙染藥品產品

藥廠對消毒劑選擇的條件

- 廣效型
- 儘可能為殺孢子劑
- 作用迅速
- 有不同的作用模式
- 不受酸鹼度及溫度的影響
- 可與清潔劑相容
- 在充填區須使用滅菌的消毒劑
- 不會殘留在物體表面
- 不會破壞物體表面
- 符合消毒劑確效規格的需求
- 使用安全
- 符合經濟效益
- 在有有機物質存在時依然具有活性

藥廠對消毒劑選擇的步驟

Phase 1 Characterization of the endogenous microbial contamination

Phase 2 Experimental evaluation of the disinfectant efficacy under practical conditions of use

Phase 3 Validation of the disinfection process

Phase 4 Microbial monitoring

Mechanism of action vs Mode of action

■Mechanism of action :

the specific biochemical interaction through which a drug substance produces its pharmaceutical effect

■Mode of action :

functional or anatomical changes, at cellular level, resulting from the exposure of a living organism to a substance

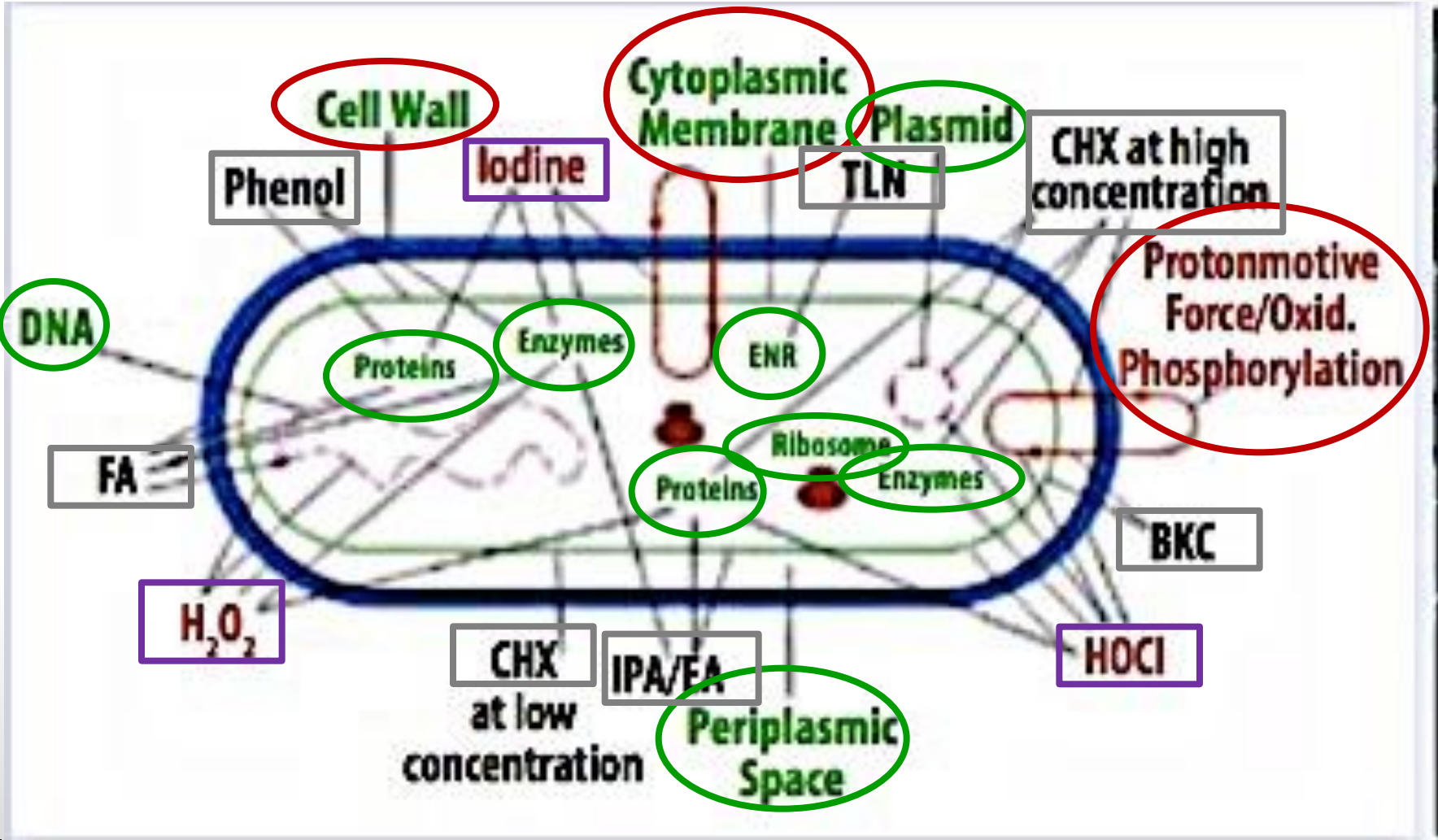
Action Mechanism of Disinfectants

- Disruption of the transmembrane proton motive force
  - Uncoupling of oxidative phosphorylation
  - Inhibition of active transport across the membrane.
- Inhibition of respiration or catabolic/anabolic reaction
- Disruption of replication
- Loss of membrane integrity
  - Leakage of cation, inorganic phosphate, pentoses, nucleotides, neuclisides, and proteins
- Lysis
- Coagulation of intracellular material

Action Mode of Disinfectants

- Action on Bacterial Cell Barriers
  - External membrane of the bacterial wall
  - Bacterial wall
  - Cytoplasmic membrane
- Interaction with cytoplasmic constituents
  - Action on energy metabolism
  - Action on the cytoplasm and nucleus
  - Action on the bacterial spore

