Pharmaceutical Industry Contamination Control

制药工业微生物污染控制- 清洁，消毒与灭菌

Thomas
Winifred International Tech Ltd.
2016-3

WINIFRED®
Our Talents, Your Solutions

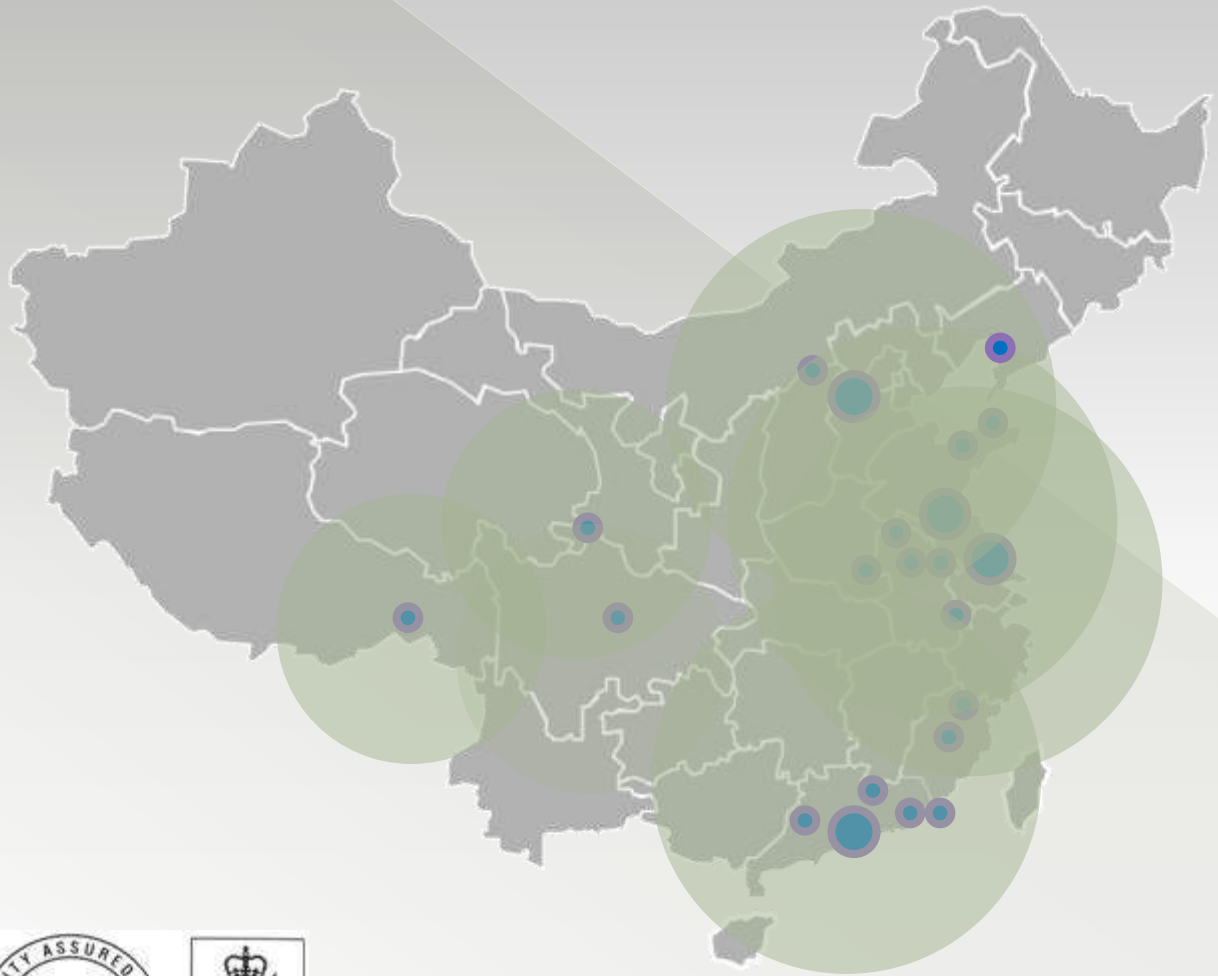
交流内容

- 污染控制---环境的洁净控制
  清洁的新理念和方法
- 污染控制---环境的消毒和灭菌
  1. 欧洲美国消毒剂管理及定义
  2. 消毒剂杀孢子剂的选择和介绍
  3. 空间消毒方案介绍及对比选择
- 消毒剂验证及确认

Winifred International Technology (Shanghai) LTD.

美商卫利

卫利国际科贸（上海）有限公司



主要业务制造与销售防静电产品、无尘净化用品以及微生物污染控制与检验产品及咨询服务，
代理世界著名公司的相关产品，总部设立在香港。
九十年代初进入中国大陆开展业务，先后在上海、深圳福田、深圳福永、天津、无锡、苏州、成都、大连、杭州、武汉、厦门、北京、西安、重庆、福州、宁波、广州、青岛、南京、昆山、东莞等地开设25个分公司和办事处,以获取更大的市场份额，提供给国内用户最优质的产品和服务。

WINIFRED®
Our Talents, Your Solutions

医药工业部

- 污染控制-微生物污染控制产品线（消毒剂灭菌剂和消毒灭菌设备）
- 污染检测-微生物污染检测产品线（生物指示剂，化学指示剂，无菌平板培养基，微生物浮游菌采样设备）
- 污染控制-洁净粒子控制产品线（各种洁净室专用清洁工具和清洁防护产品）
- 污染检测-洁净粒子检测产品线（空气和液体粒子计数器单机及在线，高效过滤器检漏系统，烟雾发生器）

- 洁净室实验室家具货架工作椅，通风橱，天平罩，称量罩及粉末防护处理工作站，真空封口机
- 水系统过滤产品，CIP清洗产品及表面清洁剂
- 制药工程验证服务，BMS，EMS设计实施
- 劳保,毒性抗癌药品身体呼吸防护和实验室常用产品

验证咨询工程服务

GLOBAL ONESOURCE LIFE SCIENCES LTD
生 科 1 站 通
Your global sourcing partner in pharmaceutical operations.
成为您在制药业务的全球外包合作伙伴

SOURCING 采购

Seamless sourcing management 无缝的全球采购管理
Supplier qualification and audits 供应商资质确认与审核
Supplier management including supplier performance review
供应商管理包括供应商绩效评估

ENGINEERING 工程

Design/build capability in China, Taiwan, Singapore, Indonesia, Vietnam
在中国，台湾，新加坡，印尼，与越南有设计和建造能力
Full range of engineering services including maintenance services and EPCM 全方位的工程服务，包括维修服务和EPCM

QUALITY/COMPLIANCE/REGULATORY
质量/合规/规管服务

Remediation services - consulting/temporary staffing
整治服务 - 咨询/临时工作人员
Project management, quality and validation support, training, marketing 项目管理，质量和验证支持，培训，市场营销
Regulatory submissions/preapproval inspection preparation/ commissioning and start-up
监管申请/批准前检查准备/调试和启动

CLEANROOM 洁净室

Cleanroom consumable supplies, monitoring equipment
洁净与无尘室耗材，监控设备
Full service support 全方位的服务支持

WINIFRED®
Our Talents, Your Solutions

消毒剂验证服务——弘知实验室

Technical and application research and service

HOZEN

专注于微生物控制领域，旨在为客户提供专业的微生物控制解决方案。

Hozen下辖Hozen Laboratories-弘知生物科技和Hozen International Trading-常化国际贸易两家子公司。在微生物控制领域与多家知名的国际公司保持紧密业务合作，为客户提供全球领先的产品和技术以及分享最新的市场和法规趋势。位于上海张江高科技园的Hozen Laboratories技术平台，可依据客户的具体情况和需求，提供创新和定制的解决方案，同时提供产品应用、配方开发、法规咨询和测试评估等技术服务。

公司与多个行业领先的国际公司保持合作，把行业最先进的产品和技术整合到我们的解决方案中。

用我们的专业和专注，提供创新和定制的方案

致力于成为消毒剂验证和微生物控制解决方案的领导者

消毒产品验证服务

- 消毒剂效力验证
- 化学残留验证
- 为客户提供一套完整的消毒剂验证解决方案
- 指导客户验证方案的设计、现场验证的实施

ZhangJiang-FuDan Union New Drug R&D Public Service Platform

公共实验室面积2700㎡，拥有气相、液相、质谱等大型检测仪器设备


vai
VELTEK ASSOCIATES, INC.


Kimberly-Clark
PROFESSIONAL
Exceptional
Workplaces


UNIVET
OPTICAL TECHNOLOGIES


vileda
PROFESSIONAL


FLOW SCIENCES, INC.


Miele


MAR COR
PURIFICATION
A Cantel Medical Company


PERFEX


ECOLAB


NAMSA


rotronic
MEASUREMENT SOLUTIONS


Tuttnauer
Your Sterilization & Infection Control Partners


TERRAGENE


laboratoires
ANIOS
Le professionnel de la désinfection


KIMO
INSTRUMENTS


TW Texwipe


Ansell


vidaro
CORPORATION


LIGHTHOUSE
WORLDWIDE SOLUTIONS


amira


MesaLabs


SISTEMA-MK


METRO

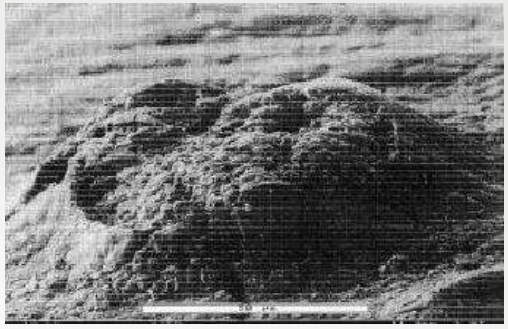

SteriTec

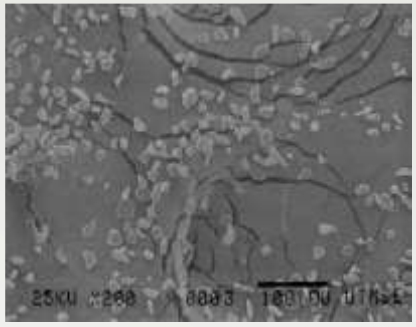

WINIFRED
Our Talents, Your Solutions

污染控制---环境的洁净控制

- 洁净室消毒和污染控制是系统方案，做好预先的清洁非常重要，因为

1. 表面清洁程度影响消毒和杀孢子效果
2. 残留物质与消毒剂产生新的未知化学产物
3. 残留促进微生物生长
4. 法规要求　酚类/次氯酸钠/季铵盐残留





Residue Levels

Residues from Disinfectants		
Chemical Tested	When Applied	After Rinse
High pH Phenol	759 ppm	61 ppm
Low pH Phenol	731 ppm	41 ppm
Quaternary Ammonium	133 ppm	11 ppm
Bleach @ 5.25%	929 ppm	66 ppm
Bleach @ 0.52%	144 ppm	14 ppm
Hydrogen Peroxide	0.067 ppm	0 ppm
Peracetic Acid/H202	7 ppm	6 ppm

Cleaning versus Disinfection
清洁Vs消毒

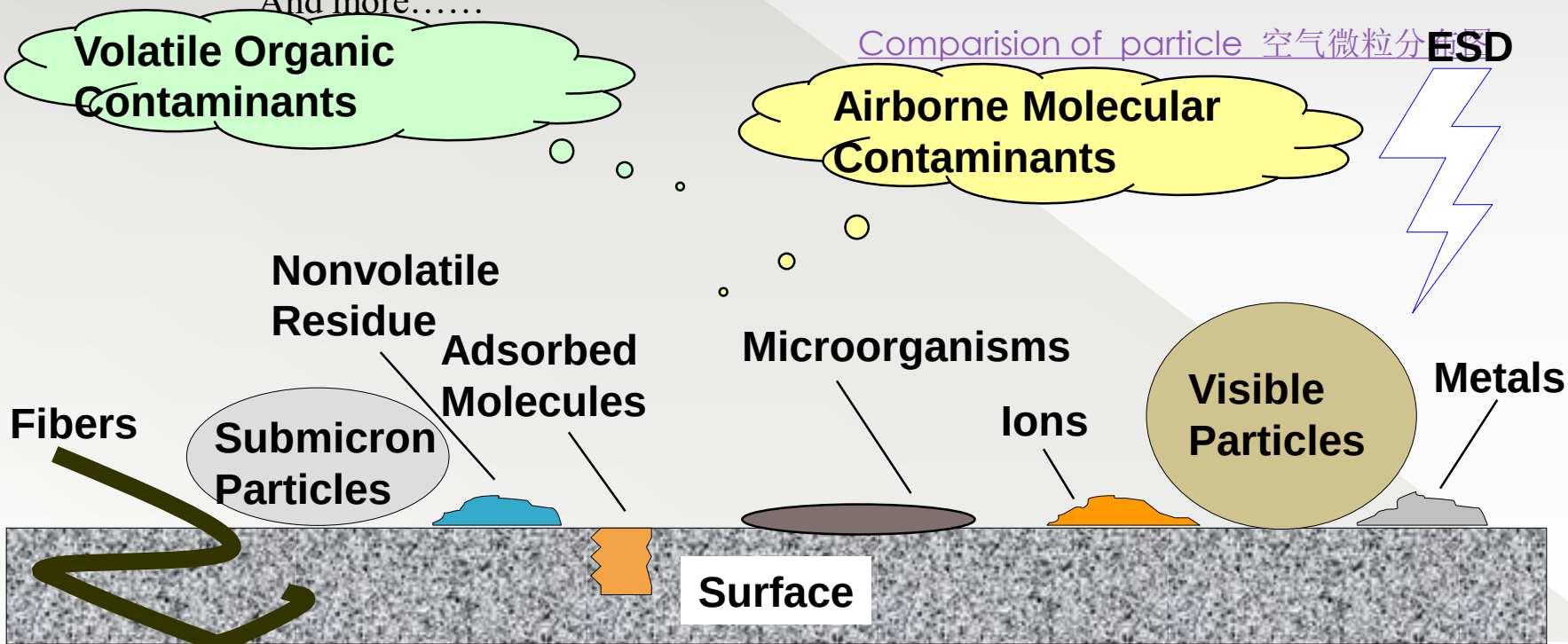
Cleaning	Disinfection
Removal of Particulate and dead microbes from the surface. 去除表面的颗粒和微生物残留组织	Saturate and Penetrate the Cell Wall 浸润并且渗透过细胞壁
Removal of Residues and buildup that can complicate Disinfection 去除掉那些影响消毒效果的残留和积累	Concern with particulate, residues and irregular surfaces 和尘埃，残留（洁净度）和不规则表面相关
	For 'X" Time Period 接触时间

Contamination control in Cleanroom

- Definition: Any foreign material or energy that has a detrimental effect on a product or process. 定义：危害产品或工艺的任何外来物质和能量。

*Particles & Fiber	微粒和纤维 *
*Microbiology	微生物及残留热源内毒素
Ions & Molecular contamination	离子&分子污染
Electromagnetic radiation	电磁辐射
*Electrostatic charge	静电荷

And more……



清洁和消毒

- 第四十一条　应当对厂房进行适当维护，并确保维修活动不影响药品的质量。应当按照详细的书面操作规程对厂房进行清洁或必要的消毒。
- 中国GMP 附录1 无菌药品

第四十三条 应当按照操作规程对洁净区进行清洁和消毒。一般情况下，所采用消毒剂的种类应当多于一种。不得用紫外线消毒替代化学消毒。应当定期进行环境监测，及时发现耐受菌株及污染情况。

- 中国GMP 附录1 无菌药品

第四十四条 应当监测消毒剂和清洁剂的微生物污染状况，配制后的消毒剂和清洁剂应当存放在清洁容器内，存放期不得超过规定时限。A/B级洁净区应当使用无菌的或经无菌处理的消毒剂和清洁剂。

- PDA NO.13 技术报告

清洁和消毒

执行清洁和消毒程序是整个工厂管理的重要组成。

要用环境监测数据来评价这些程序的有效性

- 影响消毒消毒的因素：消毒剂类型，作用时间，待消毒表面
- 消毒剂效率测试
- 残留去除

欧盟GMP的要求：清洁验证

38. 一般情况下,仅仅对于和产品接触的设备表面需要进行清洁验证。也要考虑到非接触部分。要对使用清洁间隔以及清洁再使用间隔进行验证。清洁间隔和方法应该是确定的。
39. 对于相似产品和工艺的清洁程序,选择相似产品和工艺具有代表性的范围是可以接受的。当考虑到关键结果时,可以利用"最坏情况"来进行单独的验证研究。
40. 应该使用典型的连续三次清洁程序并保证结果成功,以证明该方法是经过验证的。
41. "一直试直到干净为止"这种作法在清洁验证中是错误的。

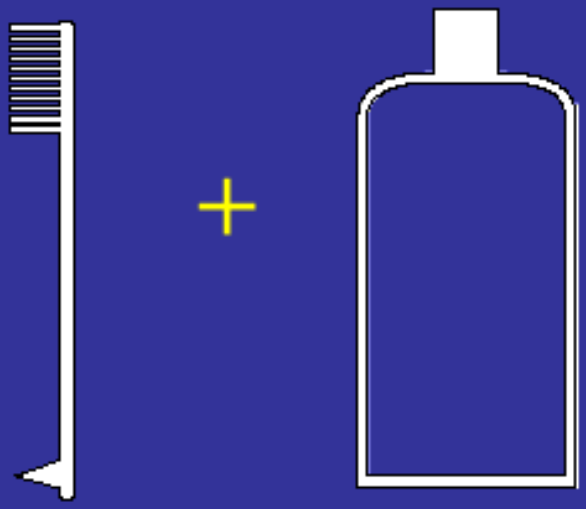
药品生产质量管理规范 (2010年修订) (卫生部令第79号) 的规定

第一百四十三条　清洁方法应当经过验证，证实其清洁的效果，以有效防止污染和交叉污染。清洁验证应当综合考虑设备使用情况、所使用的清洁剂和消毒剂、取样方法和位置以及相应的取样回收率、残留物的性质和限度、残留物检验方法的灵敏度等因素。
第一百九十七条　（六）采用经过验证或已知有效的清洁和去污染操作规程进行设备清洁；必要时，应当对与物料直接接触的设备表面的残留物进行检测；

BIOCLEAN SURFACE 新理念

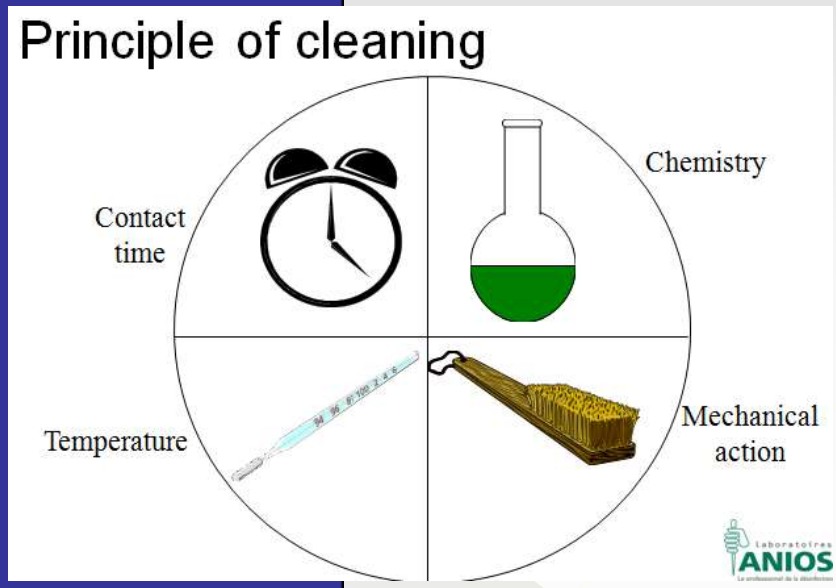
消毒液的验证方案除了化学微生物方面，还有时间温度方法的确认。

Cleaning is the Most Important Step to Successful Disinfection



Toothbrush　　Mouthwash

Too many times in this industry we just disinfect and forget to brush or clean the surface!



