新建药厂的
欧盟GMP概念设计评价

加拿大新科咨询有限公司总裁
上海新科咨询公司执行总裁
美欧GMP高级咨询师
程毓渡博士

【授课专家简介】程毓渡博士是中国著名的美欧GMP咨询师与培训师，在中国成功策划和主持了包括美欧GMP实施到文件注册在内的近百次美欧GMP公开与内部培训，近年来受美欧厂商委托经常对中国各地的原料药/制剂生产厂家进行独立第三方GMP审计，零距离了解国内药厂在GMP方面的优势与现状。程毓渡博士目前是美国ISPE（国际制药工程协会）会员、美国非肠道用药协会（PDA）会员、美国著名QUINTILES咨询公司客座咨询技术专家、美国PROTOCOL LINK咨询公司GMP审计师、中国国家药监局培训中心客座教授、国内多家制药公司首席GMP咨询师。 程博士回国之前在加拿大获化学博士学位、并在美国著名的JOHNS HOPKINS大学生物系和加拿大国家科学院生物技术研究所、加拿大新科药业等专业机构与药品开发实验室从事新药开发，建立了作为现代GMP规范基础的科学思维和验证技能。他结合近几年迅速积累的GMP审计经验开发了面向中国药企的GMP解读与实施操作系列培训课程，所到之处均受到高度评价和热烈欢迎。程毓渡博士GMP规范知识全面精深，对美欧GMP六大系统均有深入了解和解决实际问题的能力，在厂房设施方面，程毓渡博士通过GMP审计帮助各地药厂识别和整改缺陷，并为多家药企新建或改造的无菌或非无菌厂房设施进行GMP概念与风险评价，为这些药企的无菌或非无菌厂房设施GMP规范符合性提供了高度保障。关于程毓渡博士更多详情，请访问上海新科咨询（上海加中生物）网站http://www.shnovoscience.com.cn或与程博士电邮联系yudu.cheng@shnovoscience.com

培训内容提要

- 欧盟关于药厂厂房的GMP要求
- 非无菌药品/原料药厂房设施GMP概念设计
- 无菌药品/原料药厂房设施GMP概念设计
- 高活性药品/原料药厂房设施GMP概念设计
- 高致敏性药品/原料药厂房GMP概念设计

欧盟关于药厂厂房的GMP要求

欧盟药品法规现状

- **EU 人药和兽药立法（Legislation）： Vol. 1 &Vol. 5**
- **EU 人药与兽药 指令（Directives）：2001/83/EC**
- **EU 人药与兽药规范（Regulations）：EC/726/2004**
- **EU 人药与兽药指南（Guidelines）：Vol. 4**

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

General

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Area

3.6 In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities.

Production Area

3.6 (cont.) For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

Production Area

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

Production Area

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

Production Area

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

Production Area

3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

Production Area

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

Production Area

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross contamination and facilitate cleaning.

Production Area

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk for the production.

非无菌药品/原料药厂房设施GMP概念设计

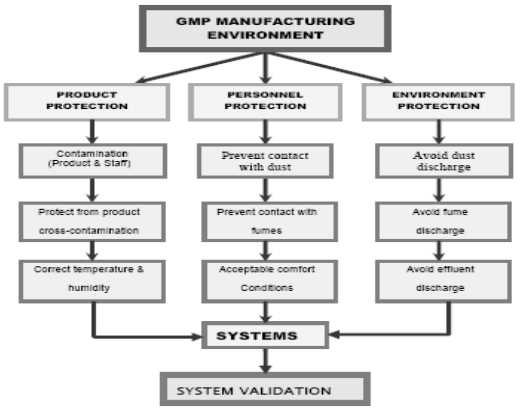
空气净化与调节系统（HVAC）的GMP概念设计

- HVAC系统：目标用途
- HVAC系统：尘埃粒子控制
- HVAC系统： 设计与构造
- HVAC系统：调试、确认与维护

HVAC系统：目标用途

- HVAC系统对产品的保护作用
- HVAC系统对人员的保护作用
- HVAC系统对环境的保护作用

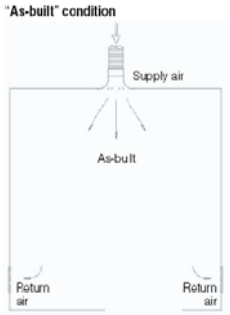
HVAC系统：目标用途



厂房设施状态与级别

级别与厂方设施状态的关系:

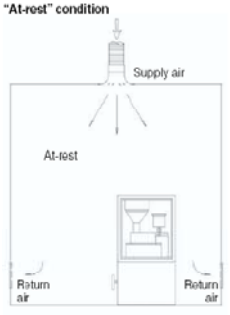
- *建成态（空置态）*
  - 空旷房间，没有设备与人员
  - 房间的级别在设备与人员进入之前必须予以确认



厂房设施状态与级别

级别与厂方设施状态的关系：

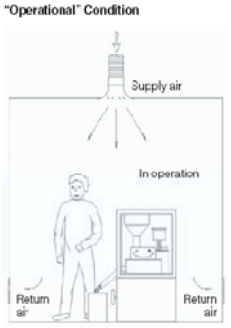
- *静态*
  - 设备已经安装且可以运行，但是没有人员操作
  - 静态时的级别需要予以确认，对固体制剂由于产尘严重，一般都确认都是静态的级别。



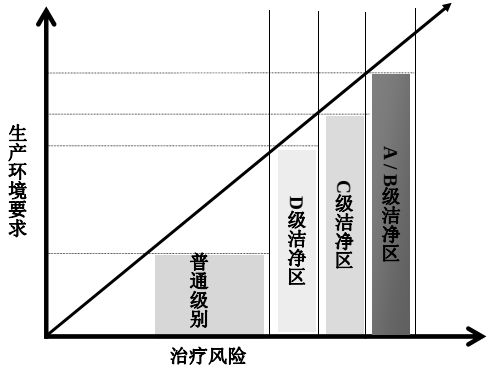
厂房设施状态与级别

级别与厂方设施状态的关系：

- *运行状态（动态）*
  - 设备与人员处于正常运行状态
  - 自净时间验证－通常20分钟左右（自净是指从运行状态即动态到静态的状态恢复）



生产环境级别与治疗风险的关系



保护级别的确认指标

影响保护级别的参数

- 空气中的尘埃粒子数、空气和表面上的微生物数目
- 每个房间的空气交换次数
- 空气流速与气流模式
- 过滤器类型与位置
- 房间之间的空气压差
- 温度、相对湿度

全球规范机构的洁净区级别

- *WHO, EU, PIC/S(世界卫生组织|欧盟|检查同盟）* *A, B, C, D*
- *US FDA（美国FDA）* *ISO5, 6, 7, 8*
- *ISPE（国际 制药工程协会）* *Level 1, 2 or 3*
- *ISO（国际标准组织）* *Class 5, 6, 7 or 8*
- *CHINA（中国）* *A,B,C,D*

