PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

PSCI Supplier Conference Shanghai

PSCI供应商会议 · 上海

19-20 September 2018

Day 2 - PSM & Industrial Hygiene Session

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会议须知 Practicalities

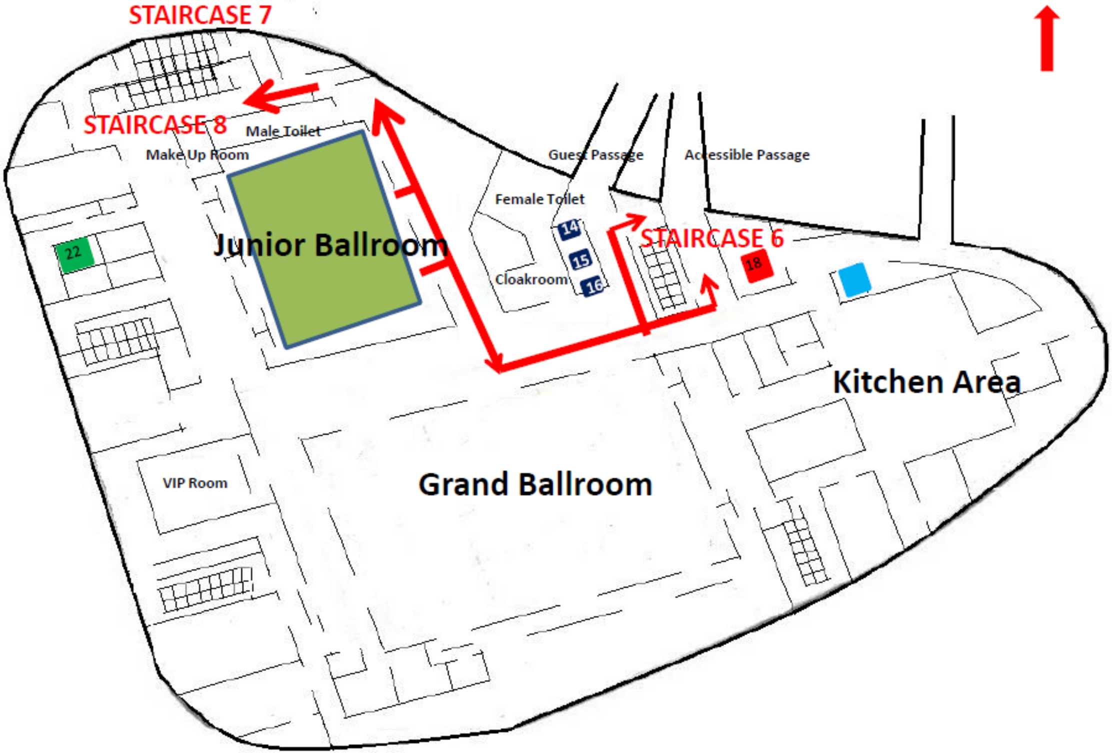
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

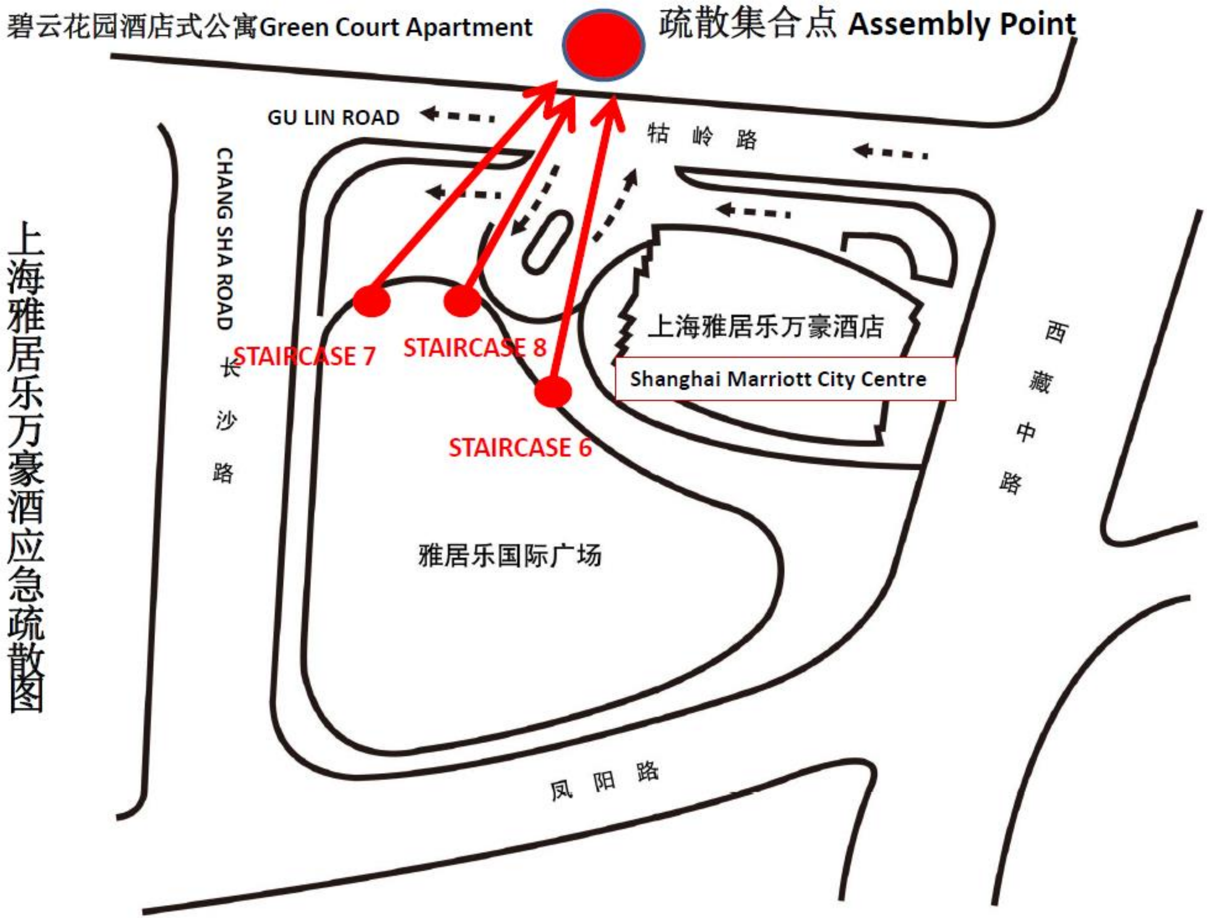
- 手机请静音 Please mute your cell phones
- 午餐及茶歇 Lunch and breaks
- 时间控制 Timings – please look at the agenda
- 反馈调查 Feedback survey
- 安全须知 Safety briefing

5F小宴会厅疏散线路图

内部厨房电梯
酒店大货梯
消防电梯
宴会厅客用电梯

Junior Ballroom Evacuation Route




上海雅居乐万豪酒应急疏散图
碧云花园酒店式公寓Green Court Apartment
疏散集合点 Assembly Point
GU LIN ROAD
牯 岭 路
CHANG SHA ROAD
长 沙 路
STAIRCASE 7
STAIRCASE 8
STAIRCASE 6
上海雅居乐万豪酒店
Shanghai Marriott City Centre
西 藏 中 路
雅居乐国际广场
凤 阳 路

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While some activities among competitors are both legal and beneficial to the industry, group activities of competitors are inherently suspect under the antitrust/anti-competition laws of the US, UK and other countries in which our companies do business. Agreements between or among competitors need not be formal to raise questions under antitrust laws, but may include any kind of understanding, formal or informal, secretive or public, under which each of the participants can reasonably expect that another will follow a particular course of action or conduct. Each of the participants in this meeting is responsible for seeing that topics which may give an appearance of an agreement that would violate the antitrust laws are not discussed. It is the responsibility of each participant in the first instance to avoid raising improper subjects for discussion, such as those identified below.

It is the sole purpose of this meeting to provide a forum for expression of various points of view on topics described in the agenda and participants should adhere to that agenda. Under no circumstances shall this meeting be used as a means for competing companies to reach any understanding, expressed or implied, which tends to restrict competition, or in any way to impair the ability of members to exercise independent business judgment regarding matters affecting competition.

Topics of discussion that should be specifically avoided are:

i. Price fixing;

ii. Product discounts, rebates, pricing policies, levels of production or sales and marketing terms customer and territorial allocation;

iii. Standards setting (when its purpose is to limit the availability and selection of products, limit competition, restrict entry into an industry, inhibit innovation or inhibit the ability of competitors to compete);

iv. Codes of ethics administered in a way that could inhibit or restrict competition;

v. Group boycotts;

vi. Validity of patents;

vii. On-going litigation;

viii. Specific R&D, sales or marketing activities or plans, or confidential product, product development, production or testing strategies or other proprietary knowledge or information

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本次会议的唯一目的是，提供一个对议程中所列出的主题表达各种观点的论坛，并且参与者应紧紧围绕这一议程进行讨论。在任何情况下，都不许将本次会议作为一种手段，让竞争公司之间达成任何明示或暗示的的谅解，从而趋向于限制竞争，或以任何可能的方式削弱成员就影响竞争的事宜行使其独立的业务判断能力。

应当特别避免的讨论主题是：

（一）限价；

（二）产品折扣、回扣、定价政策、生产水平或销售和市场营销条款、以及客户和地域分配；

（三）标准设置（如果其目的是限制产品的供应和选择，限制竞争，限制进入某一行业，阻碍创新或抑制竞争对手的竞争能力）；

（四）以一种可能抑制或限制竞争的方式管理道德准则的实施；

（五）集体抵制；

（六）专利有效性；

（七）正在进行的诉讼；

（八）特定的研发、销售和市场营销活动或计划，或保密产品、产品开发、生产或测试策略或其它专有知识或信息。

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Fire Protection 消防

Presented by
Dr. Daniel Rehm
HSE Consultant Elanco External Manufacturing EMEA & API
由Daniel Rehm博士来演讲
HSE顾问，礼来动物保健外部制造，欧洲、非洲和中东&原料药

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Fire statistics 火灾统计

Agenda 议题

1. Passive fire protection 被动防火措施
2. Fire detection 火灾探测
3. Fire Fighting 消防
4. Water Supply 供水

Sandwich panels 夹层板材
Example: Torch in Dubai
举例：迪拜“火炬塔”火灾

Passive fire protection 被动防火措施
Fire walls 防火墙

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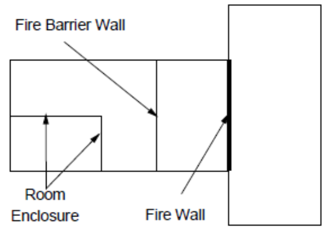
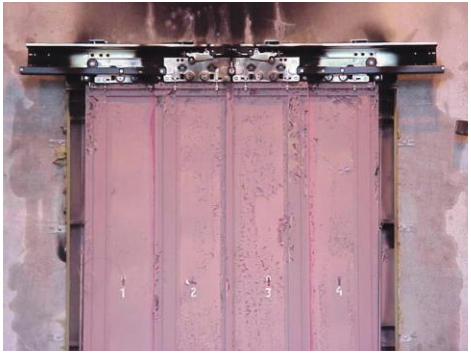
- Fire walls are barriers to keep fire limited to one area
- 防火墙是将火灾限制在一个区域的屏障
- A fire wall should offer at least 2 h of fire resistance
- 防火墙应该有至少2个小时的耐火时间
- Look for openings!!!
- 寻找开口！！！



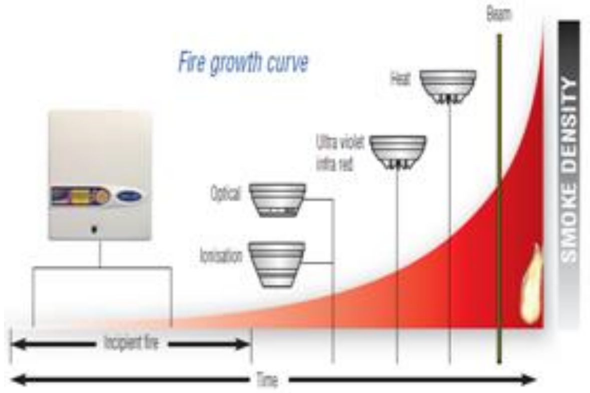
Passive fire protection 被动防火措施
Fire doors 防火门

- A fire door should offer at least 1 h of fire resistance
- 防火门应该有至少1个小时的耐火时间
- Reliability is about 80%! Monthly testing required!
- 可靠性是大约80%!需要月度测试!



Types of fire detectors 火灾探测器的类型

- Humans! 人！
- Smoke detectors 感烟探测器
- Heat detectors 感温探测器
- Beam detectors 束流探测器



Fire detection火灾探测
Smoke detector 感烟探测器

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- Different types are on the market 市场上有不同种类型
- New types can be adjusted to environment to achieve specific sensitivity 新型感烟探测器可以根据环境进行调整来达到特定的敏感度
- Correct installation is crucial: (always) on the highest point to detect smoke early 正确安装非常关键：火灾初期（总是）在最高点检测到烟雾

Fire detection火灾探测
Heat detector 感温探测器

- Correct installation is crucial 正确安装非常关键
- Alternative: heat sensitive cameras 供替代：热敏摄像机

Fire detection 火灾探测
Beam detector/Linear detector
束流探测器/线性探测器

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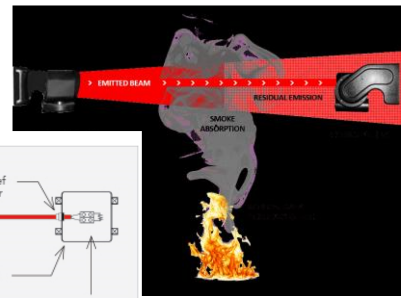
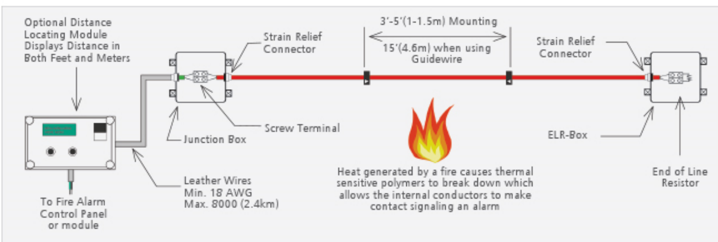
- Use in large area warehouses and workshops 用于大的区域，仓库和车间
- Very sensitive 非常敏感
- Correct installation height: at 90% of room height 正确安装高度：在房间高度90%的位置





Fire detection火灾探测
Warehouses with APIs/Pharmaceuticals
在原料药/制剂仓库

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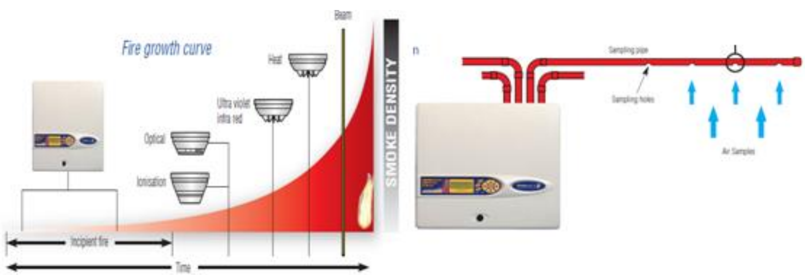
- Highly sensitive smoke detection systems 高敏感性感烟探测系统



- Alternatives 供
  - Early detection fast response sprinklers 早期检测快速响应喷头
  - Low Oxygen (13 -15% O_2) systems 低氧（13 -15% O_2）系统

Fire fighting 消防

Fire Extinguishers 灭火器
Spot the hazard 发现风险

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Fire Extinguishers 灭火器
Key points 关键点

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- Are the employees are trained to use fire extinguishers?
- 员工有没有被培训来使用灭火器？
- Are fire extinguishers of the appropriate type?
- 灭火器是合适的类型吗？
- Ensure appropriate inspections have taken place in a timely fashion per frequency determined for the facility?
- 基于工厂确定的频率，是否及时地进行灭火器的检查？
- Ensure fire extinguishers, hose reels, etc. are not blocked / obstructed, etc. Directional arrows, signs should be displayed where equipment is hidden from directional view
- 确保灭火器、消火栓等不被阻挡/阻塞。设备阻挡视线方向的区域，带有方向性的箭头、标志也应该显示出来。

Fire Extinguishers 灭火器
Types of extinguishers 灭火器的类型

Fire class	Geometric symbol	Pictogram	Intended use	Mnemonic
A			Ordinary solid combustibles	A for "Ash"
B			Flammable liquids and gases	B for "Barrel"
C			Energized electrical equipment	C for "Current"
D			Combustible metals	D for "Dynamite"
K			Oils and fats	K for "Kitchen"

Fire Extinguishers 灭火器 Standards 标准

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- NPFA 10: Standard for portable fire extinguishers
- NFPA（美国防火协会） 10：手提式灭火器标准
- Every country has its own rules concerning: amount, size and types of portable extinguishers
- 每个国家有它自己的相关规范：数量、大小和手提式灭火器的类型

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- Complex systems with many parts (pumps, valves, headers, heads etc.)
- 有很多零部件的复杂系统（泵、阀门、供水总管、喷淋头等）
- Typical systems: 典型的系统
  - Dry system 干式系统
  - Wet system 湿式系统
  - Foam systems 泡沫系统
  - Deluge system 雨淋系统
- Standards: 标准
  - NFPA 13 (US美国)
  - CEA 4001 & EN 12845 (Europe欧洲)

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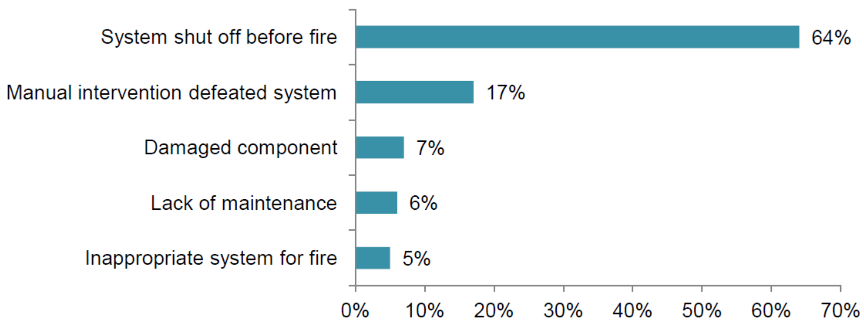
In 2007-2011 fires large enough to activate them, sprinklers operated in 91% of fires in sprinklered properties. The graph below is based on the other 9% in which sprinklers should have operated but did not.

Reasons When Sprinklers Fail to Operate, 2007-2011



Sprinkler 喷淋
What to look for 需要注意什么

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- Correct system? 系统是否正确
  - Foam system for flammable liquids? / Alcohol resistant foam needed? 针对易燃液体配备泡沫系统/是否需要抗溶性泡沫？
  - Automatic or manual? (sprinkler or deluge system?) 自动或者手动（喷淋或者雨淋系统？）
  - In-rack sprinkler (every 2.5 m in high rack storage) 货架内喷淋（高层货架储存时按照每2.5米进行配备）
- Regular testing and Maintenance by **qualified** 3rd party 需要有资质的第三方来定期的测试和维护
  - Flow test: 1/a, valve check 1/month/ visual check 1/week 流量测试：1次/年，阀门检查：1次/月，目视检查：1次/周
- Protection against freezing? 防冻保护
  - Anti-freeze can lead to leakage during summer 防冻措施在夏季可能会导致泄露
- Closed valves at foam tanks and headers!泡沫罐和供水总管上关闭的阀门
- Design documentation 设计文件
  - Correct occupancy 符合设施（用途）
- Fire load below sprinklers 喷淋下的火灾载荷
  - <1.8 m wooden pallets <1.8米的木托盘
  - < 2.5 m empty plastic container <2.5米的空塑料容器
  - <2 IBCs with flammable liquids <2个有易燃液体的IBCs
- MOC! 变更管理
  - Change of sprinkler design in case of change in occupancy 如果设施（用途）变化，喷淋设计也要变更

Sprinkler 喷淋
Other systems 其它类型的系统

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- Powder 粉末
- Water mist 水雾
- **Light and heavy foam 轻型和重型泡沫**

- Systems with only limited applications and questionabl 究应用范围有限制，（在有些情况下）不应该使用这些喷淋系统
- Foam systems for flammable storage 用于易燃（液体）存储的泡沫系统

Sprinkler 喷淋
What does not work 什么情况下不正常工作

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- Stacked IBCs with flammable/combustible liquids: max height 2 when foam is available
- 叠放的IBCs内装有易燃/可燃液体：最大高度是2层IBCs（叠放）的情况下，泡沫系统才能正常工作。

- Sprinkler protection in warehouses: 仓库内的喷淋保护
  - Sprinkler protect buildings not stored goods
  - 喷淋保护建筑，不保护储存的货物
  - Water and smoke damage render goods unusable
  - 水和烟气损害致使货物不稳定
  - Loss for electronics and pharmaceuticals: 100%
  - 电子（设备）和药物损失率：100%
- **Maintaining small fire areas is crucial to limit loss of product**
- **为了减少产品损失，维持小范围过火区域至关重要**

	Structural damage 结构毁坏	Damage to stored goods 储存的货物毁坏
No sprinkler protection 无喷淋保护	100%	100%
Sprinkler protection 喷淋保护	<10%	**50 to 100%**

Sprinkler systems 喷淋系统 Standards 标准

- NPFA 13: Standard for the Installation of Sprinkler Systems
- NFPA13：喷淋系统安装标准
- CEA 4001
- NFPA 2001: Standard on Clean Agent Fire Extinguishing Systems (CO_2, Foam, FM200 etc.)
- NFPA2001：清洁剂灭火系统标准（二氧化碳、泡沫、七氟丙烷等）

Fire brigade 消防队
What to look for 需要注意什么

- Site own fire brigade? Trained fire fighters on site? 工厂自己的消防队？工厂是否有受训的消防员
- Professional vs. voluntary fire brigade 专业的 *对比* 自愿的消防队伍
- Mutual aid available? 是否有互助？
- Equipment (no of fire trucks etc.) 设备（消防车的数量等）
- Capabilities in fighting chemical fires 扑灭化学类火灾的能力
- Distance to site 与工厂的距离
- Intervention time (time from start to full fire = 10 minutes!) 干预时机（从开始到大火阶段的时间=10分钟！）

Water supply 供水

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Water supply 供水
Minimum requirements 最低要求

- Water supply depends on occupancy 供水取决于设施（用途）
- Rules-of-thumb: 经验法则
  - Office building: 1’200 L/Min for 90 Minutes: 108 m^3
  - 办公室建筑： 1’200 升/分钟，至少90分钟：108立方米
  - Chemical plant: 3’000 L/Min for 90 Minutes: 270 m^3
  - 化学品装置： 3’000 升/分钟，至少90分钟：270立方米
  - Warehouse: 3’000 L/Min for 120 Minutes: 360 m^3
  - 仓库： 3’000 升/分钟，至少120分钟：360立方米
  - Refinery: 15’000 L/Min for 120 Minutes: 1’800 m^3
  - 炼油厂： 15’000 升/分钟，至少120分钟： 1’800 立方米
  - **Site water supply: at least 300 m^3** 工厂供水：至少300立方米

Water supply 供水
Water sources 水源

- Recommendation: 推荐
  - **Reliable water source 可靠的水源**
  - Independent from municipal supply 独立于市政供水
  - When connected to municipal supply: a ring pipeline with 2 independent connections
  - 当与市政供水连接时：一根环形管道上有两根独立的（管道）连接
- Possible other sources: 可能的其它水源
  - Rivers 河流
  - Lakes 湖泊
  - Ponds 池塘
- Water supply situation of the whole area needs to be taken in account 需要把整个区域的供水情况考虑在内

Water supply 供水
Hydrants 消火栓

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- When connected to municipal supply: a ring pipeline with 2 independent connections 当与市政供水连接时：一根环形管道上有两根独立的（管道）连接
- Test requirements: 测试要求
  - Flow test (m/s and p): 1/a 流量测试：1次/年
  - Use test: 1/m 使用测试：1次/月
  - Visual inspection: 1/w 目视检查：1次/周
- What to look for:需要注意什么
  - Condition of hydrants 消火栓的条件
  - Is the location marked? 位置是否有显著标识
  - Is the number sufficient and are all hydrants accessible?
  - 数量是否足够，以及是否所有消火栓都可接近使用？

Water supply 供水
Free access to hydrants
消火栓要不受限制的接近使用

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Water supply 供水
Water retention 水的存储

- Retention of contaminated fire water 受污染的消防水的存储
  - Assumption: 2 h fire fighting 假设：2小时消防水
  - 400 m^3 of fire water + rain water! 消防水+雨水，需要400立方米（容量）
- What to look for:需要注意什么
  - Fire water retention capacity available? 消防水存储能力是否足够?
  - How much? 有多少?
  - If not: where would the water flow? 如果不够，水会流到那里?

