GQS cGMP consultants

欧盟GMP无菌附录更新思考：厂房设施的新挑战
EU GMP Annex 1 Updating thinking: New challenge of facility

Biopharm GMP and Engineering Consulting
生物制药GMP及工程咨询

-Conceptual Design 概念设计咨询
-Q&V Consulting 确认及验证咨询
-QMS Consulting 质量体系咨询

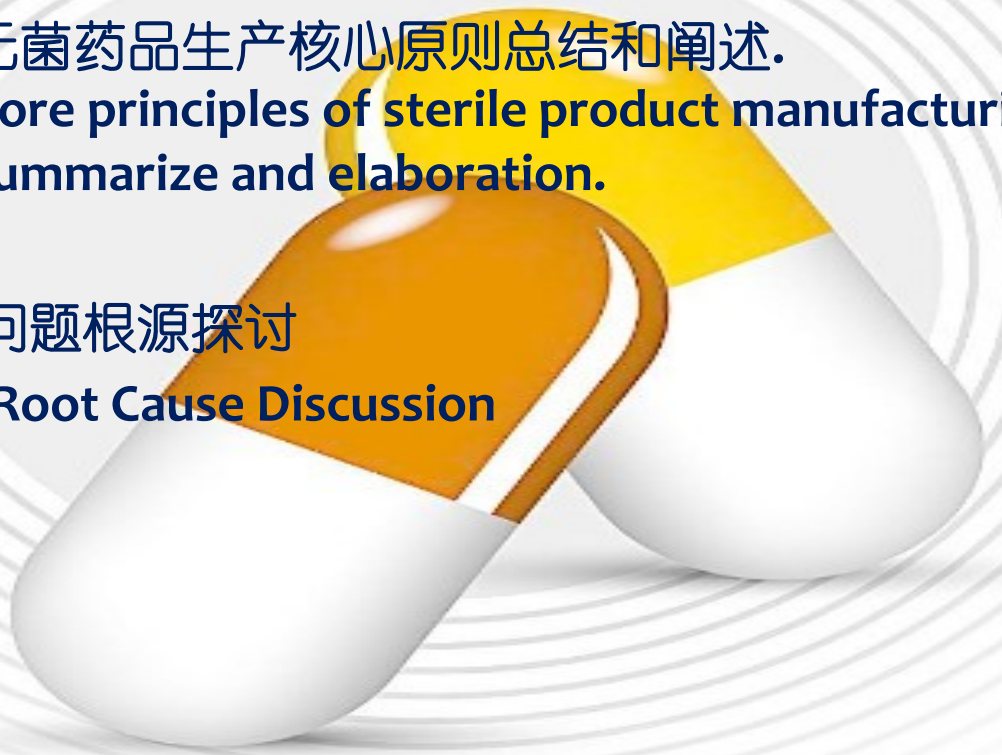
宋启国| 资深GMP咨询顾问 | 139-1557-3929 | email： gordon.song@phgqs.com

Contents :

Ⅰ 引子：附录1关键词摘录
Introduction： Annex 1 key words listing

Ⅱ 无菌药品生产核心原则总结和阐述.
Core principles of sterile product manufacturing summarize and elaboration.

Ⅲ 问题根源探讨
Root Cause Discussion



GQS
Global. Quality. Solution

I 引子：附录1关键词摘录

Introduction： Annex 1 key words listing

关键词 Key Words

- **Clean up Period**
- Up to Date
- VHP
- P&ID
- Assemble/ Connection / Preparation/ Reassemble / Filling / Capping
- Conveyor
- Portable Particle Counter
- Vent Filter
- Directly Contact Product
- Terminal / Ultimately
- Black Utilities / Clean Utilities
- **As Built / At Rest / In Operation**
- WFI / PCA / PW/ CS / Vacuum System / Process Gas System
- Seasonal Variation
- Precaution /Contamination
- Direct Support Zone
- Loading and Unloading
- Supporting Clean Area
- Drying
- Duration
- Exception
- Segregation
- LAF
- Container / Closure
- BFS / SVP / LVP / FFS
- QRM
- Condition
- Transportation and Shipping
- Calibration
- APS
- Interface
- Minimize / Maximum
- Viable and Non-Viable
- Frequency
- Investigation / Analysis / Observation / Monitoring / Control / Justification / CAPA / Interpreted / Reasonable
- RMM
- Additional
- Recommended
- PAT
- Individual
- Trend
- Inherent
- Authorized / Permitted / Listed / Documented / Approved
- Change
- PQS
- Batch
- CPP / CQA
- Sample
- Positive / Negative
- SAL
- Monitoring / control
- HEPA
- Distribution/ Mapping
- Worst Case
- Qualification and validation