WINIFRED®
Our Talents, Your Solutions

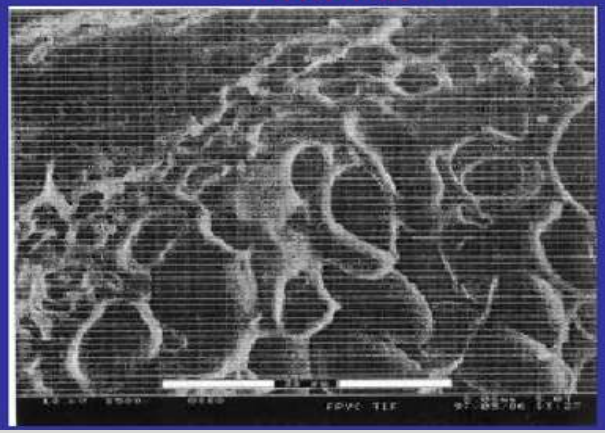
Biocleaning 欧洲

- Treatment grouping cleaning and disinfection
  清洁和消毒协同作用一步完成，效果更好
- Reinforces qualitative action of cleaning
  - Visual cleanliness 可見的清潔

  + 双重加强清洁效果
  - Microbiological cleanliness 微生物及殘留清潔
- 不適用A級，適合BCD級大面積使用，部分區域需過濾除菌，消毒剂清洁剂应该有残留测试方法和MSDS
- 北美 清洁与消毒分开进行

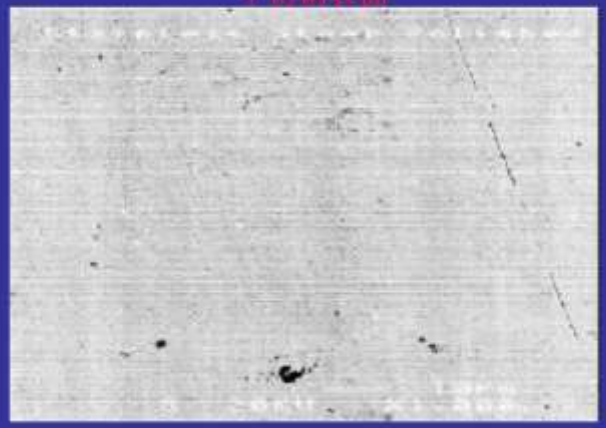
Plastic Curtains Surface #1

塑料帘表面 1



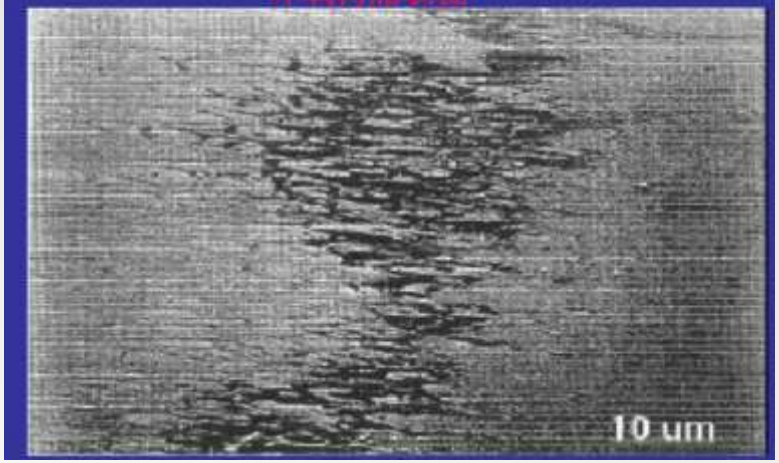
Stainless Steel Surface

不锈钢表面



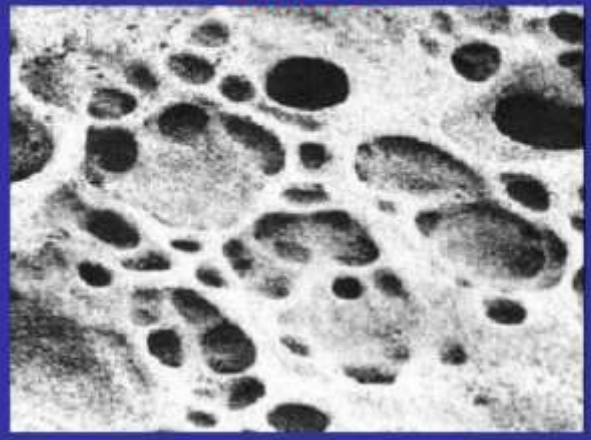
Epoxy Surface

环氧树脂表面

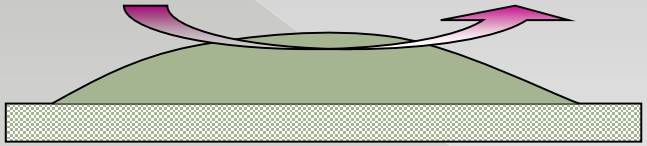


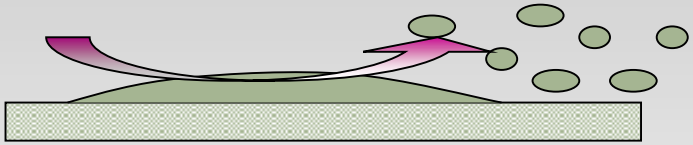
Plastic Curtain Surface #2

塑料帘表面



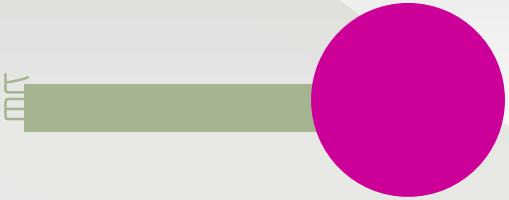
Principle of cleaning 表面活性剂



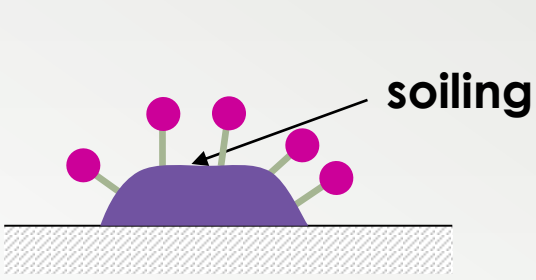


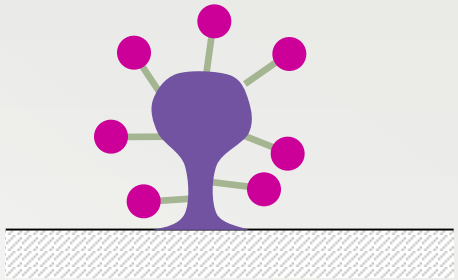
surfactants

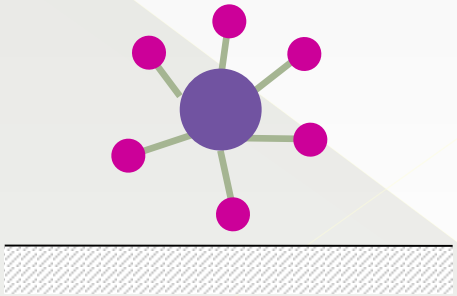
Lipophilic part親脂



Hydrophilic part疏脂



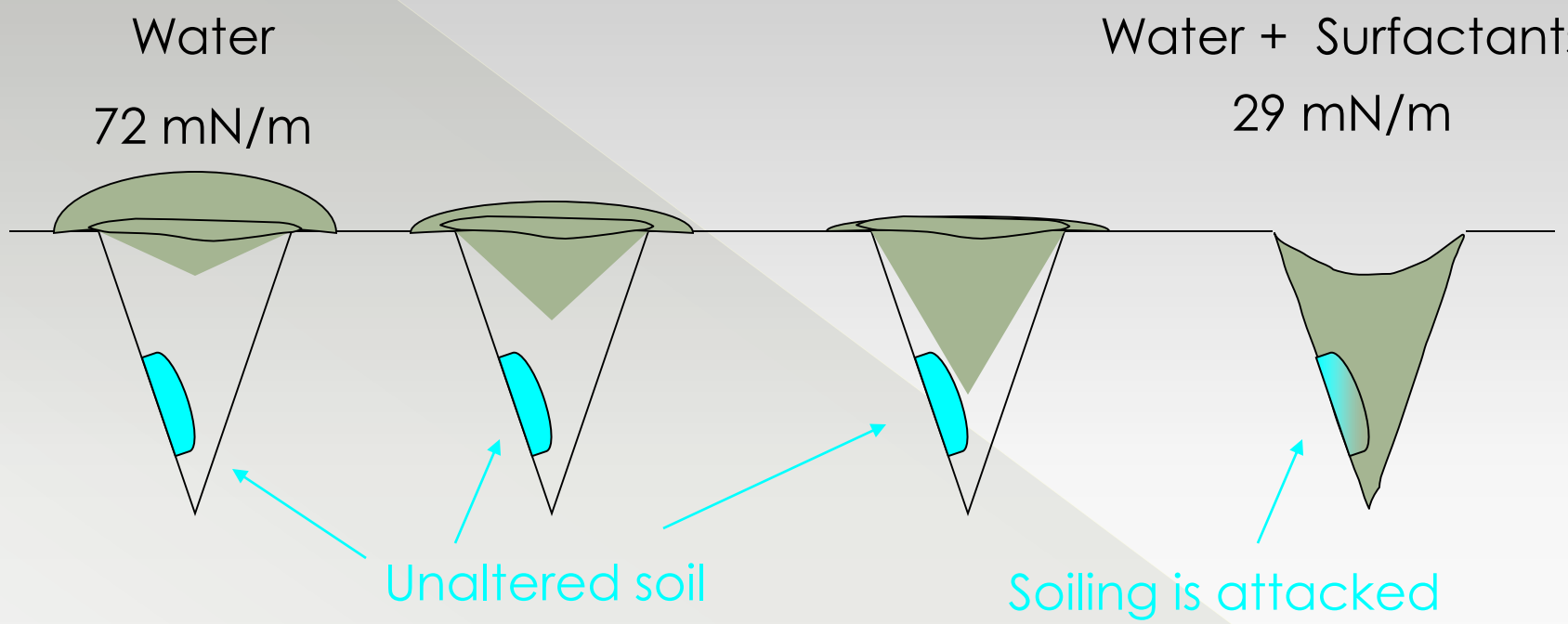




Surface to be cleaned

Surface cleaned

Wetting effect 清洁效果



Water, without the wetting effect or with a poor wetting effect, does not penetrate cracks properly.

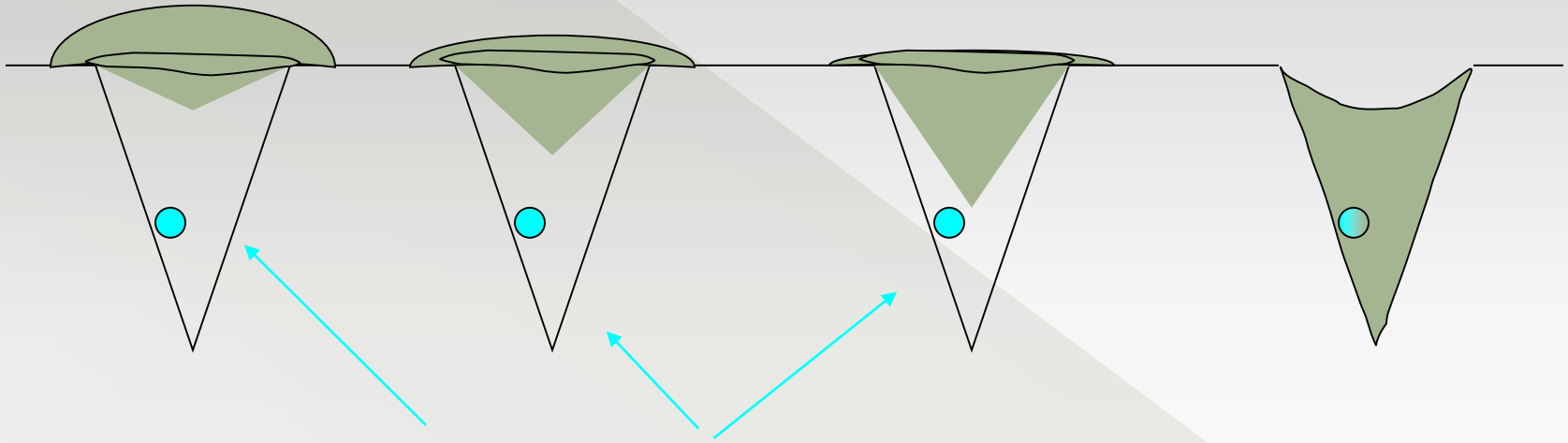
Wetting effect 消毒效果

Water

72 mN/m

Water + Surfactants

29 mN/m



No contact with micro organism

Contact hence activity

mN/m : milli Newton / meter

Surface Tension Values of Ethanol-Water Mixtures
酒精IPA的清洁消毒协同作用

优点：挥发无残留，清洁覆盖效果比纯水好
缺点：挥发快，接触时间段，用于表面消毒只能低效消毒
复合醇？乙醇+正丙醇，至少国际500强药厂很少使用
提升杀孢子剂效果：醇类+杀孢子剂

Composition % by Volume		
Ethanol	DI Water	Surface Tension (Dynes/cm)
80.0	20.0	24.5
51.0	49.0	28.2
33.0	67.0	32.7
21.5	78.5	38.4
14.3	85.7	43.7
9.3	90.7	49.7
4.5	95.5	57.6
1.0	99.0	66.6

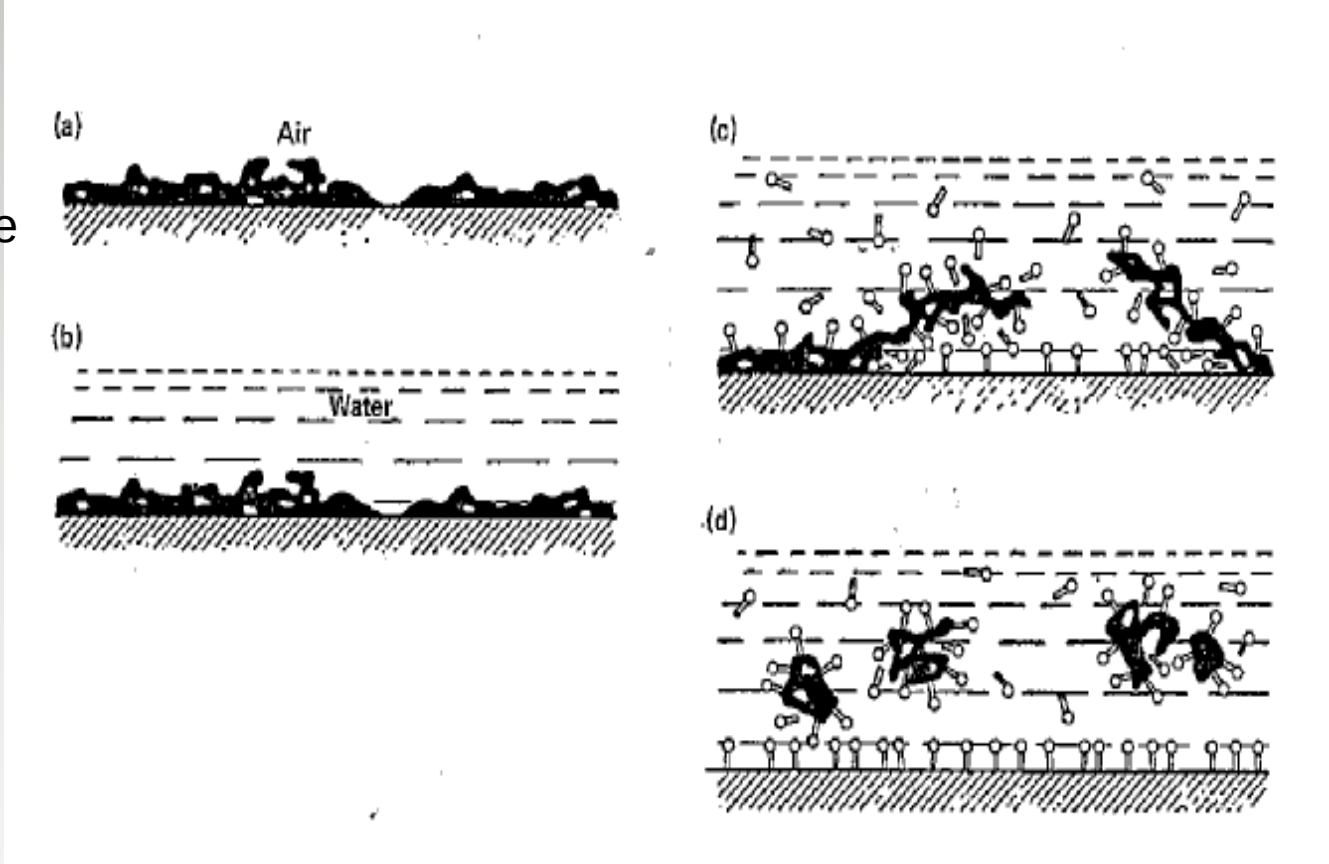
The Physics and Chemistry of Surface Cleaning

a – greasy dirt on surface

b – water alone doesn't work – high surface tension and failure to wet surface

c – detergent reduces adhesion of dirt to surface – dislodge dirt by mechanical action

d – dirt held in suspension



正确的清洁工具能带来

- 最大化的污染控制
- 节约使用成本30%以上
- 工具成本
- 清洁和消毒剂成本
- 产品报废成本
- 微生物消毒残留的清洁

内毒素热源等

洁净室清洁概要

(根据ISO 14644-5 , 操作规程建议 18.3)