Potential Targets for Disinfectants



Mode of action	Mechanism of action	Disinfectants or Biocide
On outer membrane	Change in cell hydrophobicity	QACs, CHX, PHE, CRA
	Cross-linking with phosphoproteins	GTA, OPA
	Removal of Mg^{++}, release LPS	EDTA
On cell wall	Oxidation of thiol groups	Hypochlorite, HgCl
	Cross-linking of proteins	GTA, OPA, FMA
Cytoplasmic membrane	Increased permeability	ALCs, CHX, QACs, PHE
	Membrane potential and electron transport chain	QACs, CHX, PHE, HOP
	Inhibition of enzyme activity	CHA, QACs, PHE
	Electrostatic interaction with phospholipids	QACs, CHX
Cytoplasmic constituents	General coagulation	CHX, QACs, GTA, HOP, PHE
	Action on nucleic acid	ACR, ETO, FMA, GTA, CRA
	Action on ribosomes	HOP Hg salts
	Interaction of specific groups	
	Thiol groups	ETO, GTA, HOP, CRA, OD
	Amino groups	ETO, FMA, GTA, OPA
	Sulphydryl groups	ETO, GTA, HOP CRA
	Inhibition of DNA synthesis	HOP, PAA
	Intercalation of DNA	ACR

GTA: glutaraldehye; OPA: O-phthalaldehyde; CHX: Chlorhexidine; QAC: Quaternary ammonium compd.;
PHE: Phenols; ETO: Ethylene oxide; HOP: Hydrogen peroxide; FMA: Formaldehyde;
CRA: Chlorine release agents; ACR : acridine

依據消毒劑的化學型態

非氧化類 (Non-Oxidizing Agents)

- Alcohols
- Aldehydes
- Phenols
- Quaternary Ammonium Compounds(QACs)
- Substituted Diguanides

氧化類 (Oxidizing Agents)

- Peroxides
- Halogen-releasing
- β-Propiolactone
- Ozone

非氧化型消毒劑 (Non-Oxidizing Agents）

Alcohols – Ethanol, Isopropanol, Denatured Ethanol

Aldehydes – Formaldehyde, Glutaraldehyde, O-phthalaldehyde

Phenols – Triclosan, Hexachlorophene

QACs – Benzalkonium chloride, Cetrimide, Cetylpyridinium chloride

Substituted Diguanides – Chlorhexidine, Alexidine, Polyhexamethylene biguanides

無菌製劑場所使用的消毒劑－非氧化型

Alcohols – Intermediate disinfection

70% Ethanol

70% IPA

Mechanism of Action

Dehydration
Cross-linking
Coagulation

Mode of Action

Dehydrate cells
Disrupt membrane
Coagulation of protein

Contact Times

Bactericidal	1 min.
Levurocidal	1 min. (yeasticidal)
Fungicidal	15 min.
Virucidal	30 sec.

Applications

Disinfection of surfaces and equipment/devices in cleanrooms, in particular for class A and B cleanroom areas

無菌製劑場所使用的消毒劑－非氧化型

Alcohols – Intermediate-level disinfectant

Denatured alcohol

25 g EtOH(94%) + 35 g Propan-1-ol (Schulke)

70% Denatured alcohol (5% of IPA added)

Contact Times		Applications
Bactericidal	1 min.	Disinfection of medical devices in all areas and all kind of wipeable surfaces with increased risk of infection and where short contact times are required.
Fungicidal	1 min.	
Virucidal	1 min.	
Levurocidal	1 min.	
Tuberculocidal	1 min.	
Polyoma SV40	10 min.	
Adenovirus	5 min.	

schulke – antifect N liquid

Microbiological Efficacy

Efficacy	Concentration	Contact time
bactericidal in accordance with VAH Guideline with short contact times	ready-to-use	1 min.
MRSA	ready-to-use	1 min.
tuberculocidal EN14348	ready-to-use	1 min.
levurocidal in accordance with VAH Guideline with short contact times	ready-to-use	1 min.
fungicidal EN13697	ready-to-use	1 min.
enveloped viruses (incl. HIV, HBV, HCV)	ready-to-use	0.5 min.
Norovirus EN14476	ready-to-use	1 min.
Polyoma SV40 in accordance with VAH Guideline with short contact times	ready-to-use	10 min.
Rotavirus	ready-to-use	0.5 min.
Adenovirus (type 5)	ready-to-use	5 min.

schulke – antifect N liquid

無菌製劑場所使用的消毒劑－非氧化型

Aldehydes – High level disinfectant

Glutaraldehyde (0.1-2.4%)

Mechanism of Action

Alkylation of amino-, carboxyl-, hydroxyl group
Cross-linking with phosphoproteins

Mode of Action

Outer membrane
Cell wall
Proteins and enzymes
DNA and RNA

Contact Times

Bactericidal	(20 min. at 20℃)
Fungicidal	(20 min. at 20℃)
Virucidal	(20 min. at 20℃)
Mycobacteria	(20 min. at 20℃)
Sporicidal(2%)	**(10 hr at 25℃)**

Applications

Suitable for industrial production areas and equipment disinfection(CIP)

CIDEX

無菌製劑場所使用的消毒劑－非氧化型

Aldehydes

Glutaral(10%)
Mixture(0.28%) of 5-chloro-2-methyl-2H-isothazol-3-one(CMIT) and 2-methyl-2H-isothazole-3-one(MIT) (Kathon)

Contact Times		Applications
Bactericidal (0.25-1.5%)	15-60 min.	Disinfection of equipment, floor and work surfaces, **pipes in industrial production**, personnel and material transfer areas.
Levurocidal (0.75-2.0%)	15 min.	
Fungicidal (1-4%)	15-60 min.	
Virucidal (0.5%)	5 min.	

At the end of disinfection , rinse the equipment carefully with water

無菌製劑場所使用的消毒劑－非氧化型

Phenols – Low-level disinfectant

LpH ag
O-phenylphenol(7.7%)
p-tertiary amylphenol(7.6%)
Inert ingredients(84.7%)

Mechanism of Action

Increase permeability of membrane and dissipation of PMF
Coagulation

Mode of Action

Protoplasmic poisons
Inactivation of proteins, enzymes

Contact Times

Bactericidal (1:256)	10 min.
Fungicidal (1:256)	10 min.
Virucidal (1:256)	10 min.
TB (1:256)	10 min.

Applications

For rotational use.
Because it's phosphate-free, can be used to clean and disinfect any hard, nonporous, inanimate surface in one easy step without leaving interfering residues.