保护级别概念应用范围

级别	*条件*	*区域举例*
1级	普通区	常规的洁净维护，例如仓储区、发货区等
2级	保护区	有步骤地对暴露产品实施保护的区域，例如配料区、制粒区、压片区、包装区等
3级	控制区	可以防止产品污染和降解的确定的、受控的、环境受到监控的区域，例如无菌工艺区、灭菌工艺区、注射剂生产区、毒性产品区等

保护级别概念应用范围

保护级别	*保护措施*
1级	常规的清洁与维护（例如可进行不暴露的反应罐取样）
2级和 3级	采取措施保护暴露的物料（例如密闭式过滤、洁净罐手孔、反应罐之间隔墙等）
2级和 3级	制订专门的环境条件并确保环境受控以防止对暴露物料的污染（例如在干燥区确保受控的房间压力和温度、不得同时处理多个物料、采用手套箱保护过滤器和工艺操作）

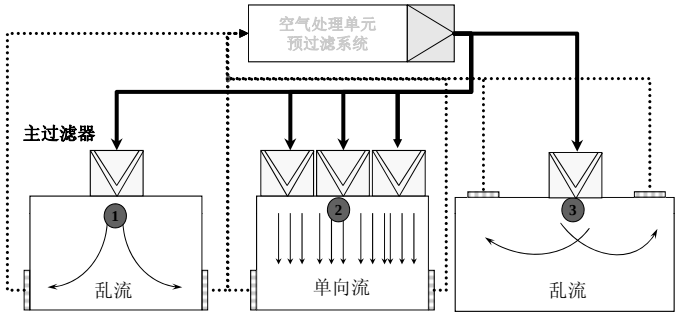
清洁生产与级别的概念

所有药厂设施内的操作都要与经过确认的洁净区级别关联起来，这就是清洁生产与级别的概念。

洁净区级别和操作举例	A	B	C	D
容器清洁				X
终端灭菌溶液配制			X	
无菌灌装溶液配制	X	X	X	
容器去热源	X			
终端灭菌灌装			X	
无菌工艺灌装	X			

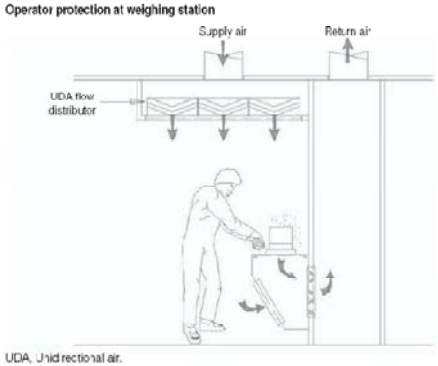
HVAC系统的空气过滤

HVAC气流模式



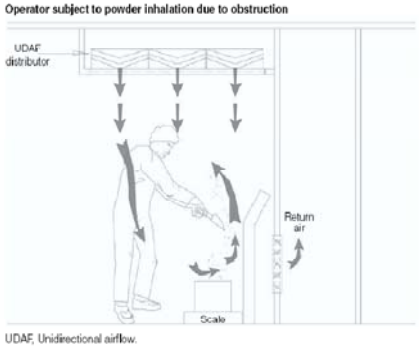
HVAC系统的空气过滤

称重区单向流概念设计

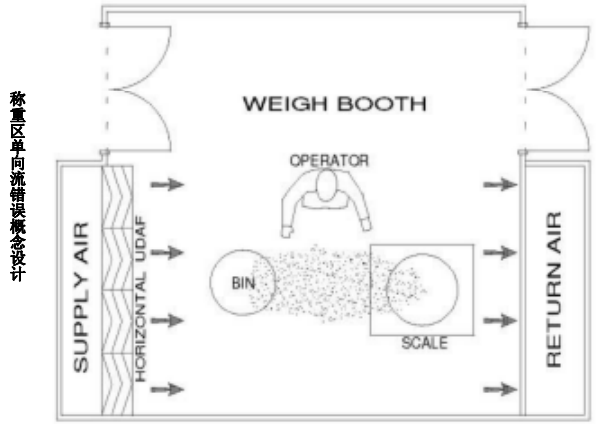


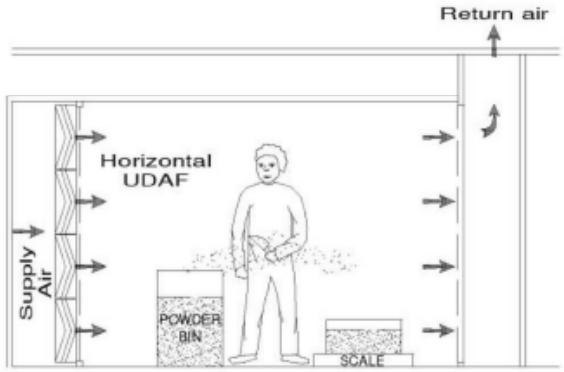
HVAC系统的空气过滤

称重区单向流错误概念设计

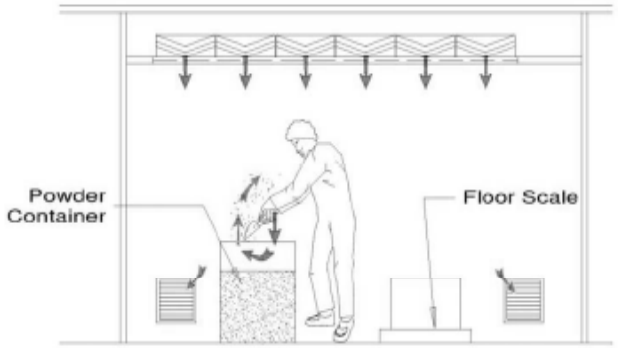


称重区单向流错误概念设计

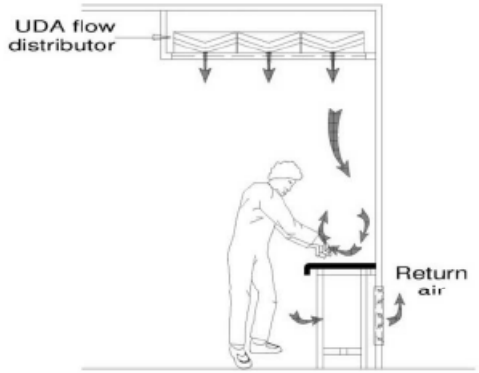




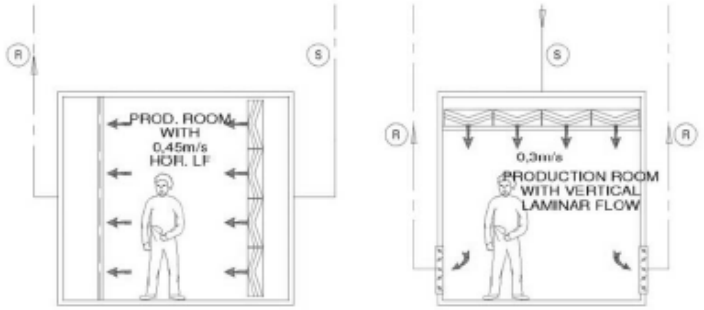
称重区单向流错误概念设计



称重区单向流错误概念设计（粉尘朝向操作员）



操作台单向流错误概念设计（粉尘回流，可让操作台与墙面保持100MM距离）



药厂可选择水平单向流或垂直单向流使粉尘污染最小化

HVAC系统的空气过滤

气流渗入

- 洁净区设施相对外界通常处在正压保护之下
- 需要防止未过滤的受污染的空气渗入洁净区设施
- 某些情况下洁净区相对外界设施保持负压（例如高致敏性药品青霉素车间）。需要采取特殊措施防止污染与交叉污染