- 01.11.1986: Schweizerhalle fire 1986年11月1日，（瑞士巴塞尔）施韦策哈勒火灾

Water retention 水的存储
01.11.1986: Schweizerhalle fire
1986年11月1日，（瑞士巴塞尔）施韦策哈勒火灾

Water supply 供水
Fire pumps 消防泵

- Fire pumps are installed to provide sufficient flow and pressure to feed sprinklers or hydrants
- 消防泵为喷淋系统和消火栓提供足够的流量和压力。
- Correct installation, testing and maintenance is crucial
- 正确的安装、测试和维护至关重要。

Fire pumps 消防泵
What to look for需要注意什么

- **Setup of pumps 泵的设置**
  - Diesel and/or electrical pumps with jockey pumps 带有稳压泵的柴油和/或电泵
  - “Standard setup”: 2 main pumps (1 electrical, 1 diesel and 2 jockey pumps) “标准设置”： 2个主泵（1个电泵、1个柴油泵和2个稳压泵）
  - Pumps are available during power cut? 停电期间泵是否可以正常供使用?
  - Pumps are in auto or manual mode? 泵是在自动还是手动模式?
- **Testing of pumps 泵的测试**
  - Flow test 1/a 流量测试：1次/年
  - Functional testing: 功能性测试
    - diesel 1/week 30 Minutes (NFPA 25) 柴油泵 1次/每周 持续30分钟 （NFPA25)
    - electrical 1/months 10 Minutes (NFPA 25) 电泵 1次/每月 持续10分钟 （NFPA25)
    - Power generator 1/months 30 Minutes (NFPA 101) 发电机 1次/每月 持续30分钟 （NFPA101)

The Pharmaceutical Supply Chain Initiative
药品供应链倡议

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Chemical Process Safety: Which parameters are important to perform a chemical reaction in a safe way

化学工艺安全：安全实施化学反应的重要参数

Liu Li 刘立
Boehringer Ingelheim China, ISEE
勃林格殷格翰中国，ISEE

Dr. Stefan Gries
Boehringer Ingelheim Corporate Center, Corp. EHS&S
勃林格殷格翰总部，总部EHS&S

AGENDA

Essential information to chemical processes 必要的化学工艺信息

Critical interactions of material 物料间的关键相互作用

Exothermic and run-away reaction 放热及失控的反应

Scale up 放大

Li Liu 刘立

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Chemist 化学背景
- 7 years with Boehringer Ingelheim China (BI CN) 勃林格殷格翰（BI）中国工作7年
- Current Position: BI ISEE China (Infrastructure, Safety & Environment, Engineering. EHS Auditor.) 目前工作： BI中国 ISEE （基础建设，安全&环保，工程。 EHS审核员）

- Former Experiences 以往经历：

  Chemical Process Research & Development 化学工艺研究开发

  Pharmaceutical Chemist 药物化学

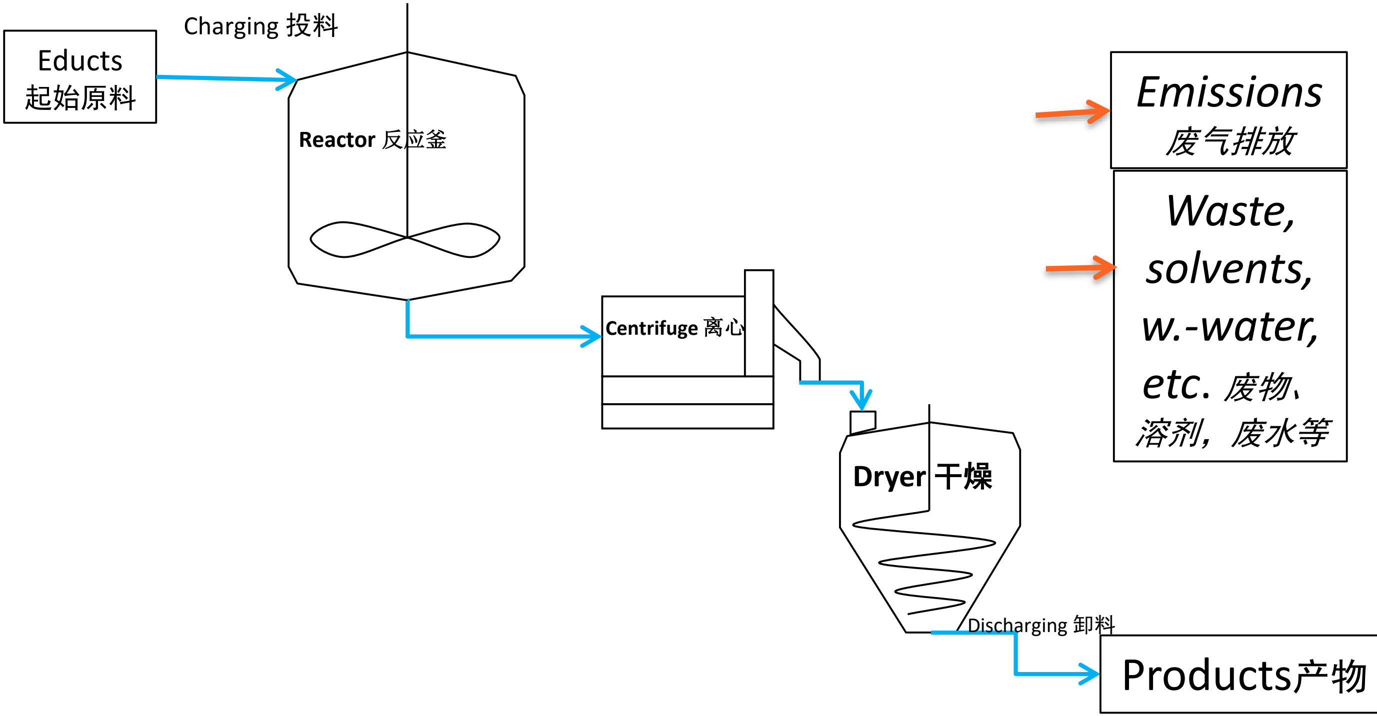
Dr. Stefan Gries

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Chemist 化学背景
- More than 25 years with Boehringer Ingelheim 勃林格殷格翰工作超过25年
- Current position: Corp. EHS & S (occupational health, exposure control, soil and groundwater protection, EHS auditor) 目前部门：BI总部EHS&S （职业健康，职业接触控制，土壤和地下水保护，EHS审核员）
- Former positions in 以往工作
  - Local EHS 当地EHS部门
  - Research & Development (head of pilot plant) 研发（中试车间负责人）
  - Chemical Production (head of production plant B) 化学生产（API工厂plant B负责人 ）

Chemical reaction in a production plant
工厂生产中的化学反应

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



Which information is necessary for a safe process?
安全的工艺需要哪些信息？

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Knowledge about the used chemicals regarding thermal stability, physical safety parameters and toxicology 所使用化学物质的信息，包括热稳定性，理化安全数据，毒性。 包括：
  - Educts 起始物料
  - Products (incl. side products) 产物（包括副产物）
  - Reagents 试剂
  - Solvents 溶剂
  - Auxiliaries 辅助试剂

- Knowledge about the chemistry 化学知识
  - Main reaction and side reactions 主反应和副反应
  - Waste streams (gas release, liquids and solids) 废弃物产生 （气体释放，液废和固废）
  - Consecutive reaction, decomposition? 连串的反应， 分解

- Reaction type 反应类型
  - Batch reaction 间歇式反应
  - Semi-batch reaction 半间歇式反应
  - Continuous flow reaction 连续反应

What is necessary for a safe process? 工艺安全的必要条件

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Calorimetric data of the chemical reaction 化学反应的量热数据
  - Adiabatic temperature rise 绝热温升
  - Gas evolution rate (→ reactor venting sufficiant?) 放气速率（反应釜泄放足够？）
  - precipitation of solids (→ reduction of heat transfer, stirrer blocking?) 固体析出（传热降低，搅拌受阻）
  - Accumulation of reactants, thermal output/time 反应物累积，放热量/时间
  - Stability of reaction mixtures, distillation residues, etc. 反应混合物、蒸馏残渣的稳定性
  - Potential for runaway reaction, abnormal operating conditions 失控反应的可能性，异常操作条件
  - If necessary: investigation of the runaway reaction 如必要：研究失控反应
- Knowledge about critical interaction between the used chemicals and other material所用化学物质和其他物料的关键反应
  - Material resistance of reactor & other equipment 反应釜和其他设备物料耐受程度
  - Possible material contact (e.g. media supply) 可能接触的物料（如介质）

What is necessary for a safe process? 工艺安全的必要条件

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Plant equipment “state of the art”: 生产设备技术水平
  - Inertisation of equipment 设备惰化
  - Materials of the equipment = > materials test, corrosive data, etc. 设备材质=> 物料测试，腐蚀数据等
  - Earthing of the equipment, explosion-proof equipment 设备接地，防爆
  - Blow-down system, pressure relief valve, rupture disc, 应急泄放系统，安全阀，防爆片
  - Heating and cooling medium 加热、冷却介质
  - Heating and cooling capacity 加热、冷却能力
  - Safety concept e. g. for electrical shut down 安全措施，如电力中断的应对

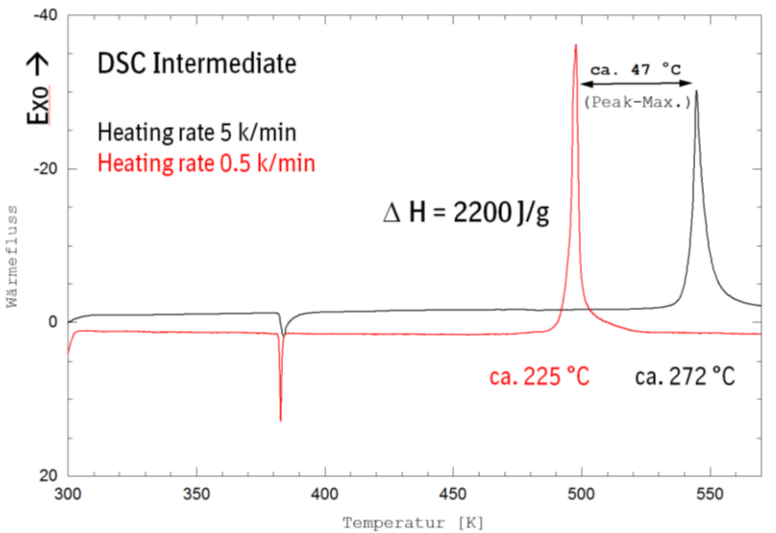
→ Process Hazard Analysis 工艺危害分析
  - Examination of the chemical properties and chemical process safety data together with the technical installation of the plant 和设备技术人员一起检查化学品性质和化学工艺安全数据

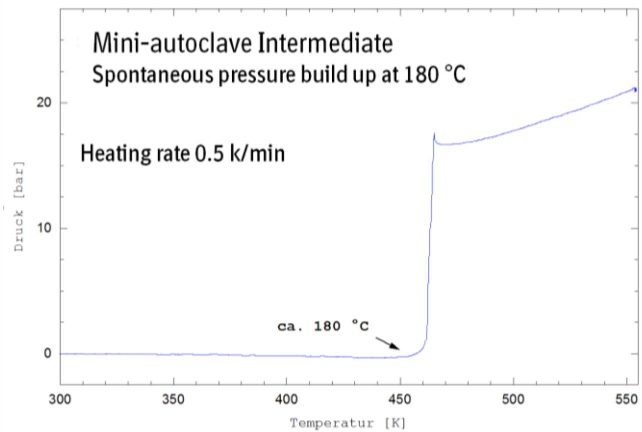
A safe chemical process is always an adequate combination of substance handling, chemical process and equipment. 物料操作、化学工艺和设备条件是实现安全化学工艺必不可少的组成部分。

Thermal stability of chemical substances and reaction mixtures
化学物质/反应混合物的热稳定性

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Thermal stability: 热稳定性
  - Differential Scanning Calorimetry (DSC) or Differential Thermo Analyses (DTA)
- Decomposition test closed vessel (pressure build-up): 封闭容器内的热分解测试（压力测试）
  - e.g. in a mini-autoclave





Known hazardous substances
已知危险物质

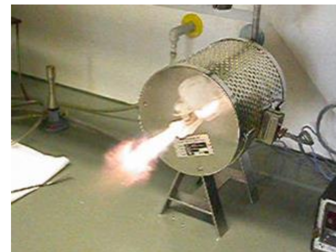
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Typical chemical functions in thermodynamically unstable compounds:
  热不稳定化合物的常见官能团：
  - $-C \equiv C-$ acetylene and acetylide
  - $-N_3$ azide and hydrogen azide
  - $-N \equiv N^+$ diazonium salts, triazene, tetrazene
  - $-N=N-$ azo compounds
  - $-HN-NH-$ hydrazide
  - $>C=N=O$ fulminates, oximates
  - $>N-X$ halogene nitrogene compounds
  - $-NO_x$ nitrites, nitrates, nitro- and nitroso compounds
  - $-O-O-$ peroxides, peroxy acids, ozonids
  - $-O-ClO_x$ (per-)chlorate, (hypo-)chlorite

General handling characteristic of substances 物料操作情况

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Additional test for thermal stability 进一步热稳定性测试
  - Thermogravimetry (TG) or combination TG/DSC; TG/DTA
  - Quasi-adiabatic heat aging in a Dewar flask (or an adiabatic calorimeter)
  - Time Pressure Test



- Flammability of solids or liquids 固体或液体燃烧性能
  - Combustion test
  - Flammability of solids
  - Smoldering temperature; minimum ignition temperature of a dust layer
  - (minimum) dust cloud ignition temperature
  - Ignition temperature of liquids
  - Flash point (of liquids)

General handling characteristic of substances物料操作情况

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Dust explosibility: 粉尘爆炸性
  - Dust explosion test
  - Dust explosion characteristics (p_{max}; $(dp/dt)_{max}$; K_{St}; explosion limits
  - Minimum ignition energy (MIE)
- Mechanical sensitivity, further safety characteristics 机械敏感度，更多安全参数
  - Sensitivity to impact
  - Sensitivity to friction
  - Self-ignition test
  - Conductivity

Critical interaction between chemicals and materials 化学品和物料的关键相容性

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Incident in a chemical production plant A: 工厂A的一次事故
- Due to an operational error a mixture of thionyl chloride, ethyl acetate and acetyl chloride have to be disposed of. For disposal the worker used the empty thionyl chloride drum. Short time later the drum exploded. 由于操作失误，用氯化亚砜空桶盛装废弃的氯化亚砜、乙酸乙酯和乙酰氯混合物。 该废液桶很快爆炸。

- Result of safety examination in laboratory: 实验室安全调查结果
- No critical reaction between thionyl chloride, ethyl acetate and acetyl chloride. 氯化亚砜、乙酸乙酯和乙酰氯之间没有明显反应。
- But, the used drum was zinc-coated
  ➔ critical reaction under pressure build-up between ethyl acetate, thionyl chloride and zinc!
  然而，这个空桶是镀锌桶。
  ➔乙酸乙酯、氯化亚砜和锌发生明显反应，并放气超压。

Critical interaction between chemicals and materials 化学品和物料的关键相容性

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Incident in a chemical production plant B: 工厂B的一次事故
  - In a process the excess of $POCl_3$ is distilled off and purged into a 200 l steel drum with a PE-inliner. Approx. 10 h later the drum burst. 蒸馏出的过量$POCl_3$倒入一个200L衬PE的钢桶中。 约10小时后，金属桶爆裂。
  - Between the batches the pipes were washed with acetone. Residual quantities of acetone remained in the pipes. 批次间清洗使用丙酮，管道中有丙酮残留。

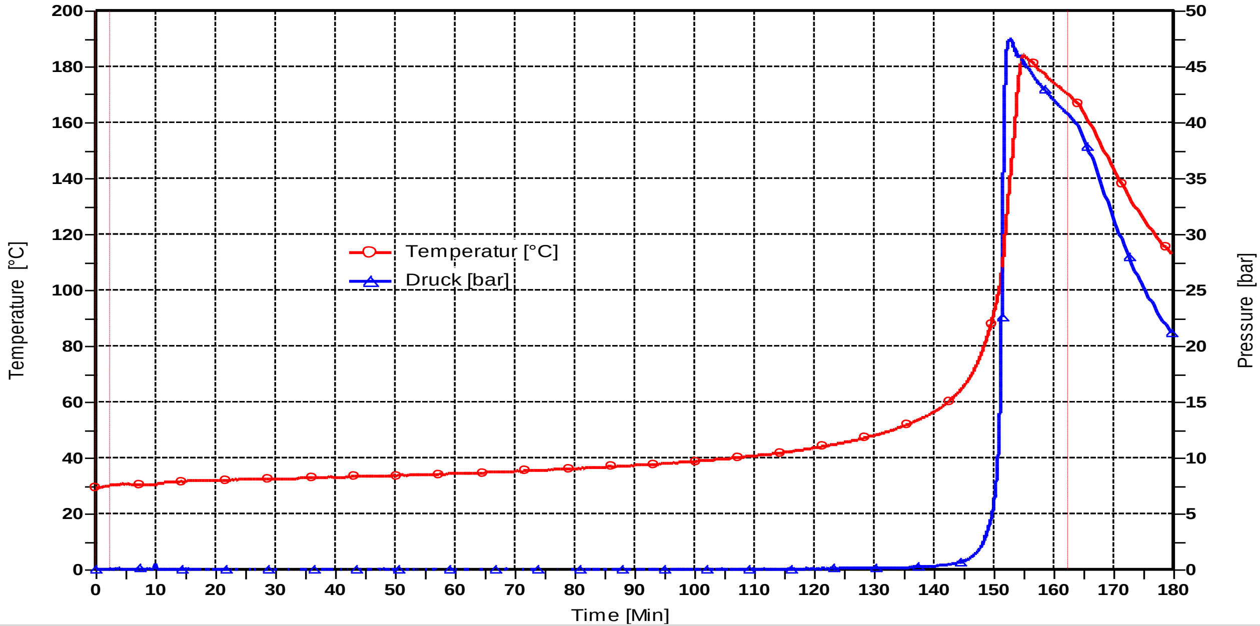
- Result of safety examination in laboratory 实验室安全调查结果:
  - Retarded critical reaction between acetone and $POCl_3$. 丙酮与$POCl_3$ 缓慢反应。

Critical interaction between chemicals and materials 化学品和物料的关键相容性

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Reaction experiment 反应测试

- closed cell test, $POCl_3$ overlay with ca. 5.8 weight-% acetone

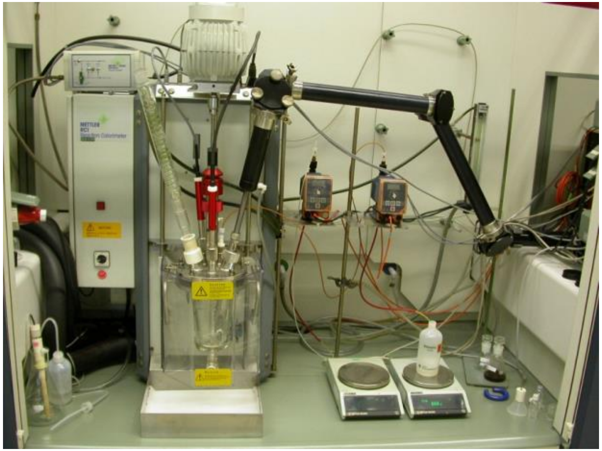


Chemical reaction parameters, calorimetric measurements
化学反应安全参数，反应热测试

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Safety investigation of reaction under process like conditions:正常反应条件下的测试
  - reaction calorimeter (e.g. Mettler RC1) with dosing, gas measurement etc.

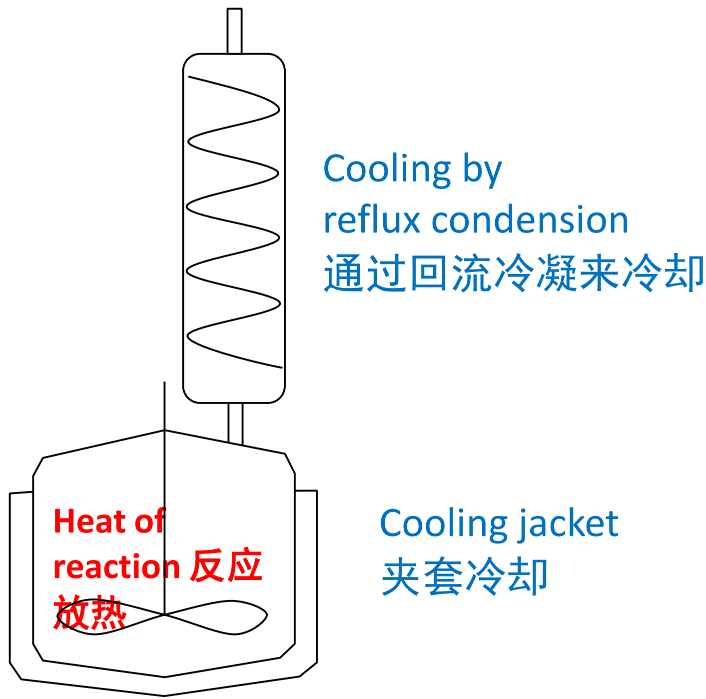
- Determination of: 测量参数
  - Heat of reaction反应热 ΔH_R [J/g] or [J/mol]
  - Heat capacity热容 C_p [J/g K]
  - Adiabatic temperature rise 绝热温升 ΔT_{ad} [K] or [°C]
  - Degree of accumulation 反应累积[%]
  - Gas release 气体释放 [l/min]



- Adiabatic investigation of abnormal operating conditions: 异常条件的绝热测试
  - determination of thermal stability under adiabatic conditions (no heat exchange between reaction mass and surroundings)

Temperature control of chemical reaction
反应中的温度控制

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



Heat balance of exothermic reactions
放热反应的热平衡

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

heat production
产生热

heat removal
消除热

Increased heat production 增加热产生的条件

- Additional energy supply 额外的能量施加 (e.g. heating, stirring, pumping如加热、搅拌、泵)
- Higher concentration of reactants 提高反应物浓度 (e. g. missing solvent 如溶剂减少)
- Presence of a catalyst 催化剂的存在 (e.g. rust, nonferrous metals)
- Initiation of other exothermic processes引发其他放热反应 (e.g. side reaction, decomposition如副反应，分解)

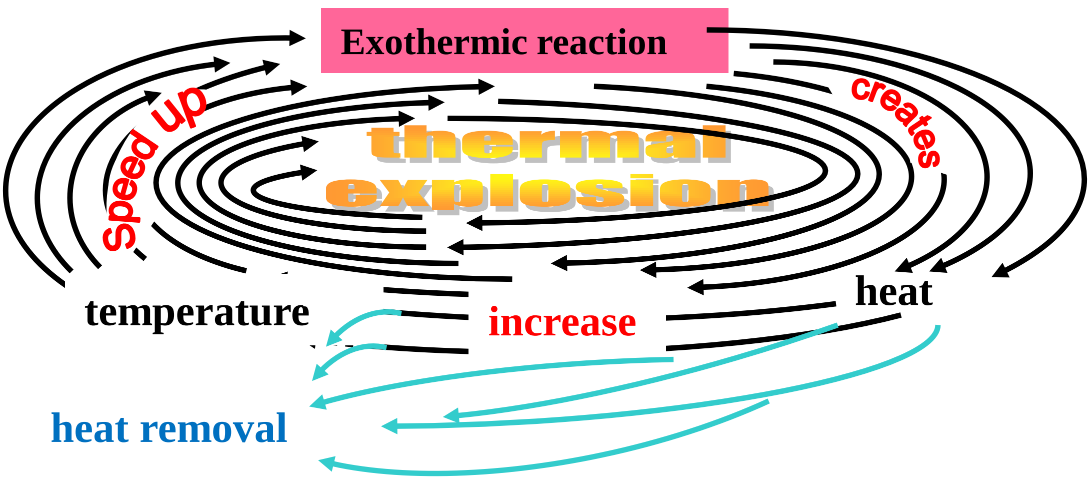
Decreased heat removal 降低热消除的条件按

- Loss of cooling冷却失效 (e.g. pump failure, solvent evaporated)
- Degrade heat transfer传热降低 (e.g. fouling, adhesion)
- Increase of viscosity 粘度增加 (e.g. higher degree of polymerization)
- Inadequate mixing 搅拌不充分 (e.g. pump failure, solvent evaporated, stirrer failure)

Exothermic and run-away reaction
放热失控反应

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- An exothermic reaction produces heat which leads to an increase of the reaction temperature if the cooling capacity is not sufficient. 如果冷却能力不够，导致放热反应的自加热，反应体系温度升高。
- A runaway reaction is an exothermic chemical process, which leads to uncontrollable reaction conditions due to an uncontrolled rise of the reaction speed. 失控反应是一个放热化学反应过程，它是由于反应条件失控导致反应温度以不可控的升高造成的。



Exothermic reaction and run-away reaction放热失控反应

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Scale up 放大
laboratory → (pilot) plant 实验室到中试车间

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Example of a heat balance change during the scale up 放大中的热平衡举例 （1L到1m³）

- From laboratory (1 l) to pilot plant (1 m^3). 实验室1L到中试1立方
- Dosing controlled reaction 加料控制反应
- Exothermic reaction 放热
- Reaction heat of 360 kJ kg^{-1} (= 0,1 kWh kg^{-1}) 反应热
- Reaction temperature 80 ° C 反应温度
- Density of reaction mass is 1 g cm^{-3}反应混合物密度
- Filling degree is 100 % 反应器容积使用率
- Heat transmission of both apparatus are 500 W m^{-2} K^{-1} 传热系数相同
- Effective temperature difference for cooling is 30 ° C 冷却温差

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Scale up 放大
laboratory → (pilot) plant 实验室到中试车间

	Laboratory	Pilot or production plant
Reactor size	1 l	1 m^3
Cooling surface	0,046 m^2	4,4 m^2
Specific cooling power	15 kW m^{-2} (= 500 W m^{-2} K^{-1} * 30 K)	
Cooling power	**0,69 kW** (= 15 kW m^{-2} * 0,046 m^2)	**66 kW** (= 15 kW m^{-2} * 4,4 m^2)
Reaction power with 3 h dosing time	0,03 kW (= 0,1 kWh kg^{-1} * 1 kg /3h) heating required	33 kW (= 0,1 kWh kg^{-1} * 1000 kg /3h) cooling sufficient
Reaction power with 2 h dosing time	0,05 kW (= 0,1 kWh kg^{-1} * 1 kg /2h) no cooling required	50 kW (= 0,1 kWh kg^{-1} * 1000 kg /2h) cooling sufficient
Reaction power with 1 h dosing time	0,1 kW (= 0,1 kWh kg^{-1} * 1 kg /2h) cooling sufficient	**100 kW** (= 0,1 kWh kg^{-1} * 1000 kg /1h) **cooling insufficient**

Factor 1000

Factor ~100

Factor ~100

Expectation of an EHS auditor
PSCI questionaire „Process safety“
EHS审核员的期望/PSCI问卷“过程安全”

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Implemented rules for „safe development“ 落实工艺开发中的安全原则
- Essential examination of the chemical reactions (ΔH_R , c_p , ΔT_{ad} …) and substances (thermal stability, minimal ignition energy, …) 对反应和物料进行必要的考查。
- Transfer protocol from research & development-- pilot plant – production 从实验室到中试，再到生产转移方案
- Risk assessement for the chemical process and defined measures to assure a safe process 工艺风险评估，以及制定相应的措施保障工艺安全。

SEPT 19-20 PSCI SUPPLIER CONFERENCE

Usefull Links
参考资料

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- https://www.bgrci.de/fachwissen-portal/topic-list/hazardous-substances/
- https://downloadcenter.bgrci.de/resource/downloadcenter/downloads/R003e_Gesamtdokument.pdf

Questions

Sources of pictures
图片来源

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Most of the pictures are taken in our laboratories or production plants (Boehringer Ingelheim)
- Pictures Page 21:
  - BG RCI, R 001 - Exotherme chemische Reaktionen (BGI 541)
  - BG RCI, R 004 - Thermische Sicherheit chemischer Prozesse (BGI 828)
  - IVSS-Broschüre "Verwechslung von Chemikalien" (ISBN 92-843-7159-7)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Create value by PSI
工艺安全信息创造价值

Sep 20, 2018

Zhejiang Langhua Pharmaceutical Co., LTD.
浙江朗华制药有限公司
Ninhua Group

AGENDA 目录

Who are we 朗华制药简介

Langhua PSI system 朗华制药PSI体系

Langhua Safety Lab 朗华制药安全实验室

Value created by PSI 工艺安全信息创造价值

LANGHUA PHARMA

- U.S.FDA/WHO/EDQM/CFDA/ANVISA approved manufacturer
- Focus on APIs, GMP intermediate & CDMO Business
- Located in National Level Pharmaceutical Industry Zone, Taizhou city， Zhejiang Province.