無菌製劑場所使用的消毒劑－非氧化型

Phenols – Low level disinfectant

Low pH polyphenolic disinfectants (pH 2.5-3.5)
O-phenylphenol(8.209%)
O-benzyl-p-chlorophenol(6.65%)
Inert ingredients(85.141%)

Contact Times		Applications
Bactericidal (1:256)	10 min.	For rotational use.
Fungicidal (1:256)	10 min.	Because it's phosphate-free, can be used to clean and disinfect any hard, nonporous, inanimate surface in one easy step without leaving interfering residues.
Virucidal (1:256)	10 min.	
TB	10 min.	

Decon LopHene

無菌製劑場所使用的消毒劑－非氧化型

Phenols

Polyphenolic disinfectants (pH 12 – 10.6)
P-tertiary amylphenol(5.25%)
O-benzyl-p-chlorophenol(3%)
O-phenylphenol(3%)
Inert ingredients(88.75%)

Contact Times (at 20 ˚C)		Applications
Bactericidal (1:128)	10 min.	Use to clean, disinfect and deordorize
Fungicidal (1:128)	10 min.	any washable inanimate, non-porous
Virucidal (1:128)	10 min.	surface in one easy step
TB	10 min.	

Decon - CiDecon

無菌製劑場所使用的消毒劑－非氧化型

Quaternary Ammonium Compounds

Didecyl dimethyl ammonium chloride (10.5%)

Mechanism of Action

Membrane active agent
Cross-linking with protein and nucleic acids

Contact Times

Bactericidal (1:128)	10 min.
Fungicidal (1:128)	10 min
Virucidal (1:128)	10 min.

Mode of Action

Inactivation of energy-producing enzymes
Disruption of cell membrane
Denaturation of proteins

Applications

For cleaning and sanitizing environmental, hard, nonporous surfaces.
Can support reduced sporicide use to control mold contamination.

Steris – Vesta-Syde SQ

無菌製劑場所使用的消毒劑－非氧化型

Biguanide

Nolvasan (Chlorhexidine diacetate,2%)

Mechanism of Action

Membrane active agent

Mode of Action

Outer membrane
Protoplasmic membrane

Contact Times

Bactericidal
Fungicidal
Viricidal

Applications

It is recommended for the disinfection of inanimate objects to aid in control of viruses infection.

無菌製劑場所使用的消毒劑－非氧化型

Poly-QACs
Alkyl(C12-C16)dimethylbenzyl ammonium chloride (ADBAC/BKC(C12-C16))
Didecyldimethyl ammonium chloride(DDAC)
Alkyl(C12-C14)ethylbenzylammonium chloride (ADEBAC(C12-C14))
(0.26% w/w respectively)

Contact Times		Applications
Bactericidal	1 min.	For cleaning and disinfection of medical devices and alcohol-sensitive surfaces.
enviloped virus	1 min.	
Norovirus	15 min.	
polyoma	1 min.	
Rotavirus	1 min.	

Schulke – mikrozid sensitive liquid

無菌製劑場所使用的消毒劑－非氧化型

QAC & Diamine

Didecylmethyl ammonium chloride
N-(3-aminopropyl)-N-dodecylpropane-1,3-diamine

Contact Times		Applications
Bactericidal (1.5%)	15 min.	disinfection of surfaces and equipment/devices in Grade A and Grade B clean areas
Fungicidal (1.0%)	120 min.	
Levurocidal (1.5%)	15 min.	
Virucidal (0. 5-1.5%)	5 min.	

無菌製劑場所使用的消毒劑－非氧化型

QAC & Aldehydes

Glyoxal
Alkyl(C12-16) dimethylbenzyl ammonium chloride

Contact Times		Applications
Bactericidal (0.5-2.0%)	15-60 min.	Disinfection and cleaning of medical devices and manufacturing areas within the pharmaceutical industry
Fungicidal (0.5%)	60 min.	
Levurocidal (0.5-2.0%)	15-30 min.	
Virucidal (0. 5-2.0%)	1-30 min.	

Schulke antifec FF

無菌製劑場所使用的消毒劑－非氧化型

QAC & Aldehydes

Glutaral
Alkyl(C12-16) dimethylbenzyl ammonium chloride
Didecyldimethyl ammonium chloride

Contact Times	
Bactericidal (0.25-0.5%)	5-30 min.
TB (2.5%)	**240 min.**
Fungicidal (1.5%)	120 min.
Levurocidal (0.5%)	30 min.
Virucidal (0. 25-0.5%)	1-60 min.
Sporicidal (2%)	**240 min.**

Applications

Disinfection and cleaning of medical devices and surfaces of all types. Ideal for use in critical/sensitive production areas within the pharmaceutical industry and in all hospital areas.

Schulke antifec extra

無菌製劑場所使用的消毒劑－非氧化型

QAC + Biguanide

Benzyl-C12-16-alkyldimethyl chloride
1,5-bis(trimethylene-guanylguanidinium) monochloride

Contact Times		Applications
Bactericidal (0.5%)	5 min.	Disinfection of surfaces and equipment/devices in cleanrooms, in particularly for class A/B areas
Levurocidal (0.5%)	5 min.	
Virucidal (0.5%)	60 min.	
Virucidal (1%)	5 min.	

Schulke perofrm sterile concentrate QB

氧化型消毒劑 (Oxidizing Agents

Peroxides

- Hydrogen peroxide
- Accelerated hydrogen peroxide(HPO +anionic and nonionic surfactants + stabilizers)
- Peracetic acid
- Ethylene oxide

Halogen-Releasing Agents

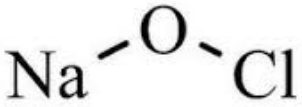
- Chlorine releasing – Hypochlorite, Chlorine dioxide, Sod. Dichloroisocyanurate(NaDCC)

β-Propiolactone

Ozone

無菌製劑場所使用的消毒劑－氧化型

Sodium Hypochlorite



Mechanism of Action

Oxidation of thiol groups
Halogenation

Mode of Action

Oxidation of sulfhydryl enzymes and amino acids, ring chlorination of amino acids
Inhibition of protein synthesis
Oxidation of respiratory components
Depressed DNA synthesis

Contact Times,

A minimum contact time of 5 minute and then allow to air dry.
A rule of thumb is 10 min. of contact time with 10% hypochlorite solution for most routine applications.