GQS
Global. Quality. Solution

关键词 Key Words

- **Air Lock**
- **Aseptic Manufacturing Area**
- **Aseptic Processing Facility**
- **Aseptic Processing Room**
- Barrier
- Clean Area
- Clean Room
- **CNC**
- Clean Zone
- Closed System
- Critical Area / Zone
- Critical Surfaces
- **Condition: At Rest / Static**
- **In Operation / Dynamic**
- **Grade A Air**
- Isokinetic Sampling Head
- Changing Room
- Separate Laundry Facilities
- Ambient Temperature & Humidity
- Lower Quality Air
- Adjacent to the Critical Area
- Local Zone
- Work Station/ Working Height
- Homogeneous Air Speed
- Guidance Value
- Localized Air Flow Protection
- Visualization Studies
- Aseptic Preparation and Filling
- Interface
- Less Critical Stages
- Without Entry
- Background Environment
- Exposed Surfaces
- Air Break
- Floor Drain
- Traps and Water Seals
- Physical Separation / Partition
- Cascade/ Bubble/ Sink
- Hands Washing Facilities
- CNC
- Time Delay
- Visual and / or Audible Warning System
- Air Flow Pattern / AFPT
- Turbulent Air Flow
- EMPQ
- Limit: Set Limits
- Between Areas
- Disinfection Regime
- Leakage / Integrity Test
- Intervention/ Exit
- Classification/ Qualification/ Grade
- Sample Points and Sample Volume
- Immediately Adjacent Environment
- Distribution-Critical / Evenly
- Expected Result
- Periodically
- Characteristics
- Washing / Clean / Disinfection / sterilization /Residue
- ……