HVAC系统的气流概念设计

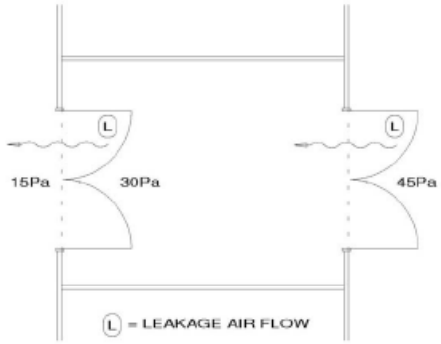
防止交叉污染

- 总体考量和概念
- 气流置换概念
  - *低压差、高气流*
- 压差概念
  - *高压差、低气流*
- 物理障碍概念

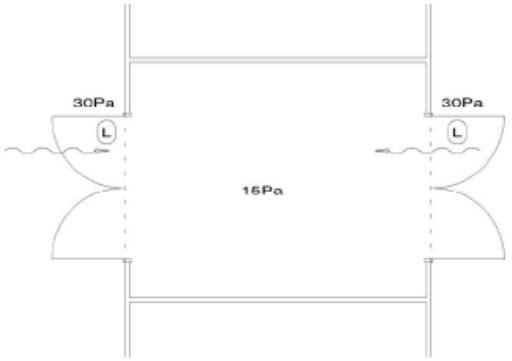
HVAC系统的气流概念设计

总体考量

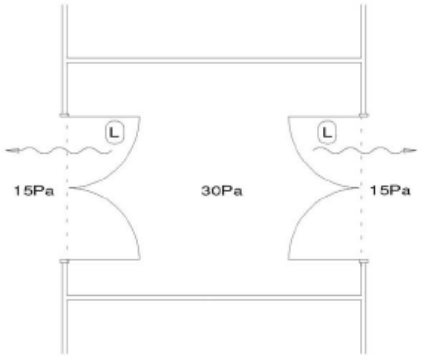
- 多产品固体制剂（OSD）生产，需要在不同产品生产的区域之间防止粉尘转移
- 有方向的空气移动和压力级差有助于粉尘控制
- 通常洁净走廊的压力高于操作间的压力，而操作间的压力高于大气的压力



级差式气闸



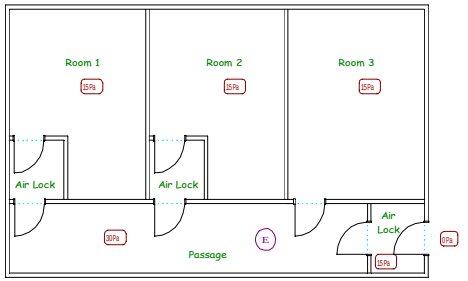
吸入式气闸



泡阻式气闸

HVAC系统的气流概念设计

固体制剂压力级差保护，防止交叉污染



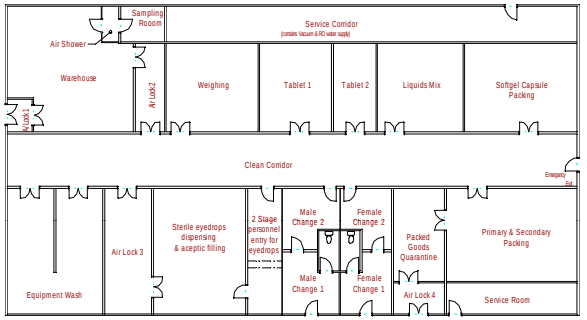
Note : Direction of door opening relative to room pressure

HVAC系统的气流概念设计

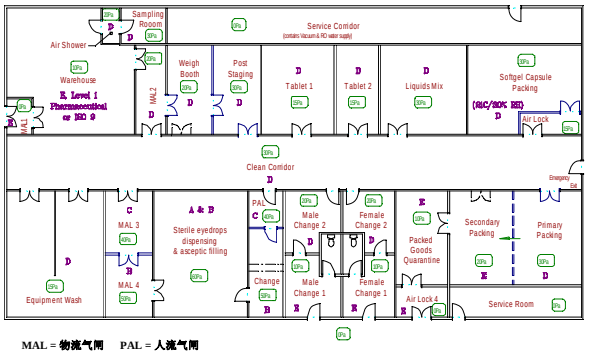
物理屏障概念设计

- 在某些情况下，使用不可渗透的屏障来防止交叉污染（例如隔离器或管道式物料传输）
- 工作点气流保护
- 通风柜

药厂洁净区级别概念设计



药厂洁净区级别概念设计



MAL = 物流气闸　PAL = 人流气闸

无菌药品/原料药厂房设施GMP概念设计

洁净区基本指标

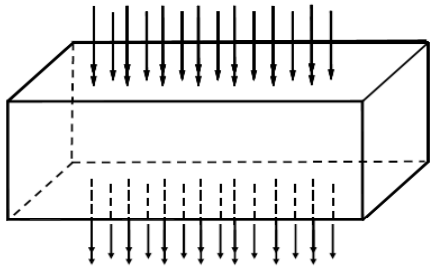
建立和控制以下指标：

- 空气质量-粒子计数（活性微粒和非活性微粒）
- 温度
- 湿度
- 房间增压
- 空气流速或换气
- 定向流动方式
- 照明
- 室内装修

FDA/ISO/EU洁净级区指南

FDA Classification (0.5 micron particles/ft³)	ISO Designation (In Operation)	EU Class	Particles/m³ = 0.5 micron or larger	Microbiological Active Air Action levels (cfu/m³)	Settling Plates Action Levels (diam. 90mm; cfu/4 hours
100	5	Grade A	3,520	1	1
1,000	6		35,200	7	3
10,000	7	Grade B	352,000	10	5
100,000	8	Grade C	3,520,000	100	50