Applications

For disinfecting surfaces in cleanroom of Grade A/B.
5.25% hypochlorite solution is free rinsing on 304L stainless-steel surface

無菌製劑場所使用的消毒劑－氧化型

Peracetic Acid

Peracetic acid (0.07%)

Mechanism of Action

Free radical oxidation
(hydroxyl radicals)

Mode of Action

Increases cell wall permeability by disrupting sulfhydryl and S-S boneds
Denatures proteins and enzymes

Contact Times

Bactericidal	5 min.
Levurocide	5 min.
Virucidal	5min.
Sporicidal	**5 min.**

Applications

For disinfecting surfaces in cleanroom of Grade A/B.

Schulke perform sterie PAA

無菌製劑場所使用的消毒劑－氧化型

Hydrogen Peroxide

Mechanism of Action

Free radical oxidation(hydroxyl radicals)

Mode of Action

Denatures proteins and enzymes, DNA
Oxidation of lipid

Contact Times

Bactericidal	30 sec. – 1 min.
Fungicidal	3 min.
Virucidal	30 sec. - 1 min.
Norovirus	**3 min.**
TB	**4 min.**

Applications

Disinfection of hard surface materials(stainless steel, glass, plastic, vinyl etc.), not recommended for use on aluminum, copper, galvanized steel and silver. Also it can be used on some soft surface materials(polyester, cotton)

Clorox Healthcare Hydrogen Peroxide

無菌製劑場所使用的消毒劑－氧化型

Hydrogent Peroxide / Peracetic Acid

Peracetic acid 5%
Hydrogen peroxide
Acetic acid

Mechanism of Action

Free radical oxidation(hydroxyl radicals)

Mode of Action

Denatures proteins and enzymes
Increases cell wall permeability by disrupting sulfhydryl and S-S boneds

Contact Times

Bactericidal (2%)	5 min.
Levurocide(2%)	5 min.
Virucidal (1-2%)	30 min.
Sporicidal (2%)	5 min.
Mycobactericidal(2%)	**5-30 min.**

Applications

For disinfecting surfaces in cleanroom of Grade A/B.

Schulke terralin PAA

無菌製劑場所使用的消毒劑－氧化型

Accelerated Hydrogen Peroxide(AHP®)

Hydrogen peroxide
Surface Acting Agents
Wetting Agents
Chelating Agents

Mechanism of Action

Free radical oxidation
(hydroxyl radicals)

Mode of Action

Contact Times

Bactericidal
Levurocide
Virucidal
Sporicidal

Applications

Clean and disinfect high-touch surfaces in 5 minutes.

VIROX

消毒劑使用的方式

液態

噴灑式 (Spray)
擦拭法 (Wipe)

氣態

薰蒸式 (Fumigation) – gas phase of liquid
霧化式 (Fogging) – tiny drops of liquid suspend in air

薰蒸法 (Fumigation)

選擇薰蒸的主要原因

- 降低潔淨室中的Bioburden
- 消除因意外或高風險管制區因維修關閉而產生的致病菌

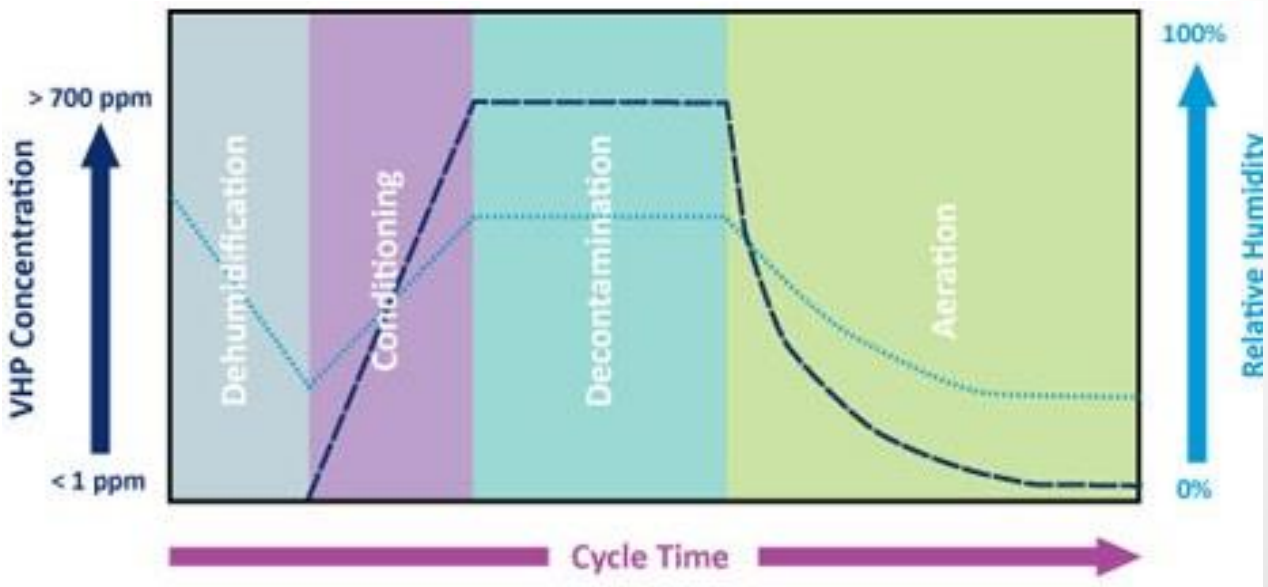
薰蒸法 (Fumigation)

Fumigation system	Pros	Cons
Vaporized Hydrogen Peroxide	Fast-acting Non toxic residue Sporicidal Fast dispersal odorless	Poor efficacy with Mycobacterium
Chlorine Dioxide	Excellent efficacy against all organisms Reproducible results Non-carcinogenic	Corrosive over time Broken down by UV light
Ozone	Very fast acting Rapid dispersal	Requires neutralization and aeration Leaves acetic acid odor challenged with high doses of pathogen

薰蒸法 (Fumigation)

薰蒸法過程

- Dehumidification
- Conditioning
- Bio-decontamination
- Aeration



市售使用的消毒劑–氧化型

Vaprox Hydrogen Peroxide Sterilant (35%, 59%)