GQS
Global. Quality. Solution

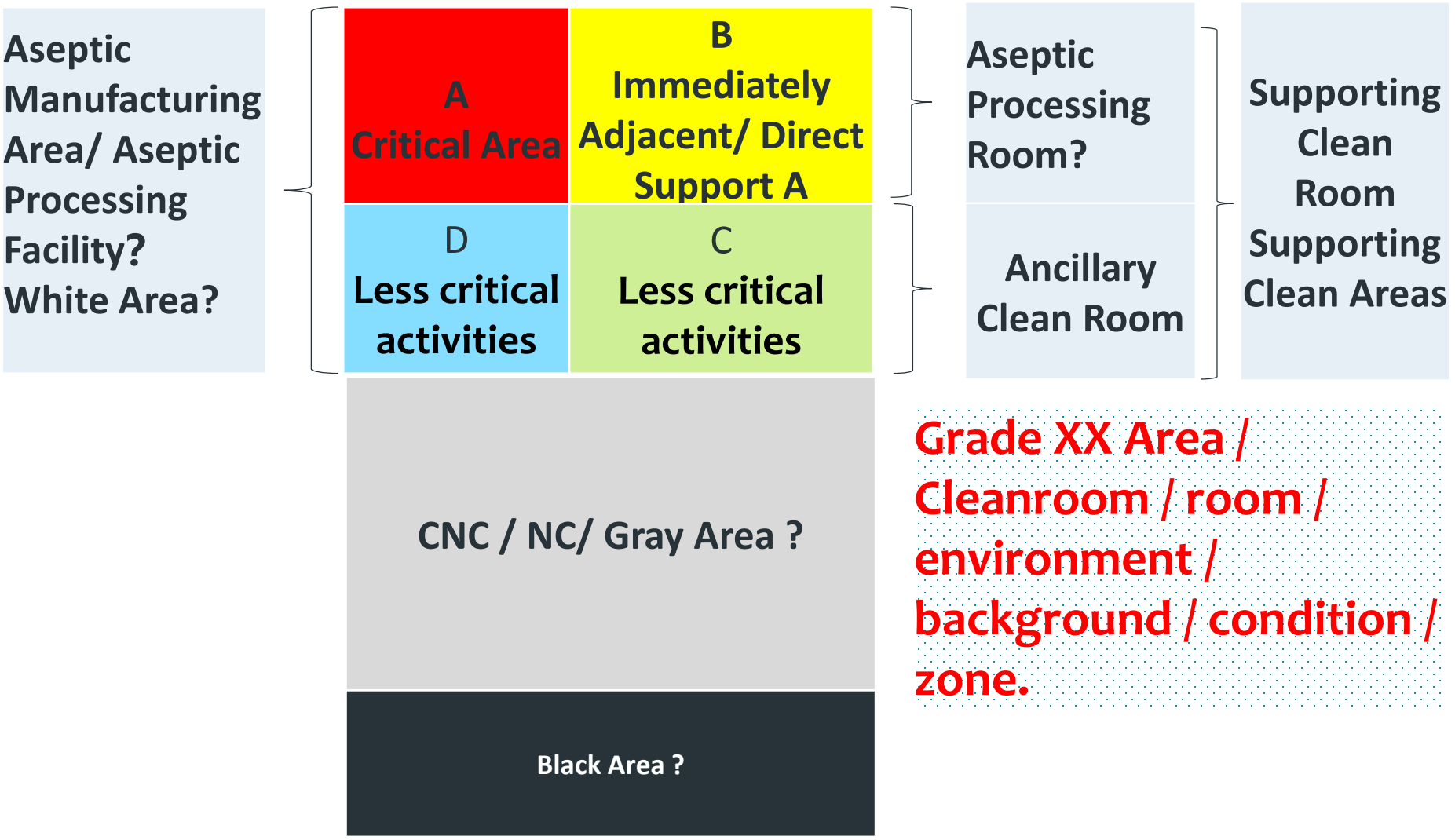
关键词 Key Words

厂房和洁净室相关关键词:我们都理解对了吗？
Facility and clean room related key words: Do we really understand them right?

- 无菌生产区域=无菌加工设施=无菌操作间？Aseptic Manufacturing Area = Aseptic Processing Facility=Aseptic Processing Room?
- 关键表面是？关键区域又是指？无菌区？**Critical Surfaces** is? How about Critical areas? How about Aseptically area ?
- A级送风（局部保护）：到底该如何定义其环境监测指标？Grade A Air Supply（Local Protection）：How to define its environment monitoring criteria ?
- 控制不分级区：新定义，环境监测的新挑战？CNC：New definition，EMPQ new challenge ?
- 单向流还是层流 Unidirectional Air Flow or Laminar Air Flow ?
- 自净时间: 如何测试？Recovery time: how to test?