垂直层流概念

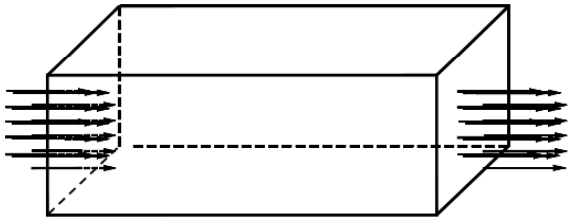


Contamination moves towards the floor 污染向地面移动

Class 100 achievable throughout the room 整个房间可以达到100级

This concept is most widely used in the pharmaceutical industry
这种设计概念在制药行业广泛采用

水平层流概念



Contamination moves from one wall to the other wall
污染从墙的一面流向另一面

Cleanest work area in the beginning
最洁净区处在起始端

Suitable where work area is near the supply wall and a large number of people present
适用于操作区靠近物流墙和操作人员比较多的情况

欧盟洁净区-“静态”和“动态”

- 为符合“动态”条件，这些区域应在“静态”状态下达到特定的空气洁净等级。
- 静态是指：生产设备安装完成，并可以运行，但是没有操作人员在现场的状态。静态条件在操作停止后15-20分钟应达到
- 动态是指：厂房设施在确定的操作模式下并有特定数量的人员进行工作的状态。

EU洁净区分级

每立方米允许的等于或小于的最大粒子数目

	At Rest		In Operation	
	0.5 µm	5 µm	0.5 µm	5 µm
Grade A	3,500	0	3,500	0
Grade B	3,500	0	350,000	2,000
Grade C	350,000	2,000	3,500,000	~~20,000~~
Grade D	3,500,000	20,000	Not defined	Not defined

FDA和EU洁净区级别规定差异

- FDA没有D级
- FDA2004年的指南中，没有指明百级区域的速度，EU则做出了明确规定（0.45m/s+20%,FDA1987年指南中制订的规定）。
- 所有FDA的要求均是针对动态
- 活菌计数：FDA与EU行动限对比（FDA更严格）
- EU将粒子分为0.5微米和5微米，FDA只有0.5微米的分类
- EU空气取样：更具有专属性和广泛性，EU：空气取样（0.5和5微米），沉降皿，接触皿，手套印记；FDA：空气取样（0.5微米）和沉降皿。

无菌洁净区GMP概念设计要点

- 百级和万级区域有终端HEPA过滤器
- 百级、万级、更衣室和气锁间的保持低回风量
- 注射剂工厂中
  - 有挂帘和进出受限隔离(Closed RAB & Open RAB)，周围环境为万级
  - 采用 隔离器技术时周围环境可以为10万级
- 有足够的空气交换速率以稀释粒子

万级 40-50空气交换,，十万级 20-25空气交换 气锁 60空气交换

- 渗入/渗出允许值（与压差输送一致）

单门 370CFM，双门 520CFM

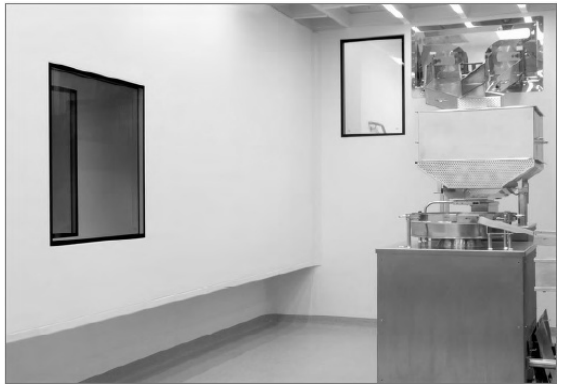
无菌洁净区GMP概念设计要点:洁净区构造

- 构架式建造-更灵活，可以在后期增加设计
- 设嵌板-高级装饰
- 预设有HVAC系统的组件
  - 高级建造
  - 可能更贵
  - 平行建造
  - 非常适合于技术落后地区使用
- 包含所有HVAC、管道和设备并类似上述设计的标准模块厂房

无菌药品/原料药厂房设施
洁净区不同级别应用举例

- 气墙模块系统
- 培养基配制，C级
- 20k生物反应器，C级
- 层析柱，B/C级
- 超滤纯化系统，B/C级
- 无菌灌装工艺洁净区GMP概念设计

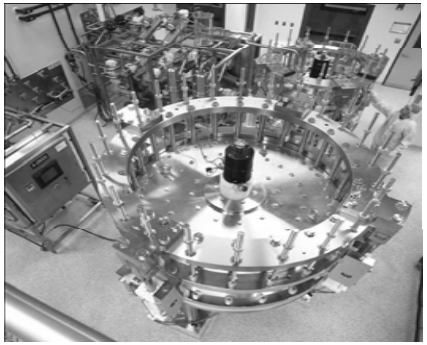
气墙模块系统



培养基配制 C级

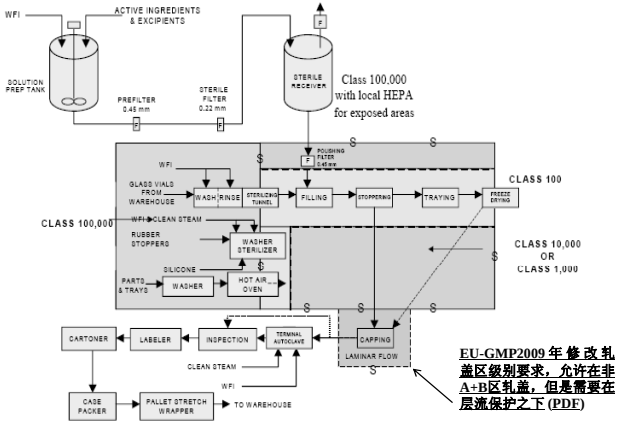
20k生物反应器，C级

B/C级层析柱



B/C级超滤纯化系统

无菌灌装工艺厂房设施GMP概念设计



中国新版GMP无菌药品/原料药厂房设施规范

为了确保无菌药品的安全性，中国新版GMP按照欧盟和WHO标准进行了修改，无菌药品附录采用了欧盟和最新WHO的A、B、C、D分级标准，并对无菌药品生产的洁净度提出了非常具体的要求。特别对悬浮粒子的静态、动态监测，对浮游菌、沉降菌和表面微生物的监测都设定了详细的规定并对监测条件给出了明确的说明。细化了培养基模拟灌装、灭菌验证和管理的要求，增加了无菌操作的具体要求，强化了无菌保证的措施，以期强有力地保证无菌药品的安全和质量提高法规和科学依据（中国新版GMP附录-1无菌药品解读）

高活性药品/原料药厂房设施GMP概念设计

NIH Contaminant Classifications Guidelines
NIH包容区分类指南

Labs	Production Plants	Severity	Containment
BSL1	BSL1-LS	Minimal	Primary
BSL2	BSL2-LS	Low	Primary
BSL3	BSL3-LS	Moderate	Primary + Secondary
BSL4		High	Primary + Secondary