Applications

Room/facility decontamination
Isolators
Pass-through chamber
Biological safety cabinet
Material airlocks
Equipment

Equipment and Accessaries

VPH Biodecontamination System
H_2O_2 Sensors
Chemical Indicators
Biological Indicator
(Geobacillus stearothermorphilus Culture media)

Microbial efficacy of biocidal actives

	Bactericidia		Mycobac-tericidia	Sporicidia	Fungicidia		Virucidia
Spectrum of action	Gram+ bacteria	Gram- bacteria	Myco-bacteria	Bacterial spores	Yeasts	Moulds	Viruses
Alcohols	+++	+++	+++	-	++	++	++
Quats	+++	++	-	-	+++	+++	++
Guanidines	+++	+++	-	-	++	++	++
Aldehydes	+++	+++	+++	+++	++	++	++
Active oxygen	+++	+++	+++	+++	+++	+++	+++
Peracetic acid	+++	+++	+++	+++	+++	+++	+++

消毒劑的交替使用

Microbial Resistance
vs
Rotation of Disinfectants

Descending Order of Resistance to Antiseptics and Disinfectants

Bacterial Spores
(B. subtilis, Cl. sporogenes)

↓

Mycobacteria
(M. tuberculosis)

↓

Nonlipid-coated Viruses
(Polioviurs and rhinovirus)

↓

Fungal spores and vegetative molds and yeast
(Trichophyton, Cryptococcus, Candidas spp.)

↓

Gram(-) Bacteria
(Pseumonas, Providencia)

↓

Gram(+) Bacteria
(S. aureus)

↓

Lipid-coated Viruses
(Herpes simplex, HBV, HIV)

Mechanisms of Microbial Resistance

- Insusceptible
- Tolerance
- Co-resistance
- Cross-resistant
- Multi-drug resistance

Development of Resistance to Disinfectants

- **Insusceptible**

  H. pylori resists to 3% hydrogen peroxide/60 min.

- **Tolerance**

A strain of P. aeruginosa survives at 1.7% H_2O_2/60 min. but <0.1% of the initial the bacteria survived

- **Co-resistant**

BMRGs in plasmids (biocide/metal resistance genes)

- **Cross-resistant**

Cross-resistance in S. aureus and E. coli against Triclosan

- **Multi-drug resistance**

消毒劑的交替使用產生的問題

- 為何要交替使用消毒劑？
- 哪一種消毒劑需要替換使用？
- 交替使用消毒劑有哪些價值？
- 交替使用的最佳頻率為何？

消毒劑的交替使用

Microbial Resistance :

When a strain is not killed or inhibited by the biocidal concentration typically used in practice

When a strain is not killed or inhibited by a concentration at which the majority of strains of that microorganism are affected

When bacterial cells are not killed or inhibited by a concentration acting upon the majority of cells in that culture

Scientific Committees(2009) Green Facts : Effects of Biocides

消毒劑的交替使用

Microbial Resistance :

The development of microbial resistance to disinfectants is less likely, as disinfectants are powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound.

The Japanese pharmacopeia, British Pharmacopeia, and European pharmacopeia do not currently address th issue of disinfectant rotation. “Sterile Drug Products by Aseptic Processing - cGMP

The rotation of disinfectant principle : true or false? **Pharm. Tech 33, Feb. 2009**

消毒劑的交替使用

Microbial Resistance :

European Commission's GMP Guidelines, Manufacture of sterile medicinal product:

"Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains"

But, the US FDA does not mention the rotation of disinfectants in the guideline "Sterile Drug Products Produced by Aseptic Processing – cGMP"

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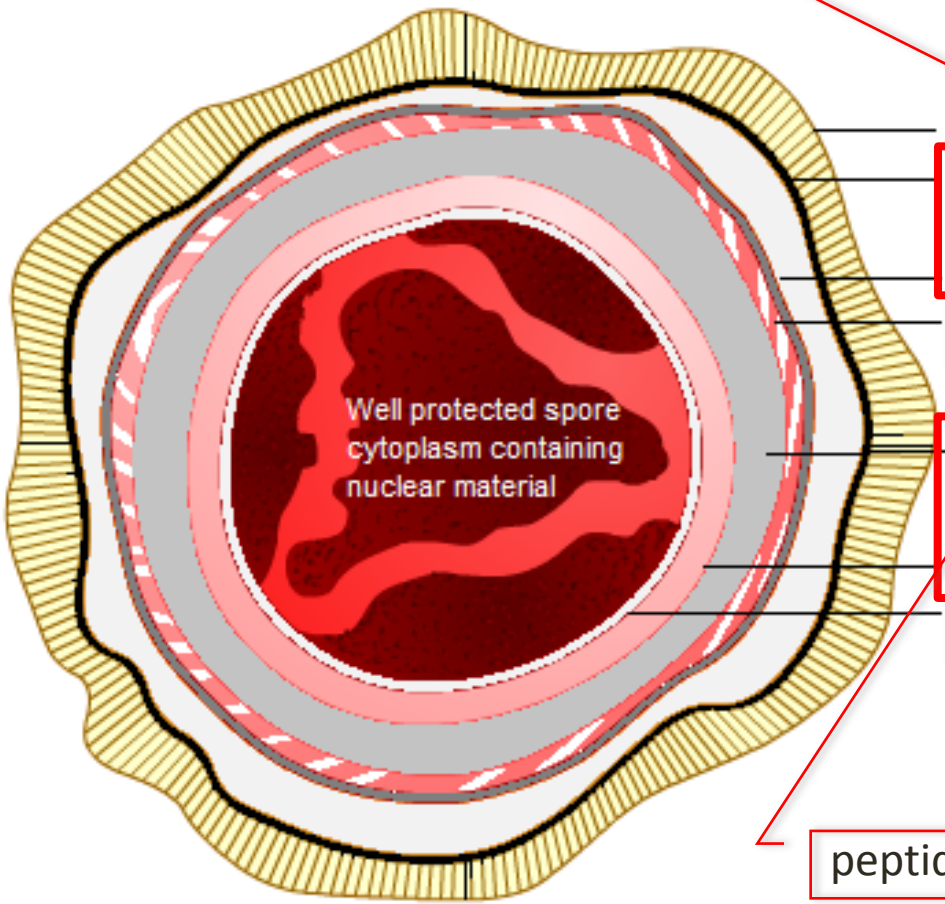
Structure of Endospore



Cot protein, lipids, carbohydrates

Exosporium

Outer spore coat

Inner spore coat

Outer membrane

Outer cortex

Inner cortex

Inner membrane

proteins cross-linked via S-S

peptidoglycan

Schematic diagram of bacterial endospore showing wall layers.