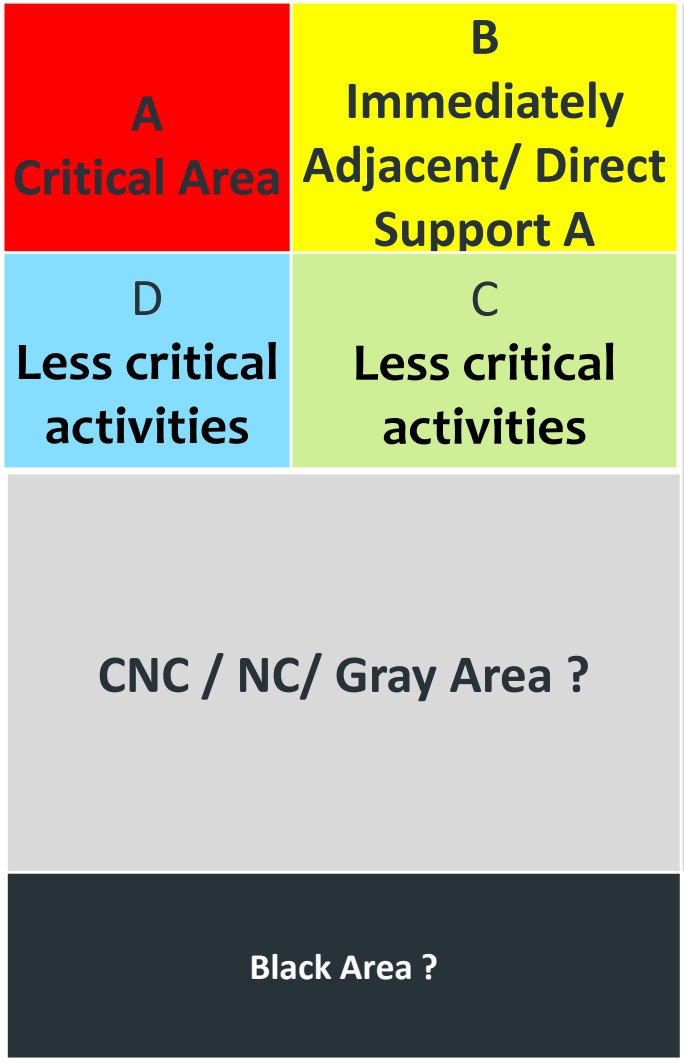
GQS
Global. Quality. Solution

关键词 Key Words



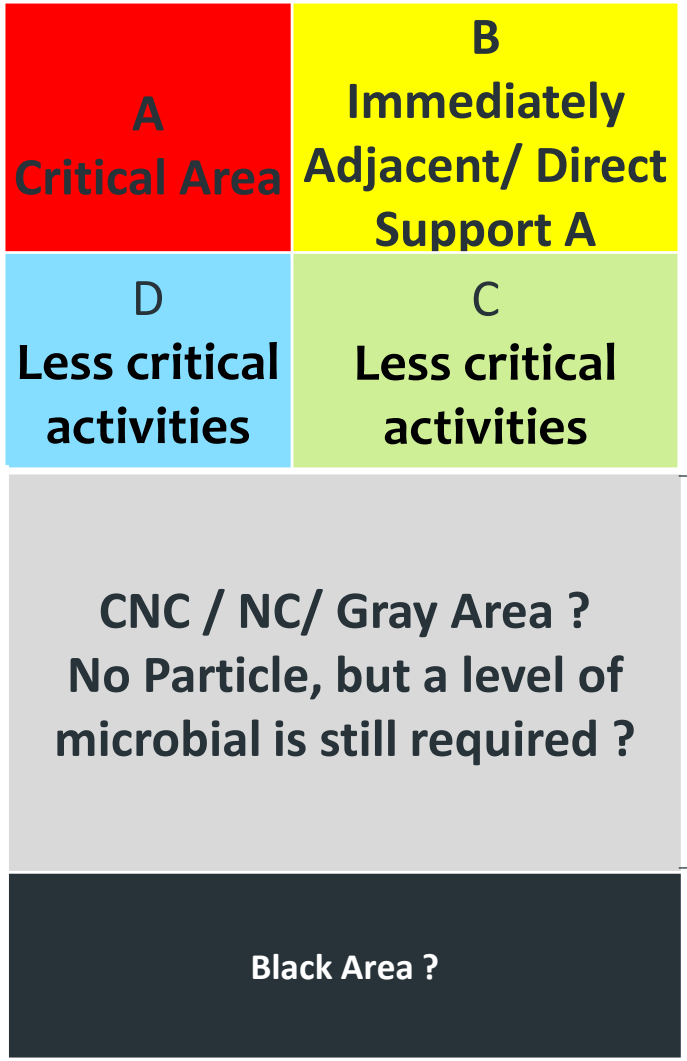
A级送风 Grade A Air Supply

Local Protection/ Grade A Air: Grade A non-viable quality air……no requirement to continuously perform non-viable monitoring or meet grade A viable monitoring limits.



- At rest should meet ISO5 at 100-150mm below filter face
- Should be capable of achieving a 1-log reduction in total particulates, below in operational background limit
- Initial qualification purposes, viable particulate limits ½ to 1/3 of the background are recommended, ……historic al EM data used for adjustment of the limits

控制不分级区 CNC



WHO TRS1010: An area where some environmental conditions or other attributes (such as temperature) are controlled, but the area has no cleanroom classification.