Lab operations are carried in less then 10L fermentor

Basis for the Classification of Biohazardous Agents by Risk Group (RG)
根据风险对生物公害进行分类的基础

Risk Group 1 (RG1) -Agents not associated with disease in healthy adult humans

1类风险（RG1）-对健康成年人无致病作用

Risk Group 2 (RG2) -Agents associated with human disease but rarely serious and for which preventive or therapeutic interventions available

2类风险（RG2）- 可引起人类疾病，但大多不严重，可进行预防或治疗干预。

Risk Group 3 (RG3) -Agents associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk but low community risk)

3类风险（RG3）-可引起人类严重或致命疾病，可能可以进行预防或治疗干预。（对于个体风险高，但对于群体风险较低）

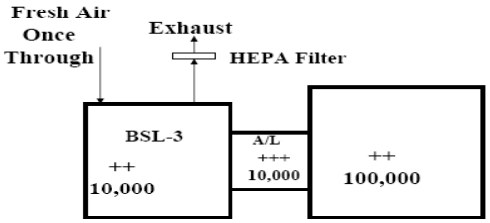
Risk Group 4 (RG4) -Agents likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available (high individual risk and high community risk)

4类风险（RG4）-可引起人类严重或致命疾病，通常无法进行预防或治疗干预。（对于个体和群体均为高风险）

Basis for the Classification of Biohazardous Agents by Risk Group (RG)
根据风险对生物公害进行分类的基础

- **Risk Group 1 (RG1)** –1类风险（RG1）-
  asporogenic *Bacillus subtilis or Bacillus licheniformis (无芽孢杆菌或苔癣样杆菌)*
- **Risk Group 2 (RG2)** –2类风险（RG2）-
  Hepatitis A, B, C, D, and E viruses（肝炎病毒A, B, C, D, 和 E）
  Herpes viruses（疱疹病毒）
  Measles and Mumps virus（麻疹与腮腺炎病毒）
  Polioviruses（脊髓灰质炎病毒）
- **Risk Group 3 (RG3)** –3类风险（RG3）-
  Yellow fever virus（黄热病病毒）
  Prions-Transmissible spongioform encephalopathies (TME) agents（动物海绵状脑病-疯牛病毒）
  Human immunodeficiency virus (HIV)（爱滋病毒）
- **Risk Group 4 (RG4)** –4类风险（RG4）-
  Crimean-Congo hemorrhagic fever virus（克里米亚-刚果出血热病毒）
  Filo viruses纤丝病毒
  Ebola virus埃博拉病毒

Containment for Biologics (BSL-3)
生物药品(BSL-3) 包容区



This concept can also be used for High Potency Compounds

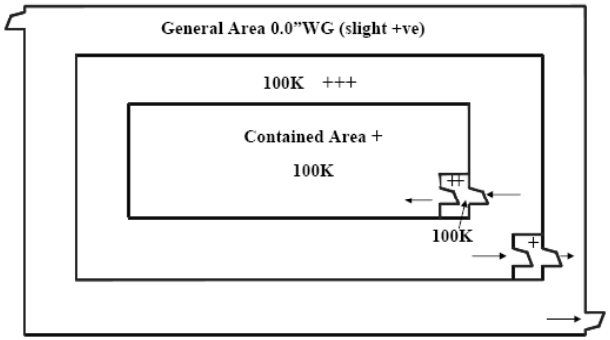
NIH Containment Guidelines NIH包容区指南
Ventilation – movement of air and filtration of air (BL3)
通风-空气流动和过滤(BL3)

- Exhaust air not re-circulated to other areas of facility. 废气不能在设施的其他区域循环
- Recommend once through air (dedicated single-pass exhaust system). 推荐一次性空气(专用单一路径排气系统)
- Discharge through HEPA filters, thermal oxidizer. 通过HEPA过滤器, 热氧化器排气
- A bag-in/bag-out (BIBO) filter or formaldehyde gas for decontamination of filters. 用袋进袋出型过滤器或甲醛气对过滤器进行除污。
- Exhaust air discharged away from supply air intakes. 废气排出应远离进气处

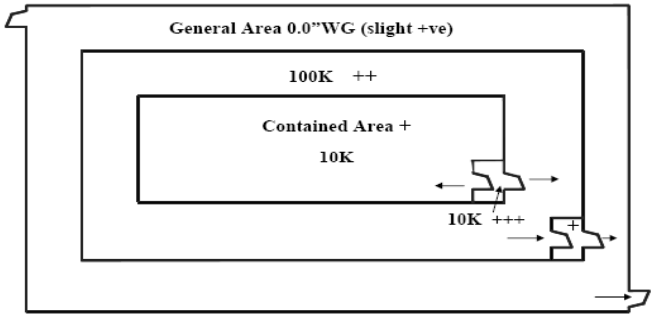
BL3-LS Design BL3-LS设计
General Considerations 总体考虑

- All doors, HVAC, light fixtures etc. carefully sealed and room leak tested. 所有的门, HVAC, 灯固定架等需仔细密封，并进行房间严密性试验
- All pipe and other services through walls welded to a plate or sealed properly. 所有墙壁管道和其他设施应焊于平板上或适当的密封。
- Provide spare openings and seal them for future use to avoid temptation to make holes. 为方便将来的使用, 应提供备用开口处, 并密封。避免打孔。
- Strictly control all future work in the room. 房间中应严格控制所有以后将要发生的工作
- Spill containment dikes and room decontamination provision. 防流堤和房间消毒设施

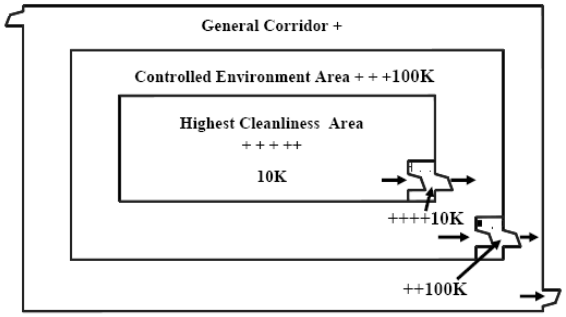
Building Pressurization Concept for Containment (e.g. BL3)
包容区域厂房压力输送概念(例如 BL3)



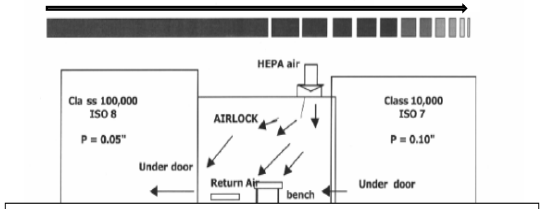
Building Pressurization Concept for Containment Cleaner Contained Area
包容区厂房压力输送概念 更清洁的包容区域