會形成孢子的微生物

Exospores

Bacillus spp –

- B. Cereus
- B. Clausii
- B. anthracis

Clostridium –

- C. botulinum
- C. difficile
- C. perfringens
- C. tetani
- C. sordellii

Methylosinus –

- M. trichosporium

Rhodomicrobium –

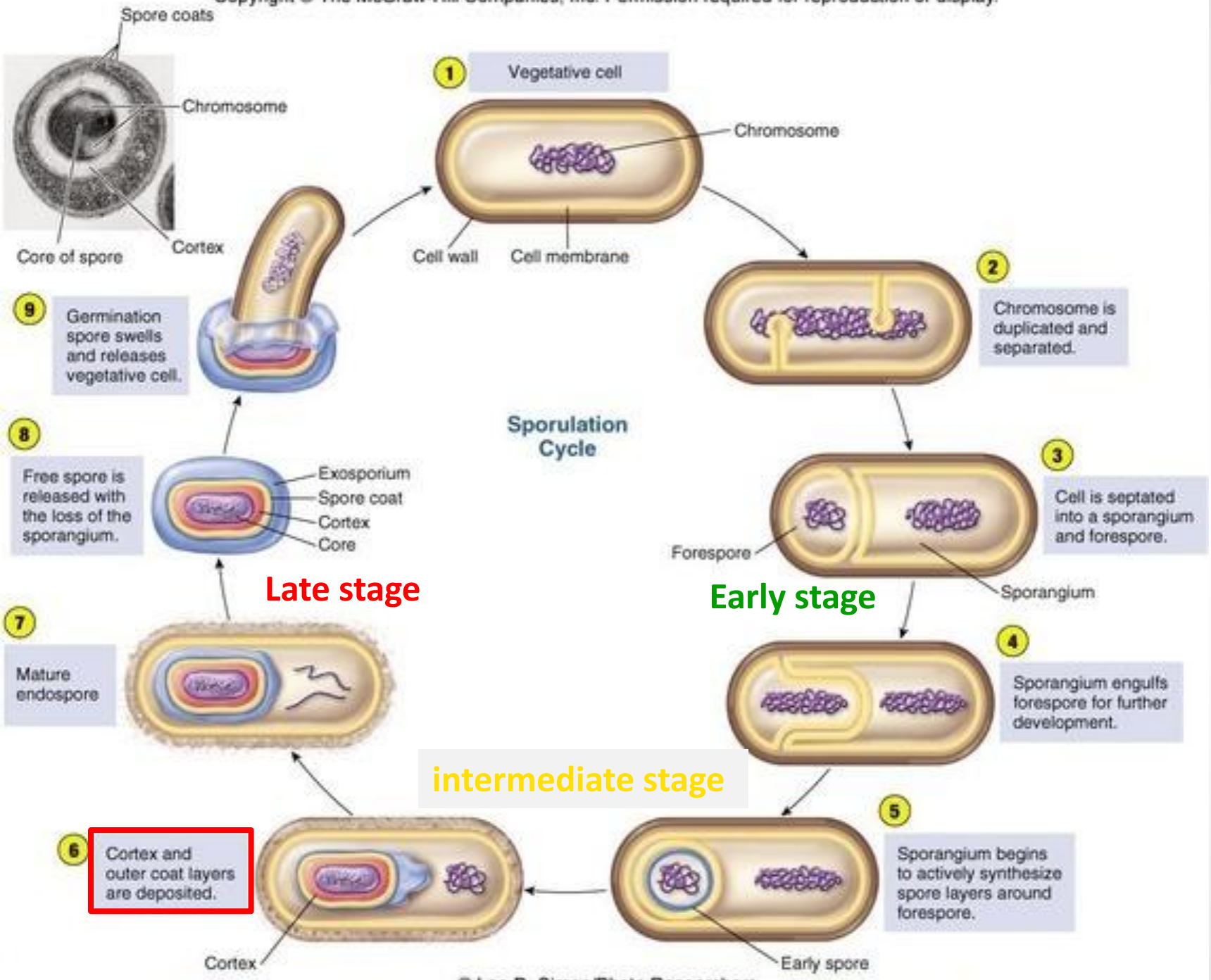
- R. vannielii

Azotobacter –

- A vinelandii

Rhodospirillum –

- R. centenum



Bacterial Spore

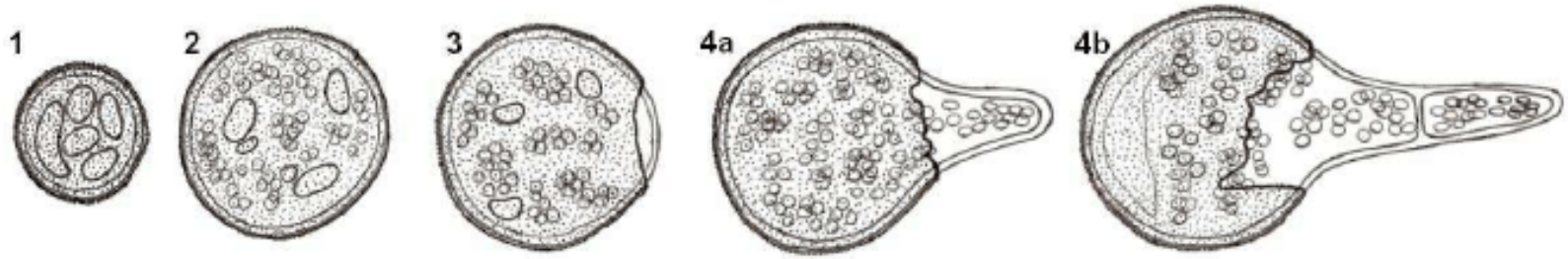
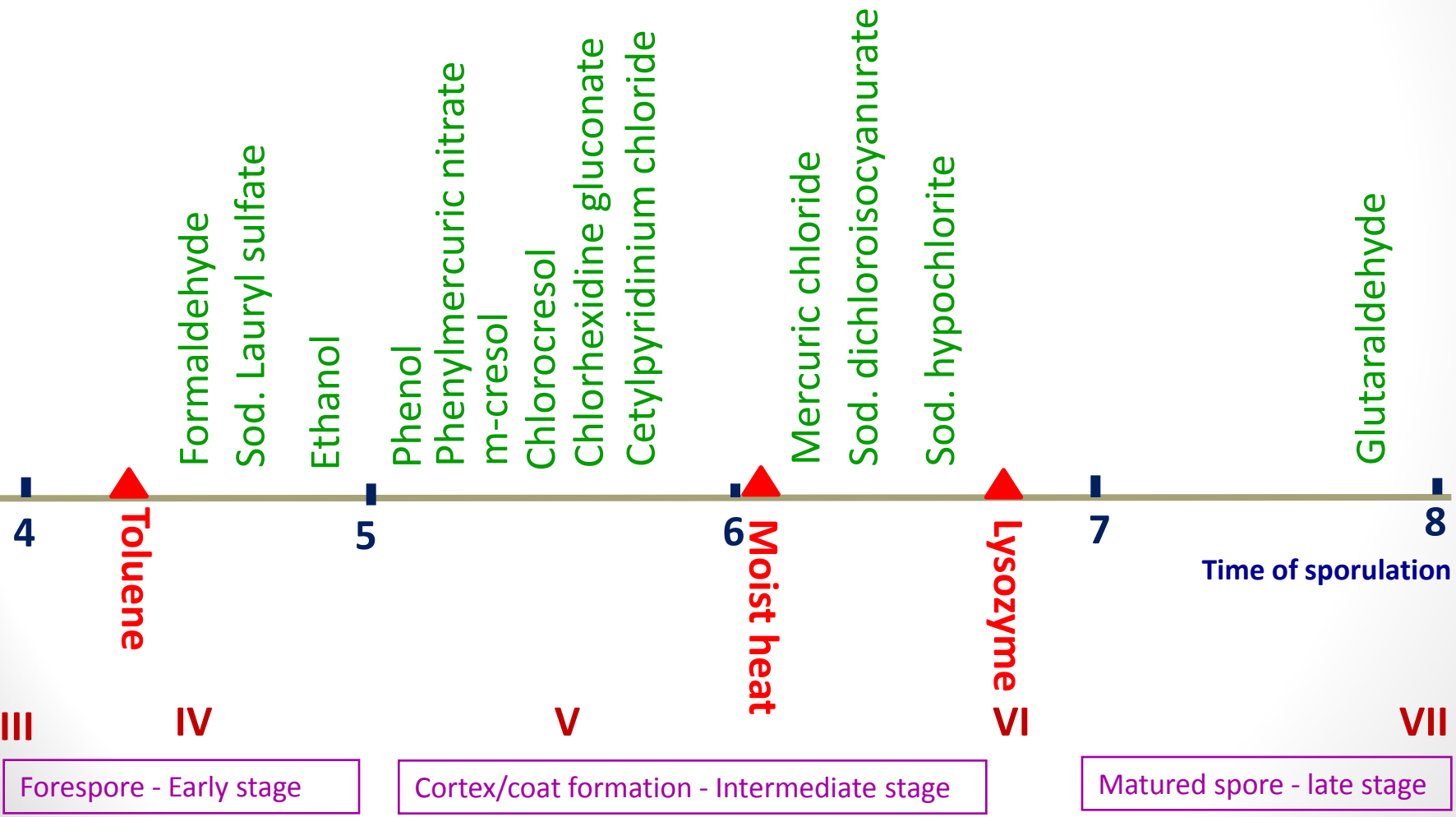


Figure 1 - Phases of spores from dispersal to germination. 1. unswollen spore, 2. swollen spore, 3. ruptured exospore, 4a. protrusion of germ tube and 4b. protonema.

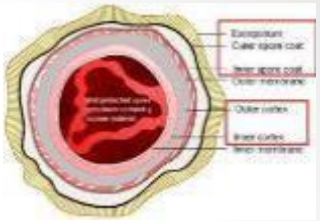
Development of Resistance of B. subtilis during Sporulation



如何管制孢子的形成

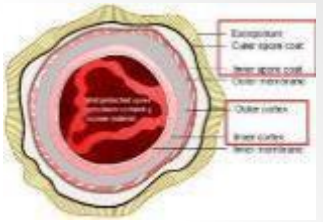
- 場所的設計
- 流向管制
- 設置適當屏障
- 溫溼度管控
- 選擇適當的材料表面
- 人員管制
- 清潔程序
- 滅菌劑的使用(Sterilant)

殺孢子消毒劑選擇



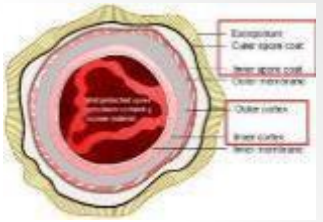
Bactericidal agents that are sporostatic	Bactericidal agents that are sporicidal	comment
Group A Phenols Organic acids and esters QACs Biguanides Organomercurials Alcohols	None in group A	Even high concentrations for prolonged periods at ambient temperature are not sporicidal; may be sporicidal at elevated temperatures
Group B Glutaraldehyde Formaldehyde ? Iodine compounds Hydrogen peroxide Peroxy acids Ethylene oxide β–Probiolactone	All in group B	Low concentrations are sporostatic; usually much higher concentrations are needed for sporicidal effect

殺孢子消毒劑選擇



Antibacterial agent	Bactericidal conc. (%, w/v)	Sporicidal conc. (%, w/v)
Chlorocresol	0.1	>0.4
Cresol	0.3	>0.5
Phenol	0.5	>5.0
Phenylmercuric nitrate	0.002	>0.02
Chlorhexidine diacetate	0.002	>0.05
Cetylpyridinium chloride	0.002	>0.05
Glutaraldehyde	<0.1	4-82.0
Formaldehyde	<1	4-8
Hypochlorite	1-2 ppm	20ppm