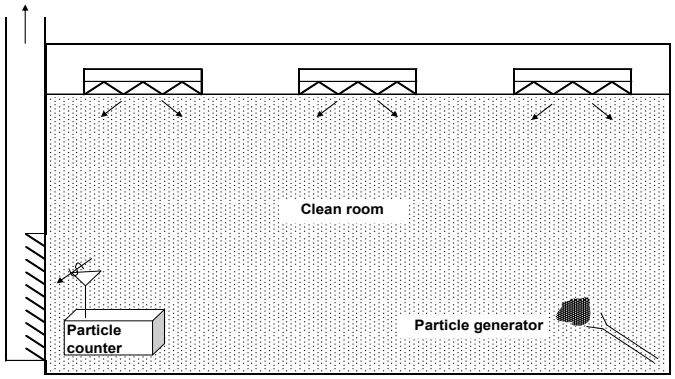
ISPE: A non-classified room environment ……CNC space is cleanable, access controlled and served with filtered ventilation air; procedural controls and personnel garment upgrades may be applied ……

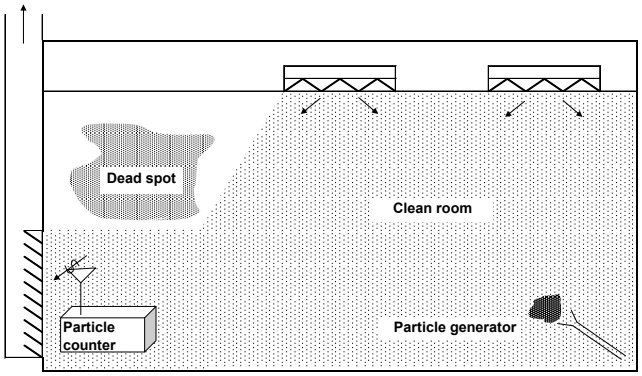
单向流还是层流 Unidirectional Air Flow or Laminar Air Flow ?

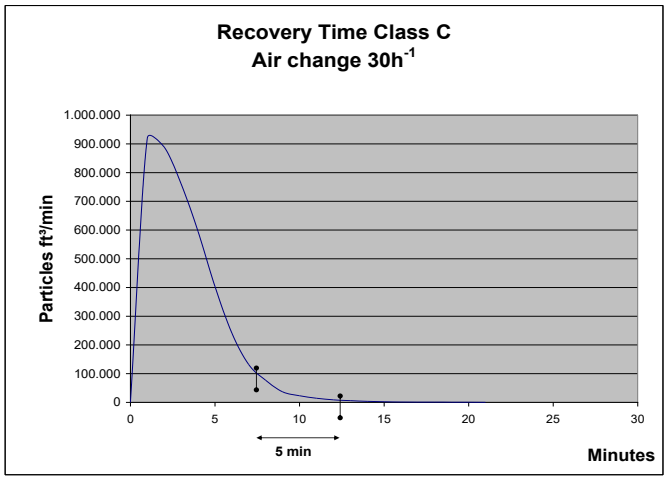
turbulent air flow. Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

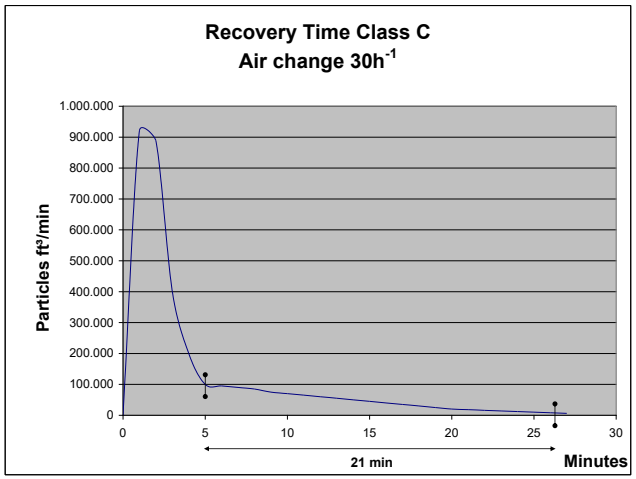
unidirectional airflow. A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also **turbulent air flow**). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