粗犷清洁

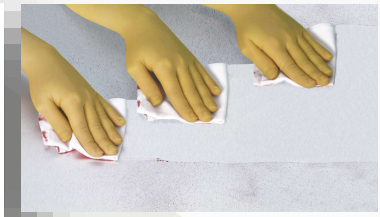
去除直径大于50 µm的大颗粒

中度清洁

去除直径在10 µm到50 µm的小颗粒

精准清洁

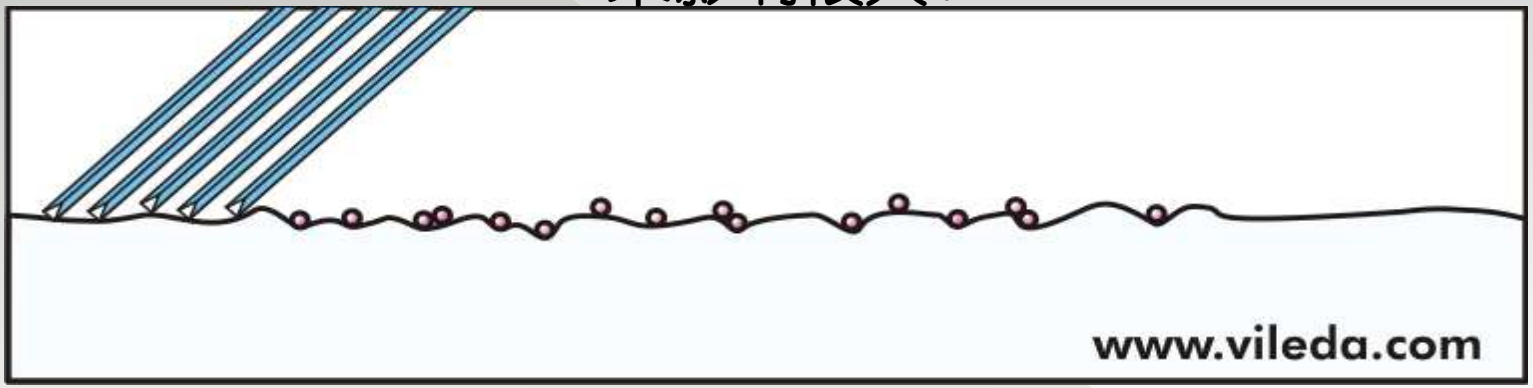
去除直径小于10 µm的微小和纳米颗粒（不仅是抹巾）



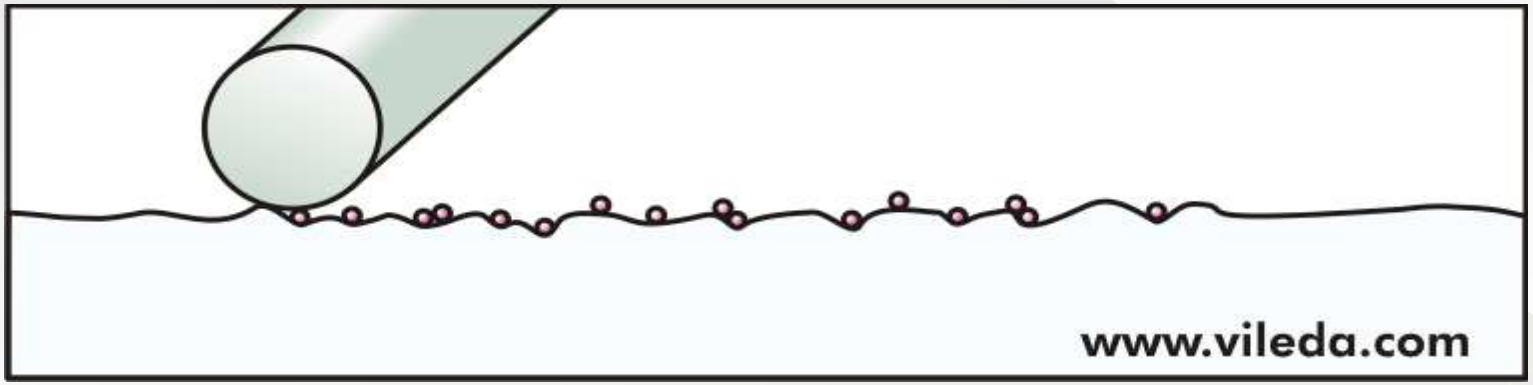
WINIFRED®
Our Talents, Your Solutions

超细纤维清洁效果

超细纤维能达到只有在显微镜下才能观察到得凹凸面结合表面活性作用，消毒液对表面的覆盖效果对杀菌效果影响很大！



超细纤维



普通
涤纶纤维

清洁方式

桶 /拧干器

消毒剂接触时间10分钟

预浸渍系统

消毒剂接触时间6分钟

Comparison of Bucket methods

Single bucket method

bucket incl. press for rinsing and wringing,
includes 16 L water plus cleaning detergent *

Working method & Cleanliness:

- rinse and wring dirty mop in bucket
- mop surface
- Mop Return a mixture of disinfectant and dirt/contamination back to the surface

Double bucket method (single wringing)

red bucket incl. press with 5L water,
blue bucket with 11 L water plus cleaning / disinfection solution

Working method & Cleanliness:

- rinse dirty mop in blue color coded bucket
- wring mop above red color coded bucket
- mop surface
- Mop Re-apply disinfectant from first bucket to surface, little contamination is returned to the surface

Double bucket method (double wringing)

red bucket incl. press with 5 L water,
blue bucket with 11 L water plus cleaning / disinfection solution

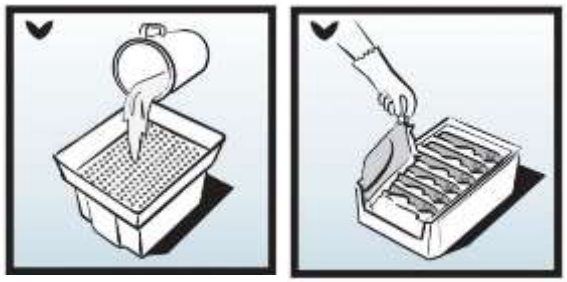
Working method & Cleanliness:

- rinse and wring dirty mop in red color coded bucket
- dip mop in blue color coded bucket
- wring mop in red color coded bucket
- mop floor
- limited contamination is returned to the surface

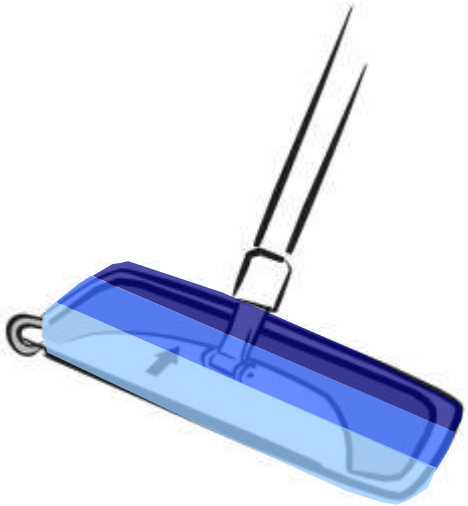
* 16 L cleaning solution, which fits in the single bucket , is the benchmark for all bucket methods. This might not be application oriented, but delivers comparable results.


MEMONA

预浸渍方式
操作方法



- *所有的替换头都吸收等量的清洁剂(消毒剂).*
- *手无需触碰替换头*
- *1个替换头最大清洁面积是25平方米*
- *一个工具全能清洁地面，墙面和天花*



拖头有不同的清洁区域

1. 预清洁区域 (弄湿污垢 – 移除松软的污垢)
2. 主清洁区域 (机械清洁)
3. 后清洁区域 (干燥地面)

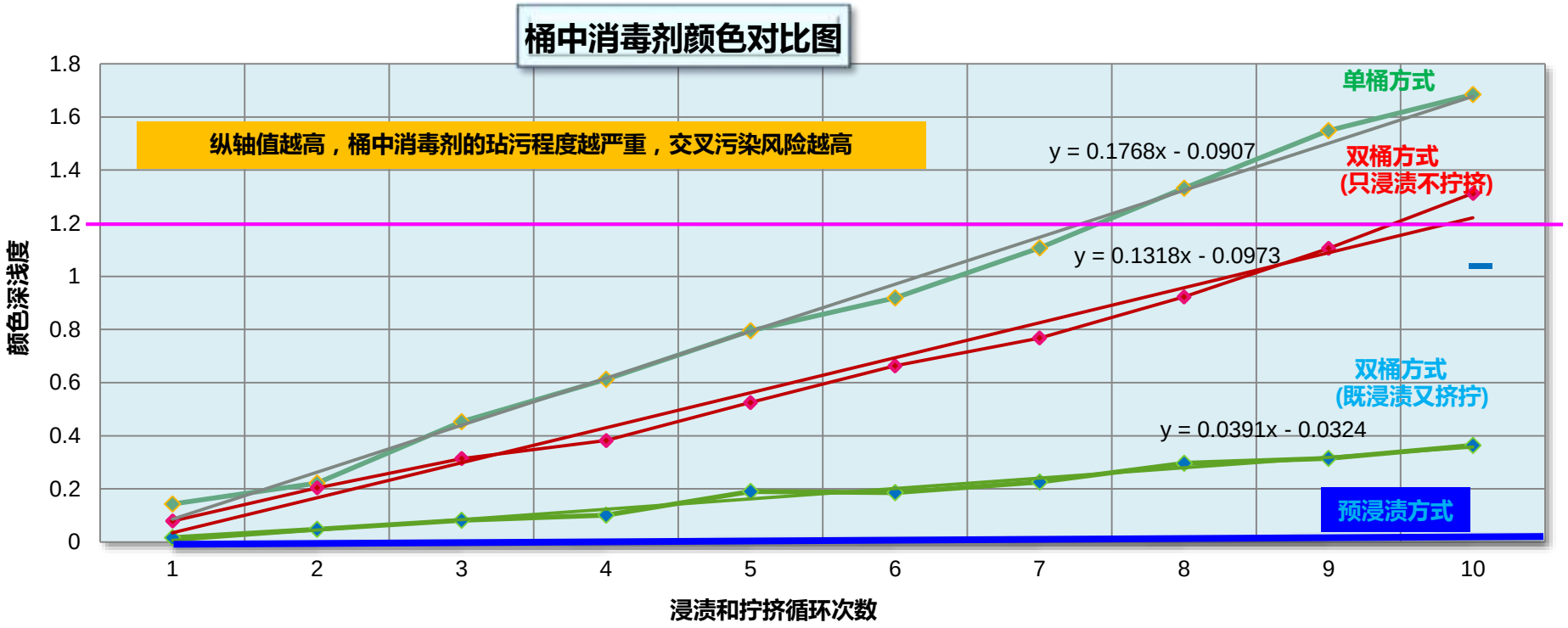
桶清洁方式对比

测试步骤

- 拖把头放在135克有颜色的容器中浸渍，模拟刚刚被污染的实际情况
- 在不同的桶（方式）中浸渍和拧干
- 在每种桶的方式中使用10个拖把替换头，均为1次浸渍和1次拧干，1次循环后换用另一个拖把替换头
- 1次循环后提取桶中的消毒液，分析比较颜色

桶清洁方式对比

结论：光度计的测量结果



Long-Term Wash Test

Where does the mops wear out?

In controlled environment the mop is used only for a short time for cleaning to avoid cross contamination.

Afterwards the mop is laundered for more than 1h in the washing machine (thermal, chemical and mechanical stress).

Therefore it is important that the mop shows a very good wash resistance.

Long-Term Wash Test

The mop was tested in the wash lab of Vileda Technical Centre

TEST CONDITIONS

- Washing Machine:Miele PW 6101FT 10 kg
- Washing Detergent: Eltra from Ecolab, powder for chemo-thermal disinfection, product: Eltra Concentration: 7g/L (210g/load)
- pH-value of wash liquor: 10.5

RESULT

After 200 cycles the mop does not show damages and is still usa

Back side after 200 washing cycles

Front side after 200 washing cycles

Long-Term Autoclaving Test

The mop was autoclaved at the lab of Vileda Technical Centre

TEST CONDITIONS

- Autoclave
- Varioklav 135 S, steam sterilizer, single pre-vacuum, usable volume 135 litres
- Test Parameter
- 121°C for 20 minutes
- Pre-vacuum: 20 kPa
- Cooling-down of product between autoclaving cycles

RESULT

After 80 autoclaving cycles the MicroControl Mop does not show any damages and FHP specification requirements. Only the white backing partially shows discoloring.

Mop after 80 autoclaving cycles

Wiping Guide 9x9 12x12

Use linear, overlapping strokes

污染控制---环境的消毒和灭菌
1. 欧洲美国消毒剂管理及定义

Terminology, Definition& Regulation

North America EPA

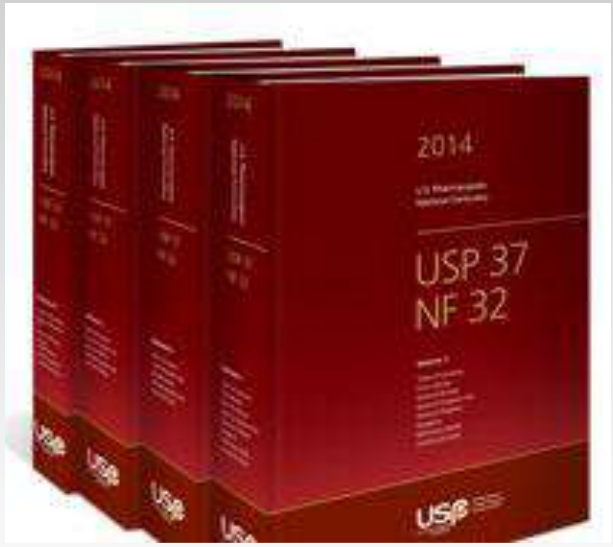
- All germicidal cleaners fall under FIFRA as amended (1988) and administrated by EPA
- Federal Insecticide, Fungicide and Rodenticide ACT (FIFRA)
- Enviromental Protection Agency (EPA)
- FDA regulation as medical device per Food Quality Protection ACT of 1996 , if used to reprocess other medical devices or if used as a steriliant for medical devices.

EPA Requirments

- Safety, use, disposal
- MSDS
- Efficacy--- Association of Official Analytical Chemists (AOAC) Official Methods of Analysis
- **ASTM E2614-08:** 美国材料与试验协会标准
- Product Labels
- Classification

USP 29 NF-24 <1072>
11 Key Factors in Selecting a Disinfectant
消毒剂选择的11个要素

U.S. PHARMACOPEIA



- **Effectiveness (6) 效果**
- **Safety (4) 安全**
- **Regulatory (1) 管理**

According to the USP 29 NF-24<1072>
Each of these 11 factor have to be evaluated by the end user

根据美国药典，使用者都必须重视这11条要素

WINIFRED®
Our Talents, Your Solutions

USP 29 NF-24 <1072>

11 Key Factors in Selecting a Disinfectant

- **Effectiveness (6) 效果**
  - Spectrum of activity 有效杀菌范围
  - Concentration required for effective performance达到效果所需浓度
  - Surface material to be disinfected 消毒表面的材质
  - Bio-burden on the surface 消毒表面的生物负载
  - Need for residual bactericidal activity 杀菌能力需要持续作用
  - Disinfectant rotational plan (if needed) 轮换消毒剂方案
- **Safety (4) 安全**
  - Corrosion issues 腐蚀性问题
  - Operator safety 操作者的安全
  - Compatibility with other cleaners or disinfectants 与其它化学品相容性
  - Steps to insure disinfectant does on contaminate product消毒步骤
- **Regulatory (1) 规定**
  - EPA Registration & Claim in the USA EPA注册并且在美国通过 (Registration according to EU Directives in Europe, etc…) (欧洲根据EU规定注册)

EN ISO Standards（不仅用于制药）

- EN 13697: 2001

  Chemical Disinfectants and Antiseptics- Quantitive non- porous surface test for the evaluation of bacterial and/or fungicidal activity of chemical disinfectants use in food, industrial, domestic and institutional areas

- EN 1276:1997

  Quantitative suspension test for the evaluation of bactericidal activity …

- EN 1650: 1998

  Quantitative suspension test for the evaluation of fungicidal activity…

Disinfectant (US Pharmacopia) 消毒剂，杀孢子剂和灭菌剂

- Chemical disinfectant--- A chemical agent used on inanimate surface and objects to destroy infectious fungi, viruses, and bacteria, but not necessarily their spores. Sporicidal and antiviral agents my be considered a special class of disinfectants. Disinfectants are often categorized as high- level, intermediate- level and low- level by medically oriented groups based upon their efficacy against various microorganisms.

效力级别	细菌芽孢	营养细孢	真菌
低	–	+	±
中	–[1]	+	+
高	+ [2]	+	+

– 表示几乎没有杀灭效果

+ 表示有相当的杀灭效果

±表示杀灭效果较温和

1有些中效消毒剂，如次氯酸盐，也能杀灭芽孢；象酒精或酚类等其它消毒剂，则不能杀灭孢子。

2用高效消毒剂杀灭高数量的细菌孢子时，须延长其接触时间。

The Ideal Disinfectant 理想的消毒剂

- Kills all micro-organisms 对所有微生物有效
- Non-corrosive 无腐蚀
- Safe to use 使用安全
- Leaves no residues 无残留
- Sterile (for Grade A and B areas) 无菌
- Fast acting 起效快
- Compatible with other agents 化学相容性好
- Compatible with cleanroom surfaces 材质相容性好
- Available in a variety of formats 多种包装形式
- Cost effective (price, time to prepare/use, PPE, wastage) 经济（价格，准备时间，使用时间，个人防护和浪费）

WINIFRED®
Our Talents, Your Solutions

The Ideal Disinfectant

- No one disinfectant will tick every box
- Compromise: "Right" disinfectant for a specific application

- 但是没有一种消毒剂是完美的，
- 针对自己的情况来做出正确的选择

WINIFRED®
Our Talents, Your Solutions

Quality Requirements 消毒剂品质控制

Points to consider….