Langhua Pharma

LOCATION

- 多次通过U.S.FDA/WHO/EDQM/CFDA/ANVISA 等官方审计
- 专注原料药、法规高级中间体与CDMO业务
- 位于浙江省台州市国家级医药园区

LANGHUA PHARMA

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

朗华制药发展历程

1986
成立之初为民营企业

2006
中宁化集团收购
(2015年中化宁波更名为中宁化集团

2012
通过FDA (USA) & WHO 审计

2013
由浙江新华制药更名为浙江朗华制药

2014
再次顺利通过EDQM
&FDA (USA) 审计

2017
多功能中试车间

2018
新QC中心实验室投入运营

AGENDA

Who are we 朗华制药简介

Langhua PSI system 朗华制药PSI体系

Langhua Safety Lab 朗华制药安全实验室

Value created by PSI 工艺安全信息创造价值

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

To avoid …
避免

Lab scale
实验室规模

Production scale
生产规模

Langhua PSI system
朗华制药PSI体系

AGENDA

Who are we 朗华制药简介

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Value created by PSI 工艺安全信息创造价值

Safety Lab Overview
安全实验室

OUR PRACTICE
实践

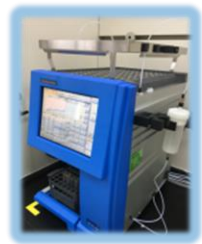
Identify
识别

Risk
风险

Process Safety 工艺安全
Thermal Stability 热稳定性
Reaction Calorimetry 反应量热
Adiabatic Calorimetry 绝热

Understanding
Control
控制

Reaction Mechanism 反应机理
Online Monitoring 在线监测
Impurity Isolation 杂质分离



Risk
风险

Process
inherent
safety
本质安全

Process Optimization 工艺优化
Reaction Condition 反应条件
(Temperature/dosing rate/pH……)
Hazardous Reaction 危险反应

OUR PRACTICE
实践

Development

Thermal Stability (DSC)
Reaction Calorimetry(RC1e)

Stage 1

- Heat of Reaction
- Heat Removal
- Thermal Accumulation
- ΔT_{ad} & MTSR & MTT & Tp

Adiabatic Calorimetry(Phi-TEC I)
Gas evolution
(Gas collection equipment)

Stage 2

- ΔT_{ad} & TMR_{ad} & TD_{24}
- Heat of Decomposition

Risk Evaluation

Now
当前

Flammability
Conductivity

Stage 3

–Burning behavior
–Flash point
–AIT
–MIT
–LIT
–Conductivity

Explosive Properties
Dust Explosion Characteristic

Stage 4

Future
未来

AGENDA

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Value created by PSI 工艺安全信息创造价值

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PROCEDURE 流程

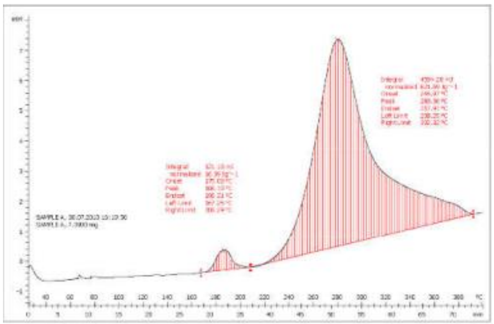
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

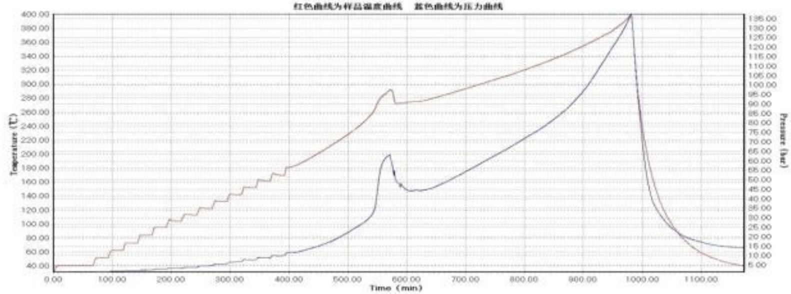
Lab Scale 实验室阶段	Pilot Scale 小试阶段	Commercial Scale 商业化
TEAM 团队		
R&D 研发 Safety Lab 安全实验室	R&D 研发 Safety Lab 安全实验室 production team 生产团队 Engineering 工程团队 EHS	R&D 研发 Safety Lab 安全实验室 Production team 生产团队 Engineering 工程团队 EHS
OUTPUT 输出		
– Screening Thermal stability 热稳定性 – Identification critical reactions 关键反应识别 – Risk evaluation 风险评估	– Thermal stability 热稳定性 – Compatibility 相容性 – Calorimetric studies (heat- and gas evolution) 量热研究 – Safety advise 安全建议 – CHA / PHA 化学品危害分析/过程危害分析	– Process safety analyses + "What-if"-questions 过程安全分析
REPORT 报告		
Risk Evaluation Report SDS Data Sheet CHA Report	Update Risk Evaluation Report Update CHA Report PHA Report	Update SDS Data Update PHA Report

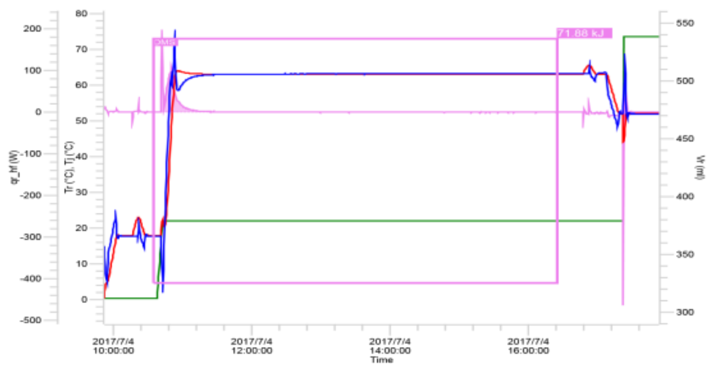
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

LANGHUA PHARMA

Risk Evaluation Report
风险评估报告







CHA Report
化学品危害分析报告

SECTION 5: Chemical Interactivity

5.1 原料之间反应活性

5.1 Reactivity between raw materials

序号 Number	化学品名称 Chemicals	1	2	3	4	5	6	7	8	9	10	11	12	13
1	A													
2	B	U												
3	C	U	U											
4	D	S	U	H										
5	E	S	U	H	S									
6	F	—	S	H, GF	U	S								
7	G	U	U	U	U	H	S,H							
8	H	S	U	U	S	S	—	U						
9	I	—	—	U	—	—	—	U	—					
10	K	—	U	H, GF	U	U	S	H	—	—				
11	L	—	U	U	U	U	—	U	—	U	H			
12	M	S	U	U	S	S	—	H	S	—	U	U		
13	N	S	U	U	S	S	S	U	S	—	U	U	S	

概括性结论 General conclusions：

XX 原辅料中，XX 会跟 XX 等物质发生剧烈反应。

注：化学品之间及与设备材料之间的反应结果按以下标注：Symbol Note:

H：放热反应：Exothermic reaction；

F：起火：Fire;

G：释放气体（无害的、不燃的气体）；Release gases(harmless, but not combustible gases)；

GT：释放气体（有毒的气体）；Release gases(toxic gases)；

GF：释放气体（可燃气体）Release gases(combustible gases).

E：爆炸：Explosion；

P：剧烈的聚合反应：Polymerization；

S：溶解或溶化：Solution；

U：有可能有风险，但不明确：There may be risky, but not clear；

H, F, GT：放热、起火、又释放有毒气体。Exothermic/Fire/Release toxic gases.

无反应用"-"标注。No reactions using"-"label.

5.2 设备及管道材料

5.2 Material of equipment and pipe

化学品 Chemicals / 材料 Materials	1	2	3	4	5	6	7	8	9	10	11	12	13
碳钢 Carbon steel	—	U	—	—	—	—	—	—	—	H, GF	—	—	—
不锈钢 Stainless steel	—	U	—	—	—	—	—	—	—	H, GF	—	—	—
瓷/玻璃 Porcelain/Glass	—	—	U	—	—	—	U	—	—	—	—	—	—
PP, PE, PB	—	—	—	—	—	—	—	—	—	—	—	—	—
PTFE, PVDF, E-CTFE (Halar)	—	—	—	—	—	—	—	—	—	—	—	—	—
PVC	—	—	—	—	—	—	—	—	—	—	—	—	—
天然橡胶 Caoutchouc	—	—	—	—	—	—	U	—	—	—	—	—	—
合成橡胶 Synthetic rubber	—	—	—	—	—	—	U	—	—	—	—	—	—
热固性塑料(EP, UP, ..)	—	—	—	—	—	—	—	—	—	—	—	—	—
石墨 Graphite	—	—	—	—	—	—	—	—	—	—	—	—	—
树脂 Jaffaite	—	—	—	—	—	—	U	—	—	U	—	—	—
润滑剂 Lube	—	—	—	—	—	—	U	—	—	U	—	—	—

概括性结论 General conclusions：

XX 生产过程中使用的物料不和生产中用到的材料反应。

注：化学品之间及与设备材料之间的反应结果按以下标注：Symbol Note:

H：放热反应：Exothermic reaction；

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G：释放气体（无害的、不燃的气体）；Release gases(harmless s, but not combustible gases)；

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GF：释放气体（可燃气体）Release gases(combustible gases).

E：爆炸：Explosion；

P：剧烈的聚合反应：Polymerization；

S：溶解或溶化：Solution；

U：有可能有风险，但不明确：There may be risky, but not clear；

H, F, GT：放热、起火、又释放有毒气体。Exothermic/Fire/Release toxic gases.

无反应用 "-" 标注。No reactions using"-"label.

CASE- PILOT SCALE
小试阶段

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

LANGHUA PHARMA

PHA Report
过程危害分析报告

目录 Contents

Update PHA Report
更新PHA报告

•4.5HAZOP 节点 Nodes of HAZOP analysis

HAZOP 评估将工艺过程分成节点列于表 4.4a。The nodes of HAZOP analysis are listed as below:

表 4.4a 确认节点 Table 4.4a List of nodes

编号 No.	节点内容 Content of Node	设计目的 Purpose of design	图纸号 No. of Diagram	评估日期 Date of analysis
节点 1 Node 1	XXXX	确保抽料和滴加过程在可控的条件下安全进行 Make sure the procedure of charging and dropping is under control.	EQ-BR00N15 0401-00	2015.07.27 09:00~11:00
节点 2 Node2	反应釜分汽包	确保分汽包操作正确，控制反应釜温度在合适范围内	EQ-BR00N15 0401-00	2015.07.27 14:00~16:00

XXXX 项目 PHA 分析行动计划

Equipement/Node 设备/节点	Sr. No. 序号	偏差	后果	Actions 行动描述	RR 风险级别	Responsible Person 责任人	Due Date 要求完成时间	Status 反馈
反应釜（R102808）	1.1.1	用抽料泵（P102814）向反应釜（R102808）中泵入 XXX 流速快	物料输送时易静电积累，静电释放存有火灾风险	1、抽料区增加接地静电夹 2、SOP 规定物料桶接地要求	III-I	XXXX	1、2015.08.07 2、2015.08.15	
	1.1.4	滴加罐 A（V102861）内 XXX 滴加进反应釜（R102808）流速快	釜内温度升高，压力聚升，反应釜内冲料，存有爆炸、火灾风险	1、SOP 规定惰化保护 2、SOP 规定滴加过程中温度要求，并进行复核 3、反应釜增加泄压装置	III-II	XXXX	1、2、2015.08.15 3、2015.09.16	

$$\mathrm{A} + \mathrm{BnBr} \xrightarrow[\mathrm{DMF}]{\mathrm{C}} \mathrm{B}$$

Problem
问题

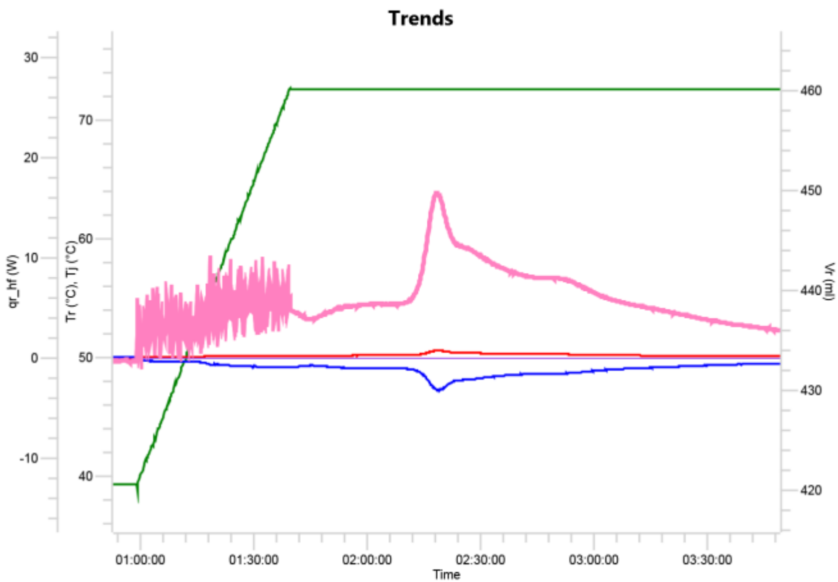
Thermal accumulation
热累积

Purity: 90%

Old process

1. Charge DMF, C
2. Charge A
3. Heat to 50 °C
4. Dosing BnCl in 40 mins

Thermal accumulation 80.2%



Process optimization -1

Add catalyst
Change BnCl to BnBr

1. Charge DMF, C
2. Charge A
3. Charge catalyst
4. Heat to 20 ºC
5. Dosing BnBr in 7 h

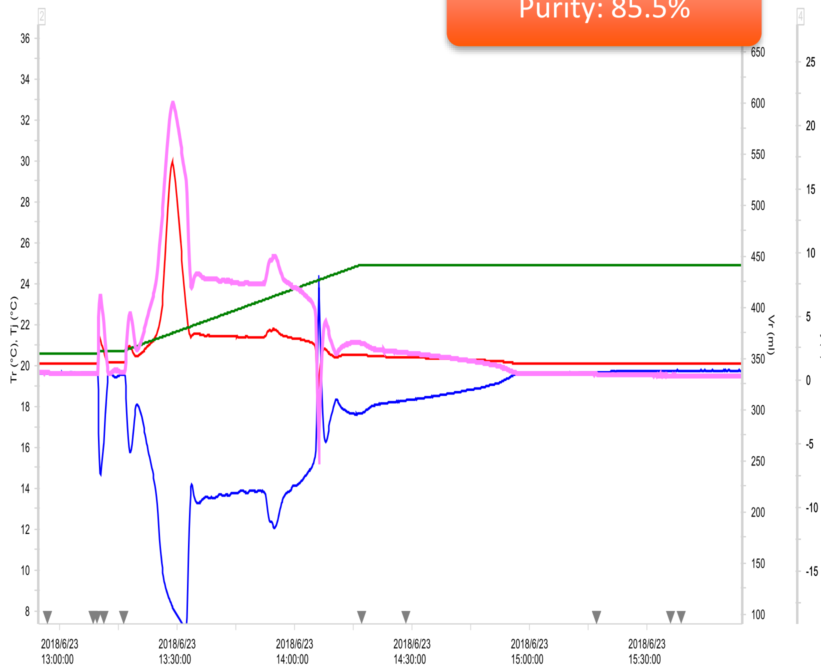
Thermal accumulation
6.68%

Process optimization - 2

1. Charge DMF, C
2. Charge A
3. Charge catalyst
4. Heat to 20 °C
5. Dosing BnBr in 1 h

Thermal accumulation 20.3%

Purity: 85.5%

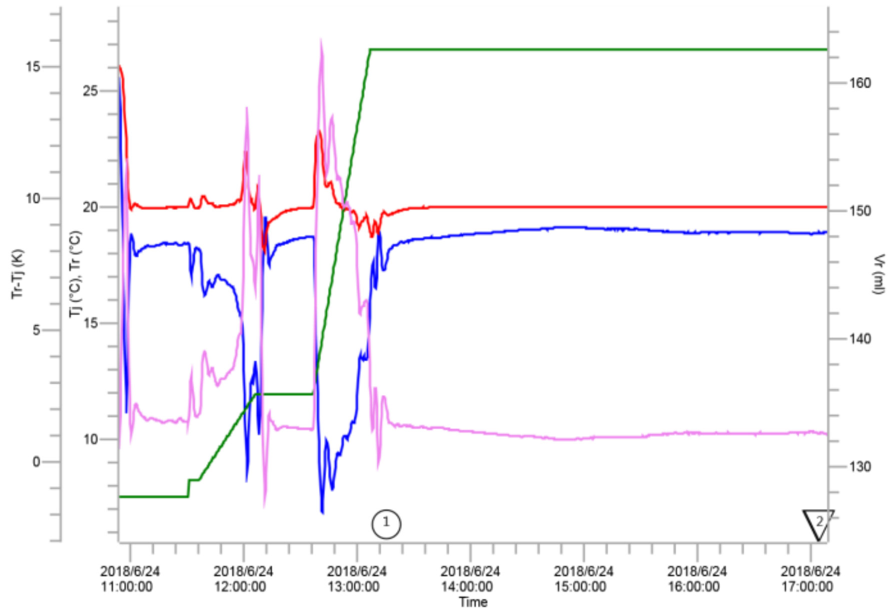


Process optimization - 3

Purity: 89.8%

1. Charge DMF, C
2. Charge A
3. Charge catalyst
4. Heat to 20 °C
5. Dosing BnBr in 1 h (20% in 30 min, wait 30 min, 80% in 30 min)

Thermal accumulation 11.2%



VALUE CREATED BY PSI
工艺安全信息创造价值

Questions?

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Tea Break 茶歇

10:30 – 11:00

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Determination of Process Safety Critical Equipment to Include in a Mechanical Integrity Program
在机械完整性程序中如何确定工艺安全关键设备

Albert Ekin, CSP
Sr. Principle PSM
Johnson & Johnson

@PSCInitiative #PSCIChina18

AGENDA 议程

- Mechanical Integrity (MI) – What is it?什么是机械完整性
- Determination of Safety Critical Equipment - A Five Step Process 安全关键设备的确定-五步法
- Documentation文件
- Recommended Resource推荐的资源
- Questions问题

Process Safety Management (PSM)
工艺安全管理

An integrated management system applied to highly hazardous processes to ensure that:一个适用于高风险工艺的综合管理体系，以确保：

- All process hazards have been identified所有工艺危害都被识别
- Risks from those hazards have been evaluated这些工艺危害带来的风险都被评估
- Controls are in place to mitigate the risks to an acceptable level采取控制措施将风险降低到可接受的水平

Mechanical Integrity is a key element in any Process Safety Management (PSM) system.机械完整性在任何工艺安全管理体系中都是一个关键要素

The US OSHA PSM Rule requires companies that process hazardous materials demonstrate process equipment is "fit for duty". (Other regulations, such as Seveso, contain similar language.)美国职业安全与健康管理局工艺安全管理规则要求处理危险材料的公司证明工艺设备"适合"。（其他规则如塞维索指令，包含类似语言）

In other words companies need to demonstrate that processing equipment handing hazardous materials has been designed, constructed and is being maintained in a manner that will prevent a catastrophic release of hazardous materials.换句话说，公司需要证明操作危险材料的工艺设备的设计，构造和维护方式应能防止危险材料的灾难性释放。

Demonstrating "fit for duty" – essential components:
证明"适合"-必不可少的组成部分

- Safety Critical Equipment list (SCE)安全关键设备清单
- Documentation of design and construction standards 设计和施工标准的文件
- Inspection, Testing, and Preventative Maintenance (ITPM) tasks based on RAGAGEP基于RAGAGEP的检查，测试和预防性维护任务
- ITPM execution & monitoring system ITPM执行和监控系统
- Equipment deficiency management system设备缺陷管理系统

Safety Critical Equipment ITPMs
安全关键设备的ITPM

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- **Inspection:** Tasks to detect the onset of a failure condition and/or assess the condition of a piece of equipment 检查：检测故障发生的任务和/或评估设备状况的任务
  - Vessel wall crack via x-ray通过X射线检测容器壁裂缝
  - Pipe wall thickness measurement 管壁厚度测量
- **Testing:** Tasks, including predictive maintenance tasks, which assess the condition of the equipment and/or detect hidden failures测试：评估设备状况和/或检测隐藏故障的任务，包括预测性维护任务
  - Detecting drift in an instrument through calibration通过校准检测仪器中的漂移
  - Function test a shutdown system停车系统的功能测试
- **Preventative Maintenance:** Tasks which help prevent the premature failure of the equipment预防性维护：有助于防止设备过早失效的任务
  - Promoting the equipment's inherent reliability (e.g. lubricating a pump)提升设备的固有可靠性（例如润滑一台泵）
  - Restoring the equipment's reliability by replacing selected parts/components通过更换选定的部件/组件来恢复设备的可靠性

RAGAGEP
公认的被普遍接受的良好工程实践

An acronym that stands for: 缩写代表：

- **R**ecognized 公认的
- **A**nd 以及
- **G**enerally 普遍的
- **A**ccepted 接受
- **G**ood 良好
- **E**ngineering工程
- **P**ractices. 实践

RAGAGEP are established design codes, standards, published technical reports, recommended practices, government regulations, manufacturers recommendations, internal company standards, or similar documents.

RAGAGEP是既定的设计规范，标准，已发布的技术报告，推荐做法，政府法规，制造商建议，公司内部标准或类似文件。

Determination of SCE
安全关键设备的确定

Safety Critical Equipment: includes process equipment, safeguards, utilities, and supporting systems that prevent or mitigate process hazards安全关键设备：包括防止或减轻工艺危害的工艺设备，安全保障措施，公用设施和支持系统。

Recommended process:推荐流程：

1. Assemble a team组建一个团队
2. Determine SCE identification criteria 确定安全关键设备的识别标准
3. Develop a comprehensive list of process equipment, safeguards, and systems制定全面的工艺设备，保障措施和系统清单
4. Apply criteria to list developed in step 3将标准应用于步骤3开发的清单
5. Document SCE selection process记录安全关键设备的选择过程

1. Assemble a Team
组建一个团队

- Members to be knowledgeable of the process and the equipment组员需要对工艺和设备有足够的了解
- Cross functional (similar to a PHA team) 跨职能部门（类似于创建一个PHA团队）
- Facilitated by an individual familiar with the process as well as the purpose and objectives of the site's Mechanical Integrity program由熟悉该工艺以及公司的机械完整性程序的目的和目标的个人带领

2. Determine SCE Identification Criteria
确定安全关键设备的识别标准

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Clear and specific criteria 明确和具体的标准
- Criteria considers the consequence of failure标准考虑失效的后果
  - If a failure could result in a High Risk event, then it should be included in the Safety Critical Equipment list. 如果失效可能导致高风险事件，则应将其包含在安全关键设备清单中
  - Companies need to define a risk evaluation methodology to define a High Risk event.公司需要定义风险评估方法来定义高风险事件
  - Risk = Severity X Likelihood风险=严重性X可能性
- The criteria documents the decision-making process of the team标准记录团队的决策过程

Criteria for Inclusion (example):
纳入标准（例子）

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

1. Equipment, if it fails, could cause or contribute to a High Risk (HR) event (i.e. vessels, piping, fans, pumps, etc.) 设备如果发生故障，可能导致或导致高风险事件（如容器，管道，风扇，泵等）
2. Safeguards that detect conditions that could lead to a (HR) event (i.e. LEL detector, pressure sensor, etc.)检测仪表方面的安全保护措施可能导致高风险事件（如可燃气体探头，压力传感器等）
3. Safeguards that prevent conditions that could lead to a (HR) event (i.e., low air flow shutdown, grounding systems)预防性层面的安全保护措施可能导致高风险事件（如低流量关闭，接地系统）
4. Safeguards that mitigate conditions that could lead to a (HR) event (explosion flaps, fire sprinklers, rupture disk)减轻后果相关的安全保护措施可能导致高风险事件（如防爆门，消防喷淋，爆破片）
5. Safeguards that contain conditions that could lead to a (HR) event (i.e. secondary containment)包容相关的安全保护措施可能导致高风险事件（如二次围堰）
6. Supporting utilities, if a failure could cause or contribute to a (HR) event (i.e. nitrogen, instrument air, electrical)支持性的公用工程系统如果故障可能导致高风险事件（如氮气，仪表空气，电气）
7. Regulatory requirements法规要求

Example criteria list for consideration
示例标准清单供考虑

3. Develop equipment list
建立设备清单

- Within the scope or boundary of the covered process, generate a comprehensive list of all equipment在涉及工艺的范围或边界内，生成所有设备的全面清单
  - Process equipment工艺设备
  - Safeguards安全防护措施
  - Associated systems相关系统
- Include supporting systems (e.g. utilities)包括支持系统（如公用工程）
- Sources for identifying equipment for consideration可以考虑的识别设备的来源
  - P&IDs管道和仪表流程图
  - PFDs工艺流程图
  - Safeguards from PHAs and LOPAs来自于工艺危害分析和保护层分析的安全保护措施
  - Field or room observations 现场观察

3. Develop a list (cont.)
建立设备清单

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Example types of equipment to be considered可以考虑的设备类型例子

- Piping管道
- Reactors反应釜
- Pressure Vessels压力容器
- Process Hoses工艺软管
- Mixing Tanks混合罐
- Storage Tanks储罐
- Filters过滤器
- Pumps泵
- Compressors压缩机
- Control Valves控制阀门
- Thermal Oxidizers热氧化器
- Dryers烘干机
- Granulators制粒机
- Nitrogen Systems氮气系统
- Compressed Air System压缩空气系统
- Ventilation通风
- Control Systems – HMIs, PLCs控制系统
- Lifting cranes and hoists起重机

4. Apply the Criteria to Everything on the List
将标准应用于清单中的所有设备

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Identify consequence of failure识别失效后果
- Systematically apply the criteria to each item on the list系统地将标准应用于清单中的每个项目
- Example: Explosion flaps on a fluid bed granulator例子：硫化床制粒机上的防爆门
  - ☐ 1. Equipment, if it fails, could cause or contribute to a High Risk (HR) event
  - ☐ 2. Safeguards that detect conditions that could lead to a (HR) event
  - ☐ 3. Safeguards that prevent conditions that could lead to a (HR) event
  - ☑ 4. Safeguards that mitigate conditions that could lead to a (HR) event 减轻后果相关的安全保护措施可能导致高风险事件
  - ☐ 5. Safeguards that contain conditions that could lead to a (HR) event
  - ☐ 6. Supporting utilities, if a failure could cause or contribute to a (HR) event
  - ☐ 7. Regulatory requirements

5. Document Safety Critical Equipment Selection Process
记录安全关键设备的选择过程

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

PSM Process: Fluid Bed Granulator
PSM工艺：流化床制粒机

Equipment	Criteria (Refer to Criteria List)							Not included rational
	1	2	3	4	5	6	7	
Explosion flaps				X				
QASVs			X					
Grounding stations			X					
Binder solution tank								Water based solution, non-hazardous
Broken bag detector		X						
Expansion Chamber	X							

Note: This is an example only 注意：这只是一个例子

Criteria for Inclusion (example):
纳入标准（例子）

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Explosion Flaps防爆门

- ☐ 1. Equipment, if it fails, could cause or contribute to a High Risk (HR) event设备如果发生故障，可能导致或导致高风险事件
- ☐ 2. Safeguards that detect conditions that could lead to a (HR) event检测仪表方面的安全保护措施可能导致高风险事件
- ☐ 3. Safeguards that prevent conditions that could lead to a (HR) event 预防性层面的安全保护措施可能导致高风险事件
- ☑ 4. Safeguards that mitigate conditions that could lead to a (HR) event 减轻后果相关的安全保护措施可能导致高风险事件
- ☐ 5. Safeguards that contain conditions that could lead to a (HR) event 包容相关的安全保护措施可能导致高风险事件
- ☐ 6. Supporting utilities, if a failure could cause or contribute to a (HR) event支持性的公用工程系统如果故障可能导致高风险事件
- ☐ 7. Regulatory requirements法规要求