自净时间测试 Recovery Time Test





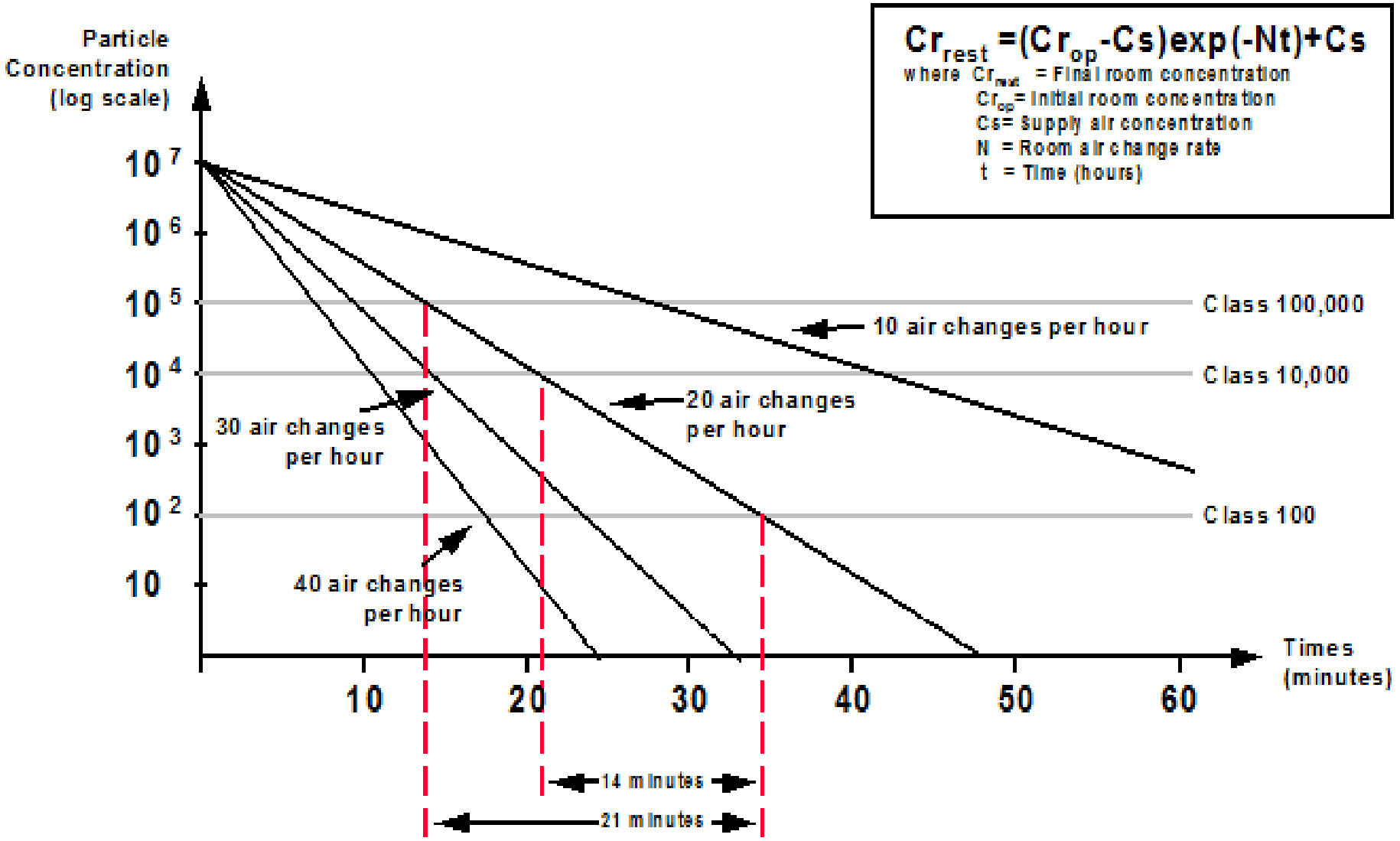




本图来自网络

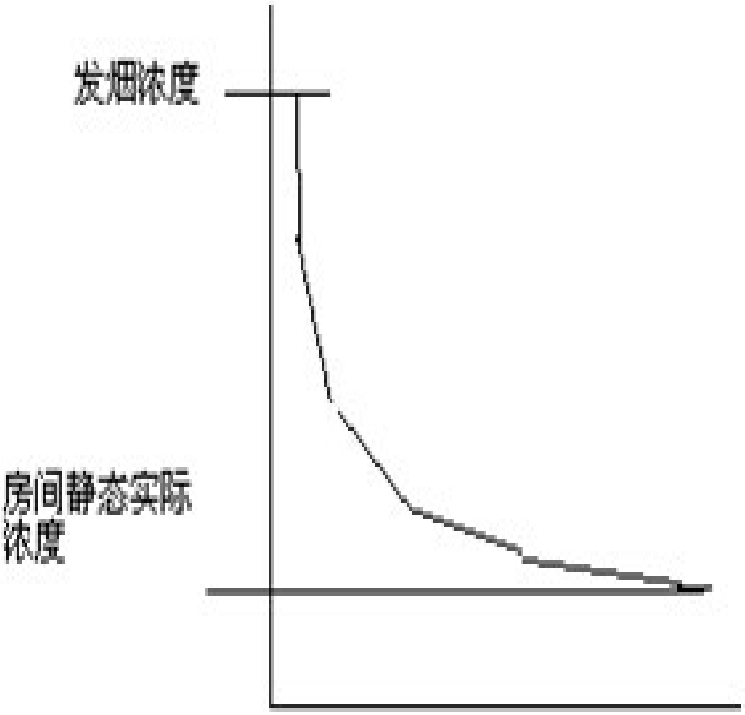
GQS
Global. Quality. Solution

GMP 要求动态至静态的自净时间为15-20分钟

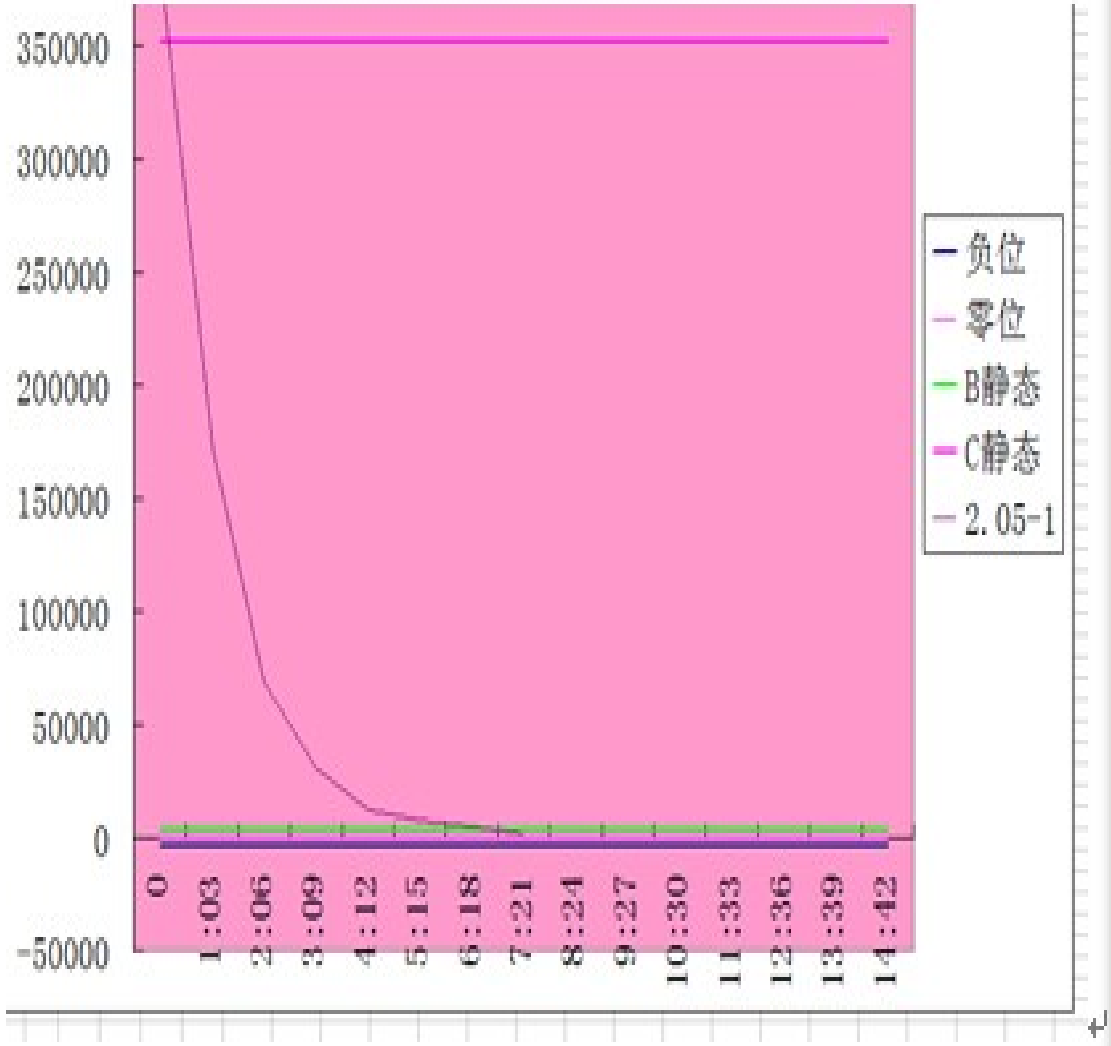


- From ISPE Baseline® for Sterile Facilities

GQS
Global. Quality. Solution



（理论图）



（实测图）

图 1-1：自净能力与房间静态浓度关系图

II 无菌药品生产核心原则总结和阐述
Core principles of sterile product manufacturing summarize and elaboration.