- How is the product manufactured, what certification does the manufacturer hold? 供应商认证系统及生产环境
- Will you be notified of changes to product formulation, specification, manufacturing process etc.? 变更通知
- Is the product supplied with a CoA or CoC?
- For product supplied without a CoA incoming QC testing should be considered 如果产品没有COA则需要做QC测试
- For product used in Grade A/B areas:
  - How is sterility assured prior to use? 使用前无菌保障
  - How is sterility assured in use? 使用中无菌保障

WINIFRED®
Our Talents, Your Solutions

Efficacy Requirements

Different disinfectants are effective against different types of organisms

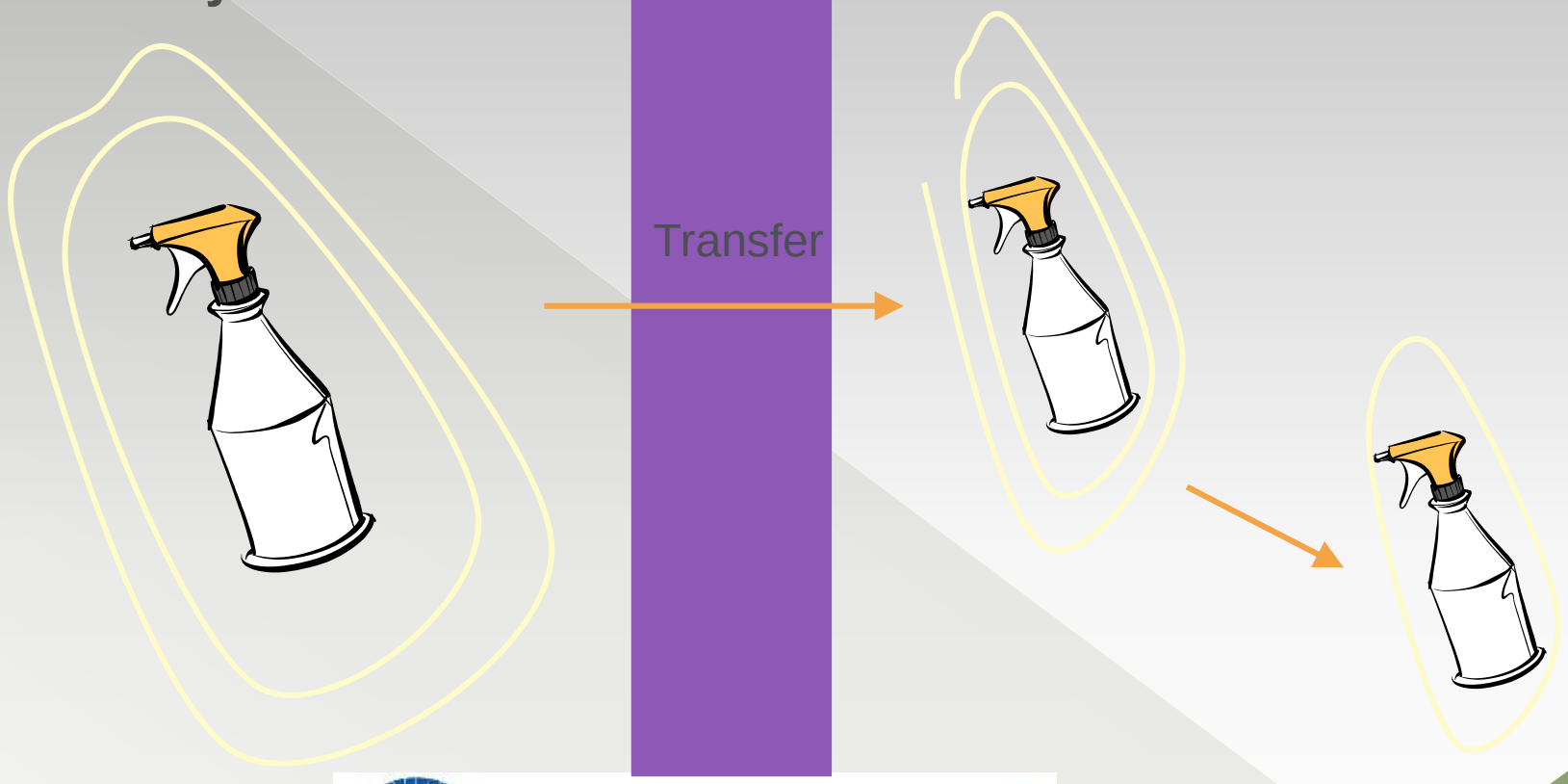
- Check the biocidal claims made by the manufacturer – what organisms is the product effective against with what contact time?
- What technical data is available to prove the efficacy claims?
- Is the spectrum of activity appropriate to the type of organisms you expect to find in your cleanroom?
- Rotation of a sporicide with a bactericide/fungicide is recommended – *USP 1072 "It is prudent to augment the use of a daily bactericide with a weekly (or monthly) sporicide"*

WINIFRED®
Our Talents, Your Solutions

Transfer Disinfection – *wrapped items*

“Dirty” Side

“Clean” Side



WINIFRED®
Our Talents, Your Solutions

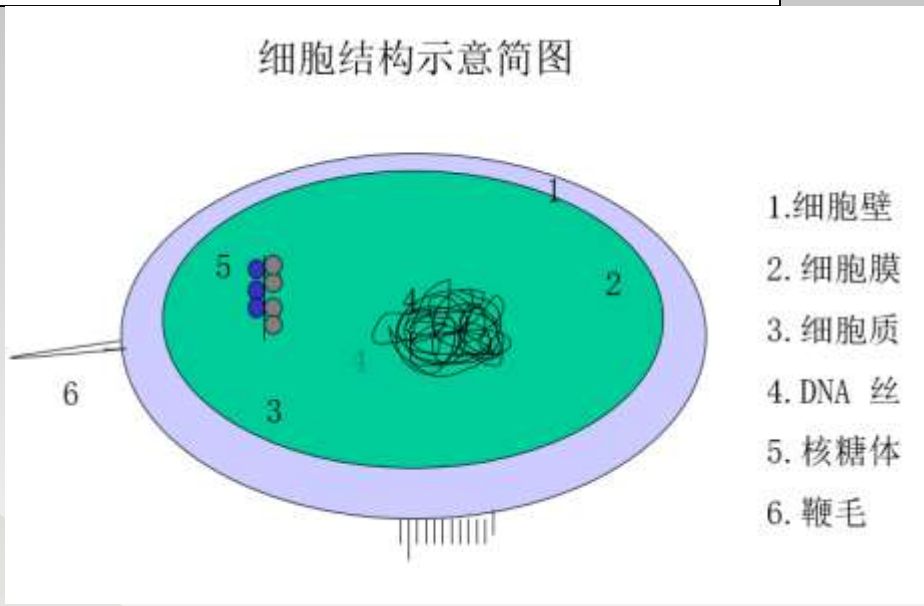
In the lower grade environment spray/wipe the exterior surface of wrapped item

In the higher grade environment open the wrapping, exposing the previously sterile inner surface

❖消毒剂是怎样发挥杀菌作用的？

破坏细胞膜类

杀菌剂，如次氯酸钠和过氧乙酸，都是强氧化剂能够引起细胞膜的全面破坏，而导致细胞内的关键细胞器流失，这个过程导致了细胞的真正死亡。



阻断细胞食物摄取和废物排泄

- 在水溶液中季铵盐基团带正电荷，它们攻击细胞上带负电荷的部份。
- 从而阻断了营养物质运输到细胞内，并阻止了堆积在细胞内的废物的排泄。使细胞被饿死和被细胞内的堆积的废物毒死。

钝化关键酶

杀虫剂类，如苯酚，酚醛类，它们进入细胞并和某些关键酶发生作用，这些酶能够支持细胞的生长和代谢活动（代谢能够为细胞的生长和裂殖提供能量）

假如钝化作用不够完全，受伤的细菌在几个小时以后能够恢复生长能力并重新污染表面。

Minncare® Mechanism of Action
过氧化氢过氧乙酸灭菌剂（杀孢子剂无需轮换）

1. Disrupts Sulfhydrl (-SH) and Sulfur (S-S) bonds in proteins and enzymes破坏蛋白和酶硫氢键和二硫键
   Important components in cells and membranes are broken by oxidative disruption.
   这样细胞和膜的关键成分都被氧化作用破坏

2. Impede cellular activity by disrupting chemosmotic function of lipoprotein cytoplasmic membrane transport through rupture or dislocation of cell walls
   通过对保护细胞功能的细胞壁的作用，从而破坏膜转运作用脂蛋白的化学透功能

3. Denature the properties of protein components by altering the nucleic acid structure of organisms.
   通过改变核酸的有机结构是相关蛋白变性

4. Damage vegetative cells by oxidation with hydroxy radicals.
   羟基的氧化作用破坏非繁殖细胞

5. Produces organic radicals that act as reducing agents for spores.产生有机键破坏孢子

Sporicidal Agent& Steriliant

- Sporicidal Agent
  - An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microoganism
  - High level disinfectant or sporcidal: bacterial spore <log4
  - In practice, spore contaminations of 10*6 are rarely recorded in life science cleanroom operations. High concentrations of H202 and high Temperature are also impractical for operational reasons. For most liquid disinfection protocols it's normally accepted that a 10*4 or even a 10*3 log reduction in spores is acceptable.
- Steriliant& Sterilization
  - An agent that destroys all forms of microbial life including fungi, viruses and all forms of bacteria and their spores. Steriliant are liquid or vapor- phase agents.
  - Bacterial spore >log6 - 7

General Classification of Antiseptic, Disinifectants and Sporicidal agents (USPC 2009)

Chemical Entity	Classification	Example
Aldehydes	Sporicidal agent	2% Glutaraldehyde
Alcohols	General purpose disinfectant, antiseptic, antiviral agent	
Chlorine and sodium hypochlorite	Sporicidal agent	0.5% Sodium hypochlorite
Phenolics	General purpose disinfectant	500ug/g chlorocresol and chloroxylenol
Ozone	Sporicidal agent	8% gas by weight
Hydrogen peroxide	Vapor phase sterilant, liquid sporicidal agent, antiseptic	4ug/ g H2O2 vapor, 10-25% solution, 3% solution
Substituted diguanides	Antiseptic agent	0.5% Chlorhexidine gluconnate
Peracetic acid	Liquid steriliant, vapor phase steriliant	0.2% Peracetic acid, 1ug/g peracetic acid
EO	Vapor- phase steriliant	600ug/g EO
Quaternary ammonium compounds	General purpose disinfectant, antiseptic	200ug/g Benzalkonium chlorite

Cleaning, Disinfection, Sporicidation& Sterilization Frequency 清潔消毒頻率

- 'The cleaning frequencies established for the walls and ceiling in the fermentation and purification areas have not been validated to ensure that these frequencies are appropriate.' GMP TRENDS, issue #556 Aug 15 2000

- Should be determined on the basis of need
  - Product risk 產品風險
  - Active level in area 活動量
  - Environmental data feedback 環境監控信息

  Should be written in SOP

USP1072关于微生物对消毒剂的抗性

- MICROBIAL RESISTANCE TO DISINFECTANTS
- The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely to occur at significant levels, as disinfectants are more powerful biocidal agents than antibiotics. In addition, they are normally 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. However, the most frequently isolated microorganisms from an environmental monitoring program may be periodically subjected to use-dilution testing with the agents used in the disinfection program to confirm their susceptibility, as there are real differences among different species in resistance to the lethal effects of different sanitizers.
- 消毒剂交替使用主要是增强对微生物杀灭效力和范围

- • *USP <1072>*
- – “研究微生物对抗生素的耐受性是得到广泛认知的。但是研究微生物对消毒剂的耐受性很少，因此消毒剂一般采用高浓度的杀灭微生物的试剂去消除低浓度的微生物污染，因此研究微生物对消毒剂的耐受性不是非常重要”.
- 对于在环境监控中经常能分离出来的特定菌株，可以使用消毒剂来进行效力确认，毕竟每种微生物对每种消毒剂的杀灭效力还是有差异的（实际上就是当怀疑的时候，做重新确认）

Alternation of antimicrobial actives

- IPA or Ethanol (surfactant& low end disinfectant, no residual) 醇類
- Bioclean- Cleaning& disinfectant 中效消毒劑
- High level disinfectant with biocide高效消毒劑
- Sterilization by Dry Fog or VHP 空間消毒滅菌
- Residual Detergent 殘留清潔劑

– Two disinfectants and a sporocide--两种消毒剂和一种杀孢子剂

– One disinfectant and a sporocide-一种消毒剂和一种杀孢子剂

– Different concentration—不同浓度，低浓度消毒剂，高浓度杀孢子剂

多种抗菌谱相似的消毒剂，交替使用无很大意义

因为消毒剂不能杀死孢子，所以和杀孢子剂的交替使用还是需要的。

Rotation of a sporicide with a bactericide/fungicide is recommended – *USP 1072 "It is prudent to augment the use of a daily bactericide with a weekly (or monthly) sporicide"*

WINIFRED®
Our Talents, Your Solutions

What's Rotation
无菌及非无菌洁净区消毒液使用方案

Alternation of antimicrobial actives

1. A级区清洁消毒：STERILE IPA or Ethanol
2. A级区杀孢子灭菌：STERILE 6% H2O2 or Vapor phase sterilant
3. 非A级和产品直接接触无菌区：季铵盐类，酚类无菌消毒液或者过滤除菌的非无菌中效消毒液
4. 非A级和产品直接接触无菌区：日常空间及表面熏蒸消毒灭菌VHP, HPVP, VPHP, Dry Fog，甲醛
5. 环境及残留清洁剂：如果不能每天及时清洁残留，或者是一些高残留的消毒剂，则定期应使用残留清洁剂 Residual Detergent

Shield Medicare --- Business Operations

UK company since 1990

Contamination Control

污染控制

Division of ECOLAB 2006

Shield Medicare

ECOLAB

Kler advantage

Mar Cor- BioScience Product

MAR COR PURIFICATION
A Cantel Medical Company

MAR COR PURIFICATION
A Cantel Medical Company
Competent, Consistent, & Compliant

Cartridge, Capsule & Crossflow Filters

Effective Against Spores, Bacteria & Viruses

Biodegradeable Solution & Short Process Time

MINNTECH · MAR COR · biolab Equipment · FS Fluid Solutions · GE Water & Process Technologies

Combined to offer Filtration, Water, and Disinfection Technologies

MAR COR PURIFICATION
A Cantel Medical Company

Combined to Offer Filtration, Water, and Disinfection Technologies

Le Professionnel de la Désinfection

110 ANS YEARS
1898 - 2008

laboratoires ANIOS
Le professionnel de la désinfection

CATALOGUE
HÔPITAUX-CLINIQUES

...IFRED®
...nts, Your Solutions

Cleanroom Expertise无尘室技术

- All Operates to
- **GMP**

ISO 9001: 2000
BS EN ISO 13485: 2001

- 8 Cleanrooms ISO 7 (Class 10,000)
- 3 Localised ISO 5 (Class 100) LAF stations
- 1 Aseptic Suite ISO 5 (Class 100)
- 1 ISO 3 (Class 10) Laminar Flow cabinet

MAR COR® PURIFICATION
A Cantel Medical Company

Competent, Consistent, & Compliant

FiberFlo® HollowFiber Filters

Cartridge, Capsule & Crossflow Filters

Actril® & Minncare® Disinfectants

Effective Against Spores, Bacteria & Viruses

Dry Fog® Clean Room Disinfection

Biodegradeable Solution & Short Process Time

Combined to Offer Filtration, Water, and Disinfection Technologies

Department INDUSTRY

Products and disinfection procedures for industrial processes (Food, Pharmaceutical and Cosmetic Industry): innovating, complete and validated answers.

A complete range of products for
Floors/Surfaces
Airborne disinfection
Hand Hygiene …

Customer Assistance:

- *Analysis of chemical substances traces in food*
- *Microbiology expertises*
- *Specific study (biofilm)*
- *Optimization of consumption*

laboratoires ANIOS
Le professionnel de la désinfection

Pharmaceutical and Cosmetic

« exigence for Hygiene without weakness: IP STERILE range»

- *Products filtered 0,2 µm*
- *Repartition in classified area*
- *Twice packaging*
- *Technical Assistance*
- *Help to validation*





1.Alcohol Features& Limitations
醇类消毒剂特性及要点

- No Residue 无残留
- Broad Spectrum 广谱
- Evaporates readily 快速挥发
- Not sporicidal 不能杀孢子低效

Limitations

- Poor Cleaner 清洁作用低
- Flammable 易燃
- Limited contact time 接触消毒时间短
- Not EPA registered
- VOC emission aerosol 挥发性吸入
- 使用过滤除菌无菌照射双层包装的醇类产品,WFI?

The best trigger on the market

- **Goal: a system with all the benefits of a trigger spray but none of the disadvantages**
- 目标：具备喷洒装置所以优点同时不会污染孢子的产品

- **Need: a system which separates the sterile liquid from the air at all times**
- 需要： 能够把无菌液体和空气分离的装置

- **Result: a bag holding and protecting the liquid inside the bottle**
- 结果： 内置袋可以保护瓶内液体

WINIFRED®
Our Talents, Your Solutions

Sterile Alcohol as a Disinfectant
无菌醇类作为消毒液需注意

- Alcohol does not kill bacterial spores
  醇类不能杀灭孢子
- Alcohol which is exposed to air could contain spores.
  醇类暴露于空气中会被孢子污染
- Alcohol should be sterile and protected when in use.
  醇类消毒液在使用中应保证无菌
- Avoid contamination of high value cleanrooms and products 避免无菌室内重要产品的污染

The most validated closed trigger spray system ever

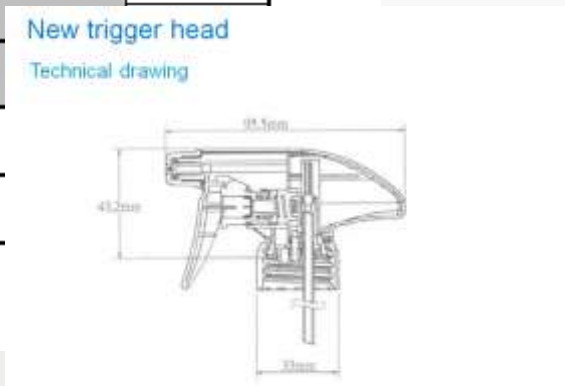
In Use Shelf Life up to 3-6 Months
开封时间超过3-6个月后的无菌测试

Shield Medicare
a division of Ecolab

Table 2: Summary of results for the SteriShield Delivery System at each time point

	Test Organism/Sample	Zero	1 month	2 months	3 months	4 months	5 months	6 months
TSB + SDS	Sample 1	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	Sample 2	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	Sample 3	-ve	-ve	-ve	-ve	-ve	-ve	-ve
FTM + SDS	Sample 1	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	Sample 2	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	Sample 3	-ve	-ve	-ve	-ve	-ve	-ve	-ve
TSB Fertility Test	*S.aureus*	+ve			+ve			+ve
	B.subtilis	+ve			+ve			+ve
	Ps.aeruginosa	+ve			+ve			+ve
	C.albicans	+ve			+ve			+ve
	E.coli	+ve			+ve			+ve
FTM Fertility Test	*S.aureus*	+ve			+ve			+ve
	B.subtilis	+ve			+ve			+ve
	Ps.aeruginosa	+ve			+ve			+ve
	C.albicans	+ve			+ve			+ve
	E.coli	+ve			+ve			
Unopened (negative controls)					-ve			
Positive Control (No SDS) TSB			-ve	-ve	+ve*	+ve**		
Positive Control (No SDS) FTM			-ve	-ve	-ve	+ve*		

* (gram +ve coccus)
** (gram +ve rod)
*** (turbidity - id Staphylococcus)



Trigger Spray Application – Advantages 喷洒装置优点

- Cost effective - all the liquid can be dispensed so eliminating wastage 所有的液体都会被利用
- Large droplets - reduced risk of inhalation
  大液滴—减小气溶胶吸入的危害
- Easy to handle adjustable spray - efficient surface coverage 可调喷嘴
- Environmentally friendly – no propellant no extra disposal costs 环保—不含任何的添加成份

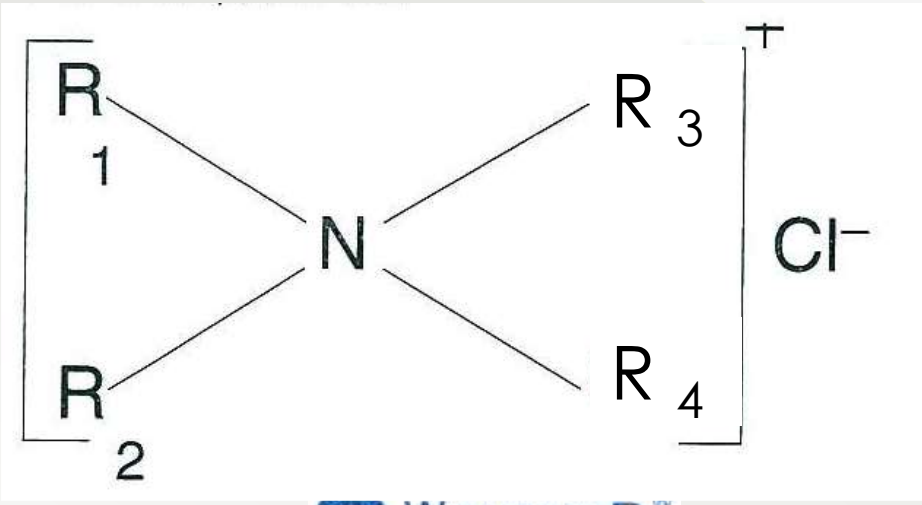
•Disadvantage with a traditional trigger spray is possible contamination of the sterile liquid through “suck back”.
传统喷洒装置一个缺点就是容易由于回吸空气导致无菌消毒液的污染，特别是對於低效的醇類消毒劑