Building Pressurization Concept 厂房压力输送概念

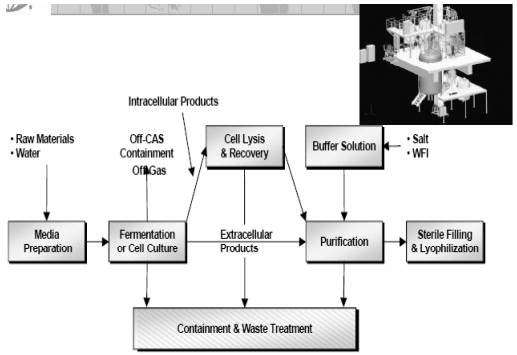


Gowning Room 更衣室



At rest level of A/L should be the same as the at rest level of higher class i.e. class 100

Typical Biology Unit Operation 典型生物操作单元



高活性包容区操作员防护服

细胞毒性操作员防护服

高活性包容区操作隔离器

高活性包容区操作隔离器与人员防护

高活性包容区操作隔离器与人员防护

高活性原料药生产操作手套箱

高活性药品/原料药生产操作手套箱

高活性药品/原料药隔离器生产操作手套箱

高活性药品/原料药生产操作人员防护

参考资料

高致敏性药品/原料药厂房GMP概念设计

高致敏性药品/原料药厂房设计GMP概念评价

Penicillin Issues

青霉素问题

Penicillin Issues
青霉素问题

- What do the CGMPs mean by separate facilities? Must the buildings be totally separated, or are the CGMPs satisfied when the floors are physically separated with separate air filtration units installed?

- CGMP规定独立的厂房是什么意思？厂房必须完全独立吗？在安装有独立的空气过滤系统的情况下，楼层之间采取物理隔离可以吗？

Penicillin Issues
青霉素问题

- CGMP regulations [21 CFR 211.42(d) and 211.46(d)] require separation of penicillins from non-penicillins during processing. The discussion of the comments in the preamble to the regulations note that "...isolation of penicillin production operations...can be achieved by sealing off...the two operations." "...does not necessarily mean...separate buildings." Thus, there can be a "building within a building"- i.e. two buildings are not required. However, there must be total separation of operations, meaning every aspect of the operations must be separate. Adequate separation should include physical barriers and separate air handling systems. Personnel and equipment from the penicillin facility should not enter the non-penicillin facility. These should operate with well established written procedures and controls. The separation should be audited, procedures validated, and where necessary monitored.

Penicillin Issues
青霉素问题

- CGMP 法规 [21 CFR 211.42(d) and 211.46(d)]要求青霉素与非青霉素产品在加工中独立。 相关的讨论观点“青霉素产品操作的隔离可以通过将两个操作完全分开而达到”，“并不需要独立的厂房”。这样，可以设计成“建筑物中之建筑物”，也就是说，两个建筑是没有必要的。然而，操作上必须完全隔离，也就是说，每一个方面都应完全隔离。充足的隔离应当包括：物理上的屏障及通风系统的隔离。青霉素厂房的人员及设备不应进行非青霉素的厂房。这些需要建立良好的书面程序并进行控制。这种隔离应进行审计，程序应经验证，如果需要还应进行监测。

Penicillin Issues
青霉素问题

- Even with separation, if any possibility of contamination exists, the non-penicillin products must be tested (21 CFR 211.176). An example of possible contamination could be inadequate controls over movement of equipment or personnel. Section 211.176 requires non-penicillin products to be tested for traces of penicillin where the possibility of exposure exists, and not marketed if detectable levels of penicillin are found.

- 即使在隔离状态下，如果存在任何被污染的可能，非青霉素产品应该经过检验。一个可能污染的例子可能是人员及设备的不充分控制。Section 211.176要求如果存在青霉素产品暴露的可能，非青霉素产品应经检查，以确定是否存在青霉素，如果检测到青霉素产品的残留，产品不应销售。

Penicillin Issues
青霉素问题

- While this section prohibits marketing of products found to be contaminated with penicillin, it does not sanction marketing of non-penicillin products based only on test results that show no detectable levels of such contamination. Other CGMP requirements must still be met. For a discussion on this issue, please review the article "Is it acceptable under section 211.176 to release products to market as long as the products are tested and no penicillin is found?" published in "Human Drug CGMP Notes" (Volume 6, Issue 2, June 1998).

- 禁止这些被青霉素污染的产品上市的同时，不能仅根据没有检测到此类污染就批准这些非青霉素产品上市，产品的上市还必须满足其它CGMP要求。关于此部分的讨论，请参照文章"Is it acceptable under section 211.176 to release products to market as long as the products are tested and no penicillin is found?"，刊登在 "Human Drug CGMP Notes" (Volume 6, Issue 2, June 1998) 上。

Penicillin Issues
青霉素问题

- Cross contamination issues have been a concern for a number of years, and continue to be problematic. In one penicillin cross-contamination case reviewed it was demonstrated how a non-penicillin facility was contaminated by a separate penicillin facility located in the same manufacturing campus. This occurred due to lack of controls regarding movements of personnel, equipment and materials. In another case, CDER concurred with a district recommendation to withhold approval on a sensitizing beta-lactam manufacturing facility that was adjacent to another drug processing building, due to the lack of containment controls which ensured against cross contamination of the other drugs.

- 交叉污染的问题多年来一直是个关注的问题，并且还会继续是个问题。下面是一个青霉素污染的例子：在同一个厂区内，使用独立厂房生产青霉素和非青霉素产品，由于人员和设备及物料控制不严格导致产品受到污染。另一个例子是，一个临近其他药品生产厂房的致敏性β内酰胺类产品生产厂房，由于缺乏足够的交叉污染控制，CDER曾经收回其批准证书。

Penicillin Issues
青霉素问题

- Is it acceptable to manufacture penicillin and non-penicillin products in the same facility on a campaign (i.e., the conversion of production facilities to a different product line on a routine basis) basis, with adequate cleaning validation procedures in place?

- 在同一个厂房里生产青霉素和非青霉素产品，在有足够清洁的前提下，可接受吗？

Penicillin Issues
青霉素问题

- No, it is not acceptable. The discussion of the comments in the preamble to the regulations state that "...it is important to make clear in these regulations that completely separate air-handling facilities for penicillin and non-penicillin production are required.". And "...because it is possible for air-handling systems between penicillin and non-penicillin production areas to be interconnected, ...the Commissioner finds it necessary to state that any such interconnection would be unacceptable."

- 不，不可接受。涉及到的法规条款是"很重要的一点需要指明：青霉素与非青霉素之间的隔离，绝对需要完全独立的空调系统"。而且，"因为青霉素与非青霉素生产区域的空气处理设施内部可能是联通的，... 委员们认为有必要明确，所有这些内部的联通是不可接受的"。

Penicillin Issues
青霉素问题

- Campaign production of penicillin and any non-penicillin product in the same facility and with the same equipment violates the CGMP regulations [211.42(d) and .46(d)]. A concern is that the cleaning validation process does not include the air handling system throughout the facility. This is important because campaign production has the potential for recontamination of the air handling systems and facilities, and can lead to cross contamination of non-penicillin products with penicillin. The concept of decontamination is broader than a typical cleaning procedure validation, in that sampling is extended to include the environment, as well as surfaces of the facility and equipment that are to be decontaminated.