5. Document Safety Critical Equipment Selection Process
记录安全关键设备的选择过程

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

PSM Process: Fluid Bed Granulator
PSM工艺：流化床制粒机

Equipment	Criteria (Refer to Criteria List)							Not included rational
	1	2	3	4	5	6	7	
Explosion flaps				X				
QASVs			X					
Grounding stations			X					
Binder solution tank								Water based solution, non-hazardous
Broken bag detector		X						
Expansion Chamber	X							

Note: This is an example only注意：这只是一个例子

Other Considerations
其他考虑因素

- Downstream process equipment and piping where hazardous materials could potentially migrate must be considered必须考虑危险材料可能迁移的下游工艺设备和管道
- Equipment and piping that is onsite but not owned, whose failure could cause or contribute to a High Risk event must be considered for inclusion in the SCE list在现场的但不属于业主的设备和管道，其失效可能导致或促成高风险事件，必须考虑纳入安全关键设备清单
    - Transportation containers (i.e. rail cars, tank trucks, tube trailers) that are owned by another company由另一家公司拥有的运输集装箱（如铁路车辆，油罐车，管道拖车）
    - Fixed equipment owned by others that provides critical utilities to plant processes (e.g. liquid nitrogen systems)其他人拥有的固定设备，为工厂工艺提供关键公用工程支持（例如液氮系统）
- Utilize MOC process to keep SCE list current利用变更管理过程保持安全关键设备清单最新
    - New equipment新设备
    - Change in service服务变更
    - Decommissioned equipment退役设备

Documentation – ITPM & RAGAGEP
文档-ITPM和RAGAGEP

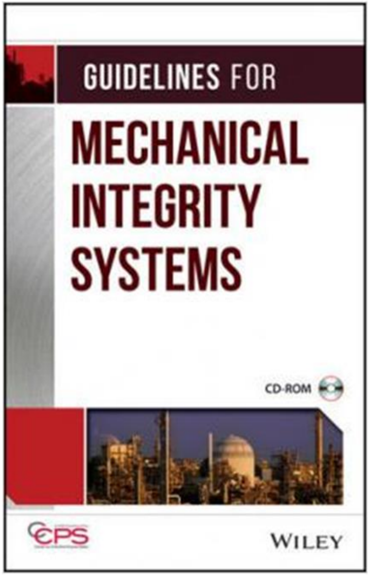
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Safety Critical Equipment: Fluid Bed Granulator
安全关键设备：流化床制粒机

Safety Critical Equipment安全关键设备	Required Activity所需活动 (ITPM)	Interval 间隔	RAGAGEP	Procedure or WI 程序或作业指导书	Assigned Department 责任部门	Comments 注释
Explosion Flaps	Servicing by Glatt	3 Years	Manufacturer's Recommendation	MI-1	Maintenance	Must be completed by authorized Glatt Technician
QASVs N2 bottles	Pressure Check	Quarterly	Manufacturer's Recommendation	MI-2	Maintenance	
QASVs N2 bottles	Replace bottles	3 Years	Manufacturer's Recommendation	MI-2.2	Maintenance	Long lead item
QASVs	Trip circuit function test	Annual	Company Engineering Standard	MI-9	Maintenance	
Broken Bag Detector	Calibration	Quarterly	Manufacturer's Recommendation	MI-3	Calibration	
Grounding Station	Verify ground	Annual	IEC 60364	MI-4	Operations	
PV-1293	Pressure Test	2 Years	Directive 2014/68/EU	MI-5	Maintenance	

Note: This is an example only注意：这只是一个例子

- CCPS publication
- 化工过程安全中心（CCPS）出版物



Questions
问题

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

爪型干式真空泵在溶媒回收中的应用

刘红心
副总经理
沈阳东瑞精细化工有限公司

AGENDA

✓爪型干式真空泵的原理及优势
✓环境保护中的作用
✓降低火灾爆炸风险
✓工业卫生中的作用

- 爪型干式真空泵的原理及优势

爪型干式真空泵的原理及优势

- 原理：螺旋反爪
- 通过转子对同步反方向旋转来产生容积变化实现吸气和排气的过程，从而实现抽真空的目的。每旋转一周吸排气各一次，吸排气口能自动关闭。

爪型干式真空泵的原理及优势

- 优势：能耗降低（以下数据来自工厂实际应用）
- 通过更换机组使电能消耗降低20%，无需油润滑，无需水降温。

机组名称	罗茨水环机组	爪型干式真空机组
额定功率	21.5KW	22.5KW
实际运行功率	16.5KW	13KW
极限真空	40Pa	10Pa

爪型干式真空泵的原理及优势

- 优势：耐用
- 不锈钢空心转子采用**17-4PH**马氏体沉淀硬化型不锈钢,密封使用复合密封技术,壳体,内表面纳米渗镍处理.平均无故障工作周期达**2**万小时。

- 环境保护中的作用

环境保护中的作用

- 无需水降温，避免了工业废水的排放，保护环境，同时降低了环保费用。

环境保护中的作用

- 尾气中所带的有机溶媒可由再泵后设置的冷凝器回收重复利用，避免了直排对空气造成污染。经工厂使用全年约多回收溶媒**55**吨。

环境保护中的作用

- 电能消耗降低20%，更换干式泵这一项全年节约电能21000度，降低了碳排放。（来自工厂实际运行数据）

- 降低火灾爆炸风险

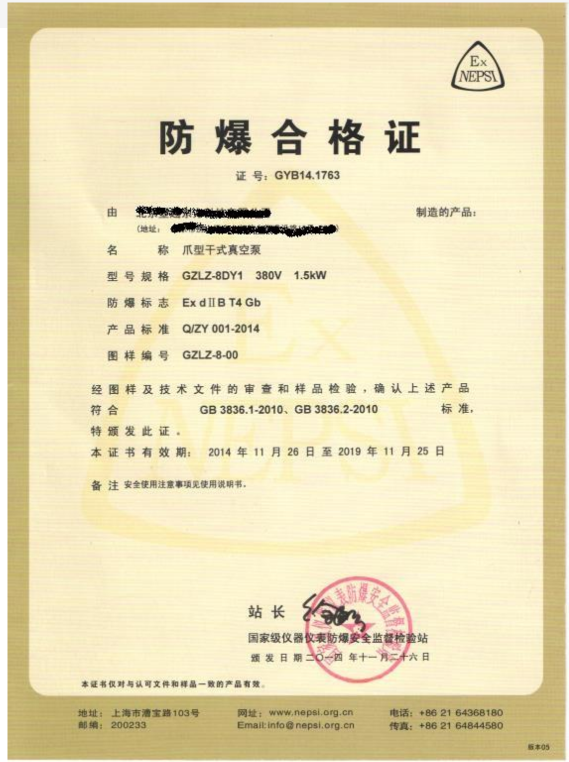
降低火灾爆炸风险

- 内部设计无接触磨损，内部无火花，消除了点火源，防爆性能好。

降低火灾爆炸风险

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 包括电机、压力传感器、操作柱等需现场设置的装置均为防爆设备，达到了真空机组设置部位的防爆要求。


Ex NEPSI

防爆合格证

证号：GYB14.1763

由 [redacted] 制造的产品：

(地址：[redacted]

名　　称　爪型干式真空泵

型号规格　GZLZ-8DY1　380V　1.5kW

防爆标志　Ex d II B T4 Gb

产品标准　Q/ZY 001-2014

图样编号　GZLZ-8-00

经图样及技术文件的审查和样品检验，确认上述产品符合 GB 3836.1-2010、GB 3836.2-2010 标准，特颁发此证。

本证书有效期：2014 年 11 月 26 日 至 2019 年 11 月 25 日

备注 安全使用注意事项见使用说明书。

站长

国家级仪器仪表防爆安全监督检验站

颁发日期 二〇一四 年十一月二十六日

本证书仅对与认可文件和样品一致的产品有效。

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版本05

降低火灾爆炸风险

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 尾气无溶媒蒸汽排放至空气中，避免了溶媒暴露，降低火灾爆炸风险。

- 工业卫生中的作用

工业卫生中的作用

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 密封性好，无泄漏，尾气做针对性回收，控制了作业环境中溶媒的暴露，避免了人员与溶媒的接触。

Questions

爆炸风险评估：防爆指令
Explosion risk assessment: ATEX Directives

PSCI Capability Building Committee
Process Safety Management Sub-team

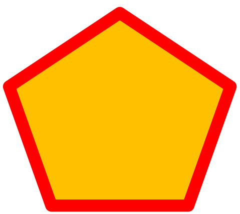
内容 Content

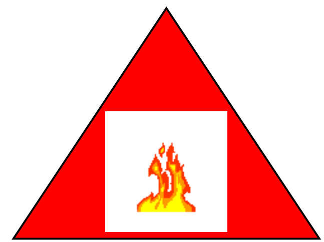
- 基本概念 Basic concepts
- 欧洲ATEX指令 The European ATEX Directives
- 其他国家的规则 Rules in other countries
- 防爆区域的划分 The zoning of hazardous zones
- 合适的电气设备 Suitable electrical equipment
- 结论 Conclusion

火灾和爆炸 Fire/ Explosion

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 燃烧三角形　The fire triangle
- 爆炸五角型　The explosion pentagon
- 爆炸比火灾更罕见 Explosion is more rare than fire

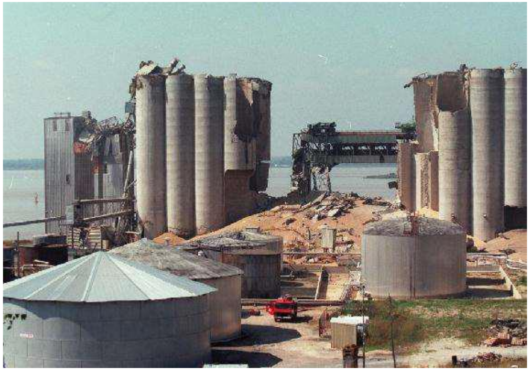




Management of Explosive Atmospheres

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 爆炸比火灾更罕见，但更危险Explosion is more rare than fire, but is more dangerous
  - 突然热释放 Sudden heat release (flash)
  - 冲击波 Shock wave (explosion)
  - 导弹效应 Missile effects (explosion)
  - 没有时间逃跑No time to escape
- 防火 Fire protection
  - 组织体制管理 Organization
  - 探测手段 Detection
  - 灭火系统 Extinguishing systems
  - 应急准备 Emergency preparedness
- 防爆 Explosion prevention
  - 风险分析 Risk analysis
  - 避免产生易爆体环境 Avoidance of explosive atmosphere
  - 减少/防止爆炸的影响Protection against explosion effects



Explosive Atmospheres of what?

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 气体可以爆炸 Gases can explode
  - 气体分组是一个国际体系 The gas group is an international system
    - 气体组 IIA Gas group IIA: 中度活跃 moderately sensitive (甲烷 methane)
    - 气体组IIB Gas group IIB: 活跃 sensitive (乙烯 ethylene)
    - 气体组IIC Gas group IIC: 高度活跃 highly sensitive (氢气hydrogen, 乙炔acetylene)
- 溶剂蒸汽也会爆炸Solvent vapors can explode too
  - 大部分的溶剂蒸汽属于重度活跃 IIA， 部分属于IIB
    Most of them belong to gas group IIA, some ethers to group IIB.
  - 如果反应温度高于闪点则危险 Danger if T process > Flash Point – 10 K
- 所有可燃性粉尘也会爆炸 All combustible dusts can also explode
  - 爆炸可能性与最小点火能量有关Explosion likelihood is linked with the Minimum Ignition Energy (MIE)
    - MIE > 1000 mJ: 很低的爆炸风险very low explosion risk
    - MIE < 10 mJ: 高的爆炸风险high explosion risk
  - 最小点火能与粉尘颗粒大小有关 The MIE is linked with the particle size.
    - 细颗粒粉尘更加危险 Fine particles are more dangerous

European ATEX Directive 1999/92/EC

- 改善可能面临爆炸环境危险的工人的安全和健康保护的最低要求 Minimum requirements for improving the safety and health protection of workers potentially at risk from explosive atmospheres
  - 与重大风管控规则无关 not linked to major risks regulations
  - 关注在工作场所的安全问题 Concerns safety at the workplace
- 只涉及工作场所条件：在空气中，在大气压力下（0.8至1.1 atm）和环境温度 （-20到+40 c）
- Only concerns workplace conditions: under air, at atmospheric pressure (0.8 to 1.1 atm) and ambient temperature (-20 to +40°C)
- 雇主的主要义务Main obligations of the employer:
  - 避免形成爆炸环境 Avoid formation of explosive atmospheres
  - 如果不能，应避免其着火 If not, avoid their inflammation
  - 如果没能，限制爆炸的影响If not, limit the effects of an explosion

European ATEX Directive 1999/92/EC

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 雇主的其他义务 Other obligations of the employer:
  - 应评估风险 Assess the risk
  - 确保工人的安全 Ensure the workers safety
  - 建立防爆分区 Establish a zoning
    - 在此过程中，能长久或短暂形成爆炸性环境
    - Permanent or transient formation of an explosive atmosphere during the process
    - 意外形成短时间的爆炸环境
    - Accidental formation of short time explosive atmospheres
  - 写报告（防爆文件）Write a report (Explosion protection document)
  - 确保设备符合防爆要求 Ensure equipment conformity (Ex class)
- ATEX指令的问题：Problems of the ATEX Directive:
  - 它没有给出明确的指示 It does not give clear indications
  - 解释因国家和公司而不同 The interpretation is very country/ company dependent

European ATEX Directive 1999/92/EC

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 防爆区域的标志：The signage of hazardous zones:
  - 在可能形成爆炸环境的地方...应该在入口处标注防爆标志
    “Places where explosive atmospheres may occur … shall be marked with signs at their points of entry in accordance with Annex III”
  - 在这些地方必须有特别工作许可证（例如动火许可证）
    Special work permit (hot work/ fire permit) is mandatory in such places.
  - 关于防爆标志的样式没有太大的限制，只要它是黄色的等边三角型，里面是黑色字体。There is a large tolerance in the form of Ex signage, as long as it is a yellow equilateral triangle with black letters.
  - 建议在标牌下注明防爆区的等级（区域1、22等）It is advisable to indicate the nature of the zone (zone 1, 22, etc..) under the sign.

The new European Directive 2014/34/EU

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 替换与设备有关的1994/9/EC号指令
- Replaces Directive 1994/9/EC related to equipment
  - 与用于爆炸环境的设备和保护系统有关的法律
  - Harmonization of the laws relating to equipment and protective systems intended for use in explosive atmospheres
  - 进口商应注明其名称和联系方式
  - Importers shall mention their names and contact details
  - 设备制造商、进口商和分销商的责任得到加强Responsibilities are reinforced for equipment manufacturers, importers and distributers.
  - 设备标识没有改变The equipment signage is not changed:

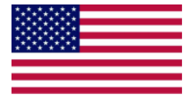
CE 1180 Ex II 2 G Ex d IIC T3 Gb

- 指令1999/92/EC没有改变Directive 1999/92/EC is not changed
  - 确保有可能面临爆炸危险的工人的保护
  - Ensures protection of workers potentially at risk for explosive atmospheres

Rules in other countries

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 美国：国家消防协会USA: NATIONAL FIRE PROTECTION ASSOCIATION
  - NFPA 70：国家电气代码NFPA 70®: National Electric code
  - 危险区的定义（第500条）Definition of hazardous zones (article 500)
    - 第一类：易燃气体和液体Class I: flammable gases and liquids
    - 第二类:可燃粉尘Class II: combustible dusts
    - 第三类：可点燃的纤维或飞絮Class III: ignitable fibers or flyings
  - 电气或电子设备的保护技术Protection techniques for electrical or electronical equipment
  - 这种逻辑与欧洲的ATEX指令相似The philosophy is similar to the European ATEX Directives
  - 主要的焦点是电气设备The main focus is on electrical equipment




भारतीय मानक
विस्फोटी पर्यावरण
भाग 0 उपस्कर — सामान्य अपेक्षाएँ
(पहला पुनरीक्षण)

Indian Standard
EXPLOSIVE ATMOSPHERES
PART 0 EQUIPMENT — GENERAL REQUIREMENTS
(First Revision)

- 印度：ATEX分区是在电气设备标准中采用的India: the ATEX zoning is adopted in the standards for electrical apparatus
  - 印度/ IEC 60079标准Indian Standards IS/IEC 60079

- 中国：爆炸危险环境电力装置设计规范 / GB 50058-2014

  爆炸性气体环境，爆炸性粉尘环境， 以及爆炸性环境的电力装置设计

ATEX/NFPA zonings

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 反映了产生爆炸性环境在设备内部和外部的可能性
- They reflect the likelihood of explosive atmosphere in/outside the equipment
- 它们必须与实际操作和条件一致
- They must be consistent with actual operations and conditions
- 美国的NFPA分区并没有明确永久/频繁和可能的爆炸环境
- The American NFPA zoning does not distinct permanent/frequent and likely

Frequency of ex. atm.	永久或频繁 Permanent or frequent	可能在正常情况下 Likely under normal conditions	罕见(意外或短时间内)Rare (accidental or short period)	特殊(意外)Exceptional (accidental)
气体或蒸汽的分区 Zones for gas or vapors (ATEX)	0	1	2	NC
气体或蒸汽的分区 Zones for gas or vapors (NFPA)	Class I, Division 1		Class I, Division 2	NC
粉尘的分区 Zones for dust (ATEX)	20	21	22	NC
粉尘分区Zones for dust (NFPA)	Class II, Division 1		Class II, Division 2	NC

Workers protection

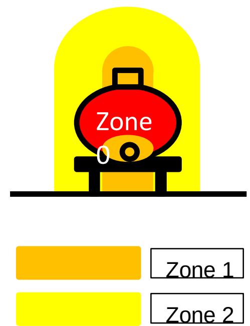
Explosive atmosphere:	永久或频繁 Permanent or frequent	可能的Likely	罕见Rare	特殊或意外 Exceptional
气体或蒸汽的分区 Zones gas or vapors	0	1	2	NC
粉尘的分区 Zones dust	20	21	22	NC

- 工人不得接触或暴露于0/20的区域/Workers shall not be exposed to zones 0/20
- 在1/21区工作必须有防护 /Work in zones 1/21 must be secured
- 2/22区主要涉及泄漏或溢出的情况/Zones 2/22 mainly concern leaks or spillage
- 分区必须反映实际的风险/The zoning must reflect the actual risk
  - 避免总括性的分区/Avoid “blanket” zoning
- ATEX区域划分本身并不是一种保障/The ATEX zoning is not a safeguard *per se*
  - 必须采取技术和组织措施/Technical & organizational measures
  - 合适的设备&以及充足的维护和保障Equipment adequacy & maintenance

ATEX zoning: solvents

爆炸环境Explosive atmosphere:	永久或频繁 Permanent or frequent	可能的Likely	罕见 Rare	特殊或意外 Exceptional
气体或蒸汽的分区 Zones for gas or vapors	0	1	2	NC

- 非惰性容器中的第0区Zone 0 in non inerted vessels
  - 桶，储罐。Drums, tanks,...
- 容器开口周围为1区 Zone 1 around vessels openings
  - 危险情况：形成爆炸环境，操作员可能产生静电释放Risky situation: the explosive atmosphere is present and the operator can create an electrostatic discharge
- 第二区 Zone 2:
  - 在第一区的周围/Around zone 1
  - 可能发生泄漏的地方Where leaks or spillage may happen



ATEX zoning: solvents

- 惰化改变分区
- Inertion modifies the zoning
  - 非惰化容器为0区Zone 0 in non-inerted vessel
  - 惰化容器为1区Zone 1 in inerted vessel
    - 需验证 Validation
  - 如果惰化是连锁的则为第二区 Zone 2 if inertion is interlocked
- 通风系统对分区有很大的影响 Premise ventilation strongly affects the zoning
  - 泄露发生在不通风的房间内 Eg: leak in non ventilated room
  - 标准EN 60079-10-1/Norm EN 60079-10-1

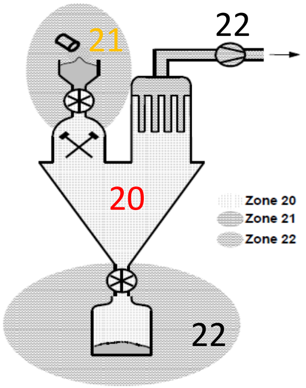
Table B.1 – Influence of independent ventilation on type of zone

Grade of release	Ventilation						
	Degree						
	High			Medium			Low
	Availability						
	Good	Fair	Poor	Good	Fair	Poor	Good, fair or poor
Continuous	(Zone 0 NE) Non-hazardous[a]	(Zone 0 NE) Zone 2[a]	(Zone 0 NE) Zone 1[a]	Zone 0	Zone 0 + Zone 2	Zone 0 + Zone 1	Zone 0
Primary	(Zone 1 NE) Non-hazardous[a]	(Zone 1 NE) Zone 2[a]	(Zone 1 NE) Zone 2[a]	Zone 1	Zone 1 + Zone 2	Zone 1 + Zone 2	Zone 1 or zone 0[c]
Secondary[b]	(Zone 2 NE) Non-hazardous[a]	(Zone 2 NE) Non-hazardous[a]	Zone 2	Zone 2	Zone 2	Zone 2	Zone 1 and even zone 0[c]

ATEX zoning: dusts

Frequency of ex. atm.	永久或频繁Permanent or frequent	可能的Likely	罕见Rare	特殊或意外 Exceptional
粉尘分区Zones for dust	20	21	22	NC

- 20区举例Zone 20 example:
  - 流化床的内部Inside the Fluid Bed Dryer
- 21区举例Zone 21 example:
  - 投料口In the charging booth
- 22区举例Zone 22 examples:
  - 在收集容器的周围Around the collecting bi
  - 过滤后的部分After the filters



电气设备Electrical equipment

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

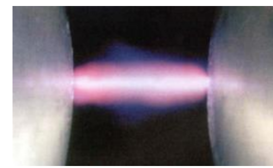
- 危险区域的非受保护电气设备造成了重大风险Non protected electrical equipment in hazardous zones create an important risk
  - 电火花可以点燃爆炸的环境Electrical sparks may ignite the explosive atmosphere
  - 过热可能会点燃粉尘或溶剂Overheat may ignite sensitive powders or solvents
- 许多规范定义了避免这种情况的建筑要求：Numerous norms define the construction requirements to avoid this:
  - 火花避免或隔离Sparks avoidance or containment
  - 密封性 Tightness
  - 外壳温度Body temperature (例如T3 意思是外壳温度小于200度eg T3 means body T < 200°C)

- 标牌定义了危险区域的设备设计 The signage defines for which hazardous area the equipment is designed
  - ATEX Directive: CE 1180 Ex II 2 G Ex d IIC T3 Gb
  - NEC standard: Class I, Zone 1, AEx d IIC T3 Gb

Electrical equipment: warning

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 设备成本取决于分级The equipment costs depend on the class
  - 不要把用于0区的电气用于2/22区 Do not use equipment for zone 0 in zones 2/22!
- 电气的可靠性并不能永远保证The electrical compliance is not guaranteed for ever
  - 振动可以改变密封性Vibrations can alter the tightness
  - 线路不得更改shall not be modified
  - 完整性检查是强制性的Integrity check is mandatory
- 电气设备不是唯一的引燃源Electrical equipment is not the only source of ignition
  - 静电的释放Electrostatic discharges
  - 电气连续性，接地是强制性的Electrical continuity, grounding are mandatory
  - 发热的电机或马达Thermic motors
  - 摩擦,分解反应Friction, decomposition reactions
- 电气合规性是强制性的，但这还不足够。
- Electrical compliance is mandatory, but this is not sufficient.