2. Quats 季铵盐类

- Broad Spectrum activity
- EPA registered alkaline (and acid)
- Catronic surfactancy provides excellent cleaning
- Limitation
  - Not sporicidal
  - Not always TB结核 effective
  - Activity affected by incompatible chemical agents

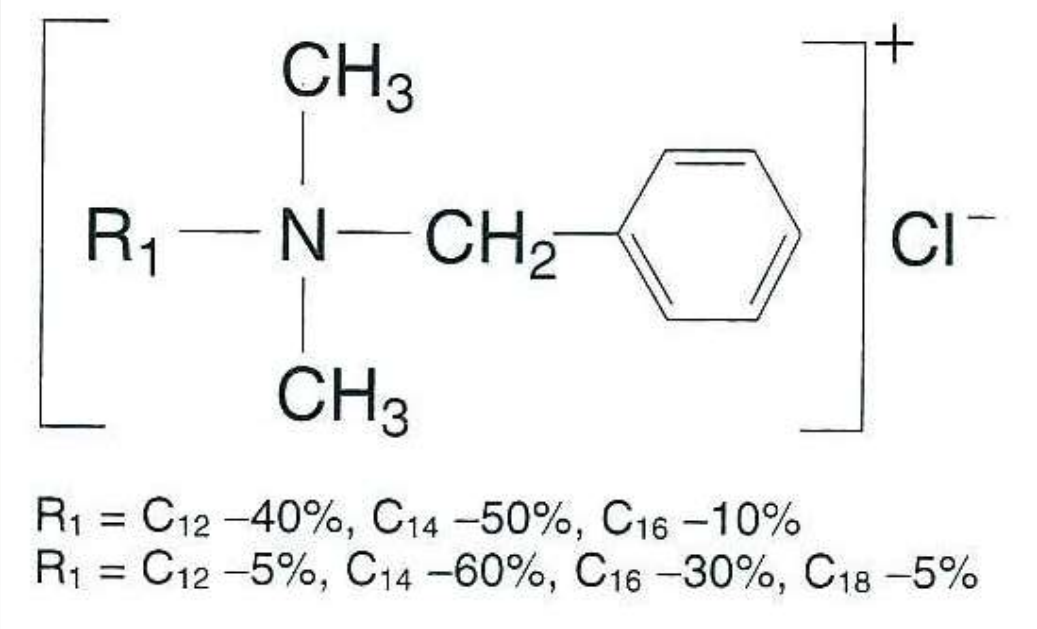
Quaternary ammonia
第四代季铵盐新的化合物性质具有新的清洁消毒功效

- Group of compounds
  - Central atome of natrium 钠原子为中心
  - Quaternarization: cationic 阳离子季铵反应
  - Disinfect action / structure 消毒功能结构



Quaternary ammonia

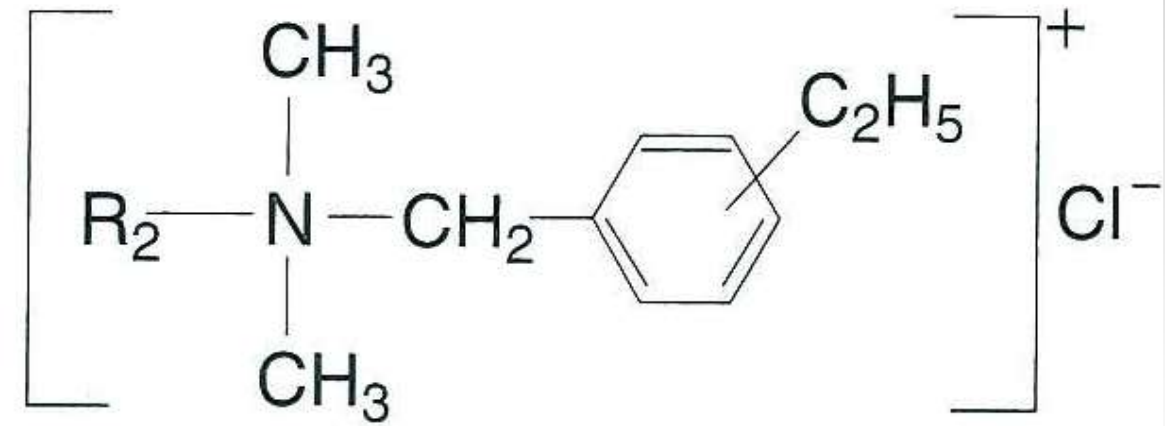
- Benzalkonium chloride:氯化苯甲烃铵；苯扎氯铵
  - 1st generation 第一代双链季铵盐



- Lipophilic 亲脂基
- Spectrum uncomplete
  不广谱
- 不建议作为消毒剂使用因为易造成残留和污染

Quaternary ammonia

- Substituted Benzalkonium chloride:
  - 2nd & 3rd generations 第二三代苯扎铵



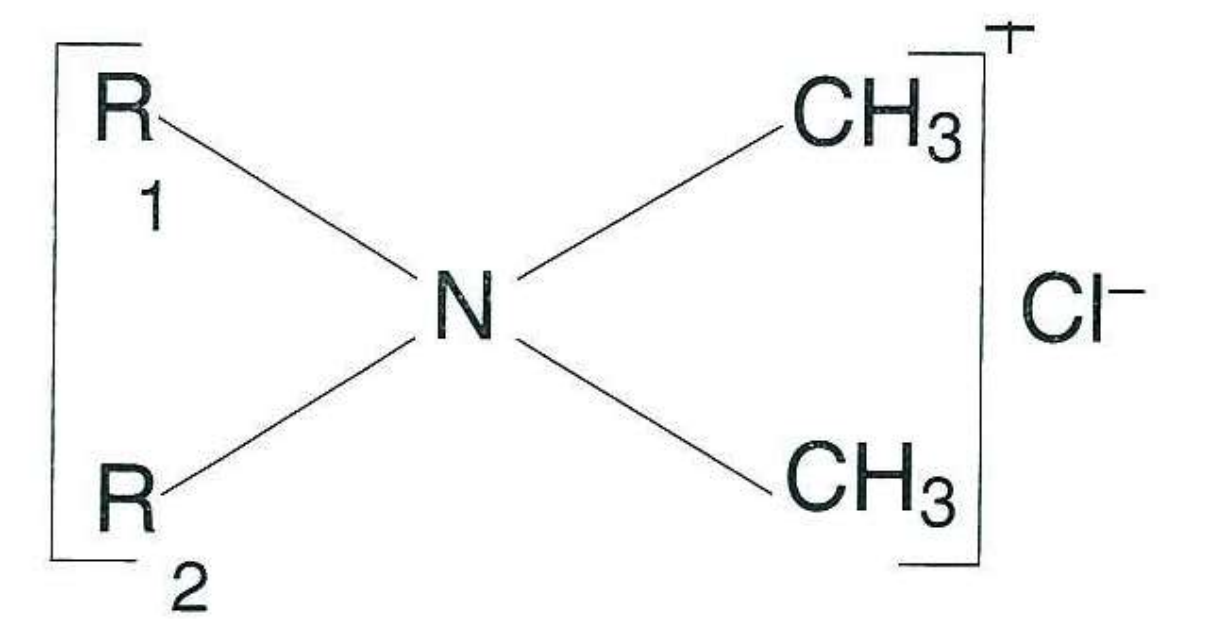
$R_2 = C_{12}$ –50%, C_{14} –30%, C_{16} –17%, C_{18} –3%
$R_2 = C_{12}$ –68%, C_{14} –32%

- Lipophilic
- Spectrum uncomplete

Evolution of the 1st generation towards less toxic and more biocidal compounds相比第一代毒性降低效力增加功效

Quaternary ammonia

- 4th generation: less toxical & more active



Dioctyl 25%, didecyl 25%, octyldecyl 50%

Quaternary ammonia

第四代季铵盐在欧洲广泛作为中效消毒剂，特别是对霉菌有很好的消毒效果，在较低浓度下发挥高效的消毒作用，同时降低毒性和残留

- 4th generation:
  less toxical & more active
  - Acute toxicity
    - D.L. 50 = 1000 to 2000 mg/kg
  - Local toxicity
    - IPC non irritant at the use dose: < 200ppm
    - Not much sensitising

- Not “mutagenous” 不含诱变剂
- Not “teratogenous”不会导致畸形

WINIFRED® Our Talents, Your Solutions

laboratoires ANIOS Le professionnel de la désinfection

Quaternary ammonia

- 4th generation:
  less toxical & more active

- Bactericidal (EN 1040)
  - Pseudomonas aeruginosa: 0.1%
  - Staphylococcus aureus: 0.05%

- Fungicidal (EN 1275) 对霉菌有效！！！！
  - Aspergiluus niger: 0.1%
  - Candida albicans: < 0.005%

- Virucidal: variable according to strains

- Algicidal
  - Approx. 0.005 to 0.020%

Benzalkonium Chloride
Here below publications to illustrate the potential of sensitization & contact dermititis

- http://www.ncbi.nlm.nih.gov/pubmed/22548403
- http://www.ncbi.nlm.nih.gov/pubmed/22385765
- http://www.ncbi.nlm.nih.gov/pubmed/18416759
- http://www.ncbi.nlm.nih.gov/pubmed/11358732
- http://www.ncbi.nlm.nih.gov/pubmed/11233718
- http://www.ncbi.nlm.nih.gov/pubmed/7843962
- http://www.ncbi.nlm.nih.gov/pubmed/7924299
- http://www.ncbi.nlm.nih.gov/pubmed/1839276

SURFANIOS
SURFANIOS CITRON

Detergent disinfectant for floors and surfaces

SURFANIOS
SURFANIOS CITRON

Detergent disinfectant for floors and surfaces.

INSTRUCTION FOR USE

1 Fill a washing bucket and a rinsing bucket with 8 litres of water. **0.25 % dilution:** Pour a 20 ml dose of SURFANIOS in the washing bucket.

2 After a wet sweeping of the room, proceed with cleaning respecting the draw: from the back to the exit (do not rinse surfaces).

3 Rinse and wring the mop before re-soaking in the washing bucket. (the cleaning trolley has to stay in the corridor, outside of the room).

3) CLEANING and DISINFECTANTS CONCENTRATED PRODUCTS

- **SURFANIOS IP**
- **BACTERANIOS SF IP**

- **Blow Fill Seal technology** Aseptic filling
- 15 ml sterile single-doses
- Double bagged
- Gamma radiated
- Concentration :1 to 4 doses / 6 l water
- Box of 15 strings of 8 doses of 15ml.

Laboratoires ANIOS
Le professionnel de la désinfection

COMPOSITION

lecylopropane-1,3-diamine
dammonium chloride (25 mg/g),
ttors, non ionic detergent.

MICROBIOLOGICAL PROPERTIES

Active against	Standards	Contact time
Bacteria	EN 1040, EN 13727, EN 1276, T 72-300 (EMRI), EN 13697 NF T 72-170, NF T 72-190, T 72-300 (L. pneumophila)	5 minutes 15 minutes
Mycobacteria	Mycobacterium tuberculosis (TB)	15 minutes
Yeasts / Moulds	EN 1275 (Candida albicans), T 72-300 (A. niger, A. fumigatus) EN 1650 (C. albicans)	15 minutes 5 minutes
Viruses	HIV-1, BVDV (surrogate of HCV) Influenza virus (H1N1) PRV (surrogate of HBV)	5 minutes 15 minutes 30 minutes

IS FOR USE

v the instructions for use
with European Directive 99/45/CE).
he Safety Data Sheet and the label.
PC.

Ref. 350.129
ch Ref. 350.092
dosing pump of 20 ml Ref. 350.036

Ref. 347.129
ch Ref. 347.092
dosing pump of 20 ml Ref. 347.036

Pavé du Moulin
59260 Lille-Hellemmes - France
Tel. +33 3 20 67 67 67 - Fax : +33 3 20 67 67 68
www.anios.com

非无菌消毒液选购要点

1. 产品成分, MSDS（毒理性测试）及认证
2. 残留验证方法HPLC, TOC是否提供
3. 微生物效力验证AOAC or EU ISO
4. 过滤方法及滤芯材质相容性研究
5. 是否有交替使用方案和清洁方案(相容性研究)
6. 消毒效果及残留的关系(稀释比例)
7. 残留量,是否可以少清洗或者易于清洁,颜色,黏度等等
8. COST=國產一二代季銨鹽產品

3. Phenolics

- TB effective and broad spectrum 消毒效果
- EPA registered
- Anionic/ neutral surfactants provide good cleaning ability 有清洁作用
- Alkaline or acidic formulas available 酸碱
- Limitation 局限性
  - Not sporicidal 不能杀孢子
  - Residues 残留
  - Activity affected by incompatible chemical agents 易被干扰

Problem of compatibility

- Not compatible with 相容性问题
  - Non ionic surfactants 非离子表面活性剂
  - Cationic surfactants 阳离子表面活性剂
  - PEG 聚乙二醇
  - PVPI 碘伏
  - Hypochlorites 次氯酸盐
  - Rubber 橡胶
  - Silicone 硅胶
  - Neoprene 聚丁橡胶
  - …

Safety issue

LVPE / COUNTRIES	Average for 8 hours		Value for 15 min.	
	ppm	mg/m³	ppm	mg/m³
France	2	7,8	4	15,6
Europe	2	7,8		
USA	5			

LVPE: Limit Value for Professional Exposure

The Sporicidal Solution 对细菌孢子的解决方案

Currently used chemical products化学法:
Formaldehyde based 甲醛类
Hydrogen Peroxide & Peracetic Acid
过氧化氢与过氧乙酸
Sodium Hypochlorite (Bleach)次氯酸钠
Stabilised ClO_2二氧化氯

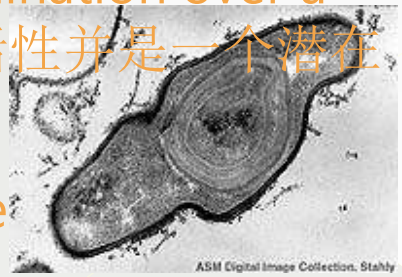
- Dormant state, which some bacteria assume during stress.

  Eg Bacillus sp. Clostridium sp. 细菌在受到外界压力情况下产生的休眠体

- Extremely resistant to destruction by most chemical biocides, heat, UV, radiation, desiccation, etc. 对大部分的化学杀菌剂，加热，紫外，放射和干燥有极强的抵抗能力

- Can remain viable and a potential source of contamination over a long period of time 在很长的时间内仍能保持孢子活性并是一个潜在的污染

- Under suitable conditions will germinate to become vegetative bacteria 在合适的条件下孢子会恢复活性



USP 29 NF-24 <1072> Lists the Effective Sporicidal Agents:

- Aldehydes: Most of them are listed carcinogenic and Mutagenic 大多数醛类致癌引发诱变
- Bleach (HClO): More and more mentioned as potential Carcinogenic and Mutagenic 漂白剂潜在致癌和诱变
- Ozone: Toxic and corrosive 臭氧有毒腐蚀性
- Hydrogen Peroxyde: Sporicide at high concentration过氧化氢是高浓度下的杀孢子剂
- Ethylene Oxide: Toxic EO有毒
- Peracetic Acid: Effective at low concer and listed as a potential **Cold Sterilant**
  过氧乙酸低浓度下就是高效的冷灭菌剂

液体杀孢子剂综述

- A级无菌区一般只能使用IPA或者酒精等低效消毒液，VHP气体又不能频繁使用，所以定期或者穿插使用无菌包装6% H2O2
- 大面积表面高效消毒剂杀孢子剂应该与两种日常中低效消毒剂结合使用，推荐过滤除菌的过氧化氢过氧乙酸，特点高效低浓度经济
- 过氧乙酸+过氧化氢> 纯过氧化氢
- 为保护洁净室材质，液体杀孢子剂一般浓度较低，配合空间气体灭菌使用，频率1-2个月，杀孢子剂无需轮换

H2O2/ Hydrogen Peroxide 无残留

- Sporicidal 6%
- High level deinfection
- EPA registerd
- Limitations:
- Corrosive to soft material
- Precleaning required预清洁影响消毒杀孢子效果
- Temperature sensitive
- May only be a disinfectant, not a steriliant杀孢子剂中效果最弱
- Corrosive to eyes and skin

Premier-WFI Klercide-CR Sterile Biocide C

6% hydrogen peroxide (H_2O_2) blended with WFI

- Sterile filtered into pre-irradiated containers
- 1 litre trigger spray
- 5 litre capped
- Sporicide with no residue for use c critical
- product contact surfaces
- o not require rinsing after u

Shield Medicare
a division of Ecolab

ECOLAB

WINIFRED®
Our Talents, Your Solutions

H2O2/ Peracetic acid blends

- Fast, broad spectrum activity, sporicidal
- Less corrosive than comparably effective oxidizers
- EPA registered
- Safer for personal
- Self sterilizable
- Limitation
  - Corrosive to soft metals
  - Precleaning required
  - Temperature sensitive
  - Pungent odor (vinegar)

过氧化氢过氧乙酸杀孢子剂

Steris
Spor-klenz

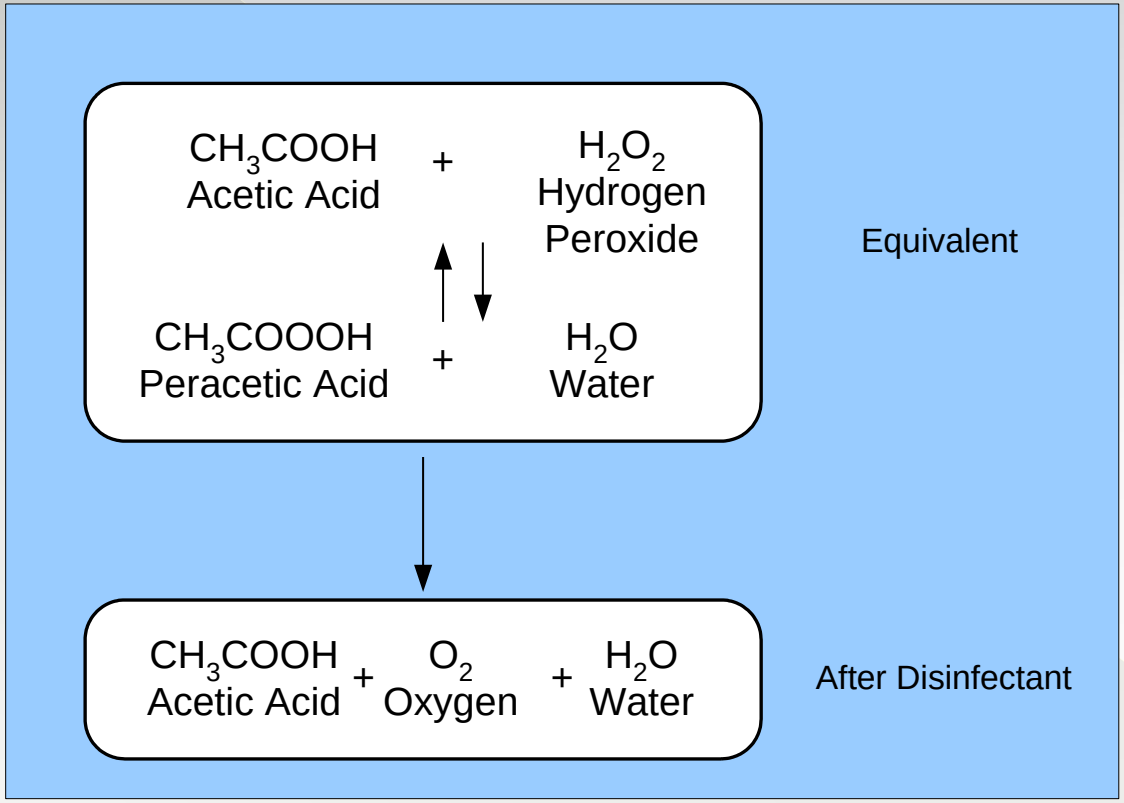
Minncare
Cold
Sterilant

组成成份：过氧化氢＋过氧乙酸

Component：Hydrogen Peroxide 22.0%
Concentrate Peracetic Acid 4.5%

“Sterilant and high-level disinfectant uses which provide flexible options depending on facility needs
-Sterilant 11 hrs 20° C
-Board Spectrum Disinfection 10 min 20° C”