Penicillin Issues
青霉素问题

- 使用同一厂房和同一设备生产青霉素和非青霉素产品违背了CGMP法规，[211.42(d) and .46(d)]。需注意的一点是清洁验证并不包括厂房的所有空调系统，这一点是非常重要的，因为这种生产方式可以造成潜在厂房和空调的再污染。去除污染的概念可能要比典型的清洁的概念要宽泛的多，取样可能扩大至大环境，厂房和设备的表面。

Penicillin Issues
青霉素问题

- A facility contaminated with penicillin could not begin non-penicillin production until extensive decontamination and clean-up of the facility is accomplished in accordance with the established procedures, and representative environmental samples demonstrate that the facility conforms with its decontamination protocol/specifications.

- 一个已经被青霉素污染的厂房不能再被用于生产非青霉素产品，除非依照既定程序完成了最广泛的去除污染和清洁工作，并且有代表性的取样表明厂房已符合既定的去污染方案/规格。

Penicillin Issues
青霉素问题

- Current technology makes decontamination of air handling systems difficult. This is because the decontamination/cleaning procedures would necessitate sampling and residual testing of other parts of the air handling system, to include the ductwork. This would be difficult because the air handling system throughout its length has uneven areas and crevices that create the possibility of penicillin residue build-up, with slough-off at undetermined periods during the non-penicillin production period. Thus penicillin contamination would not be uniformly distributed in the air handling system, and "representative" samples (retain, surface and/or air) may not be an accurate portrayal of the level of contamination.

Penicillin Issues
青霉素问题

- 现在的技术要想去除空调系统的污染非常困难，这是因为去除污染而进行的残留检测需要对空气处理系统进行取样，包括管道。这是非常困难的，因为空气处理系统的不规则的面积，其内部的沟沟角角有可能使青霉素残留，而这些残留有可能在生产非青霉素产品时溶解出来。因为青霉素的污染在空气处理系统里的不均匀分布，而使得取样的不能代表污染的水平。

Penicillin Issues
青霉素问题

- 21 CFR 211.176 indicates that where the possibility of exposure exists, non-penicillin products must be tested for traces of penicillin and not marketed if detectable levels are found. This means that representative samples from all batches of non-penicillin products produced in each campaign must be tested with an acceptable method and found non-detectable for the penicillin product produced prior to the start-up of the non-penicillin campaign.
- 21 CFR 211.176指明当可能存在污染时，非青霉素产品必须被检测是否存在青霉素。如果发现有残留则不能销售。 这意味着这一个生产阶段的所有批号应取样检测，这些取样应有代表性，且方法应可接受。检测结果为未检出，方可进行下一阶段的生产。

Penicillin Issues
青霉素问题

- One case we reviewed demonstrated a positive environmental surface sample from the fan blade of an exhaust hood in the repack room for beta-lactam residue, even though the most recent beta-lactam repackaging operation had been performed more than six months prior to sampling.
- 我们遇到的一个例子是，尽管在取样时包装操作已经超过6个月，从包装室排风扇的翅子上擦试头孢残留依然呈阳性。

Penicillin Issues
青霉素问题

- Is it acceptable to manufacture penicillin products in the same facility as cephalosporin?
- 在同一个厂房内生产青霉素和头孢产品可以接受吗？

Penicillin Issues
青霉素问题

- Beta-lactams are products with a chemical substructure that contains the beta-lactam ring. They have the potential to sensitize and cause allergic response in humans. Hypersensitivity, due to intolerance of beta lactam ingredients, can trigger reactions which range from a rash to life-threatening anaphylaxis. There is evidence that cross-sensitivity exists between penicillins and cephalosporins. Thus, patients who are intolerant of penicillin may also be intolerant of cephalosporins, and further, cephalosporins may induce anaphylaxis in patients with a history of penicillin anaphylaxis.

- β内酰胺类产品是一类具有β内酰胺环化学结构的产品，具有潜在过敏性可导致人过敏。由于对β内酰胺类的不耐受性，超敏性可能引发从皮疹至有生命危险的过敏性反应。有例子表明青霉素和头孢类之间存在交叉污染。因此，不能耐受青霉素的病人也可不耐受头孢产品，而且，头孢也可诱发有青霉素过敏史的人过敏。

Penicillin Issues
青霉素问题

- The immune system is exquisitely sensitive and can distinguish between very subtle changes in chemical composition. Patients may be tolerant of a given drug but intolerant of another drug with closely related chemical structures. There is evidence that patients tolerant of penicillin may be intolerant of cephalosporins. CDER recognizes the considerable potential for cross-sensitivity and the possible life-threatening consequences of unintended exposure. Therefore, although not a specific requirement of sections 211.42 (d), 211.46(d) and 211.176, it is recommended that manufacturing operations for cephalosporins, penems and cephems, be separated from non-beta-lactam products and other beta-lactam drug products. For example cephalosporin type products would be separated from penicillin type products or non-beta-lactam products.

Penicillin Issues
青霉素问题

- 免疫系统非常敏感，可以识别化学物质的细微变化，病人可以耐受一个给定的药物，而可能不能耐受化学物质非常相近的另一个物质，也有证据表面有的病人能耐受青霉素而不能耐受头孢。CDER认识到很大的可能存在交叉过敏现场，从而由于非预期的泄漏导致威协到人的生命安全，因此尽管在211.42 (d), 211.46(d) 和 211.176里对头孢的生产没有特殊的要求，但是推荐头孢、青霉烯及头孢烯的生产操作，也应与其它非β内酰胺类产品及其它β内酰胺类产品分开生产，例如，头孢类产品与青霉素类产品或非β内酰胺类产品隔离生产。

Penicillin Issues
青霉素问题

- Production of cephalosporin type products can be approached from two different regulatory/compliance perspectives:

- 头孢类产品可以通过以下两种方法达到法规上的符合性：

Penicillin Issues
青霉素问题

- 1) If cephalosporins are considered to be non-penicillin drugs, they could not be manufactured in a facility lacking adequate separation from penicillin products. 2) For cephalosporin production with other non-beta-lactam drug products, similar health concerns exist for patients sensitive to cephalosporins who should not be exposed to it in a non-beta-lactam product.