Conclusion

- 气体，溶剂蒸汽，并且可燃的粉尘能形成爆炸/Gases, solvent vapors but also combustible powders can create an explosion
- ATEX指令1999/92，旨在保护工人/ATEX Directive 1999/92 EC aims at protecting workers
- 要点Priorities:
  - 避免爆炸环境/Avoid explosive atmospheres
  - 防止其点火/ Prevent their ignition
  - 限制爆炸的后果/Limit the consequences of explosion
- ATEX分区是基于风险分析的/The ATEX zoning is based on a risk analysis
- 分区只是一个风险划分，而不是保护本身。/Zoning is only a risk mapping, not a protection *per se*.
- 它必须反映出具有爆炸性环境的实际风险/It must reflect the actual risk of having an explosive atmosphere
- 电气设备必须是合规的并且很好的维护/Electrical equipment must be compliant and maintained

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Lunch Break 午餐

12:30 – 13:30

请带好贵重物品和餐券，用餐请到3楼Shanghai City Bistro

Please take your own belongings and lunch ticket.
The restaurant is Shanghai City Bistro on 3rd floor

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Inerting – Key Considerations in Design and Validation
惰化- 在设计和验证过程中的关键注意事项

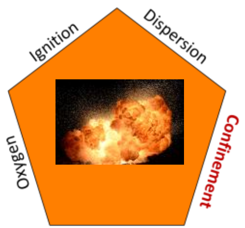
Albert Ekin, CSP
Sr. Principle PSM
Johnson & Johnson

AGENDA日程

- Inerting as a Basis of Safety
- 安全基本要求-惰化
- Inerting Methods & Design Considerations
- 惰化的手段&设计注意事项
- Testing and Verification
- 测试和验证
- Management System
- 管理系统
- Other Considerations
- 其它注意事项
- Questions
- 问答

Inerting is used to prevent fires and explosions in processing equipment.
惰化用于工艺设备过程中，预防火灾和爆炸。

- Eliminates one leg of the fire triangle or explosion pentagon
- 消除火灾三角形和爆炸五边形的一个要素
- Inerting is used where it is challenging or impractical to eliminate all ignition sources
- 惰化用于在消除所有点火源有困难或难以实施的情况下
- The objective of inerting is to reduce the O_2 concentration below the Limiting Oxygen Concentration or LOC of the fuel
- 惰化的目的是降低氧气浓度，至燃料极限氧气浓度LOC以下



In general, it is almost impossible to eliminate all possible sources of static electricity in manufacturing, particularly in processes handling nonconductive solvents and/or powders

For Example:

- Handling and storage of non-conductive flammable liquids
- Addition of powders to flammable liquids

通常，消除生产过程中所有可能的静电是不可能的，特别是在操作非导电的溶剂和/或粉料

比如：

- 操作和储存非导电的可燃液体
- 将粉料投加至易燃液体

Other inerting applications

- Solvent granulation
- Flammable liquids heated above their flash point
- High speed grinding of combustible or explosible powders

其它惰化的应用:

- 溶剂相下的造粒
- 易燃液体加热至超过闪点
- 高速研磨易燃或易爆的粉料

Inerting Gasses 惰化的气体

Commonly used Inerting gasses 常用的惰化气体

- Nitrogen 氮气
- Carbon Dioxide 二氧化碳
- Argon 氩气
- Helium 氦气
- Steam 蒸汽
- Flue Gas 废气

Selection Considerations 选择注意事项

- Cost 成本
- Availability 可用性
- Compatibility 兼容性
- Reliability of supply 供给的可靠性

Limiting Oxygen Concentration
极限氧气浓度

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- LOC is defined as the limiting concentration of oxygen below which combustion is not possible, independent of the concentration of fuel. It is expressed in units of volume percent of oxygen.
- LOC表示氧气浓度低于该限值，燃烧不会发生，它和燃料的浓度无关。用氧气百分比表示。
- LOC values for many flammable gases and vapors are available in reference materials (e.g. FM Data Sheet, FM-DS-7-59, NFPA 69)
- 在相关的参考资料中可以查询到可燃气体和蒸汽的LOC值。（如：FM 数据表， FM-DS-7-59, NFPA 69）

Limiting Oxygen Concentration
极限氧气浓度

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- LOC varies with different inert gasses LOC值与不同的惰性化气体

	N2-Air Mixture	CO2-Air Mixture
Flammable Vapor 易燃蒸汽	LOC O_2 volume %	LOC O_2 volume %
Acetone 丙酮	10	12.5
Ethanol 乙醇	9	11.5
Heptane 庚烷	10.4	13
Methanol 甲醇	8.5	10.5

Adapted from NFPA 69, 2014

- LOC varies with temperature and pressure
- LOC 值随着温度和压力也在变化
- For hybrid mixture use LOC of lowest constituent
- 对于混合物，使用LOC值最低的

Operating Parameters
工作参数

- Recommended key parameters for system design
- 系统设计时，推荐的主要参数
  - Limiting Oxygen Concentration (LOC)极限氧气浓度LOC
  - Maximum Permissible Oxygen Concentration (MPOC)最大允许氧含量
  - Alarm 报警
  - Normal operating level 常规操作
- In practice, a safety margin must be maintained between the LOC and the MPOC
- 在实践中，安全余量必须维持在 LOC 和 MPOC 之间
- Immediate corrective action should be taken if MPOC is exceeded
- 如果超过MPOC限值，必须立即采取措施。

Operating Parameters
工作参数

- Determination of MPOC
  - For an LOC > 5%, LOC minus 2% - 4% (2% is common), up to a maximum of 8%
  - If LOC < 5%, and O2 continuously monitored, MPOC = 60% LOC
  - If LOC < 5%, and O2 not continuously monitored, MPOC = 40% LOC

- MPOC 取决于
  - 如果LOC>5%, MPOC=LOC - 2% - 4% (2%较常见), 最高值8%;
  - 如果LOC<5%, 同时有O2的持续监测， MPOC = 60% LOC;
  - 如果LOC<5%, 没有O2的持续监测， MPOC = 40% LOC

Operating Parameters
工作参数

- Determination of alarm level 报警的设定
  - Can be set at MPOC or some margin lower
  - Consider response time of the system to avoid spurious alarms
  - If not using O2 analyzer, some other parameter is used, i.e. flow or pressure
  - Define operator actions and/or automated control response and time required
  - 可以设定在MPOC值或者再低一些
  - 为了防止避免误报，考虑系统的响应时间
  - 如果不使用氧含量探测仪，可以使用其它的参数，比如，流量、压力
  - 定义操作工的响应动作和/或自控系统的响应动作和时间
- Determination of normal operating level 常规操作的设定
  - Same considerations as determining alarm level
  - 同上

Inerting Methods
惰化手段

Common inerting methods (but not all) 常用的方法（但不是所有）

- Initial O_2 purging 初始的氧气置换
  - Vacuum purging 真空置换
  - Pressure purging 压力置换
  - Sweep through purging 吹扫置换

- Maintaining inert condition 维持惰化
  - Fixed rate addition 固定流量供气
  - Variable rate addition 根据需求供气

Vacuum Purging
真空置换

- Most common
- Draw a vacuum to target level and break vacuum with inert gas
- Repeat until target oxygen concentration is reached
- Equipment must be able to handle the vacuum

- 最常见
- 对设备拉真空到一定真空度，然后用惰化气体破空
- 反复操作，直至事先设定的氧含量要求
- 设备必须可以拉真空

Vacuum Purging
真空置换

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Oxygen concentration x_k after k purge cycles
- 经过k次置换，氧含量x_k的计算

$$x_k = x_o \left(\frac{P_L}{P_H} \right)^k$$

- Quantity of inert gas, V_2, required for k cycles
- K次置换，惰化气体体积V_2的计算

$$V_2 = k \frac{(P_H - P_L) V_1}{P_H}$$

Note: Equations and nomenclature used in this presentation are readily available in technical reference literature.
注：资料中所用的公式及术语，在相关技术参考文献中均可查到

Vacuum Purging Example
真空置换的例子

Assume a vessel initially contains air at atmospheric pressure. Determine the number of cycles to lower the O_2 concentration to 4%. A vacuum pump is used that reaches 0.4 bar absolute. Nitrogen is used to break the vacuum back to atmospheric pressure.

假定该容器初始态为空气，大气压力。需要将氧含量降至4%。真空泵绝对真空度0.4bar. 使用氮气进行破空至大气压力。

$$x_k = x_o \left(\frac{P_L}{P_H} \right)^k$$

$X_0 = 20.9$ % O2, $P_H = 1$ bar, $P_L = 0.4$ bar

After 1 cycle, $x = 0.209 \dfrac{(.4)}{(1)} = 0.084$ or 8.4% O_2

After 2nd cycle, $x = 0.084 \dfrac{(.4)}{(1)} = 0.034$ or 3.4% O_2

Therefore, it takes 2 purge cycles to reduce the O_2 concentration below 4%.
通过计算，氮气置换2次可以将氧含量降到4%以下。

Pressure Purging
压力置换

- Pressure purging is the opposite of vacuum purge, add inert gas under pressure, then depressurize
- Repeat until target oxygen concentration is reached
- Equipment must be able to handle the pressure

- 压力置换与真空置换顺序相反，先加入惰化气体，然后减压至常压
- 反复操作，直至事先设定的氧含量要求
- 设备必须能够承压

- Oxygen concentration *x* after *k* purge cycles
- 经过k次置换，氧含量x_k的计算

$$x_k = x_o \left(\frac{P_L}{P_H} \right)^k$$

- Quantity of inert gas required for *k* cycles
- K次置换，惰化气体体积V_2的计算

$$V_2 = k \frac{(P_H - P_L) V_1}{P_H}$$

Same equations as for vacuum purging.
计算公式与真空置换一样。

Pressure Purging Example
压力置换例子

Assume a vessel initially contains air at atmospheric pressure. Determine the number of cycles to lower the O_2 concentration to 4%. Nitrogen is available to pressure the vessel to 3 bar.

假定该容器初始态为空气，大气压力。需要将氧含量降至4%。氮气可以打到3bar。

$$x_k = x_o \left(\frac{P_L}{P_H} \right)^k$$

x_0 = 20.9 % O2, P_H = 3 bar, P_L = 1 bar

After 1 cycle, $x = 0.209 \dfrac{(1)}{(3)} = 0.070$ or 7.0% O_2

After 2nd cycle, $x = 0.070 \dfrac{(1)}{(3)} = 0.023$ or 2.3% O_2

Therefore, it takes 2 purge cycles to reduce the O_2 concentration below 3%.
通过计算，氮气置换2次可以将氧含量降到3%以下.

For previous examples, assume the same vessel with a volume of 1000 L.
使用前面的例子，假定容器体积为1000L.

$$V_2 = k\frac{(P_H - P_L)V_1}{P_H}$$

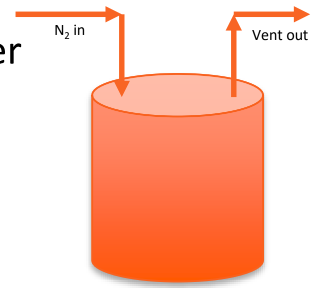
For vacuum purging 真空置换

$$V = (2)\,\frac{(1 - 0.4)}{(1)}\,(1000) = $$ 1,200 L of nitrogen 需要1200L氮气

For pressure purging 压力置换

$$V = (2)\,\frac{(3 - 1)}{(3)}\,(1000) = $$ 1,333 L of nitrogen 需要1333L氮气

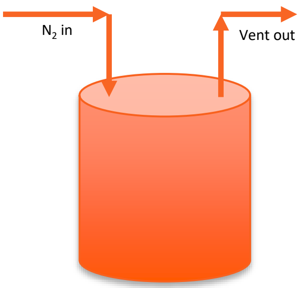
Sweep Though Purging
吹扫置换



- Inert gas is added at one opening and vented at another opening, "sweeping out O_2"
- Openings to be as far apart as possible
- Commonly used when equipment is not rated for pressure or vacuum
- Inert gas is added and vented at atmospheric pressure

- 惰化气体从一个开口进，另一个开口出，“扫出氧气”
- 进口和出口相隔越远越好
- 通常用于设备不承压，也不能拉真空情况下
- 惰化气体进出都是大气压力

Sweep Though Purging
吹扫置换



- Assuming perfect mixing
- 假定气体完美混合

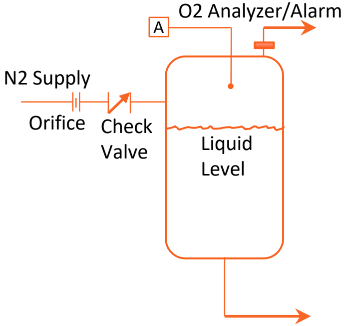
$$Qt = V\, ln\left(\frac{C_1}{C_2}\right)$$

- However, perfect mixing is normally not attained, a correction factor *K* is used
- 但是，完美的混合现实中是无法实现的，所以引入矫正系数*K*

$$Qt = \frac{V}{K}\, ln\left(\frac{C_1}{C_2}\right)$$

- Appropriate *K* factor is based on geometry of equipment
- 恰当的矫正系数取决于设备的结构

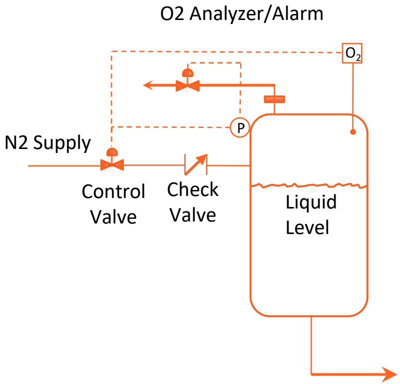
- Fixed rate addition
  - Inert gas added at a constant rate and vented
  - Constant rate must meet peak demand
  - Orifice plate typically used to set flow



- 固定流量供气
  - 惰化气体以恒定流速通入和排出
  - 恒定速率必须满足设备最大需求
  - 孔板常用来调节流量

Maintaining Inerting
维持惰化

- Demand rate addition
  - Inert gas is added at a rate equal to demand
  - Maintain constant pressure
  - Addition capacity must meet peak demand
  - Pressure controller used to set flow
  - O2 analyzer can be used to increase inert gas flow if needed
  - Uses less nitrogen
- 根据需求供气
  - 惰化气体根据需求来供气
  - 设备维持恒定的压力
  - 供气能力必须满足最大需求
  - 压力控制器用来调节惰化气体流量
  - 氧含量分析仪可以用来调节惰化气体的流量
  - 氮气用量会更少



Design Considerations
设计注意事项

- Consult an expert
- 咨询专家
- Perform risk assessment (i.e. HAZOP) on design prior to implementation
- 在使用前对于设计做风险分析（如，HAZOP）
- Reliability of inerting system based on risk assessment or LOPA
- 基于风险分析或LOPA需求，设计惰化系统的可靠性
  - Integrity level 完整性
  - Levels of protection 保护层级
  - Redundant backup may be needed 冗余设计

Design Considerations
设计注意事项

- Maintaining inerting during powder addition to vessels needs special consideration
- Centrifuges processing non-conductive solvents require special consideration
- Inerting gas supply quantity and reliability
- 在投加固体粉料时，需要特别考虑如何维持惰化
- 离心工艺过程中使用非导电溶剂，需要特别考虑
- 惰化气体的供气量和可靠性

Initial Verification 初始验证

- Completed before introduction of hazardous materials
- 在加入危险物质之前完成
- Leak check of system
- 系统的气密性验证
- Qualification document 验证文件
  - Verify equipment installed as per design
  - 验证设备是否按照设计安装
  - Verify target O2 concentrations are achieved
  - 验证目标的氧含量是否可以实现
- Training 培训
- Procedures 程序规定

Verification during operation 在操作过程中验证

- Oxygen monitoring 氧含量监测
- Validated procedures 有效的程序
- Other operating parameters to verify MPOC not exceeded
- 利用其它的操作参数来验证没有超过MPOC限值
  - Flow 流量
  - Pressure 压力

Testing and Verification
测试和验证

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Verification during operation 在操作过程中验证

- Oxygen monitoring 氧含量监测
  - Continuous 持续监测
  - Scheduled 间隔监测
  - Random 随机测试
  - Analyzer Compatibility with gas environment
  - 氧含量分析仪应该适用于所测试的气体环境
- Pressure indication 惰化气体压力读数
- Flow indication 惰化气体流量读数
- Vacuum indication 真空读数
  - < 100 mbar absolute, continuous O_2 monitoring not needed
  - 绝对压力<100mbar, 不需要进行持续的氧含量监测
  - < 50 mbar absolute not capable of supporting combustion
  - 绝对压力<50mbar, 无法支持燃烧
- **Following a validated procedure with no means of verification is discouraged**
- **仅仅是按照程序操作，而没有进行验证是不充分的**

A documented management system is critical to ensure the inerting system continues to function properly

文件化的管理系统，是惰化系统持续正确运行的关键

- Basis of safety 安全基础
- Design basis and calculations (including key parameters, i.e. LOC) 设计和计算基础（包含关键参数，如LOC）
- Required level of integrity
- 需要的完整性等级
- Verification procedure (initial and ongoing)
- 验证程序（初始和生产过程中）
- Maintenance and inspection Procedures
- 维护和检查程序
- Training 培训
- Annual Management System review process
- 年度管理系统的评审

Other Considerations
其它注意事项

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- Inert gases are asphyxiants
  - Evaluate hazard of potential leakage in surrounding area, ensure adequate ventilation
  - Consider area oxygen monitoring with alarm
  - Employee training
  - Emergency procedures and equipment to respond to oxygen deficient atmosphere
  - Strict adherence to confined space entry rules
  - Labeling and signage

- 惰化气体是窒息性气体
  - 评估如果发生泄露，周边区域的潜在风险，确保有足够换风
  - 考虑区域加氧含量监测和报警
  - 员工培训
  - 对于缺氧环境，建立应急流程和准备应急设备
  - 严格遵守受限空间进入准则
  - 标签和标示

Other Considerations
其它注意事项

- Vent exhausts to safe location
- 排气排放到安全区域
- Cross connections between inert gas and other utilities are not allowed
- 不可以将惰化气体和公用气体交叉连接
- Isolate inert gas from process with check valve(s)
- 利用止回阀隔离惰化气体和工艺

Recommended Resources
推荐资料

- Factory Mutual data sheet FM DS 7-59

  "Inerting and Purging of Tanks, Process Vessels, and Equipment"
- NFPA 69

  "Standard on Explosion Prevention Systems" Chapter 7
- EN 50271

  "Electrical apparatus for the detection and measurement of combustible gases, toxic gases or oxygen"
- EN 50204

  "Performance Standard for Oxygen Measurement System"
- UK HSE Codes

Questions

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

高效化合物项目管理 - 共同挑战和隔离控制范例

Angelo Chinni, CIH, CSP
Manager, Industrial Hygiene & Safety
SAFEBRIDGE Consultants Inc.,
A Trinity Consultants Company

Chao Wang

AGENDA议程

Potent Compound Program Management
高效化合物项目管理

What Does It Take to Manufacture Potent Compounds?
高效化合物的制造需要什么？

Elements of a Potent Compound Management Program
高效化合物项目管理的要素

Case Examples of Containment
隔离控制案例

SafeBridge Consultants, Inc. - A Trinity Consultants Co.

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Group of environmental, health and safety professionals with expertise in:
  - Toxicology
  - Health and safety
  - Industrial hygiene
  - Analytical chemistry
  - Occupational medicine
  - Product safety and risk assessment
  - Developing programs to recognise, evaluate and control occupational exposures to potent pharmaceuticals
- Expertise is in pharmaceutical safety and health consulting
- Offices in SF Bay Area, New York City, Pennsylvania & Europe; also staff located in Toronto, Canada and Raleigh, NC
- Trinity Office in Hang Zhou

- 团队的专业领域:
  - 毒理学
  - 健康和安全
  - 工业卫生
  - 分析化学
  - 职业医学
  - 产品安全和风险评估
  - 制定计划以识别，评估和控制对强效药物的职业暴露
- 制药安全和健康咨询
- 旧金山湾区、纽约市、宾夕法尼亚州和欧洲办公室; 加拿大多伦多和北卡罗来纳州罗利市也有工作人员
- 杭州办公室

制造高效化合物需要什么？

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Common Question from:
- Contract Manufacturing Organization (CMO)
- Contract Research Organization (CRO)
- Analytical Laboratories

常见问题来自:
- 生产企业（CMO）
- 研究机构（CRO）
- 分析实验室

Manufacturing and R&D:
- API Manufacturing (Chemical Synthesis)
- Pharmaceutical Oral Solid Dosage (tablets and capsules)
- Sterile Injectables
- Creams, Gels, Patches

制造与R&D:
- API制造（化学合成）
- 药物口服固体制剂（片剂和胶囊）
- 无菌注射剂
- 乳剂、凝胶、贴剂

制造高效化合物需要什么？

Common Questions to SafeBridge :

- Do I have the right facility?
- Do I have the right controls?
- Can I just put my employees in airline respirators?
- I want to manufacture Category or Band 4 Material – can I do this in my facility?
- How do I make <Potent Compound Product> safely?

常见的咨询SafeBridge的问题:

- 我有合适的设施吗？
- 我有正确的控制吗？
- 我可以只是把我的员工放在供气式呼吸器里吗？
- 我想制造Category或Band 4材料 - 我可以在我的工厂生产吗？
- 如何使得<高效化合物的生成>变得安全？

解决方案

A Comprehensive Program is required to safely handle potent compounds.

需要一个全方位的过程控制来确保安全处理高效化合物

高效化合物的定义

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- An API or pharmacologically active intermediate with a therapeutic dose at or below 10 milligrams;
- An API or pharmacologically active intermediate with a SafeBridge OHC of 3 or 4;
- An API or pharmacologically active intermediate with an Occupational Exposure Limit (OEL) at or below 10 micrograms per cubic meter of air as an 8-hour TWA;
- An API or pharmacologically active intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects or reproductive toxicity at low doses; or
- A novel compound of unknown potency and toxicity

Note that ALL Pharmaceutical Compounds need to be handled with proper controls and procedures – even "non-potent" compounds have health effects.

- 治疗剂量小于等于10毫克;
- SafeBridge OHC为3或4;
- 职业暴露限值（OEL）小于等于10微克/立方米空气，8小时TWA;
- 具有高选择性的API或药理学活性中间体（即结合特定受体或抑制特定酶的能力）和/或具有在低剂量下引起癌症，突变，发育效应或生殖毒性的潜力
- 一种未知效力和毒性的新化合物

请注意，所有药物化合物都需要通过适当的控制和程序进行处理 - 即使是"非高效"化合物也会对健康产生影响。

采用系统和科学的方法

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- **Recognize the Hazard**
  - Occupational Health Categorization (OHC)
  - Occupational Exposure Limit (OEL)
- **Evaluate and Control the Risk**
  - Use advanced engineering controls due to unique toxicity and potency
  - Select/Design Controls appropriate for risk
  - Develop Procedures
- **Verify the Controls through Measurement**
  - i.e. Surrogate Monitoring
- **Industrial Hygiene Monitoring - API**
  - Develop Quantitative Tools to Measure Worker Exposure
- **Other Program Elements**
  - Medical Surveillance/Reproductive Health, Cleaning and Maintenance, Waste Handling and Disposal, Training

Apply similar approaches to Quality endpoints to prevent cross-contamination

- **认识到危害**
  - 职业健康分类（OHC）
  - 职业暴露限值（OEL）
- **评估和控制风险**
  - 由于独特的毒性和效力，使用先进的工程控制
  - 选择/设计适合风险的控制
  - 制定程序
- **通过测量验证控制**
  - 即替代监测
- **工业卫生监测 - API**
  - 开发量化工具来衡量工人暴露
- **其他计划要素**
  - 医疗监督/生殖健康，清洁和维护，废物处理和处置，培训

对质量末端应用类似的方法以防止交叉污染

Recognize the Hazard
认识到危害

化学品的毒性/效力分类（SafeBridge系统）

Occupational Health Categorization (OHCs) and Handling Practice System

职业健康分类（OHCs）和处理实践系统

- Category 1: Low Toxicity 低毒性
  OEL >0.5 mg/m^3 (aspirin)
- Category 2: Intermediate Toxicity 中毒性
  OEL 10 µg/m^3 - 0.5 mg/m^3 (insulin, oxycodone)
- Category 3: Potent 高效 (default)
  OEL 30 ng/m^3 - 10 µg/m^3 (estradiol 17-β, paclitaxel, fentanyl)
- Category 4: Highly potent 非常高效
  OEL $\leq$ 30 ng/m^3 (nafarelin, leuprolide, sufentanil)

职业健康分类（控制范围）

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- **Understand the Banding / Categorization System Used**
  - If Customer says "This is a band or Category 3" don't assume you know what that means. Ask questions, get the baseline information used to make the decision. Make your own judgments and decisions.
- Develop System for your organization with defined Criteria for setting the categories.
- Use an experienced Occupational Toxicologist to set the bands or categories.
  - Want to get band "just right". Not too conservative to limit manufacturing flexibility but still be protective of worker safety.

- **了解所用的范围/分类系统**
  - 如果客户说"这是范围或类别3"，请不要假设您知道这意味着什么。 提出问题，获取基线信息，以便做出自己的判断和决定。
- 使用已定义的条件开发系统以设置类别。
- 使用经验丰富的职业毒理学家来设置范围或类别。
  - 想让范围"恰到好处"。 不太保守而限制制造灵活性，但仍能保护工人的安全。

医药OELs例子

40小时工作时间或短期暴露的可接受水平;
类似于英国WEL，OSHA PEL或ACGIH TLV

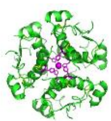
Drug/Material	OEL L
Naproxen (NSAID)	5,000 μg/m^3
Nicardipine (cardiac drug)	400 μg/m^3
Isotretinoin (Accutane for acne)	5 μg/m^3
Paclitaxel (anti-cancer)	0.8 – 10 μg/m^3
mAbs	1 - >100 μg/m^3
Fentanyl (synthetic opioid)	0.7 μg/m^3
Thalidomide	0.25 μg/m^3
17β estradiol (natural estrogen)	0.1 μg/m^3
Ethinyl estradiol (synthetic estrogen)	0.035 μg/m^3
Camptothecin (anti-cancer)	0.03 μg/m^3
Nafarelin (peptide hormone)	0.001 μg/m^3

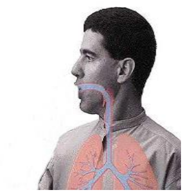
Evaluate and Control the Risk

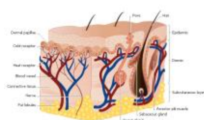
评估和控制风险

职业暴露途径

1. Inhalation 吸入
2. Dermal Absorption (ASLs) 皮肤吸收
3. Ingestion 食入
4. Inadvertent Contact with Skin & Mucous Membranes
   无意中接触皮肤和粘膜







Exposure Pathways

Source – Pathway – Target

风险 - 导致重大风险的因素

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Physical form of the material
- Labor intensive steps
  - manual transfer of materials
  - weighing active materials
- High energy operations
  - milling, sizing, fluidising, spraying
  - over-pressurisation
- Poor work practices
  - carelessness or lack of awareness
- Cleaning and maintenance operations

- 材料的物理形式
- 劳动密集型步骤
  - 手动转移材料
  - 称重活性物质
- 高能操作
  - 研磨，上浆，流化，喷涂
  - 超压
- 错误操作
  - 粗心或缺乏意识
- 清洁和维护操作

控制 – 与危险相关联（OHC / OEL）

- Facility Design 设施设计
- Ventilation 通风
- Gowning/Degowning 洁净服/去换衣
- Engineering Controls 工程控制
  - Controls – Hoods 控制 - 引擎盖
  - Containment – Enclosed process, Isolators 隔离 - 封闭的过程，隔离器
- Work Practices 实际操作
- Gowning / PPE 洁净服/PPE

设施基础元素

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Negative differential air pressure in processing rooms relative to surrounding areas.
- Room air locks/anterooms are recommended
  - Provide an air pressurisation barrier
  - Serve as a gown/degown area
- Recirculation of air into non-production areas is not permitted
- HEPA filtered room air exhaust should not be recirculated
- Designated areas should be posted with appropriate notification and hazard warning
  - Controlled access to the work area is required.
- Segregate personnel and material/equipment flows
- Locker rooms and showers contiguous with processing/work areas are recommended for manufacturing suites.
- Air showers are not recommended
- Mist/water showers are preferred and recommended.

- 处理室相对于周围区域的负压差。
- 建议使用室内空气锁/前室
  - 提供空气加压屏障
  - 作为换衣区域
- 禁止将空气再循环到非生产区域
- HEPA过滤室内空气排气不再循环
- 指定区域应张贴适当的通知和危险警告
  - 需要对工作区进行受控访问。
- 隔离人员和材料/设备
- 建议让加工/工作区与更衣室和淋浴间相邻。
- 不建议使用风淋室
- 喷雾/水淋浴是首选和推荐。

高级工程控制方法

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Process containment
  - barriers/isolators (equipped with RTPs)
  - bag techniques (bag w/in a bag)
- Closed transfer systems
  - vertical process trains
  - intermediate bulk containers (IBCs)
    - specialised connectors and valves (SBVs)
- Ventilated enclosures
  - powders weighing hoods
  - enclosures for subdividing, filling, sizing

- 流程隔离
  - 屏障/隔离器（配备RTP）
  - 包装技术（袋装袋）
- 封闭式传输系统
  - 垂直运输车
  - 中型散装容器（IBCs）
    - 专用连接器和阀门（SBVs）
- 通风的遮罩
  - 粉末称重遮罩
  - 用于细分，填充，筛分的遮罩

隔离

灵活的控制和隔离

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

通风平衡安全柜

个人保护设备

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Powered air purifying respirators (PAPRs) 动力空气净化呼吸器
  - With combination cartridges
    配有组合式滤筒
  - Hood covering
    遮光罩
- Skin protection 皮肤保护
  - Tyvek® coveralls and sleeve covers
    Tyvek®工作服和袖套
  - Booties
    短靴
  - Double gloves
    双层手套

控制和隔离的良好流程

- Movement of material into and out of the control / containment
- Cleaning of work surfaces
- Proper use of controls
- Use of control for purposes designed
- 材料进出控制/隔离装置
- 清洁工作台面
- 正确使用控制
- 将控制用于设计目的

Verify the Controls through Measurement

通过测量验证控制方法

控制/隔离验证

- Surrogate Monitoring
- Factory Acceptance Testing
- Site Acceptance Testing
- Statistical Analysis
- Comparison to Control/Containment Performance Target (CPT)
- 替代监测
- 工厂验收测试
- 现场验收测试
- 统计分析
- 控制/隔离性能指标（CPT）的比较

Industrial Hygiene Monitoring – API
工业卫生监测 - API

健康与安全工业卫生暴露评估

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Requires sensitive air sampling analytical methodology
  - RIA, ELISA, HRGCMS
  - goal is to detect 10% of OEL in 15 minute sample
- Task oriented monitoring
  - identify worst case and representative cases
  - careful observation of controls and work practices
- Data analysis
  - calculate and compare to OEL or CPT
- Report and Recommendations
- Periodic reassessment

- 需要敏感的空气采样分析方法
  - RIA， ELISA， HRGCMS
  - 目标是在15分钟内中检测10％的OEL
- 面向任务的监控
  - 确定最坏情况和代表性案例
  - 仔细观察控制和工作实践
- 数据分析
  - 计算并与OEL或CPT进行比较
- 报告和建议
- 定期重新评估

设置空气监测方法目标

Preferred Sensitivity 首选灵敏度

Principle原理: Quantitate 10% of the OEL in a 15 minute air sample 在15分钟的空气样品中定量10％的OEL.