The Chemistry of Minncare® and Actril®



Peracetic Acid Efficiency Compared to H2O2 (Liquid form on B. atrophaeus (subtilis) spores)

对比过氧乙酸和过氧化氢效果（液态中菱缩芽孢孢子）

Contact times	Minncare (1%) 0.2% H202	H2O2 0.2%	H202 (5%)	H202 (10%)
0 Minutes	**2.3×10^6**	2.2×10^6	2.1×10^6	2.0×10^6
15 Minutes	**1.1×10^6**	2.3×10^6	2.0×10^6	2.0×10^6
30 Minutes	**3.0×10^1**	2.3×10^6	2.0×10^6	2.0×10^5
60 Minutes	**< 10**	2.0×10^6	1.0×10^5	< 10
2 Hours	**< 10**	2.0×10^6	< 10	< 10
4 Hours	**< 10**	1.5×10^6	< 10	< 10
6 Hours	**< 10**	1.0×10^6	< 10	< 10
12 Hours	**< 10**	1.0×10^3	< 10	< 10
24 Hours	**< 10**	< 10	< 10	< 10
D-values minutes	**6 minutes**	250 minutes	22 minutes	11
6D	**36 minutes**	1500 minutes	132 minutes	66 minutes

WINIFRED®
Our Talents, Your Solutions

What is the difference between Minncare and Actril Cold Sterilants

结论低浓度过氧乙酸加入过氧化氢，消毒效果大幅提升，腐蚀性刺激性降低

Product	Composition	Usage	Shipping
Minncare	22% Hydrogen Peroxide 4.5% Peracetic Acid	Diluted 32x, 100x, 320x	Hazardous, Ground
Actril	1% Hydrogen Peroxide 0.08% Peracetic Acid	Ready-to-use	Air, Regular

Sodium Hypochlorite (Bleach)

- High level of disinfectant efficiency
- Sporicidal at 600ppm- 1000ppm
- Corrosive to soft metals and Stainless steel
- Limitations
  - Precleaning required
  - Temperature and light sensitive
  - May only be a disinfectant, not a steriliant
  - Safety concern with chlorine gas
  - Corrossive to eye and skin
  - May produce THM in presence of organic material
  - General not EPA registered

Premier Klercide-CR Sterile Biocide E

Sodium Hypochlorite (NaOCl) blended with DI yields 0.5% w/v available chlorine (Cl_2)

- Terminally sterilised by gamma irradiation
- 1 litre spray
- 5 litre capped RTU
- Available as a unit dose concentrate in tablet form (NaDCC)–

Premier Klercide-CR Sterile Biocide S

Shield Medicare
a division of Ecolab

ECOLAB

WINIFRED®
Our Talents, Your Solutions

Rinsing- Residue Removal 残留与清洁

- Do residues support harbor microbial growth 化学残留促进微生物生长
- Do residues inhibit preceding chemistry activity 化学残留抑制消毒和杀孢子效果
- Sticky and opaque surface due to residues 国产季铵盐使用浓度过高，表面变色，变黏

"Facilities must be periodically cleaned to remove any disinfectant residue" USP 29 NF-24 General Chapter <1072> disinfectants and anticeptics

- Rinsing
  - IPA or water
  - Formulated cleaner 残留清洁剂

Premier Klerclean-CR™ Sterile Neutral Detergent 中性无菌去污剂

- 该产品是一种非离子中性，PH＝6.7-7.3，去离子水和脂肪醇乙氧基化合物的混合物，经0.2u过滤，在Class10,000（ISO Class7）净化间进行封装，并经不低于25Kgy Gamma射线照射。保质期2年。

- 适用于具有严格要求的净化间，隔离间，生产设备和所有非渗水的表面。尤其对于溅有油腻和粘性物质的表面或者是一般养护之后的清理有效。

- 采用无菌防护递送装置的专利技术及可调式喷嘴在使用过程中形成封闭系统，以确保内容物的完整性。该产品备有1升即开即用喷雾器装，对于大面积有50ml浓缩装，然后用合适品质的水进行稀释。

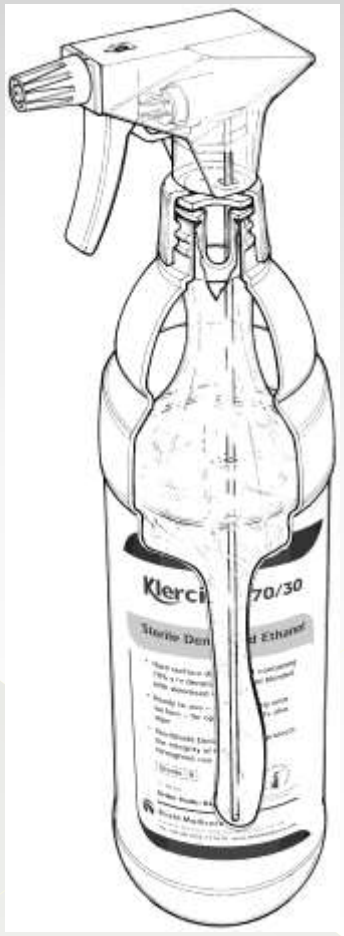
Shield Medicare
a division of Ecolab

ECOLAB

Your logo here
WINFRED®
Our Talents, Your Solutions

手消毒与手套消毒HAND GEL

- 更衣间戴无菌手套前的手清洗消毒无需无菌消毒液，但需要对皮肤亲和性好
- 对无菌手套的消毒和洁净室无菌消毒剂没有区别
- 手清洗培训和检验



WINIFRED®
Our Talents, Your Solutions

Space air and fogging **sterilization**
空间消毒灭菌

Wet fog

Dry fog

Vapor/air phase

Room Space

Electronic Compress air

Strategy

- Cleanroom Fog& Vapor products
  - 闪蒸法 Steris VHP BIOQ （适合A级无菌小密闭环境）
  - 文丘里效应压缩空气Minncare Dry Fog system （适合大空间ABC级环境）
  - 醛类熏蒸方案 （有条件的逐步取代）
  - 其它湿雾，超声波发生器 （适合实验室等小密闭空间）

  - 空间灭菌要素：气体，验证，残留，腐蚀

甲醛消毒的问题

VHP, HPV, VPHP

- Multinational Company
  Sterilization & Disinfection Equipment + Sterilants
- Pure (30%) H_2O_2 Vaporization
- Only Vapor Phase (> 1.000 ppm)
- Room Volume: Liminted
- Required ducting installation in premises
- Price: $50,000 - $125,000

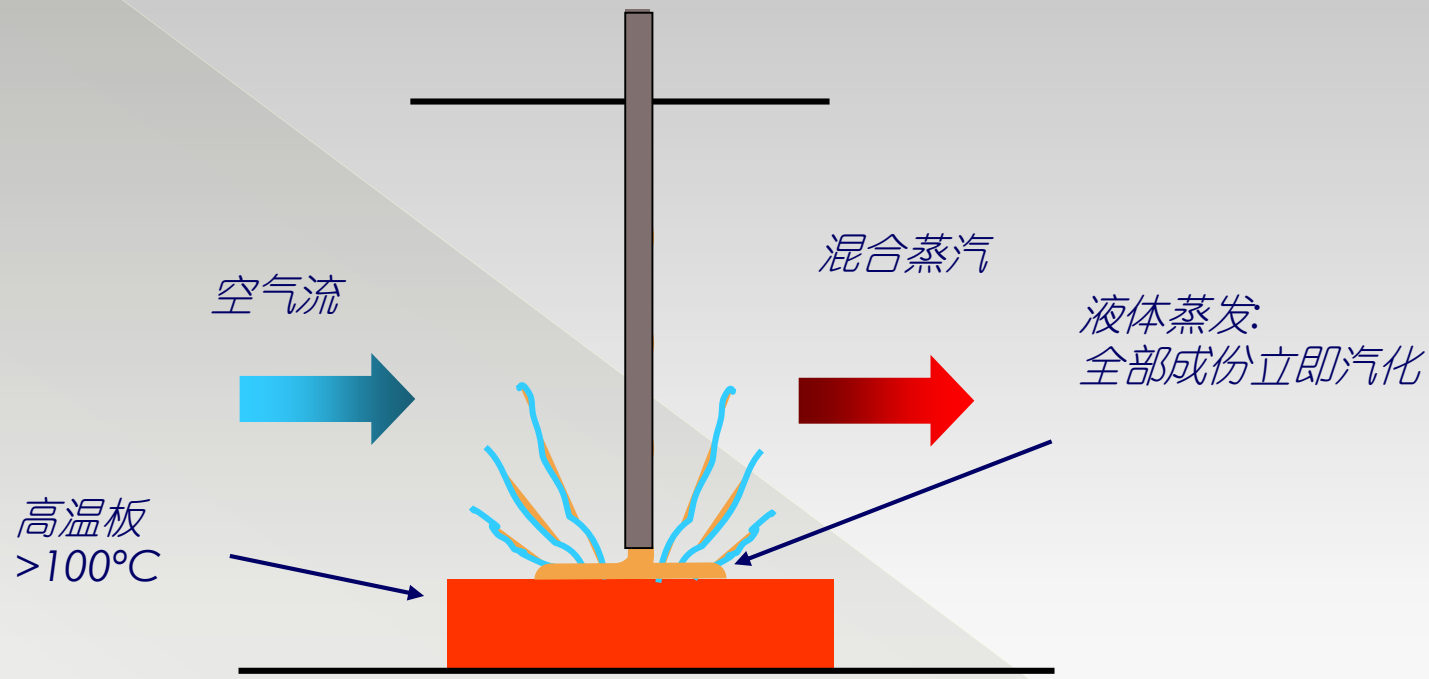
WINIFRED®
Our Talents, Your Solutions

amira
Innovative solutions for life sciences

闪蒸过氧化氢系统(如*Bioquell*和*Steris*):

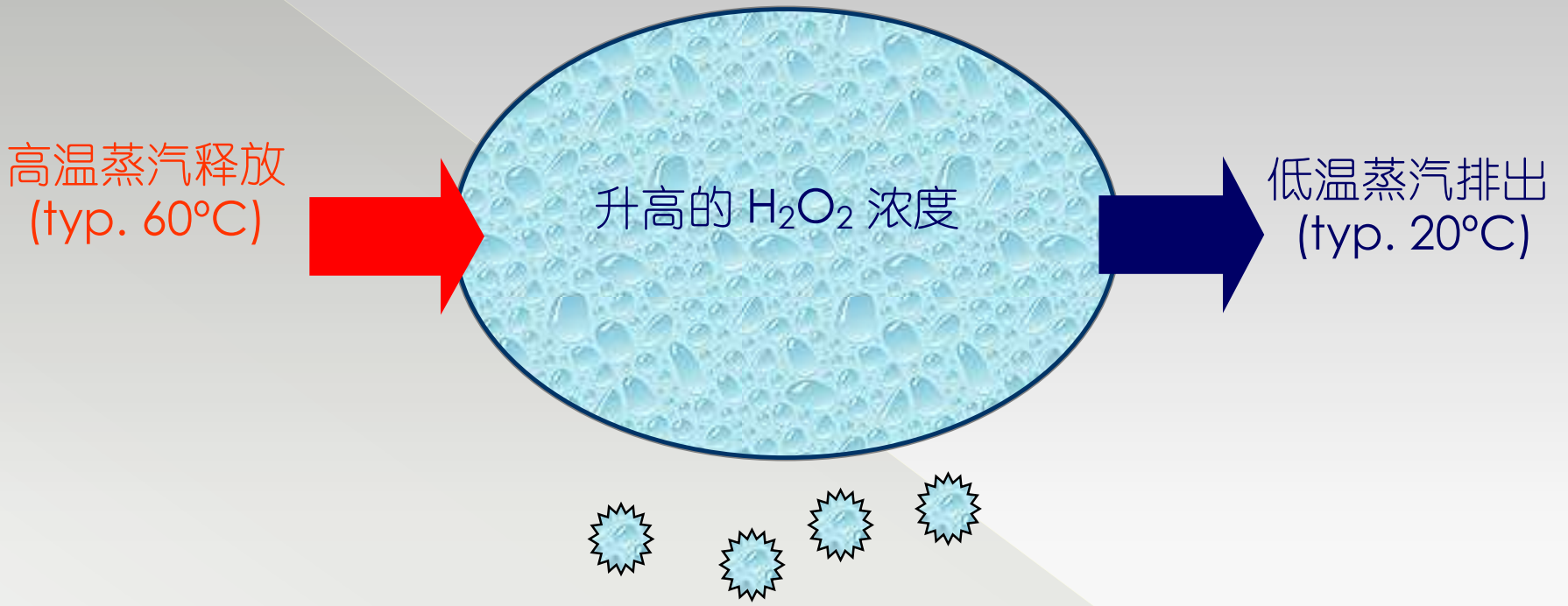
- 使用异常复杂
- 系统脆弱，需要经常和复杂的维护
- 一台机器往往不能覆盖超过500立方米的空间
- 需使用高浓度药液(30至35%)
- 尤其是对喷漆表面有特殊风险，无法风险评估及老化试验