- 1）如果头孢被理解为非青霉素药品，则不能在缺少足够隔离的生产青霉素的厂房内生产。 2）当头孢产品和其它非β内酰胺产品一同生产时，对那些对头孢过敏的人来说，也存在类似的健康问题，他们不能在使用非头孢类产品时，接触头孢类产品。

Penicillin Issues
青霉素问题

- For fundamental CGMP reasons and because of the difficulties in demonstrating and validating appropriate sampling and testing methodology for measuring cross-contamination, penicillin production should be performed in facilities separated from non-beta-lactam drug products and other beta-lactam drug products unless adequate separation is demonstrated. We don't know of a satisfactory shared facility as of today.

- 出于基本的CGMP考虑，以及交叉污染取样及检测方法验证的困难性，青霉素产品的生产应在独立的设施内进行，与非青霉素产品和其它β内酰胺产品分开，除非有足够的隔离。我们至今为止还没有了解到一个令人满意的共用厂房。

Penicillin Issues
青霉素问题

- Furthermore, if necessary, other sections of the CGMP regulations [i.e., 211.28; 211.42(b) & (c); 211.46(c); 211.67; and 211.80(b)] could be applied to control contamination between beta-lactam and non-beta-lactam drug products. In summary the Agency considers the separation of production facilities for sensitizing beta-lactam based products to be current good manufacturing practice.

- 此外，如果需要，其它CGMP的法规部分211.28; 211.42(b) & (c); 211.46(c); 211.67; and 211.80(b)可适用于控制β内酰胺和非β内酰胺产品之间的交叉污染。总之，本局是基于CGMP的生产实践要求来考虑过敏性产品β内酰胺产品的生产问题的。

Penicillin Issues
青霉素问题

- Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin solid dosage forms provided there is no further penicillin production in the renovated facility?

- 一个生产青霉素制剂的厂房，不再生产青霉素产品，是可否在去除污染和改造后用于生产非青霉素产品？

Penicillin Issues
青霉素问题

- Yes. However, the decontamination process is extremely difficult and we are unaware of any firm that has successfully decontaminated a penicillin facility and converted it to production of non-penicillin products.
- 可以。但是，去除污染是极为困难的，我们至今还没有了解到任何一个公司成功的去除了青霉素厂房的污染，转而生产非青霉素产品。（参考资料：头孢菌素和青霉素的清洁）

Penicillin Issues
青霉素问题

- Note that at section 211.176 the CGMP regulations require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and not marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present where decontamination has not been conducted effectively. That would put the responsible firm in a position of having to test each and every lot of non-penicillin product for the presence of penicillin.
- 注意到CGMP法规的211.176部分要求：如果非青霉素产品可能存在与青霉素产品交叉污染问题，必须检测非青霉素产品中的青霉素含量，如果用合法的方法检测到青霉素，则产品不能销售。如果不能有效的去除污染，则青霉素是可能存在的，这就使得企业有责任检测每一个批号的非青霉素产品。

Penicillin Issues
青霉素问题

- In sum, while the CGMP regulations would not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues makes the chore daunting.
- 总之，尽管CGMP并不禁止这种去污染和转产的做法，青霉素清洁残留的难度也会使人望而却步。

Penicillin Issues
青霉素问题

- Is there an acceptable level of penicillin residue in non-penicillin drug products?
- 在非青霉素药品中青霉素的残留标准是多少？

Penicillin Issues
青霉素问题

- Any detectable levels of penicillin residue are considered violative because 21 CFR 211.176 indicates that a non-penicillin drug product must not be marketed if detectable levels of penicillin are found when tested according to procedures specified in The Procedures for Detecting and Measuring Penicillin Contamination in Drugs.
- 任何可检查出的水平都是不可接受的，因为21 CFR 211.176指明：依据“检测和衡量药品中青霉素污染规程”中特定的程序进行检测，如果在非青霉素产品中发现任何水平的青霉素污染，则此产品不能销售。

Penicillin Issues
青霉素问题

- The current analytical standard for demonstrating adequate decontamination of facilities, separation within the same building, or measurement of cross-contamination is codified at 21 CFR 211.176 and 436.104 and has a limit of detectability of 0.006 ppm (as Penicillin G using S. Lutea) and a violative detection amount of 0.03 ppm. Note that the latter amount reflects the method's limits with respect to confidence and reproducibility and does not represent a tolerance level. This analytical methodology is limited to the detection of Penicillin G and ampicillin in a limited number of products listed in the referenced method, not including other beta-lactam antibiotics. In situations where this methodology is not workable, it is the firm's responsibility to develop, validate, and use other methodology with similar sensitivity.

Penicillin Issues
青霉素问题

- 目前针对证明厂房能被足够去除污染，同一个建筑物内的隔离，或者交叉污染检测的分析标准在21 CFR 211.176 和436.104中作了规定，LOD为0.006 ppm，不可接受的检测量为0.03 ppm。注意后者反应了方法的可信度及重现性，但不代表而耐受水平。这种分析方法仅适用于参照方法中列出的部分产品的青霉素G及氨苄青霉素检测，不包括其它beta-内酰胺类抗生素。如果此方法不适用，企业有责任开发、验证并使用其它类似灵敏度的方法来检测产品中的头孢。

Penicillin Issues
青霉素问题

- If a firm's only operation is performing finished packaging operations for bulk tablet and capsule drug products, must it still maintain separate facilities and equipment for packaging penicillin products?
- 如果一个公司的操作仅是片剂和胶囊的包装，也必须是独立的厂房及设备吗？

Penicillin Issues
青霉素问题

- Yes. The CGMP regulations explicitly require that operations relating to the manufacture, processing and packaging of penicillin be performed in facilities that are separate from those facilities used for other drugs. The regulations also require separate air-handling systems in facilities used for penicillin products. Furthermore, if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, CGMPs require that the non-penicillin drug be tested for the presence of penicillin. The CGMPs make no exceptions from the foregoing for operations that are limited to repackaging solid oral dosage forms.

Penicillin Issues
青霉素问题

- 是的，CGMP法规明确要求有关青霉素的生产，加工及包装的厂房应与其它的药品厂房分开。法规也要求在生产青霉素的厂房内应设有独立的空气处理系统。而且，如果存在非青霉素产品被青霉素产品污染的可能，CGMP要求应检测非青霉素产品中的青霉素含量，CGMP没有将固体制剂的包装排除在外。

Penicillin Issues
青霉素问题

- It should be noted that the requirement for separate facilities does not necessarily mean that operations relating to penicillin products must be conducted in separate buildings from other drugs. A separate area dedicated to penicillin products within a larger facility may be acceptable if penicillin containment can be established and validated.

- 应当指出，青霉素生产需要隔离的设施并不意味着需要独立的建筑，如果青霉素的污染程度可以确定且经过验证，则可以接受在一个较大的设施内使用青霉素专用隔离区域。

咨询联系信息

- 张顺杰经理
- MP:13636336667
- TEL：021 6426 2161
- Email: jack@shnovoscience.com

- 程毓渡博士
- MP：13818112430
- TEL：021 6426 2161
- Email: yudu.cheng@shnovoscience.com