Assumptions假设: Sensitivity in ng/filter;
Sampling rate = 2 L/min; and
OEL = 0.5 μg/m^3

Sensitivity灵敏度:

$$\frac{(0.1)\,(0.5\ \mu g/m^3)\,(1000\ ng/\mu g)\,(2\ L/min)\,(15\ min)}{1000\ L/m^3}$$

$$=1.5\ ng/filter$$

其他计划要素

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Medical Surveillance/Reproductive Health
- Cleaning and Maintenance
- Waste Handling and Disposal
- Training

- 医疗监督/生殖健康
- 清洁和维护
- 废物处理和处置
- 培训

Case Studies – Examples
案例

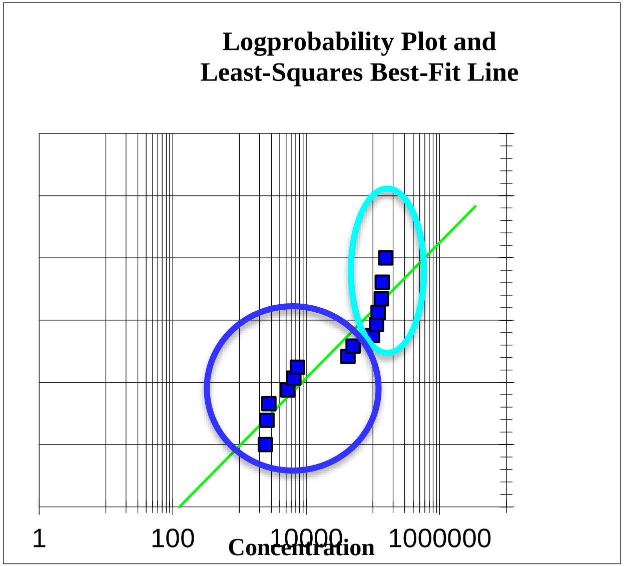
研磨
(案例：非高效，但并非罕见……)

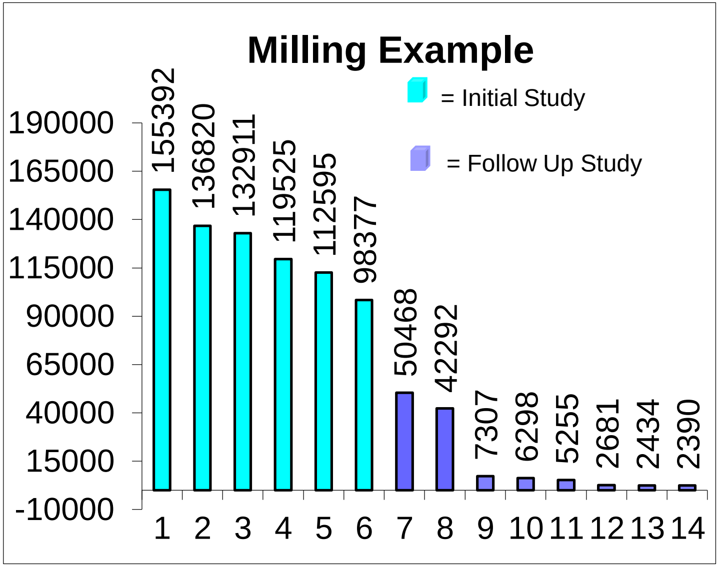
- Pin Mill Technology
- “Hand Scooping” to load mill
- Poor/No Containment
- Milling in small room with low air changes
- “Product Recovery” sweeping bags from dust collector using a hand broom
- Exposure Exceeded Maximum Respiratory Protection (> 1000x the OEL)
  - OEL = 1000 ug/m3

- 针磨技术
- “手舀”加载磨机
- 差/无隔离
- 在空气变化较小的小房间内研磨
- “产品回收”使用手持扫帚从集尘器中清扫袋子
- 暴露超过最大呼吸保护（> 1000倍OEL）
  - OEL = 1000ug / m3

研磨数据对比示例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE





Intervention: Improved local exhaust ventilation and cleaning practices. 干预：改善局部排气通风和清洁操作。

(~ 80% reduction in mean exposures, ~ 60% reduction in 95th Percentile)

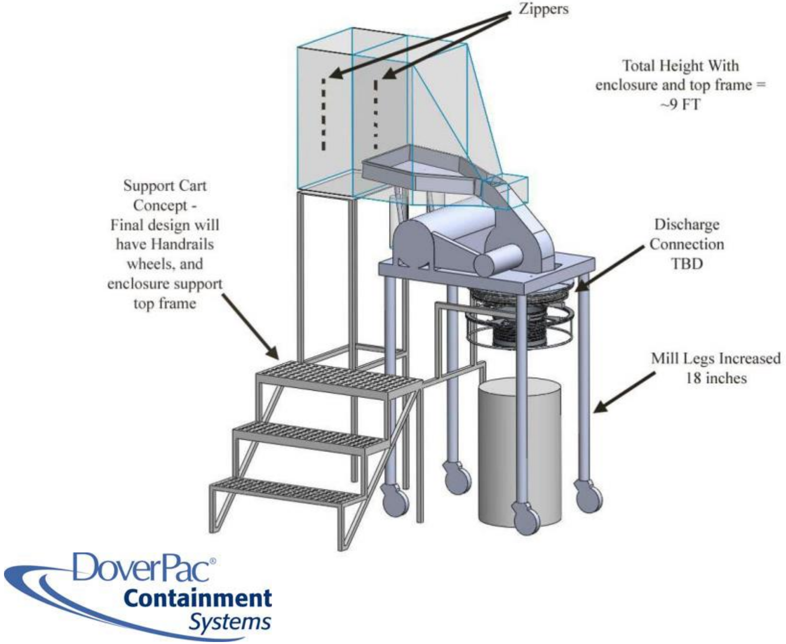
（平均暴露减少约80％，95百分位减少约60％）

研磨

- Previous Example: (Non-Potent)
  上一个例子:(非高效）

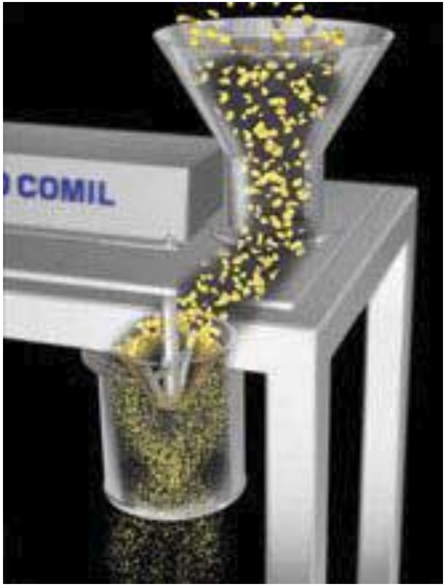
- Potent Handling:
  (Needs More!!!)
  高效处理：需要更多

研磨-Fitzmill


Zippers
Total Height With enclosure and top frame = ~9 FT
Support Cart Concept - Final design will have Handrails wheels, and enclosure support top frame
Discharge Connection TBD
Mill Legs Increased 18 inches
DoverPac Containment Systems

研磨- *Over Drive Comil*

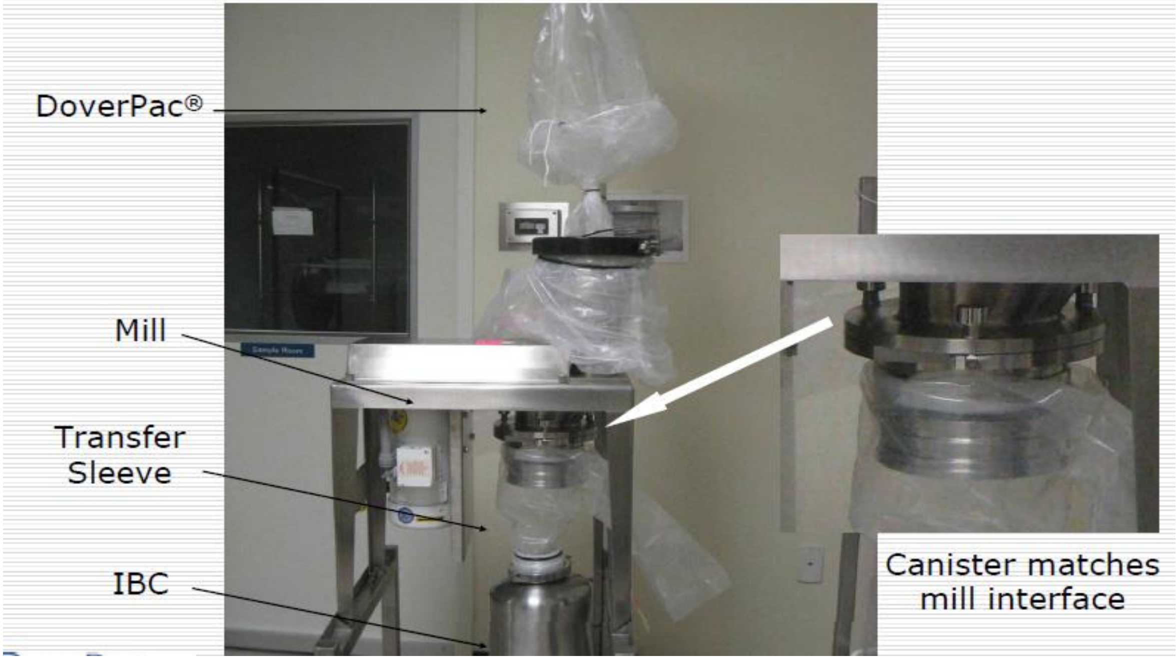
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



Assembly Not Sealed

DoverPac® Containment Systems

研磨- *Over Drive Comil*



DoverPac® Containment Systems

研磨- *Over Drive Comil*

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Location 位置	Sample Time (min.) 样品时间	Conc. ug/m3 浓度
Area Sample: Milling Located at glovebox 区域样品：研磨位于手套箱	7	<0.076
Operator 1 Breathing Zone 操作员1呼吸区	7	<0.072
Area Sample: Milling Located at glovebox 区域样品：研磨位于手套箱	7	<0.074
Operator 2 Breathing Zone 操作员2呼吸区	7	<0.074

DoverPac® Containment Systems

制粒和干燥

DoverPac® Containment Systems

ILC Dover Enclosure System	Test Material	OBZ	*OBZ-TWA (μg/m³)	Comment (No. of operators)
Granulator	Lactose	0.1120-0.0108	0.0026-0.0027	Operation (2)
Granulator	Lactose	0.0247-0.3000	0.0027-0.0331	Cleaning (2)
Drying Oven	Lactose	0.0395-0.0416	0.0026-0.0028	Operation (2)
Drying Oven	Lactose	0.0142-0.0630	0.0026-0.0037	Cleaning (3)

DoverPac® Containment Systems

示例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- UNLOADING IS MANUALLY PERFORMED OPENING THE CENTRIFUGE AND TRANSFERRING INTO DRUMS
- 卸载是手动操作开放离心机并转移到桶

示例

- UNLOADING IS MANUALLY PERFORMED OPENING THE CENTRIFUGE AND TRANSFERRING INTO DRUMS
- 卸载是手动操作开放离心机并转移到桶

DoverPac® Containment Systems

示例

示例

示例
(改进前)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

BTL Glovebox 手套箱:

- Compound is a gonadotropin-releasing hormone agonist (GnRH agonist) with an OEL of 1 ng/m³.
  化合物是促性腺激素释放激素激动剂（GnRH激动剂），OEL为1ng / m3
- Old containment could not adequately protect employees and breaches led to surface to surface contamination.
  旧的隔离措施无法充分保护员工和违规行为，导致各个表面的接触污染。

Courtesy of Corden Pharma
由Corden Pharma提供

示例2
(改进前)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Courtesy of Corden Pharma

示例2
数据 (改进前)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

OPERATION 操作	SAMPLE TYPE 样品类别	SAMPLER LOCATION 样品位置	DURATION (minutes) 时长	REPORTED CONCENTRATION[1] 报告浓度 (ng/m^3)[2]	ESTIMATED 10-HOUR TWA[3] 估计10小时TWA3 (ng/m^3)
Sampling and Packaging at Glovebox 手套箱的采样和包装	Personal Partial Period	Personal breathing zone.	69.5	50.0	5.79
	Area	Pump placed on top of Glovebox	71.5	6.0	0.71
	Area	Pump placed on chair set	19	3.1	0.098

Courtesy of Corden Pharma

示例2
数据 (改进前)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

OPERATION 操作	SAMPLE TYPE 样品类别	SAMPLER LOCATION 样品位置	DURATION (minutes) 时长	REPORTED CONCENTRATION 报告浓度 (ng/m^3)	ESTIMATED 10-HOUR TWA 估计10小时TWA3 (ng/m^3)
NAF-9 Humidification at Glovebox RA-BTL-GB1 手套箱RA-BTL-GB1的NAF-9加湿	Area	On top of CPU located on desk in laboratory.	88	10.3	1.5
	Area	Pump placed on chair set off the Northwest corner.	83	6.8	0.94
	Area	Cassette on bottom West corner of drying rack	58.5	96.8	9.4
	Area	Pump placed on top of Glovebox	82	25.7	3.5

Courtesy of Corden Pharma

示例 2 (改进后)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

由科登制药公司提供

示例 2
(改进后)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

由科登制药公司提供

示例 2
(改进后)

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Engineering Control: 工程控制	Operation 操作	Sample type 样品类别	Sampler location 样品位置	Duration (minutes) 时长	Reported concentration 报告浓度 (Ng/m³)	Estimated 10-hour TWA 估计10小时twa3 (Ng/m³)
RA-GBX-BTL	Package NAF 9	PBZ	202.0	599.8	1.3	0.36
		PBZ	203.0	600.5	0.90	0.25
	Package NAF 9	PBZ	83.0	245.3	0.41[3]	0.047[3]
		PBZ	83.0	244.4	0.41[3]	0.047[3]
	Package NAF 9	PBZ	129.0	384.2	0.58	0.10
		PBZ	129.0	382.2	0.26[3]	0.070[3]

由科登制药公司提供

感谢

我们由衷感谢以下机构为这次演讲提供了示例和数据

Scott Patterson –ILC Dover

www.ilcdover.com

Amy VanAntwerp

Corden Pharma Colorado, Inc.

www.cordenpharmacolorado.com

提问

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Typical Containment Solutions and Performance
典型密闭解决方案与控制效果

SPEAKER NAME： Junbo Zhao
TITLE: EHS Director
COMPANY: Porton Pharma Solutions Ltd.
演示人： 赵军波
职位: EHS 总监
公司: 重庆博腾制药科技股份有限公司

@PSCInitiative #PSCIChina18

AGENDA 议程

Controls Hierarchy 控制层级

IH Assessment Flow 工业卫生评估流程

Typical Operation Performance 典型单元操作控制效果

Controls Examples 控制方案实例

Engineering Enhancement 工程改造

About Porton关于博腾

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Vision愿景:
To build the world's leading Pharma Solutions platform, enabling the transformation of molecules to medicines with continuous improvements in speed and cost
成为全球领先的制药服务平台，让新药更快惠及更多患者

Mission使命:
Help people live long and healthy lives!

健康每一天，再活一百年!

Founded in 2005, Porton is a top-tier **CDMO** company with 4 R&D centers + 3 Sites globally, who reliably helps global **pharmaceutical & biotech** companies more efficiently deliver improved health outcomes across the **whole drug life cycle** through End-to-End API development and manufacturing solutions
重庆博腾制药科技股份有限公司成立于2005年，在全球拥有4个研发中心，3个生产基地，是一家按照国际标准为跨国制药公司和生物制药公司提供医药中间体及原料药定制研发生产服务（CDMO）的高新技术企业
为全球制药企业客户提供端到端的API开发和生产服务

API Process R&D 工艺路线开发及优化	**Analytic Development 分析方法开发**	**Crystallization Solution 药物结晶技术**	**Process Validation 工艺验证**	**API manufacturing 原料药生产**
GLP Operation GLP生产	**Method Validation 分析方法验证**	**High Potent Handling 高活性物质合成**	**Biotransformation 生物转化技术**	**Flow Chemistry 连续反应技术**

Business Positioning
业务定位

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Global Market Focus - Pharmaceutical and Biotech Innovators
全球业务聚焦 – 创新药制药和生物制药公司

J-STAR RESEARCH A Member of the PORTON Group

CDMO: How We Help You Succeed
CDMO: 助力新药成功

PORTON

Drug life cycle 药品生命周期

Discovery 药物发现

Preclinical 临床前

Clinical 临床期

On-patent 专利期

Off-patent 专利期后

API value chain API价值链

Starting Materials 起始物料

GMP Intermediate GMP中间体

API 原料药

CRO strategic partner
CRO战略合作伙伴

BIODURO

CODEXIS® PROTEIN ENGINEERING EXPERTS™

Tech strategic partner
技术战略合作伙伴

*Industry-Leading Preclinical Solutions Offered via BioDuro
保诺科技—行业领先的药物发现和制剂CMC服务CRO

*Leading biotransformation technology via Codexis
全球领先的生物催化技术 -- Codexis

Controls 控制

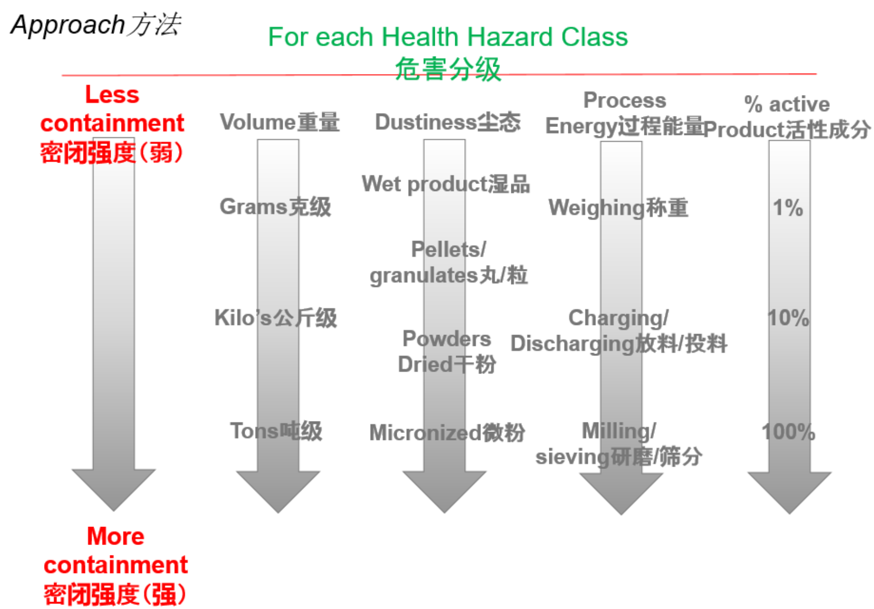
Respect hierarchy of controls 遵循控制层级

- Focus product transfer 关注产品转移
- Primary containment: 一次密闭：
  - Isolator technology 隔离器技术
  - Flexible containment: big bags, endless liner, … 柔性密闭：大包袋、连续袋
  - Containment devices: PTS/DCS, powder feed unit, split butterfly valves, … 密闭手段：PTS/DCS、进料单元、分体式蝶阀
  - Ventilation systems: cabinet, down flow booth, LAF 通风系统：隔间、层流罩、洁净层流罩
- Secondary Containment: 二次密闭：
  - Separation areas: control flow air pressure difference 独立的区域：控制空气流向和压力差
- Personal Protective Equipment 个人防护用品
- Importance of on the job training & maintenance 培训与维护的重要性

Controls 控制

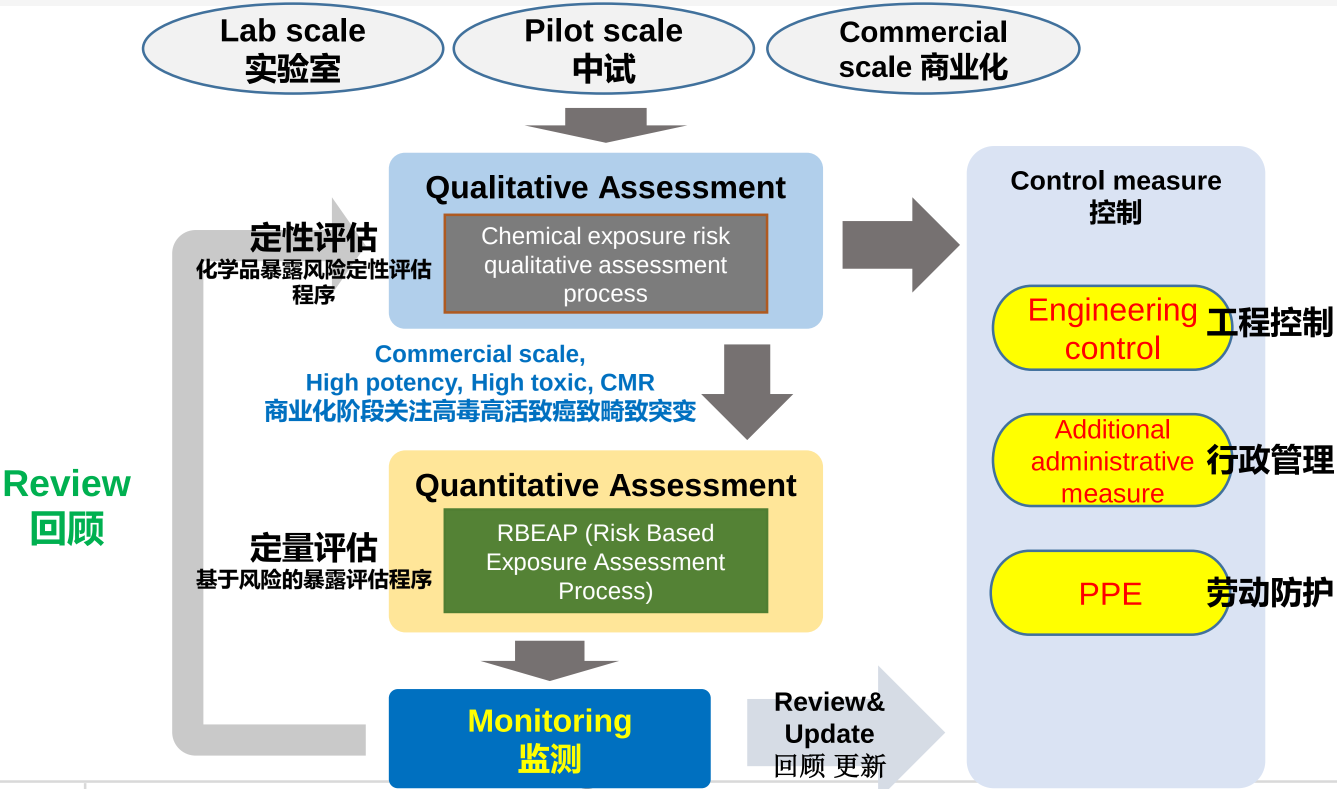
Respect hierarchy of controls 遵循控制层级

Controls



IH Risk Assessment
工业卫生风险评估

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



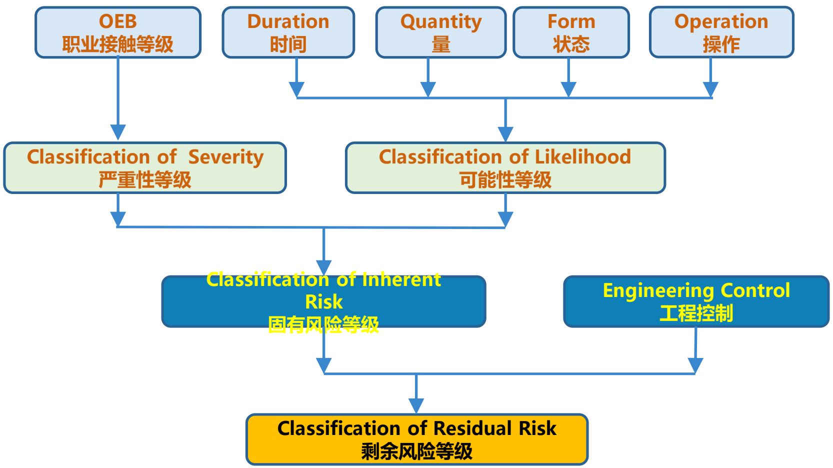
IH Risk Assessment

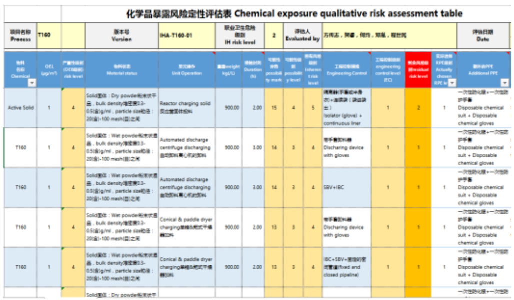
-Qualitative Assessment with Residual Risk

定性风险评估与剩余风险

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

For active ingredients (API/IPI), IH Risk Qualitative Assessment is applied to assess Inherent Risk and Engineering Control
定性风险评估程序用于评估活性成分的固有风险和工程控制





Internal tools for qualitative assessment
基于博腾现状开发的定性评估工具
Focus on: OEL/OEB, character, containment , process, unit operation, etc
关注：OEL/OEB、物质性质、密闭、单元操作等

IH Risk Assessment

-Quantitative Assessment
定量风险评估

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Monitoring 采样监测

Porton follows SMEPAC guide to figure out test proposal and perform the sampling.

采样遵循SMEPAC指南

- Testing 样品分析

All the samples are sent to Bureau Veritas North America Inc. for testing.

Bureau Veritas实验室分析样品

- Data Processing 数据处理

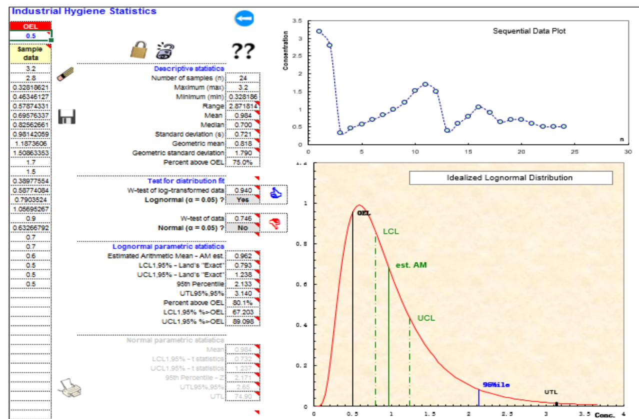
AIHA IHSTAT software is used to process results data.

Focus on peak date and 95% possibility limit data.