液体蒸发



获得比平衡状态更高的H2O2 蒸汽浓度

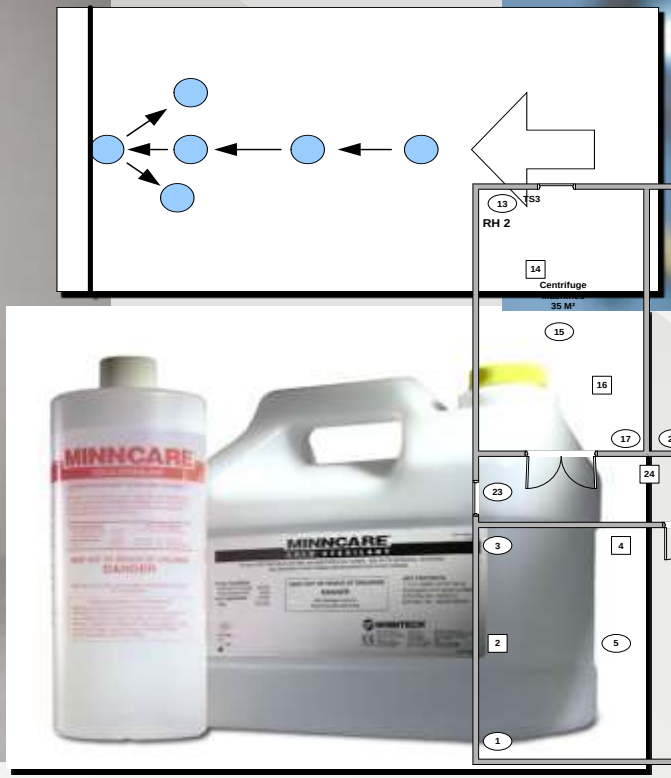
微冷凝的形成

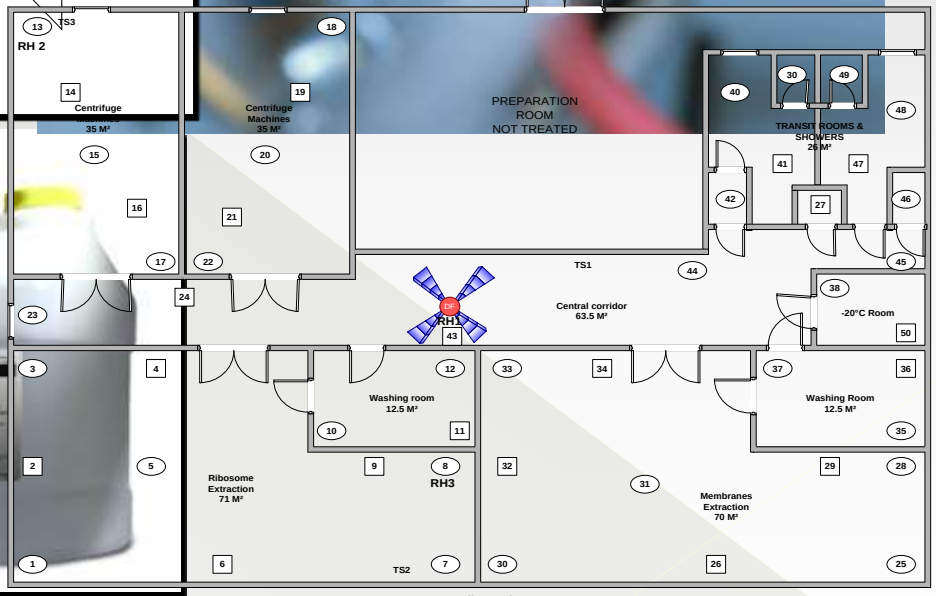


微冷凝的形成

- 达到杀菌所必需
- 微冷凝过程经常是看不见的

MINNCARE DRY FOG SYSTEM



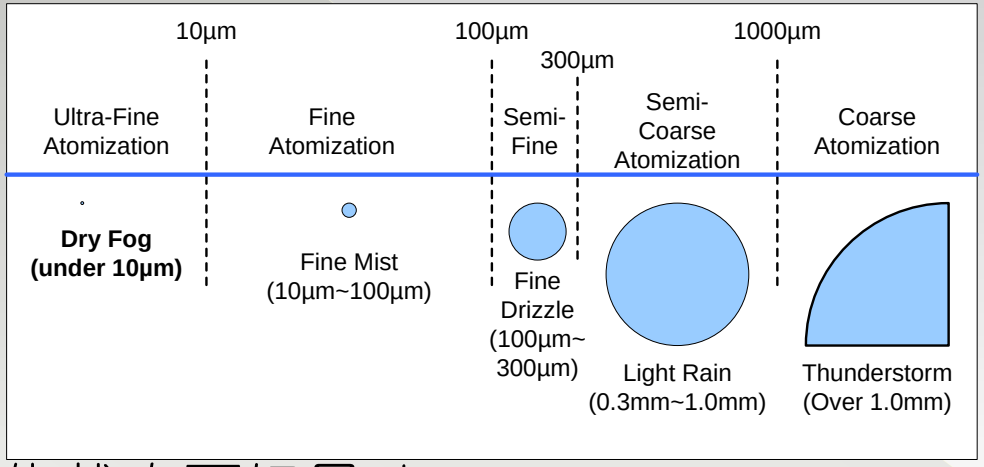


WINIFRED®
Our Talents, Your Solutions

空间灭菌需要考虑

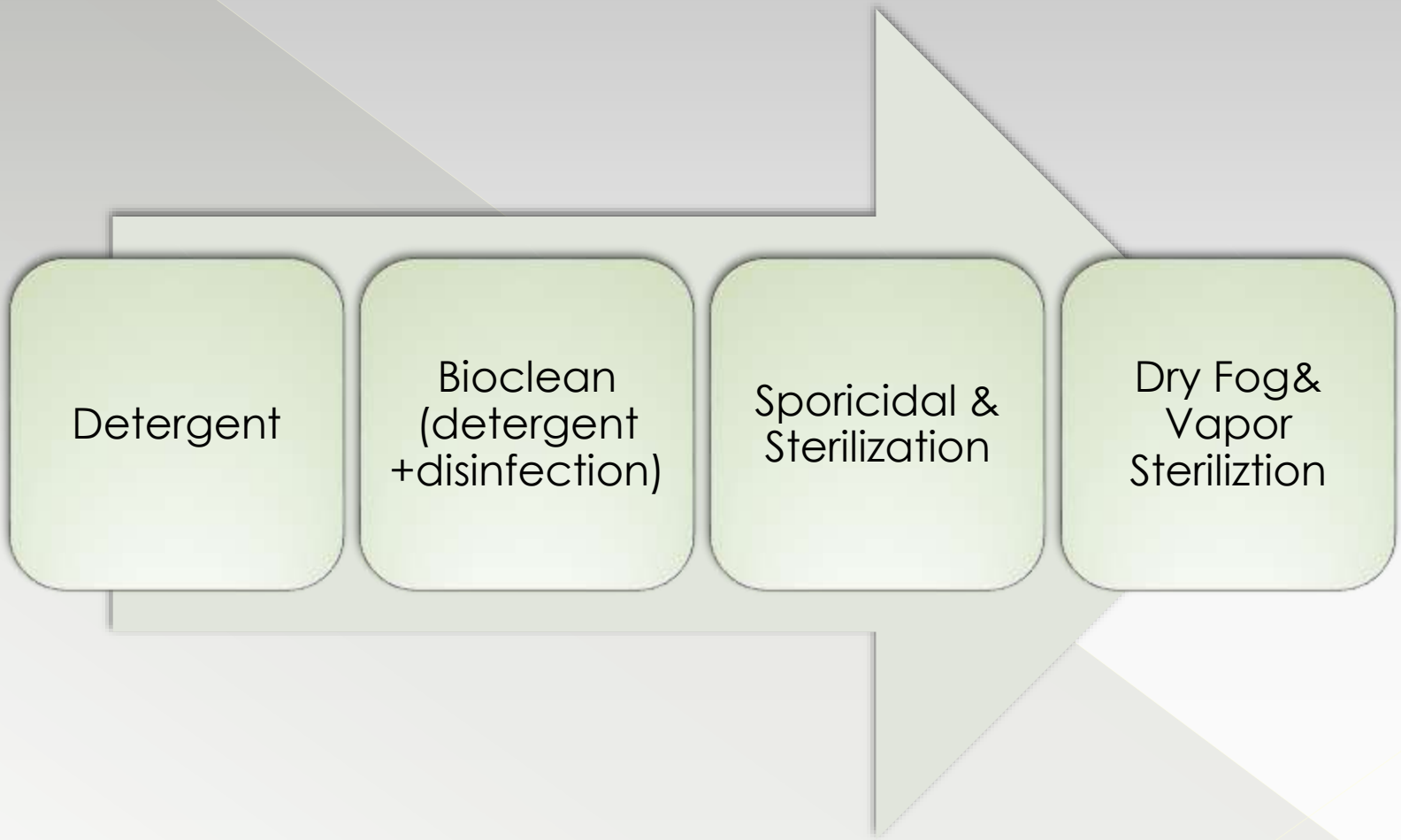
- 日常环境清洁消毒及杀孢子剂方案的选择直接影响空间灭菌的频率
- 频率应该尽量低，系统采用前必须考虑相容性，做必要的相容性挑战实验
- 小型密闭空间和大型洁净区应采取不同的方案和理念：
- ✓ 环境是否和产品直接接触，是否易于清洁残留
- ✓ 环境需要达到STERILIZATION的灭菌或者只需要高效消毒
- ✓ 采用的空间气体灭菌剂或者杀孢子剂本身是否洁净
- ✓ 采用的表面高效消毒剂（不是灭菌）本身是否无菌
- ✓ 大环境空间灭菌考虑成本，服务，验证，不会造成二次污染
- ✓ 验证建议LOG4与LOG6的生物指示剂作为最终标准，辅助过程参数

小型空间灭菌设备气化效果差适合用于密闭小房间局部气化大部分属于液体状态



气化状态不好导致：

- 腐蚀性增加，设备数量增加，工作复杂
- 过氧化氢和过氧乙酸在液态状态下灭菌及消毒作用均下降，需增加灭菌时间
- 可通过CONTACT TIME判断是否是真正气体灭菌，一般在一小时以内，超过2个小时都是液体作用



消毒剂验证及确认 定义

VALIDATION

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

QUALIFICATION

Action of proving that any equipment works correctly and actually leads to the expected results. The word *validation* is sometimes widened to incorporate the concept of qualification.

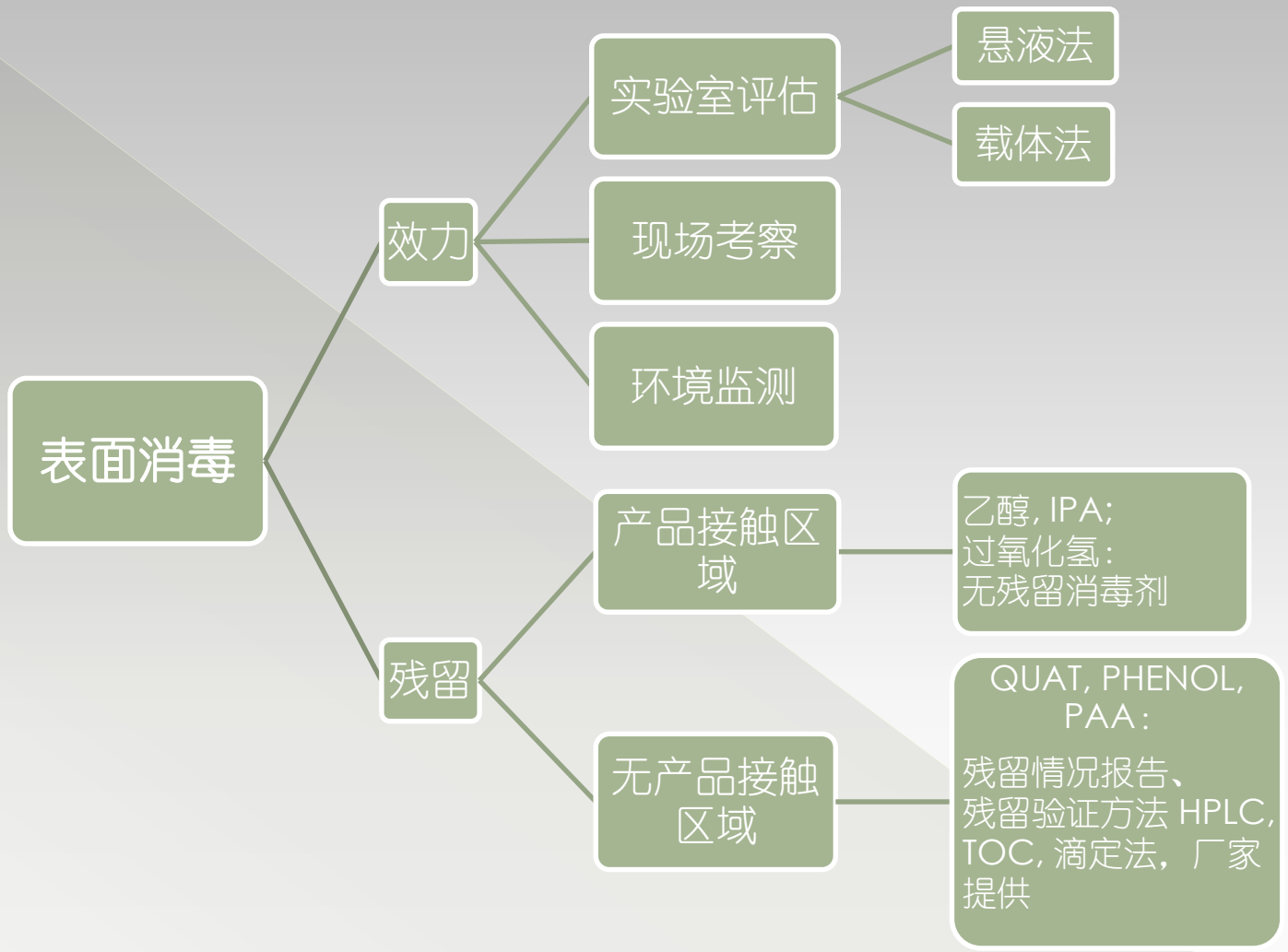
对清洁剂消毒剂进行效力确认QULIFICATION,
对清洁步骤进行验证VALIDATION,包括消毒的步骤

清洁验证是法规强制要求，而不是根据GMP对消毒剂进行验证，而是效力确认

What is Validation of a Disinfectant?
什么是消毒剂验证？步骤如下：

论证选定的消毒剂可以减少环境的生物负载水平到一个可接受的限度

1. Screening tests (various disinfectants/different concentrations) 选定成分和浓度
2. Challenge tests using cleanroom surfaces and EM isolates 介质或表面挑战实验
3. Field Trial - Study of organisms isolated (frequency and type) before and after implementation of a new cleaning/disinfection regime 消毒前后环境监控对比



Directives and Guidance

USP36-NF31 Chapter <1072>

“The selection of suitable disinfectants and the verification of their effectiveness in surface challenge testing is critical in the development of a cleaning and sanitization program.”选择合适的消毒剂并确认其表面消毒效力对洁净室的消毒清洁方案非常关键

“To demonstrate the efficacy of a disinfectant within a pharmaceutical manufacturing environment, it may be deemed necessary to conduct the following tests:制药生产环境对消毒剂效力的测试以下这些实验非常必要:

(1) use-dilution tests… 菌悬液测试

(2) surface challenge tests… 表面测试

(3) a statistical comparison of the frequency of isolation and numbers of microorganisms isolated prior to and after the implementation of a new disinfectant.” 对一个消毒剂使用前后微生物的出现频率和数量的统计对比

“It is prudent to augment the daily use of a bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent.” 每周或者每月交替使用杀孢子剂(明确)

Regulatory Requirements

USP <1072> Antiseptics and Disinfectants

Provides some very useful theoretical and practical information regarding the use and testing of disinfectants in a pharmaceutical setting 消毒剂使用和测试的理念和实施建议

The test design should take into account: 测试应考虑

- Representative model organisms from standard cultures

  标准菌株中的代表菌株
- Common environmental isolates 一般环境野生株
- Predominant surfaces in the cleanroom 洁净室中的常见表面材料
- Performed under “clean” conditions 在洁净的环境中进行验证

Types of Disinfection Efficacy Test

There are 3 basic types of disinfectant efficacy testing:

- Suspension Test 悬浮液测试
- Surface Tests 表面测试
- Carrier Tests 介质测试

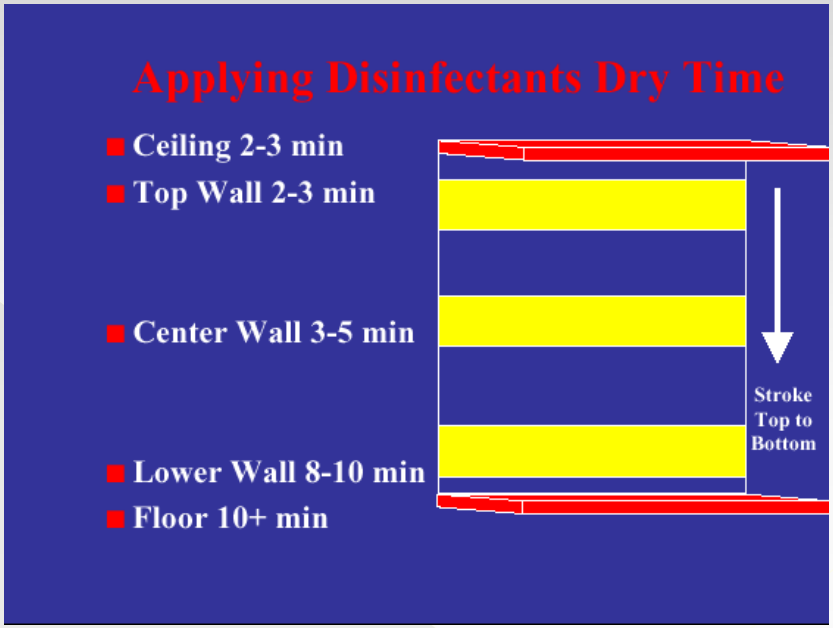
All tests involve exposure of a test inoculum to a biocide under controlled conditions. The biocidal activity is a measure of the difference between the test inoculum count and the number of surviving organisms. 所有测试都是消毒剂和培养液暴露在受控环境中，然后测试这过程前后的微生物计数变化

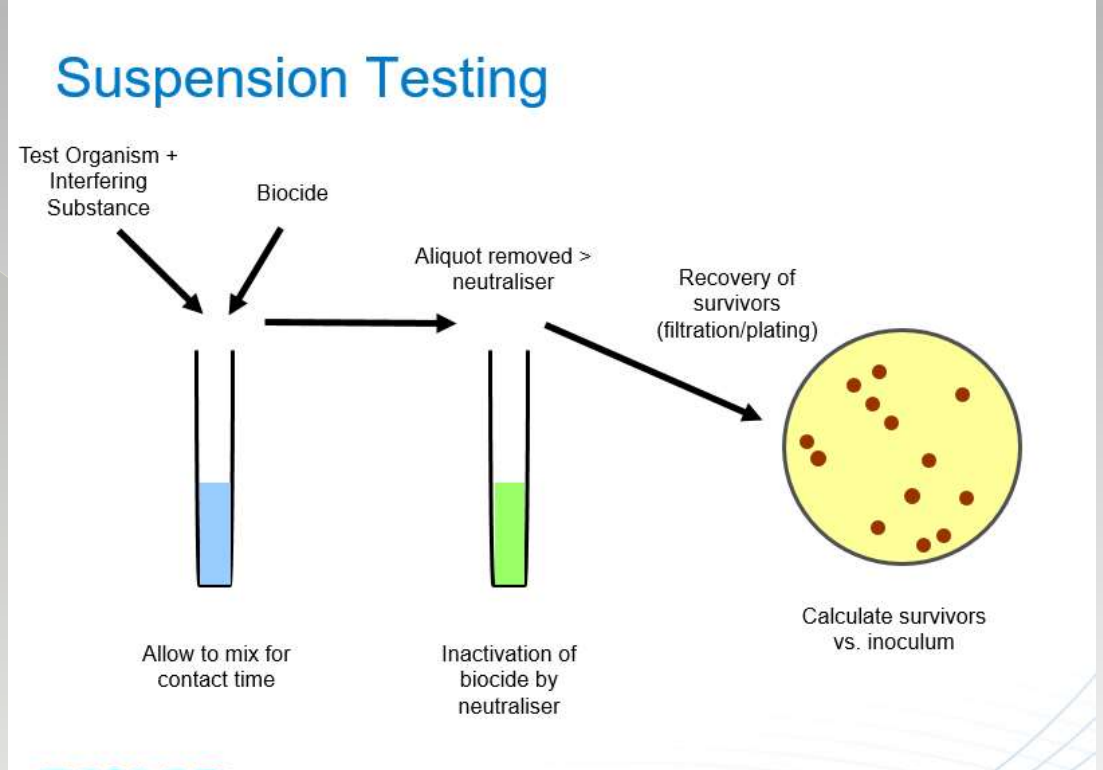
Each test type has advantages and disadvantages and may be more or less suitable depending on the intention of the testing 每种方法都各有优缺点，是否适合主要取决于测试的目的

The CEN Standards (Industrial Area)

CEN TC 216: European Committee for Standardisation Technical Committee 216 (1991)

- **Phase 1** – Basic suspension tests 一般悬浮菌测试 no challege
  - EN 1040/1275/14347
- **Phase 2，模拟实际**
- **Step 1** – Quantitative suspension tests 定量悬浮菌测试
  - EN 1276/1650/13704/14476
- **Step 2** – Surface test and hand wash/rub methods 表面和洗手测试
  - EN 13697/1499/1500
- **Phase 3** – Field tests under practical conditions 模拟环境实地测试





- Simple tests, easy to perform, useful for screening 初选简单，能够准确、规范的对所考察的消毒剂进行微生物效力的横向对比。
- The biocide is diluted as part of the test, by the addition of the bacterial suspension 消毒剂和菌悬液混合
- The amount of inoculum is known 菌量已知
- High degree of reproducibility due to good mixing between the suspension and biocide 接触混合充分重现性好
- Can be a poor predictor of how the biocide will perform practice (i.e. on surfaces) 不实际

Phase 2, Step 1 – Quantitative Suspension tests 定量悬浮菌测试

- Take into account environmental parameters 考虑环境参数
  - Water hardness 水的硬度
  - Organic soiling有机污染干扰物

- Simulated “Clean” and “dirty” conditions using Bovine Serum Albumin (BSA)- Clean 0.03% 使用BSA模拟洁净和污染环境，洁净的是0.03%

- Pass criteria: 5 log reduction for bacteria, 4 log reduction for fungi and 3 log reduction for spores

  通过标准：细菌log5，真菌log4，孢子log3

Standard Organisms used in Industrial Methods 工业标准菌株

- EN 1276/EN 13697 Bactericidal细菌类
  - *S. aureus* ATCC 6538 金葡
  - *E. hirae* ATCC 10541 希拉肠球菌
  - *P. aeruginosa* ATCC 15442 绿脓
  - *E. coli* ATCC 10536 大肠
- EN 1650/EN 13697 Fungicidal 真菌类
  - *C. albicans* ATCC 10231 霉菌白念
  - *A. brasiliensis* ATCC 16404
- EN 13704 Sporicidal 细菌芽孢
  - *B subtilis* ATCC 6633 Spores 枯草