无菌药品生产的核心原则 Core Principles

- 源头控制；
- 梯度递减；
- 隔离/遏制保护；
- 无菌制造；
- 工艺和环境监测；
- 及时恢复；
- 人员培训和监测；

恰当的污染控制策略

界面和传递 Interface & Transfer：

- 维护结构：门、窗、管道开孔、灯具、插座、开关、安装的压差表、互锁、洁净电话等的密封情况；
- 系统使用终端：空气系统高效送风、回、排风口、气体系统：压缩空气、氮气等；液体系统：WFI\PW,工艺管道、PS\SIP\CIP；真空系统：真空管路；
- 传送轨道：隧道烘箱、灌装线同包装线的连接轨道等
- 传递窗、缓冲室：物料传递、穿着洁净服的人员、灭菌柜
- 人员着装/手套

完整性/密封性测试 Integrity Test :

- 过滤器完整性： HEPA Filter/ Vent Filter/ Sterilize Filter
- 包装和容器完整性： Package / Container / CCIT
- 管路完整性： Pipe / Duct
- 隔离器/手套完整性： Isolator / Glove
- 工作服: Garment
- 厂房设施： Facility

专业的技术

丰富的经验

严谨的态度

才能表现出正确的行为

产生需要的结果

GQS
Global. Quality. Solution

问题根源 Root Cause

- 传统开放洁净室 **VS** RABS **VS** ISOLATOR
- 欧派 **VS** 美派
- 其他行业（电子/汽车等） **VS** 医药行业

问题根源 Root Cause

- ISO14644.1定义: 空气悬浮粒子浓度受控的房间，其建造和使用方式使房间内进入的、产生的、滞留的粒子最少，室内温度、湿度、压力等其他相关参数按要求受控。
- GMP定义（WHO TR 937 Annex）：一个洁净区（或房间）有着规定的微粒、微生物污染的环境要求，它的 建造是为了在这个特定区域里减少污染物的带入、生成。
- FDA无菌药品生产指南2004/欧盟附录1（征求意见稿）：A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.
- 从定义上可看出医药洁净室的关注点同普通洁净室相比，多了对微生物污染的要求。从设计、施工、测试到使用都需要考虑微粒和微生物两方面的问题。

问题根源 Root Cause

A, 并不是所有测试项，GMP都给出了详细的测试方法和接受标准；

B, 以上标准中很多并不完全是针对制药行业的，并不完全适用于制药行业，遵照执行的话，可能会造成测试和接受标准不能很好的满足GMP要求;

C, 一些标准虽然是专门针对制药行业的，但由于发布时间较早，有些内容已同当前GMP不一致;

D, 由于起草组织以及标准适用范围不一，导致即使针对同一问题各标准之间也不能保持完全一致。

GQS
Global. Quality. Solution

问题根源 Root Cause

E, 不同经历的从业人员，由于知识和理解的局限性，仅以其所了解的某个标准或指南上的规定为依据来理解洁净室的相关指标和要求。沟通过程中经常出现不同人员参考的标准或指南不一致造成对同一问题不同理解而产生的无谓争论。

以上问题造成不同层次混乱现状：

- **无标准；**
- **有标准但无细节要求；**
- **有标准规定但标准本身就有问题，标准之间冲突；**

GQS
Global. Quality. Solution

谢谢大家 Thank you！

Contact Information

SHANGHAI GQS PHARMACEUTICAL TECHNOLOGY Co., Ltd.

上海誓炬医药科技有限公司

公司地址：中国上海奉贤区奉城镇川南奉公路9198号1幢1118室

苏州地址：苏州工业园区若水路388号D栋207室

公司电话：0512—67223121

移动电话：139-1557-3929

E-mail: gordon.song@phgqs.com

GQS GMP咨询微信公众号