关注最高值和95%置信度值

Static sampling 定点采样

Personal sampling 个体采样



IH Risk Assessment
-Quantitative Assessment
定量风险评估

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Documentation 记录

IH report is used to document assessment process in Porton. The key elements are as below

博腾使用工业卫生报告记录评估过程。关注：

- ✓ Purpose 目的
- ✓ Executive Summary 总结
- ✓ Chemicals & Surrogate 化学品&替代物性质
- ✓ Ventilation & Containment 通风&密闭
- ✓ Operation &Observations 操作&观察内容
- ✓ Result & Interpretation 结果&数据解读

- Communicate Data & Review 告知&回顾

PORTON EHS-SAT Report

EHS-SAT Report EHS-SAT Report #: SAT-006-A(EN)

Site Acceptance Test (SAT) Report
Assessing Containment Performance of Glovebox & Continuous liner in Mini plant

Location:	Mini plant
Room:	Chemical area dispense room2
Product:	——
Process:	Dispense
Surrogate:	Lactose

Written by James Zhu Aug. 30, 2017 Reviewed by Carl Deng Aug. 30, 2017

1. Executive summary

Glovebox with continuous liner in Mini plant was designed for dispense operation to control high active substances (OEB5). Site acceptance test was performed to determine if the containment equipment was able to achieve the Design Exposure Limits (DEL) of OEB5 < 1 μg/m³.

Sampling results showed that all personal samples and X0.95 (95% possibility limit data) were not exceed the DEL, Glovebox with continuous for dispense could achieve OEB5 < 1 μg/m³.

2. Purpose

The DEL of the glovebox is < 1 μg/m³. The purpose of site acceptance test (SAT) was to determine the containment performance of Glovebox with Continuous liners by using surrogate of Lactose.

3. Surrogate

Lactose
CAS#: 63-42-3
Brand: BELGIOIOSO
Particle size: 50 % of particles are < 60μm.

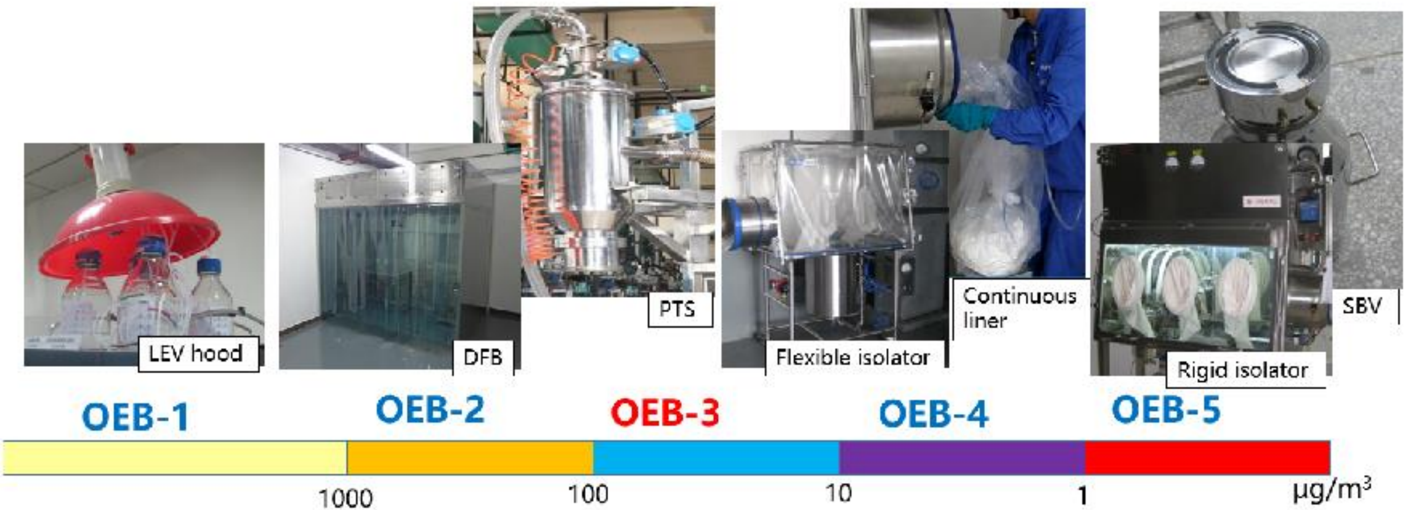
4. Glovebox and continuous liner description

IH report 工业卫生报告

Typical Operation Performance
典型单元操作的控制效果

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

In general, better containment performance mostly means more complex operation and higher cost.
Containment equipment combination is always based on target value.
更好的密闭控制往往意味着更高的成本和更复杂的操作。
应基于目标控制值，选用合适的密闭设备。



Typical Operation Performance
典型单元操作的控制效果

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Scale 规模	Unit operation 单元操作	Controls 密闭控制	Volume 批重量 (per batch)	Containment performance (μg/m3) 密闭控制性能
Workshop 车间	Dispensing分料	Down flow booth层流罩	100KG	800
	Reactor charging反应釜进料	Flexible isolator柔性隔离器	5KG	10
	Reactor charging反应釜进料	Flexible isolator, PTS 柔新隔离器、PTS	25KG	10
	Discharging, milling ,packing 双锥出料、粉碎、包装	PTS，Flexible isolator 柔新隔离器、PTS	50KG	1
Pilot plant 中试	Dispensing分料	Rigid isolator硬质隔离器	10KG	1
	Reactor charging反应釜进料	Rigid isolator硬质隔离器	10KG	1
	Reactor discharging反应釜出料	Glovebox, continuous liner 手套箱、连续袋	5KG	1
	Drying干燥	Rigid isolator硬质隔离器	5KG	1
	Milling transfer粉碎转料	SBV分体蝶阀	5KG	10
R&D Center 研发中心	Lab operations实验室操作	Rigid isolator硬质隔离器	500g	0.5
	Weighting称量	weight cabinet称量罩	500g	0.5

Controls Examples
控制实例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Lab operations (Dispensing, drying, weighting)
单元操作：实验室内操作（分料、干燥、称量等）
Controls: rigid isolator, weight cabinet 密闭控制：硬质隔离器、称量罩
Weight scale： 500G 批重量：500G
Containment performance ： ＜0.5 μg/m3 密闭效果： ＜0.5 μg/m3

Rigid isolator 硬质隔离器

Weight cabinet 称量罩

Controls Examples
控制实例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Miller charging/discharging
单元操作：粉碎机进/出料

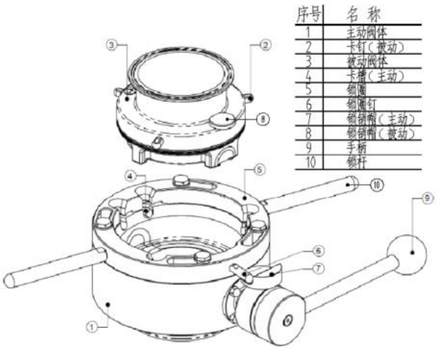
Controls: Split butterfly valve 密闭控制：分体式蝶阀

Weight scale： 5KG 批重量： 5KG

Containment performance：＜ 10 μg/m3 密闭效果:＜ 10 μg/m3

Charging via SBV进料

Discharging via SBV出料



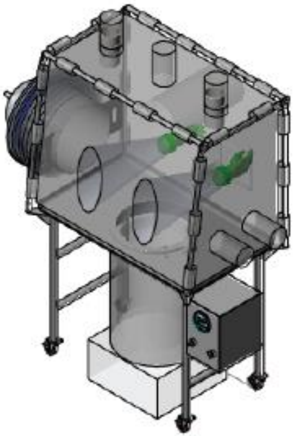
Controls Examples
控制实例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Reactor charging 单元操作：反应釜进料
Controls: PTS， Flexible isolator, continuous liner
密闭控制：PTS、柔性隔离器、连续袋
Weight scale：25KG 批重量：25KG
Containment performance ：＜10 μg/m3 密闭效果：＜10 μg/m3

Operation outside isolator
隔离器外

Operation in isolator
隔离器内



Controls Examples
控制实例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Reactor charging 单元操作：反应釜进料

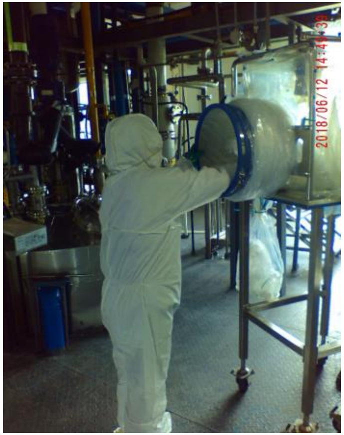
Controls: Flexible isolator, continuous liner

密闭控制：柔性隔离器、连续袋

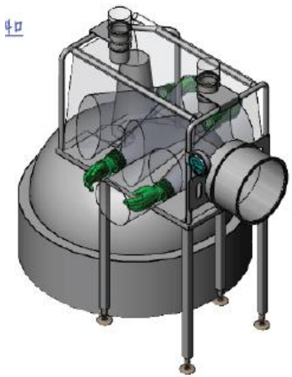
Weight scale： 5KG 批重量：5KG

Containment performance ：＜ 1 μg/m3 密闭效果： ＜1 μg/m3

Operation outside isolator
隔离器操作



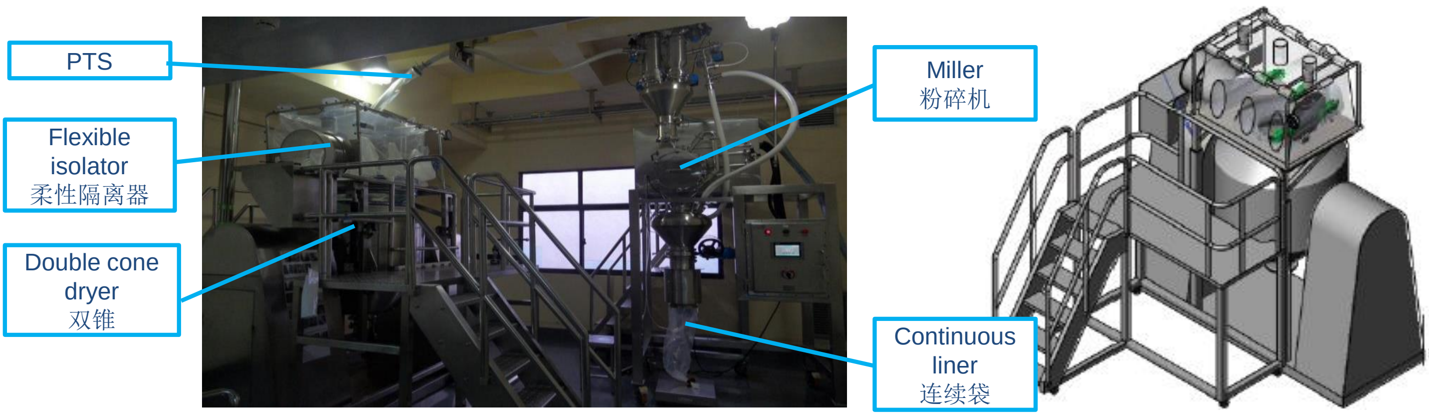
Transfer into isolator
物料传入隔离器



Controls Examples
控制实例

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Discharging, milling ,packing
单元操作：双锥出料、粉碎、包装
Controls: PTS, Flexible isolator, continuous liner
控制：PTS、柔性隔离器、连续袋
Weight scale: 50KG 批重量：50KG
Containment performance : ＜1 μg/m3 密闭效果：＜1 μg/m3



Controls Examples
控制实例

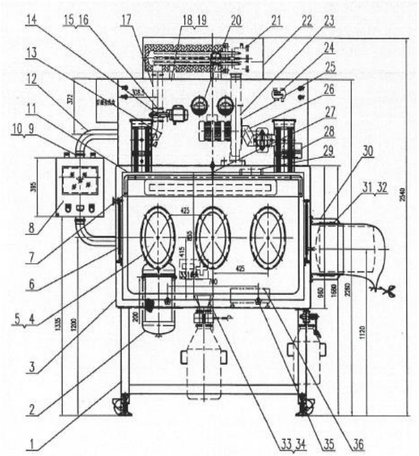
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Unit operation: Drying 单元操作：干燥

Controls: Rigid isolator, continuous liner
密闭控制：硬质隔离器、连续袋
Weight scale：5KG 批重量：5KG
Containment performance ：1 μg/m3密闭效果：＜1 μg/m3

Operation outside isolator
隔离器外

Operation in isolator
隔离器外



Before改造前

After改造后

Before：chuck connection
After： flange
多处抱箍升级为法兰，强化设备连接处的密闭性

Set a automatic valve to control the dust feeding valve to minimize the dust flying
增加自动阀，控制下料速度，降低扬尘量

Set two flexible connector to absorb the vibration of the milling to minimize the dust escape.
增加两处软连接以减少震动，减少因震动引起的连接处密封松动造成的泄漏

42 µg/m3

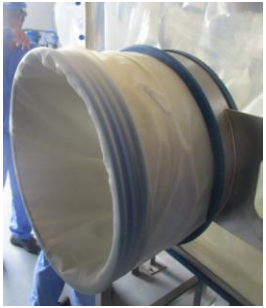
< 1 µg/m3

Engineering Enhancement
工程控制升级

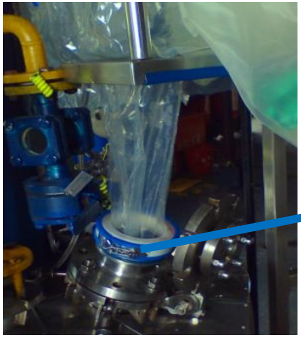
PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Before改造前

After改造后



Improve the connections between liners and isolator to minimize the dust escape
Before：Rubber rings
After：C-Type clasp
O型环改为C形抱箍
改变连续袋固定方式以减少物料污染干净连续袋的可能性



Improve the connections to the reactor
Before：Rubber rings
After：Hopper+C-Type clasp
在进料口加设漏斗型环直接固定在连续袋外部，减少进料口物料堆积

7 µg/m3 → **< 1 µg/m3**

Questions
问题讨论

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Industrial Hygiene Risk Management in Pharmaceutical Industry
制药行业工业卫生风险管理

Dan Wang
EHS Senior Manager, EHS SME
SynTheAll Pharmaceutical Co., Ltd.

AGENDA

Introduction of STA 公司简介

Qualitative Assessment 定性评估

Quantitative Assessment 定量评估

Challenge 挑战

"At WuXi STA, **we enable bold innovators by arming them with the industry's most comprehensive pharmaceutical development and manufacturing platform equipped with very latest technologies** to aid their quest to design, develop and manufacture the innovative medicines."

"End-to-End" Small Molecule CMC Platform

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- WuXi STA has invested in building capability to support your process R&D and manufacturing needs from preclinical to commercial. Our comprehensive one-stop platform enables us to move your project forward faster throughout the product development cycle.

PRE CLINICAL	PHASE I	PHASE II	PHASE III	COMMERCIAL
DS PROCESS RESEARCH & DEVELOPMENT				
DS CLINICAL MANUFACTURING			DS COMMERCIAL MANUFACTURING	
FORMULATION RESEARCH & DEVELOPMENT				
DP CLINICAL MANUFACTURING & PACKAGING			DP COMMERCIAL MANUFACTURING & PACKAGING	
ANALYTICAL DEVELOPMENT AND QUALITY CONTROL				

A Culture of Quality and Regulatory Excellence

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

WuXi STA has an **ingrained quality culture,** not a passive approach to simply meeting existing standards.

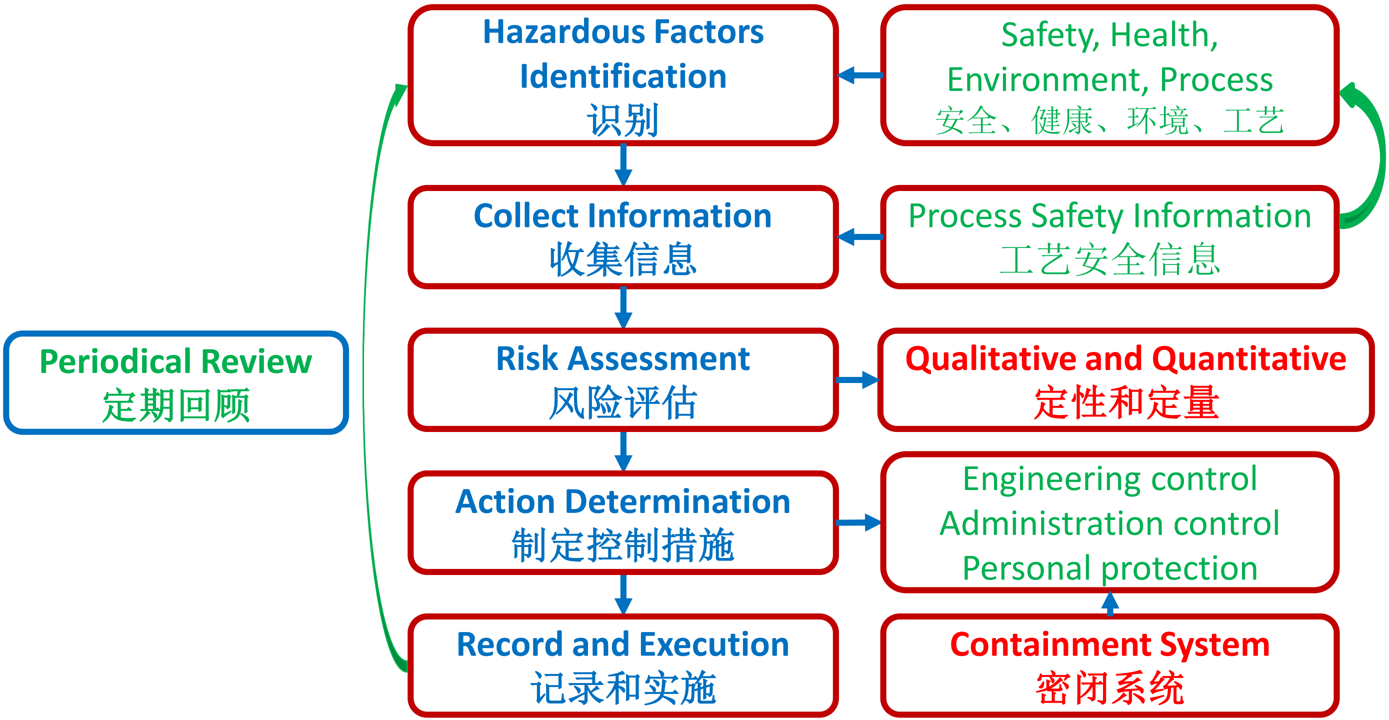
First CMC platform in China that passed FDA inspection for new chemical entities.

6 successful FDA inspections across 3 sites in 2013, 2014, 2016 and 2018.

First CDMO to support the approval of an innovative drug in China through the "MAH" pilot.

Industry leading R&D and Manufacturing Centers

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE


Hazardous Factors Identification
识别
Safety, Health, Environment, Process
安全、健康、环境、工艺
Collect Information
收集信息
Process Safety Information
工艺安全信息
Periodical Review
定期回顾
Risk Assessment
风险评估
Qualitative and Quantitative
定性和定量
Action Determination
制定控制措施
Engineering control
Administration control
Personal protection
Record and Execution
记录和实施
Containment System
密闭系统

Identification and Information Collection

- **New Product Introduction Evaluation新产品引入评估**
  - Intermediate and API toxicological data: NOAEL, LOAEL, OEL, OEB, MTD……
    中间体和API毒性数据: NOAEL, LOAEL, OEL, OEB, MTD……
  - Route of entry (oral, injection)
    给药途径（口服，注射）
  - Absorption, metabolism and excretion
    吸收、代谢、排泄
  - Special API: β-lactams, steroid, hormone, cytotoxic……
    特殊API：β-内酰胺、甾体类、激素类、细胞毒……

- **MSDS安全技术说明书**
  - Section 2 Hazard identification 危害性
  - Section 8 Exposure controls/personal protection基础控制和个体防护
  - Section 9 Physical and chemical properties理化特性
  - Section 11 Toxicological information毒理学信息

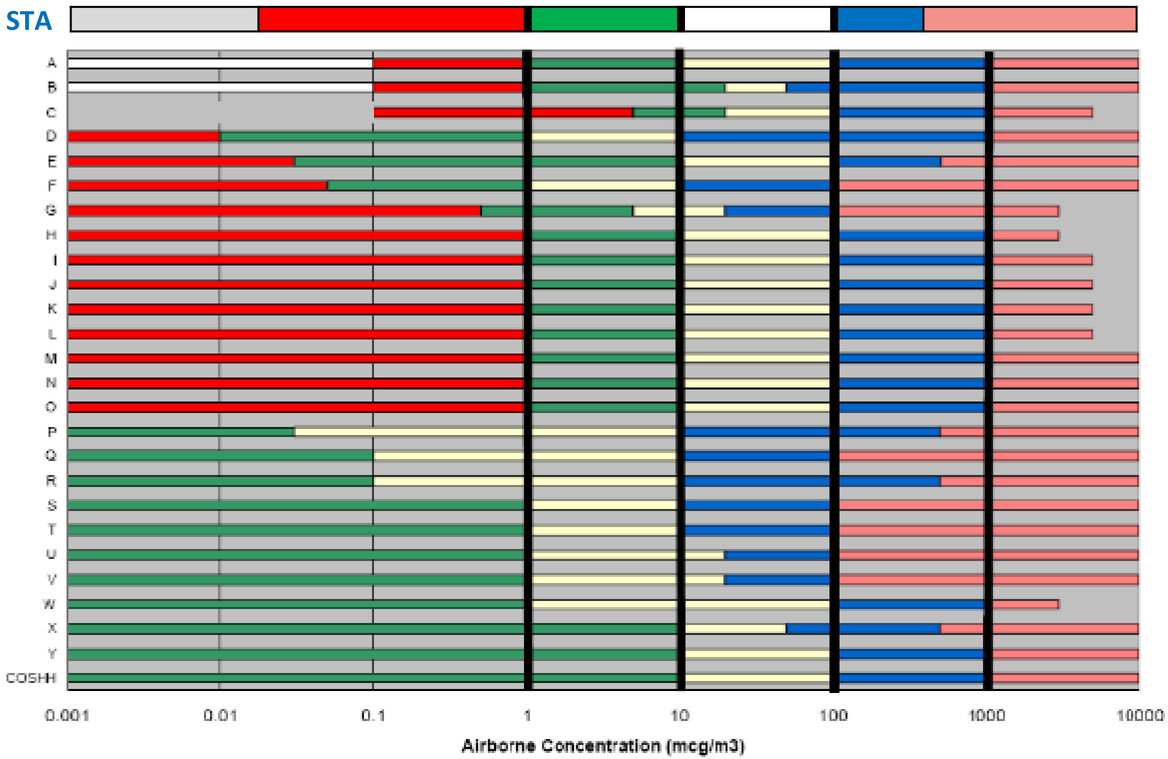
- **Handling操作:**
  - Physical form: dusty, solid, wet cake, flaky, viscous, liquid……
    物理形态：粉状、固体、湿饼、絮片状、粘性、液体……
  - Pressure, temperature, composition……
    工艺压力、温度、化合物组成……
  - Lab(small)/pilot/commercial scale?
    规模：实验室级别、研发中试、商业化……
  - Open/enclose handling?
    操作方式：开放式？密闭？
  - Manual/ mechanized/automatic?
    人工？机械化？自动化？
  - Continue/intermittent process or batch?
    连续作业/批次？间断作业/批次？
  - Routine/temporary/shift task?
    日常/临时/班组制作业？
  - Long-term/short-term process?
    长期/短期工序？
  - ……

- **Cleaning清洁:**
  - Manual/ mechanized/automatic (CIP/WIP)? 人工/机械/自动化（在线清洗）？
  - Continue/intermittent? 连续/间断作业？
  - Routine/temporary/shift task? 日常/临时/班组制作业？
  - Long-term/short-term process? 长期/短期工序？
  - Deactivate for High Potent API? 高活API失活处理？

- **Personal impact个体影响：**
  - Age: youth, elder 年龄：年轻人、中老年人
  - Gender: male, female 性别：男性、女性
  - Life habit: smoking, drinking, overnight, sport 生活习惯：吸烟、饮酒、熬夜、运动……
  - Potential disease: diabetes, hypertension 潜在疾病：糖尿病、高血压……
  - Individual habitus: allergy…… 个人体质：敏感体质……
  - ……….