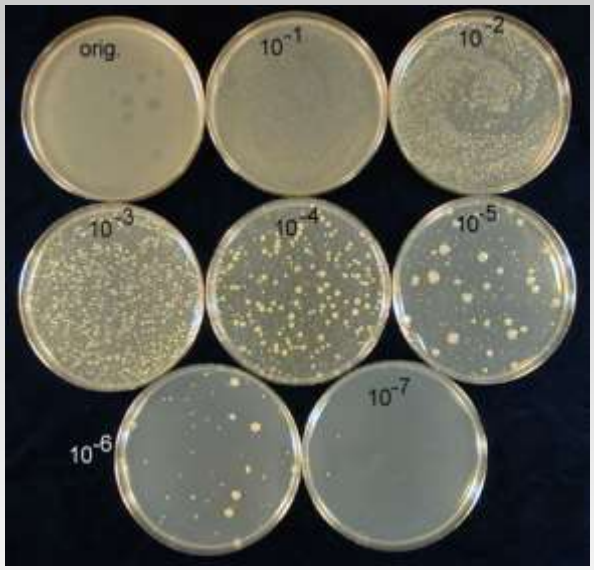
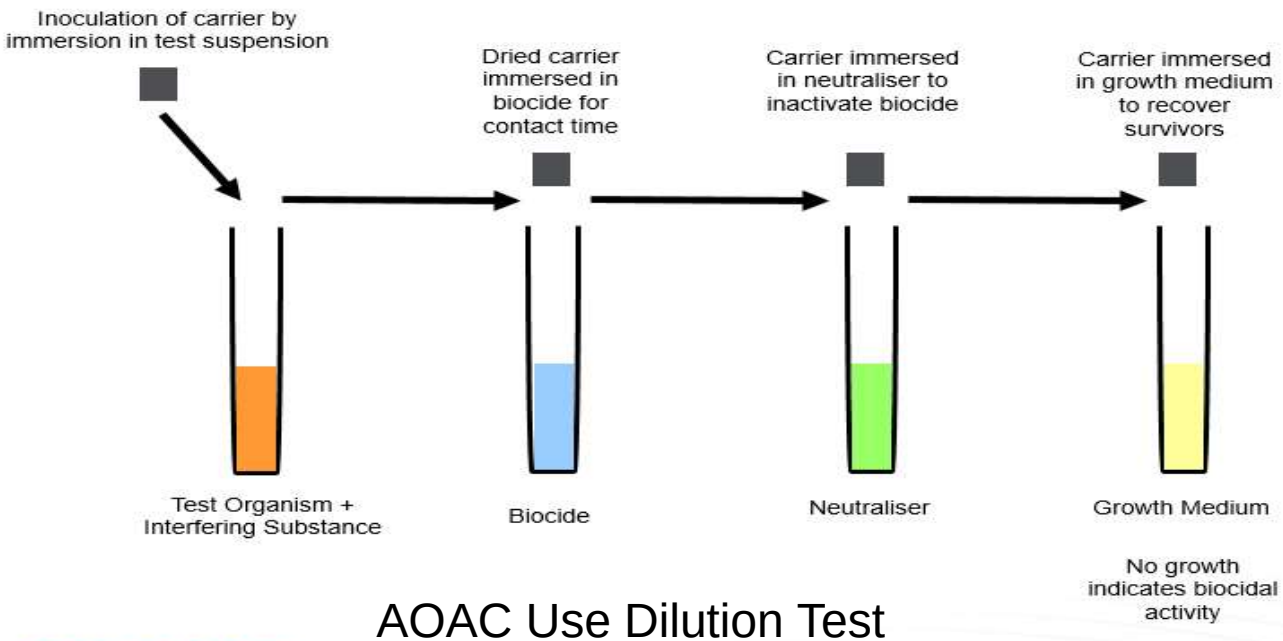


Table 5. Typical Challenge Organisms

AOAC Challenge Organisms	Typical Environmental Isolates
Bactericide: *E. coli*, ATCC 11229; *S. aureus*, ATCC 6538; *P. aeruginosa*, ATCC 15442	Bactericide: *M. luteus*, *S. epidermidis*, *Coynebacterium jeikeium*, *P. vesicularis*
Fungicide: *C. albicans*, ATCC 10231 or 2091; *Penicillium chrysogenum*, ATCC 11709; *A. brasiliensis*, ATCC 16404	Fungicide: *P. chrysogenum*, *A. brasiliensis*
Sporicide: *B. subtilis*, ATCC 19659	Sporicide: *B. sphaericus*, *B. thuringiensis*

Carrier Testing



AOAC Use Dilution Test
AOAC Sporicidal Carrier Test

- By varying the biocide concentration and contact times, a potentially active concentration-time relationship can be determined 确定消毒剂浓度和接触时间
- The amount of inoculum dried onto the carrier is unknown 接种量未知
- The number of survivors is usually not constant 接到载体后数量不稳定
- Due to this variability a high number of replicates is required (e.g. AOAC In-use Dilution method requires 72 individual carriers to be tested for one organism at one biocide concentration) 所以需要做很多的样本
- Does not reflect how the biocides are used in practice 也偏离实际情况

Observed Practices 无菌生产监控

For sterile drug manufacture:

- Surface/coupon testing is performed 表面测试
- Most commonly encountered surfaces included

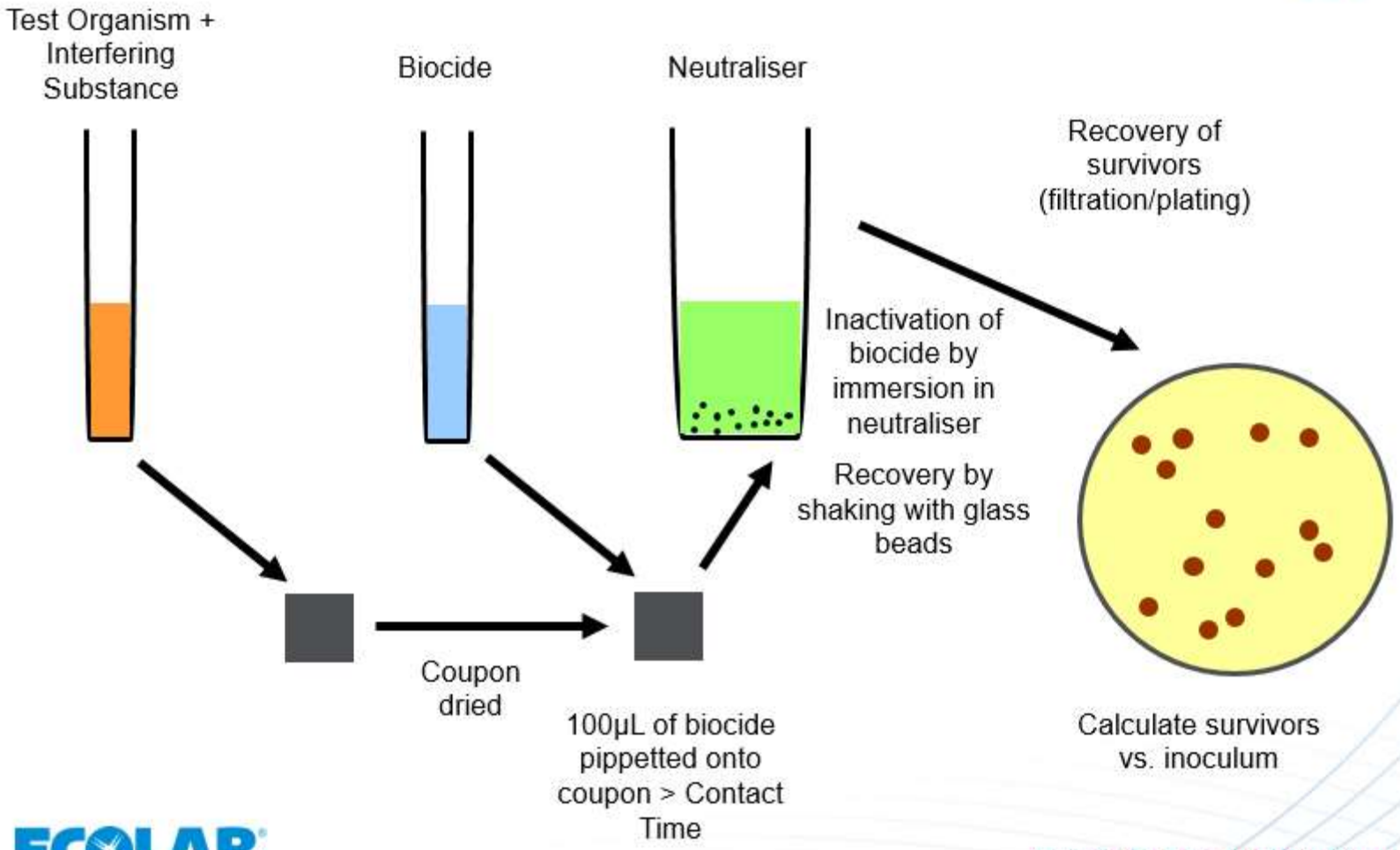
  常见表面材质
- Organism test panel includes in-house isolates

  环境分离菌株

Phase 2, Step 2 – Quantitative Surface Test (EN 13697) 定量表面测试

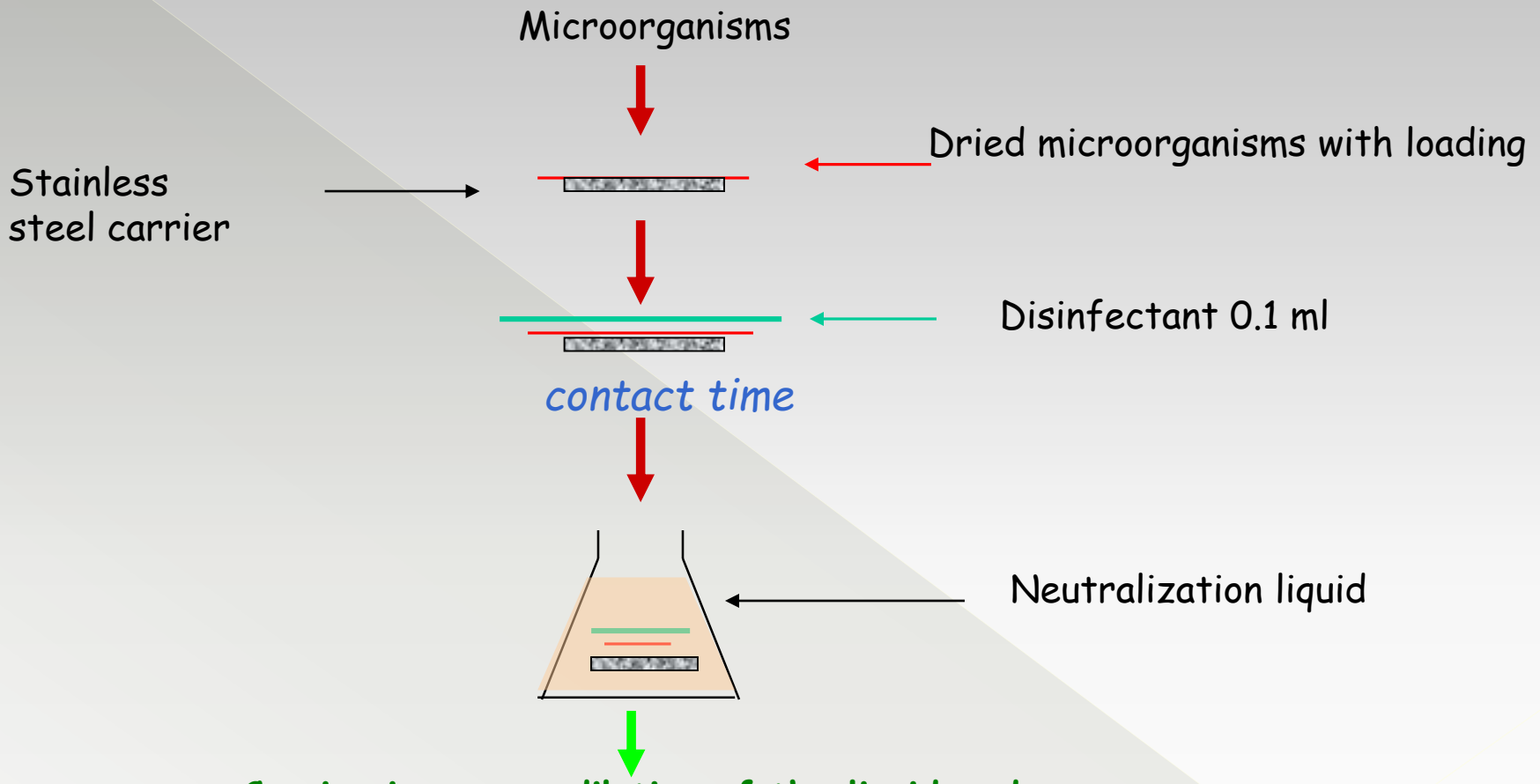
- Simulates practical in-use conditions as far as possible尽量模拟实际环境
- Organisms dried onto a stainless steel surface prior to the application of the disinfectant and recovery　在喷洒消毒剂和培养前微生物在不锈钢介质表面风干
- Is performed under “Clean” OR “Dirty” conditions　根据环境选择洁净或者非洁净的环境测试
- Uses the same organisms as EN 1276/1650
- Pass criteria: 4 log reduction in 5 minutes for bacteria, 3 log reduction in 15 minutes for fungi 通过标准：细菌4分钟log4，霉菌15分钟log3
- No provision in the surface method or acceptance criteria for testing bacterial spores 细菌孢子表面测试没有统一标准

Surface Testing



ECOLAB

Principle of a carrier test EN 13697



Surface Testing 表面测试

- The number of survivors when treated with water is compared to the number of survivors when treated with biocide = Log Reduction 对比消毒剂和水处理的LOG变量
- The amount of inoculum dried onto the carrier is known介质上的接种量已知
- The amount of biocide used is known 使用的消毒剂量已知
- Reflects how the biocides are used in practice (organisms dried onto a surface, surfaces wetted with biocide and allowed to dry, the in-use dilution of biocide is used) 可模拟消毒剂使用实际情况（微生物在表面干燥，表面用消毒剂湿润，可以风干）
- EN 13697 – Quantitative Surface Test for bacteria and fungi， NOTE: there is currently no approved surface test method for sporicidal activity

Points to Consider – Acceptance Criteria
通过限度需考虑因素

The standard methods were not designed for cleanroom disinfectants – a lower log reduction than that specified by the standards may be acceptable in practice. Acceptance criteria should be set accordingly: 标准方法不是专为洁净室消毒剂设计的，所以相比标准接受限度低的结果根据实际环境监控数据可以降低，标准如下：

EN 13697 (Surface)

- Fungi - 3 log
- Bacteria - 4 log

EN 13704 (Suspension)

- Spores - 3 log

USP <1072>

- Bacteria - 3 log
- Spores - 2 log

Points to Consider – Acceptance Criteria

USP <1072> "*The disinfectant efficacy test must have realistic acceptance criteria*":
USP: 消毒剂效力测试要设定现实的通过标准，适当降低原因：

Reduced acceptance criteria are permitted because:

- Disinfectants are less effective against the high numbers of organisms used during testing than against the low numbers expected in a cleanroom environment洁净室环境微生物数量很低，所以消毒剂效力相比微生物数量很高的测试时强
- Stressed environmental organisms are not easier to kill than the cultures using in testing 微生物在测试的不利环境下变得更难杀
- In reality disinfectants are applied by wiping/moping which physically removes organisms enhancing the "kill"* 实际消毒过程消毒剂使用中有擦拭和清洁的机械作用，加强了杀菌效果

Points to Consider – Test Controls

Each of the different efficacy tests will include the following controls: 效力测试过程中的控制

- Control to check that the test conditions are not lethal to the test organisms (i.e. that the organisms will not die anyway without biocide contact and cause a false positive result) 测试环境不会对微生物致死（微生物如果没有接触到消毒剂是不会就杀死了导致假阳性）
- Control to check that the neutraliser is working effectively 监控中和剂以下两点
  - 毒性试验：证明中和剂不会影响微生物的生长
  - 效力试验：证明中和剂能消除消毒剂的抑菌性，具有足够的中和效力

Technical Report

DATE OF ORIGINAL TEST WORK:

January 2016

DOCUMENT No: **TR1601R**

TITLE: **Neutralization Study of Microbiological Media Using Ecolab Contamination Control Products**

Table 1: Test Organisms

Test Strain	ATCC Number
Pseudomonas aeruginosa	9027
Bacillus subtilis	6633
Staphylococcus aureus	6538
Candida albicans	10231
Aspergillus brasiliensis spores	16404

ble 2: Culture Media

me	Supplier	Article Number	Lot Numbe
A w/lecithin, Polysorbate 80, dium thiosulphate, L-Histidine	Oxoid (Thermo Scientific)	P05510D	1653104
A contact + LT-ICR eipha ref 2284e)	Merck Millipore	1.46195	133806
A contact + LT-ICR eipha ref 2284e)	Merck Millipore	1.46195	134765
IR Con TS 1.6% Agar L/T db	Cherwell Laboratories	103153	1508253
A contact + LTHTh – ICR eipha ref 2283e)	Merck Millipore	1.46231	135660
unt – Tact 3P Irradiated 55mm tact plates	Biomerieux	43691	10041711

ble 3: Disinfectant

infectants	Test concentration	Batch

Points to Consider – Soiling 污染

- The presence of organic soiling can reduce the efficacy of a biocide 有机污染物会降低消毒效力
- “Clean” and “dirty” conditions may be simulated by adding BSA to the test culture 通过加入BSA到培养基来实现
- EN Norms include some interfering substance in testing of all disinfectants. “Clean” conditions more accurately reflect level of soiling of cleanroom surfaces EN介绍了一些测试消毒剂干扰污染的物质，洁净环境更符合洁净室表面环境

  “Clean” conditions = 0.03%

  “Dirty” conditions = 0.3%

Points to Consider – Acceptance Criteria

The log reduction obtained will be impacted by the starting inoculum.
In both examples below a log 2 reduction is achieved, but the actual number of organisms killed is very different: 实际洁净区内初始接种量不要太高

- TEST A
  - Test inoculum: 1 X 10^7cfu
  - Survivors: 1 X 10^5cfu
  - Log reduction: 2 log
  - Organisms killed: 9.9 x 10^6 cfu

TEST B
Test inoculum: 1 X 10^5cfu
Survivors: 1 X 10^3cfu
Log reduction: 2 log
Organisms killed: 9.9 x 10^4 cfu

- Temperature： The efficacy of biocides is temperature dependant. Standard test methods are conducted at 20° C. Use of biocides at lower temperatures may require longer contact times (e.g. in refrigerated store rooms etc.).低温时长
- Water for Dilution of Biocide Concentrates：The EN Norms use “water of standard hardness”. This should be substituted for the water which will be used in practice (e.g. WFI, DI, PWTR etc.) 替换为实际用水
- Test Surfaces：Surfaces must be non-porous. Porous surfaces will soak up the test suspension/biocide so that the test conditions can not be adequately controlled. In addition, porous surfaces are not appropriate for a cleanroom environment 非孔表面

Field Trials

The equivalent of “PQ” testing of disinfectants.

- Verifies that the cleaning agents/disinfectants, frequencies and method of application are appropriate
- Ideally conducted under worst case conditions (e.g. after shut-down/break in asepsis)
- A baseline is established prior to and then during implementation of the new regime using intensive EM* sampling.
- Statistical evaluation of the EM data before and after implementation of the new regime (results should be equivalent or better)
- * Contact plates should contain validated neutralisers appropriate for disinfectants being used
- ➨ 模拟最糟糕的情况，如空调系统停机等，消毒前后进行取样对比微生物数量变化。
- ➨ 较为方便的方式：在污染严重区域如更衣间、清洁间等做现场考察
- 消毒剂及相应的清洁方法正常使用后的日常监测。
- ➨ 经常回顾监测数据，有助于评估消毒剂的使用效果，以及洁净间微生物的季节性波动。

Requirement for Re-validation 重新验证

Validation is not a one-off exercise. Re-validation should be considered when there is: 消毒剂验证不是一劳永逸的

- A significant change in the number and/or type of organisms identified (efficacy of current biocides against any new predominant organisms should be established) 发现新的微生物(对现有消毒剂效力再验证)
- Change to the predominant surface types in the cleanroom: e.g. refurbishment, new equipment (efficacy of current biocides on new surfaces should be established) 环境表面变化，例如重新粉刷喷涂表面，引入新设备等
- Change to the formulation of the biocide (requirement for full re-validation should be considered) 消毒剂成分改变

Questions and Answers

- .
- .
- .

- Thank you !

- 李铁林
- Winifred International Technology Ltd.
- EMAIL: thomas@winifred-hk.com
- Tel: 0086-022-23787898-621 Fax: 0086-022-23787896
- Mobile Phone: 0086-13370336099
- Website: www.winifred-hk.com/pharma/