殺孢子消毒劑選擇



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Hypochlorite	1-2 ppm	20ppm

? Not sporicidal at this concentration at ambient temperatures

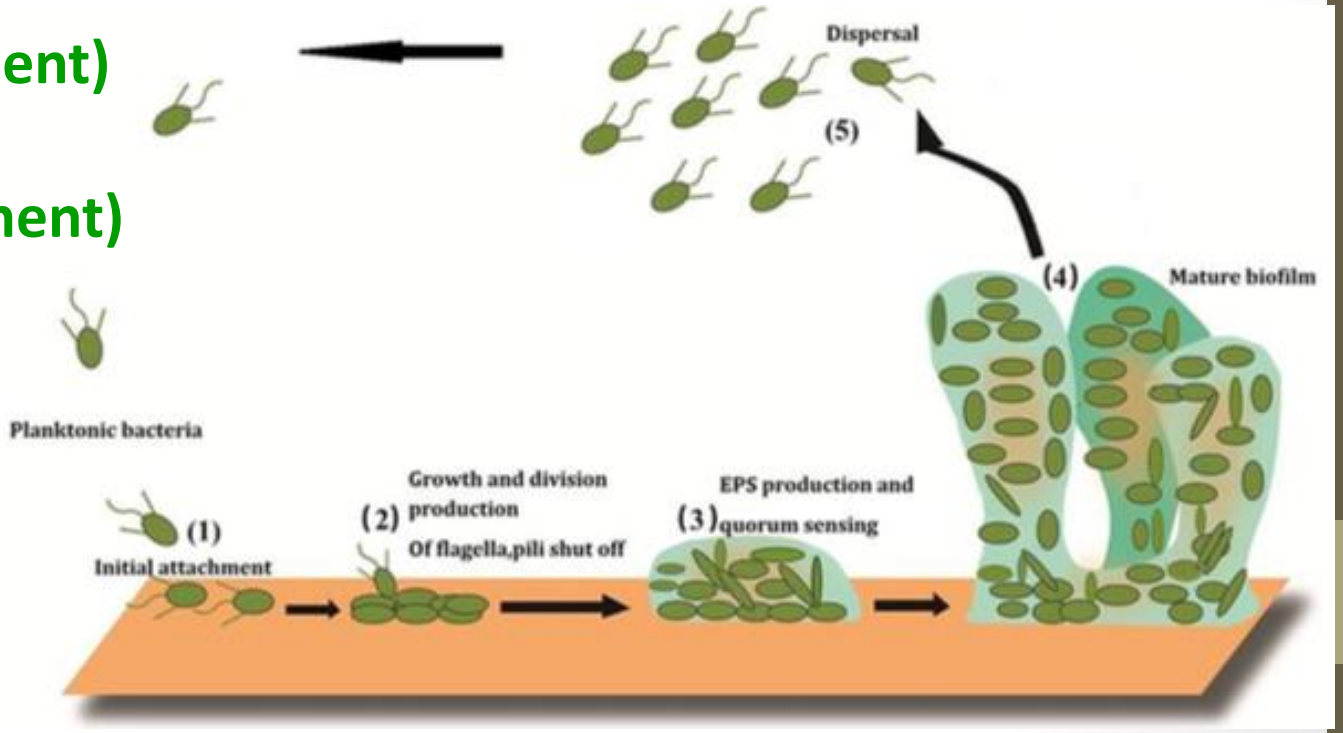
生物膜 (Biofilm)

生物膜是微生物存活的一中方式，當環境變得惡劣時，有些微生物為了生存會附著在固體表面，與其他的微生物結合在一起，並產生一種多醣體(extracellular polymeric substance,EPS) 加將微生物包覆在其內加以保護。生物膜多產生於液體與固體表面相接處。

生物膜 (Biofilm)

生物膜的形成過程

附著(attachment)
生長(growth)
脫離(detachment)



生物膜 (Biofilm)

微生物的生物膜無所不在

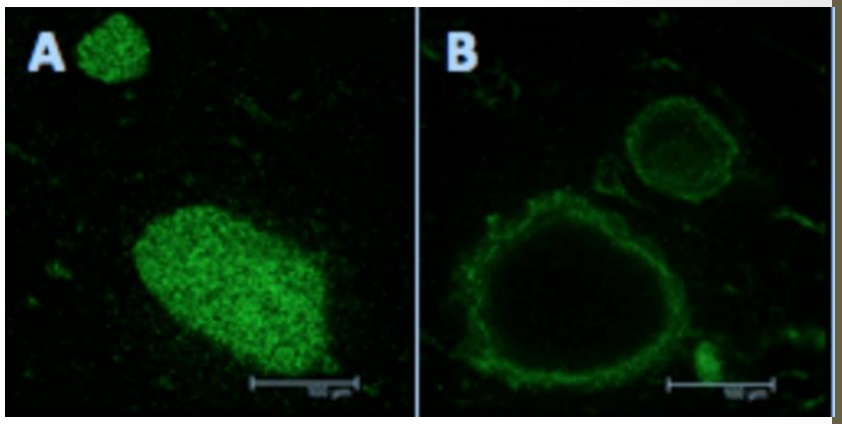
自然環境中如，水，土壤
設備表面，冷水塔，水管
人造物，義肢，假牙
人體內組織，血管，泌尿道，牙齒

生物膜 (Biofilm)

如何對抗微生物生物膜

- Hydrogen Peroxide Silver - Accepta 8101
  Effective against Legionella bacteria
- Plant Extracts
  incartin(from Epimedium breviocornum), resveratrol (Polygonum cuspidatum)
- Honey
- Essential Oil and Other Plant Oils

生物膜 (Biofilm)



未來對抗生物膜的趨勢

- 研發新的材質使得微生物無法附著。或在材質表面塗抹消毒劑，抗生素等使得醫療儀器適合微生物停留。
- 透過給予特定化學訊號去干擾生物膜內各微生物間的溝通 - Quorum Quenching(furanone, patulin and penicillic acid)
- 使用噬菌體(bacteriophages)來處理生物膜

感謝聆聽