Occupational Exposure Band

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



- **The purpose 目的:**
  - Anticipate/estimate the risk level 预估风险等级
  - Develop inventory of operation units, hazards, controls……
    建立操作单元、危害因素、控制措施的数据库/清单
  - Develop Similar Exposure Group (SEG) and IH monitoring plan
    建立相似暴露组和IH监测计划
  - Review the effectiveness of the current controls
    回顾目前控制措施的有效性
- **Qualitative assessment tools 常用定性评估工具:**
  - Risk Based Exposure Assessment
  - ILO Chemical Control Toolkit
  - COSHH Essential - UK
  - AIHA - USA
  - GBZ/T 298 - China
  - ……
- **Limitation: depends on IH experience judgment**
  局限性：依赖IH人员的经验判断

Quantitative Assessment

- **Why conduct IH monitoring 为什么进行IH监测？**
  - To assess compliance with relevant control limits or exposure standards
    评估是否满足控制限值或暴露标准的要求
  - To check the effectiveness of control measures
    确认控制措施的有效性
  - To assess the suitability of respiratory protective equipment
    评估呼吸防护用品的适用性

- **What shall be conducted by IH monitoring 哪些需要进行IH监测？**
  - All new and improved equipment, operation units, containment facilities, processes……
    所有新的和改进/改造的设备、操作单元、密闭设施、工艺等
  - Personal exposure
    个体暴露水平
  - Periodically monitoring
    定期监测

- **Personal sampling 个体样品**
  - To check the effectiveness of control measures in place to control chemical release
    确认目前实施的控制措施的有效性
  - To assess the suitability of respiratory protective equipment being worn
    评估呼吸防护用品的适用性

Tube 溶剂采样管（**charcoal/silica gel**）（活性炭/硅胶）

IOM
粉尘采样器

Pump
采样泵

Calibrator
流量校验器

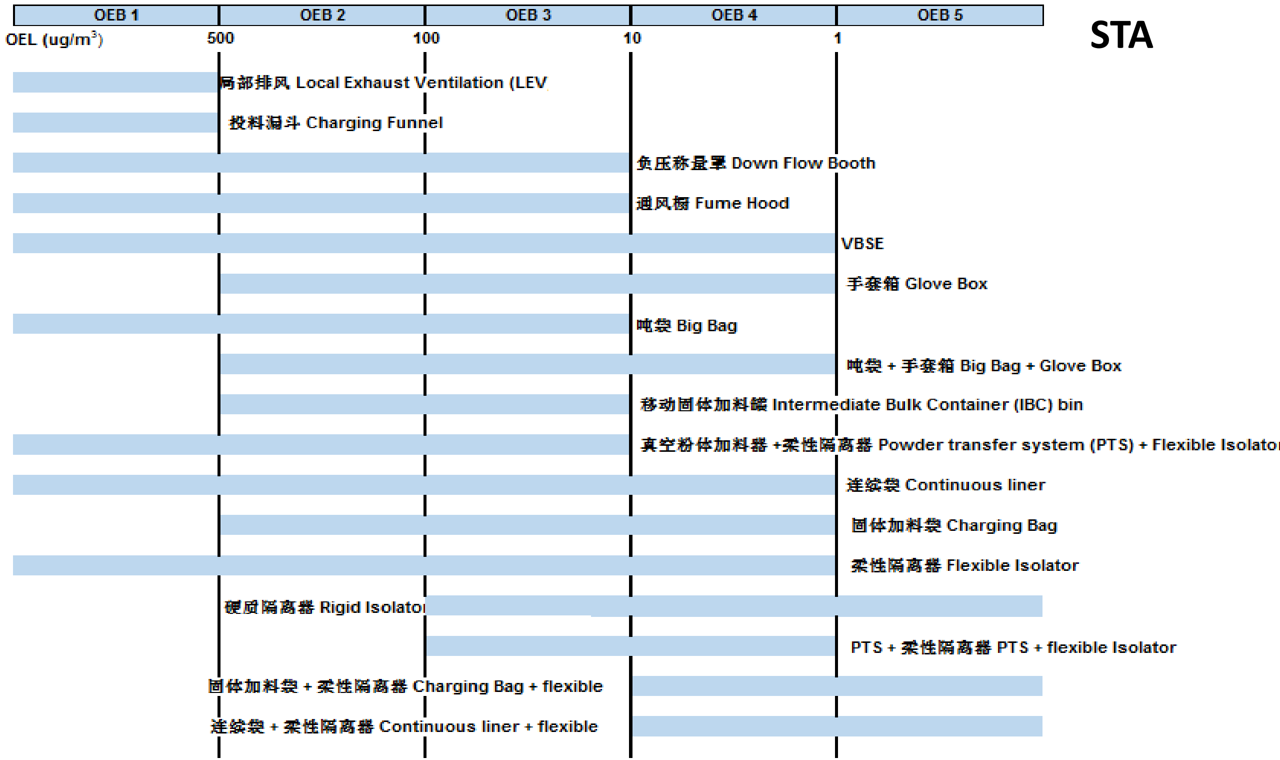
- **Static sampling 定点样品**
  - Background sampling 背景样品
    - Before operation or/and during operation 操作开始前或/和操作过程中
    - To establish chemical concentrations that may lead to airborne chemical release into work area 操作区域范围内可能的暴露的化学品浓度
  - Leak monitoring 泄漏监测
    - To confirm that the controls in use are sufficient to prevent the spread of chemical and that the integrity of the enclosure is being operated 确认采取的控制措施的有效性，以防止化学品扩散和使用的密闭设备的完整性
  - Cleaning process monitoring 清洁过程监测
    - To assess the suitability of personal protective equipment during cleaning process 评估清洁过程个人防护用的适用性
    - As part of a cleaning qualification procedure to verify an area is suitable for re-occupation 清洁验证的一部分，以确认区域可以用于再次作业
    - Air sampling or/and wipe sampling 空气样或/和擦拭样

（ISPE guidance ISPE指南）

- **Criteria of the monitoring results 监测结果判断标准：**
  - Containment Performance Target (CPT) usually is the lowest limit of each OEB
    密闭性能目标值通常是每个OEB的下限值
  - The statistic calculated 95th percentile of a dataset with three or more samples shall be compared against the CPT
    三个或以上个体样品采用统计学进行判断，与CPT直接进行比较
    - IHSTAT – AIHA统计工具
    - Bayesian decision analysis (IH DA Lite software) 贝叶斯统计工具
  - If a dataset with one sample, the measured result shall be compared against the 10% of CPT
    只有一个个体样品，与10%CPT进行比较

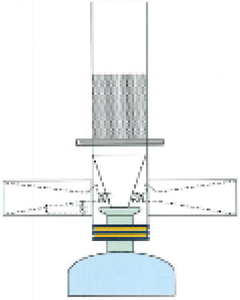
- **Establish Similar Exposure Group 建立相似暴露群组**

Containment Guideline



Containment Example

- **Small scale – Charging bag for** charging/ discharging
- **Pilot scale – Flexible isolator with continuous liner** for dispensing/ weighing/ charging/ discharging/ milling/ sieving/ packaging
- **Commercial scale – Big-bag with liner system for** charging/ discharging



Glove Bag
Photo from ONFAB

Flexible Isolator
Photo from STA

Containment Big Bag System
Photo from ILC Dover

Continuous Liner
Photo from ONFAB

Challenge to CRO/CMO/CDMO

Challenge	Problem
• Handle new chemicals safely • 安全地操作新化学品	• No or limited toxicological data • 毒性数据没有或有限
• Cost balance: production, equipment and manpower • 费用平衡：生产、设备、人力	• Old facilities VS new design containment equipment • 旧生产设施 VS 新型密闭设备
• High EHS requirements • 高EHS要求	• Efficiency VS EHS requirements • 生产效率 VS EHS要求

Questions

Tea Break 茶歇

15:45 – 16:15

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

IH Case Study - Reactor Charging & API Kilo Lab
工业卫生案例- 反应釜投料和公斤级实验室

William Zhu, CIH

Associate, IH Service Manager

Golder Associates

AGENDA

Reactor charging improvements 反应釜投料的密闭改善

IH Controls at a Kilo Lab 公斤级实验室活性药物成分的工业卫生控制措施

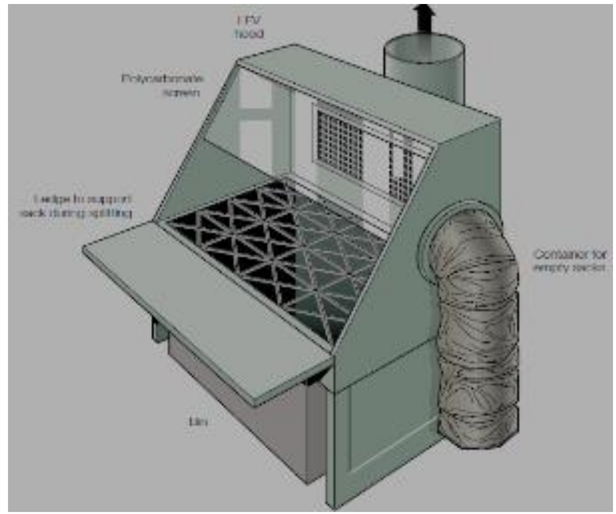
Containment Performance Assessment 密闭性能评估

Exposure Control Options for Reactor Charging
反应釜投料工程控制措施的选择(活性粉尘的控制)

- Open process with local exhaust hood (captor hood)
  开放式操作，配局部排风系统(外部排风罩)
- Open process with local exhaust hood (partially enclosed hood)
  开放式操作，配局部排风系统(局部密闭排风罩)
- Powder Transfer System (negative pressure) 真空上料系统
- Split Butterfly Valve (SBV) 分体式蝶阀系统
- High Containment Flexible IBC 高密闭吨袋系统
- Glovebox 手套箱
- Isolator (hard-walled or flexible) 硬质或柔性隔离器

Exposure Control Options for Reactor Charging
反应釜投料工程控制措施的选择

Improved Local Exhaust Ventilation 局部排风系统的优化



picture from BOHS LEV Guide

Reactor charging- Level I
反应釜投料- 方案I

Glovebox: 手套箱

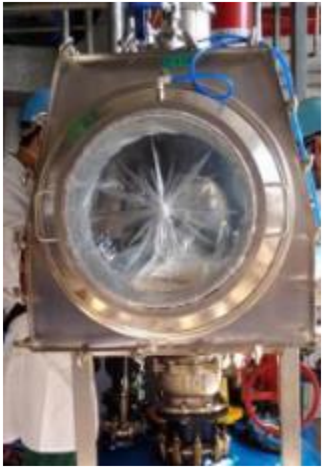
- Single chamber 单舱体
- Open door (right side) to transfer bags in 打开舱门，传入物料袋
- Bag-out port to transfer empty bags out 投料后空袋通过“袋出”方式传出
- Negative pressure inside by LEV 舱体内保持负压(通过LEV系统)
- Better containment performance than local exhaust ventilation 密闭性能优于常规局部排风罩

Reactor charging- Level I
反应釜投料- 方案I

- Containment assessment results (2 bags of surrogate lactose, 25kg/bag): highest personal exposure 47.8μg/m^3
  密闭性能：用2包乳糖(每包25kg)进行模拟操作，个体接触浓度最高达47.8μg/m^3

- Problem: Re-opening the door to transfer the 2nd bag in could cause dust exposure.
  改善机会：第二包物料传入时，需要打开舱门，可能导致舱体内的粉尘逸散

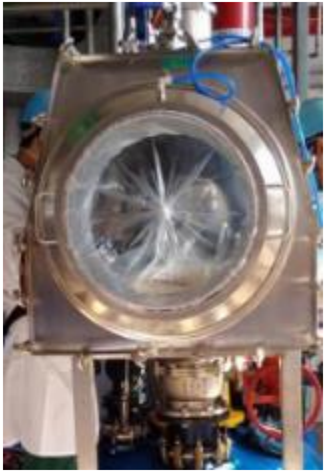
Reactor charging- Level II
反应釜投料- 方案II



Improvement: 改善方法

- Bag-in/Bag-out port to transfer bags in
  "袋进"法传入物料
- Can transfer more than one bags in while maintaining good containment.
  可连续传入多包物料，同时保持良好密闭

Reactor charging- Level II
反应釜投料- 方案II



- Containment assessment results (2 bags of surrogate lactose, 25kg/bag): highest personal exposure 2.82μg/m³

  密闭性能：用2包乳糖(每包25kg)进行模拟操作，个体接触浓度最高为2. 82μg/m³
- Further improvement opportunities 进一步改善机会：

✓ Negative pressure maintained by fan 使用自动调节的风机，而不是LEV系统维持舱体负压

✓ Leakage test 舱体泄漏测试

✓ Two chambers (passing & charging) 双舱体(传递舱/投料舱)

✓ HEPA for air in/ out 进出舱体的气体经高效过滤器

✓ Safe change of gloves 手套安全更换

✓ Washing in place 在线清洗

Reactor charging- Level III
反应釜投料- 方案III

- Hard-walled isolator 硬质隔离器
- Containment assessment results (lactose surrogate):

  highest personal exposure 0.782μg/m^3

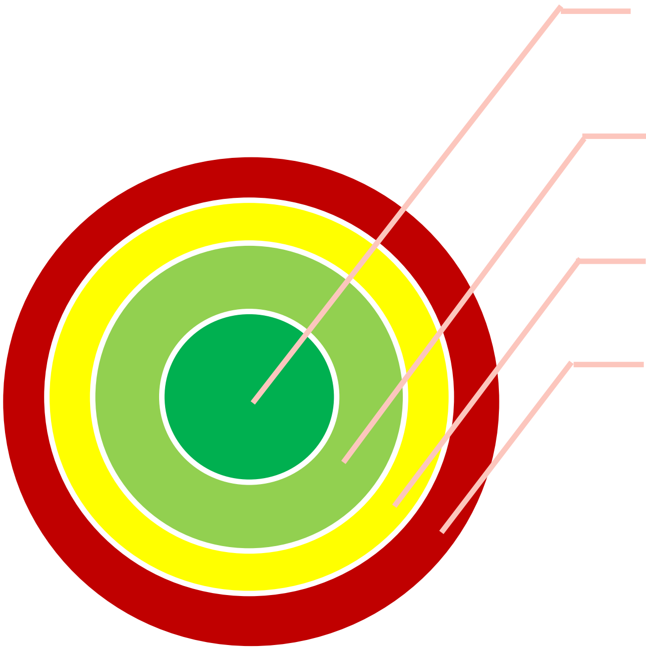
  密闭性能：个体接触浓度最高为0.782μg/m^3

Containment design 密闭设计要点

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- OEL/OEB 职业接触限值/职业接触等级
- Material quantity and physical state 物料用量、物理状态
- Process/ unit operation 单元操作类型
- How materials are transferred in and out? 物料如何传进、传出？
- Any possible leakage during the process operation? 设备运行过程中是否有泄漏可能？
- Exposure during QC sampling? QC取样时是否有接触风险？
- Exposure during troubleshooting? 设备故障排除时是否有接触风险？
- How to deal with residual inside equipment? 设备内剩余物料如何处理？
- Exposure during equipment cleaning? 设备清洗、清洁过程中接触风险？
- Weakness of a specific containment technology 某一特定密闭技术的弱点？
- Emission control/ waste disposal 大气排放控制/废物处置
- Productivity 密闭操作对生产效率的影响
- Ergonomics 密闭操作的工效学问题
- Cost 密闭措施的成本
- Safety issues 密闭措施的安全风险

API Exposure Control
活性药物成分职业接触控制



Primary containment 设备密闭

Secondary containment 设施密闭

PPE 个人防护用品

Emergency containment 应急处置

API Exposure Control for a Kilo Lab (OEL 1 μ g/m³)
某公斤级实验室活性药物成分(OEL 1 μ g/m³)接触控制

- Primary containment: hard-walled isolator for the whole process from reactor charging to packing (containment performance verified).
  设备密闭：加料、反应、干燥、包装均在硬质隔离器内进行，密闭性能经验证
- Secondary containment: Entry/ Exit; Airlock; Dedicated HVAC system; No air recirculation; Air changes; Air filters safe change; mist shower.
  设施密闭：人/物进、出通道；独立HVAC系统；全新风；换气次数；排风过滤器安全更换；雾淋
- Respirator during routine work: disposable N95 dust mask (half facepiece respirator with cartridge for solvents)
  常规作业的呼吸防护：防尘口罩（或半面罩呼吸器）
- Respirator during chemical spill: Airline respirator or SCBA
  应急状态的呼吸防护：长管呼吸器或正压式空气呼吸器
- Emergency containment: Vacuum cleaner (with HEPA), Spill kit, Deactivation, PPE decontamination
  应急处置：真空除尘器(配HEPA)；泄漏处置工具；灭活液(如适用)；PPE洗消

ISPE (International Society for Pharmaceutical Engineering) “Assessing the Particulate Containment Performance of Pharmaceutical Equipment”
国际制药工程协会出版物 -- 《制药设备颗粒物密闭性能的评估》

- Simulated operation 模拟操作
- Surrogate material (lactose, naproxen sodium, mannitol, acetaminophen, etc.)替代物 (乳糖，萘普生钠，甘露醇，对乙酰氨基酚等)

- Occupational Exposure Limit (OEL) 职业接触限值
- Occupational Exposure Band (OEB) 职业接触等级
- Design OEL (DOEL) 密闭设计限值
- Containment Performance Target (CPT) 密闭性能目标

- Air samples (task-based) 空气样(基于单元操作)

Area: background; during operations 定点样(操作前背景样；操作过程样)

Personal: during operations 个体样

- Surface samples (swab) 表面擦拭样

- Sample analysis by accredited laboratory 样品分析
- Data interpretation and statistical analysis 数据解读和统计学分析

Questions
问题

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

呼吸器选择及滤毒盒使用寿命

Kelvin Jiang
Application Engineer
3M China R&D Center

AGENDA

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 呼吸危害因素
- 呼吸器标准与认证
- 呼吸器的种类
- Case Study 1：呼吸器的选择
- Case Study 2：滤毒盒的使用寿命?
- 总结

呼吸危害因素

- 存在空气污染物
  - 颗粒状

粉尘

烟

雾

  - 气态

有毒有害气体

有毒有害蒸气

- 缺氧

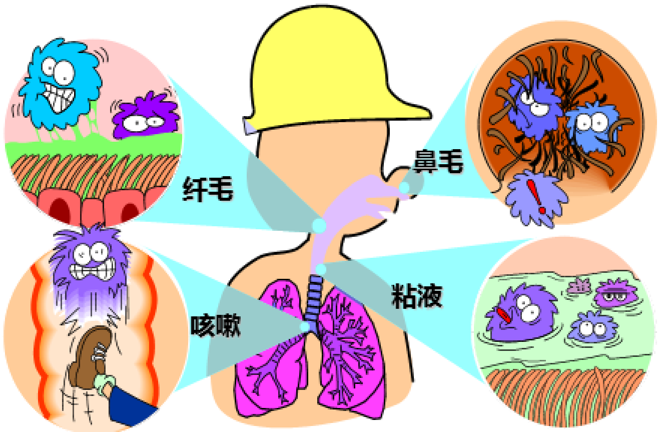
$O_2<19.5\%v/v$

GB8958-2006

呼吸危害因素

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

人体对抗空气传播性颗粒物的防御机理



人体自身呼吸防御系统的局限

1. 颗粒物数量巨大

（能够冲破防御系统）

2. 有毒、传染性颗粒

（能够伤害肺脏和身体的其他器官）

3. 致过敏性颗粒

（能够引发过敏反应，比如哮喘）

4. 粒径很小的颗粒

（能够绕开防御系统到达肺脏 ）

5. 人体自身呼吸防御系统无法阻挡有毒有害的气体

3M呼吸器概览

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

口罩

9502+/KN90
可折叠式

9042V/KN90
可折叠式，有机异味减除

8210 / N95
杯罩式

8862 / KN95
可折叠杯罩式

9334 / FFP3
三面板式

1860 / N95
杯罩式，医用

面具及过滤元件

防颗粒物呼吸器标准

- GB 2626-2006 自吸过滤式防颗粒物呼吸器

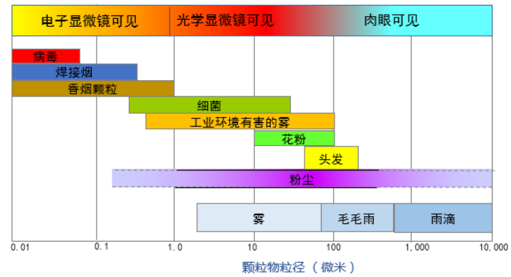
分级		颗粒物过率效率		
		90%	95%	99.97%
分类	KN 类	KN90	KN95	KN100
	KP 类	KP90	KP95	KP100
适用面罩类型		全面罩不适用	适合各类面罩	

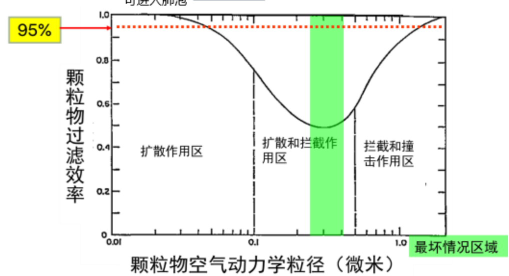
- NIOSH 42 CFR 84 Respiratory protective devices

分级		颗粒物过滤效率		
		95%	99%	99.97%
分类	N类	N95	N99	N100
	R类	R95	R99	R100
	P类	P95	P99	P100

- EN 140-2001 Filtering half masks to protect against particles

颗粒物过滤效率	80%	94%	99%
EN 149 分级	FFP1	FFP2	FFP3





过滤元件分类

过滤元件分类

- A型：某些有机蒸气，防苯、甲苯、二甲苯等，如3M的6001CN
- B型：某些无机气体，防氯气，如3M的6002CN
- E型: 二氧化硫和其他酸性气体，防二氧化硫、氯化氢、氟化氢等，如3M的6002CN
- K型：氨及氨的有机衍生物，如3M的6004CN
- CO型：一氧化碳气体
- Hg型：汞蒸气，如3M的6009CN
- HS型：硫化氢气体，如3M的6002CN
- P：防颗粒物滤烟层，如3M的2091/5N11
- 以上各类的任意组合，如3M的6003CN（A/B/E）和60926CN(A/B/E/K/P)

防护对象	颗粒物	有机蒸气	酸性气体	硫化氢	无机气体	碱性气体	特殊气体甲醛	汞	低沸点(<65℃)有机蒸气
美国标准 NIOSH/ANSI	P100 N/R/P	黑	白			绿	黑	橙	无规定
欧洲标准 EN140	P	A褐	E黄		B灰	K绿	FM 橄榄绿	Hg红	AX褐
GB2890-2009	P	A棕	E黄	HS蓝	B灰	K绿	无规定	HG 红	无规定

说明：

- 不同标准在过滤元件分类中有细微差别，性能不一定都等效。
- 一个同时符合几个标准的过滤元件会同时按照相应标准进行标识、标色。
- 每种防毒过滤元件所适用的具体的有毒气体/蒸气种类应咨询制造商。

正压型呼吸器

送风过滤式呼吸器

长管呼吸器

自给式空气呼吸器

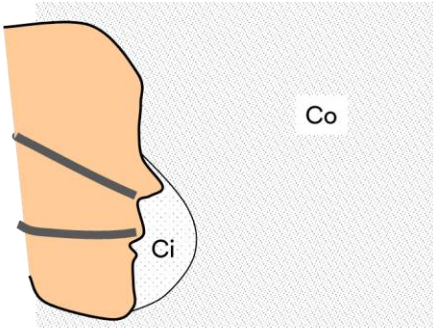
Case Study - 1

呼吸器的选择

防护因数

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 防护因数 = C_o / C_i
- Co = 呼吸器外的空气污染物浓度
- Ci = 呼吸器内的空气污染物浓度

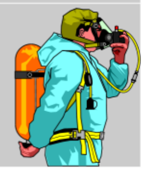
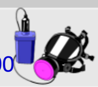


指定防护因数 APF

- 定义：一种或一类功能适宜的呼吸防护用品，在适合使用者佩戴且正确使用的前提下，预期能将空气污染物浓度减低的倍数。
- APF=10的防尘半面罩可将粉尘浓度降低10倍。若作业场所粉尘浓度是卫生标准的5倍，防尘半面罩就适合；若粉尘浓度超标10倍，就不适合。

GB/T18664危害因数(HF)

- 现场浓度与职业接触限值(OEL)的比值
- 危害因数 HF>1，空气污染物浓度超标；HF越大，危害水平越高，需要的防护水平越高。
- 呼吸器 APF > 危害因数 HF

过滤式呼吸器			隔绝式呼吸器
自吸过滤式呼吸器 密合型面罩	半面罩（半面具）	随弃式面罩 DR APF=10 	长管呼吸器 SAR APF=25-1000 
		可更换式半面罩 RR APF=10 	
	可更换式全面罩（全面具）RR APF=100 		携气式呼吸器 SCBA APF>1000 
送风过滤式呼吸器 PAPR APF=25-1000   			

呼吸器选用举例

铅尘OEL: PC TWA = 0.05 mg/m^3

现场A监测: 0.3 mg/m^3

危害因数 = 0.3 ÷ 0.05 = 6

可选：半面罩、全面罩

过滤元件：至少KN95

APF = 10 > HF = 6

现场B监测: 0.7 mg/m3

危害因数 = 0.7 ÷ 0.05 = 14

只能选全面罩

过滤元件：至少KN95

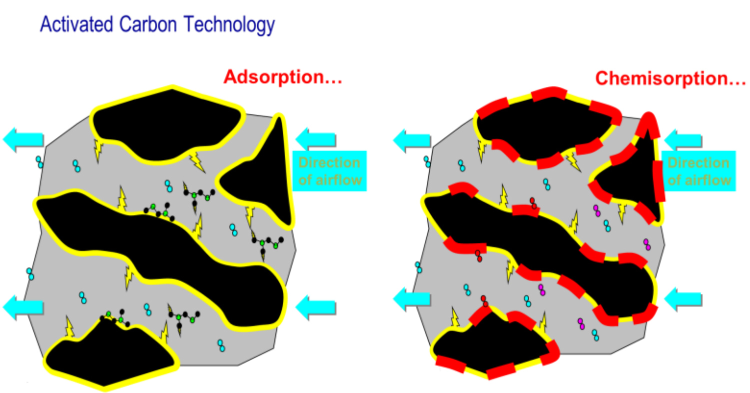
APF = 100> HF = 14

Case Study- 2

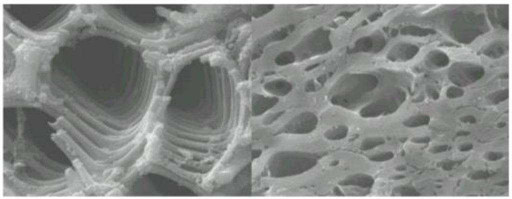
滤毒盒的使用寿命?

活性炭对气态物质吸附机理

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE



活性炭微观结构



物理吸附：适合某些有机蒸气，靠范德华力，无化学反应。

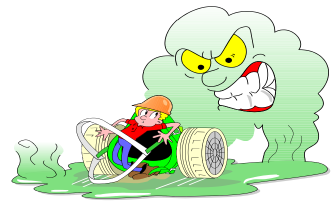
化学吸附：适合某些无机类气体、甲醛、汞蒸气等，靠催化剂，有化学反应。

对某些物质尚缺少有效的吸附过滤技术。

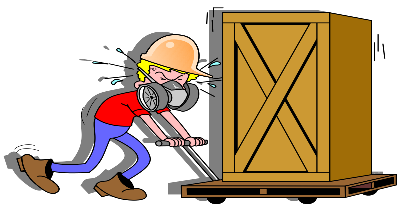
滤毒盒使用寿命的影响因素

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

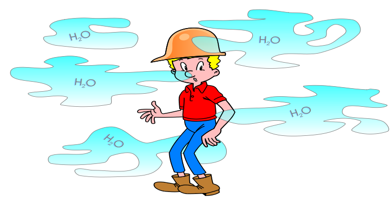
污染物的性质



污染物浓度



配戴者劳动强度

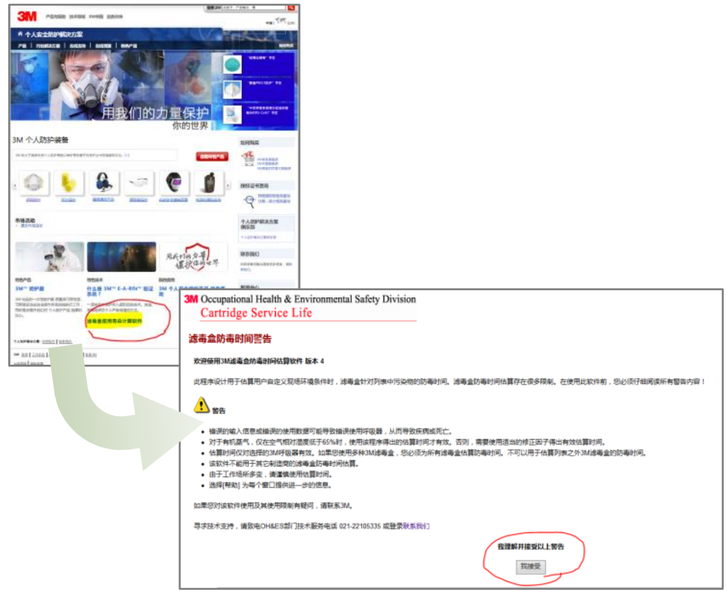


环境温湿度

3M防毒过滤元件
使用寿命估算软件

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- 提供全中文界面，用于3M产品选用
- 毒物目录
  - 职业接触限值信息
  - 嗅阈、沸点等
- 选择毒物及混合物组分、浓度、环境条件、劳动强度和3M产品，测算防护时间，用于滤毒盒更换时间表的建立；
- 提供根据环境湿度折算防护时间的方法。



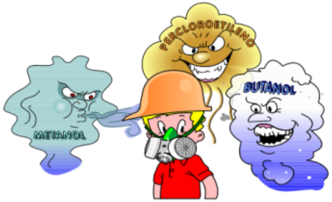
有机蒸气滤毒盒使用寿命的影响因素
——有机蒸气种类

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

用相同浓度不同种类的有机蒸气计算3M 6001CN有机蒸气滤毒盒的使用寿命：

有机物种类	浓度mg/m³	6001CN使用寿命（小时）*	沸点℃
苯	30	93	80
甲苯	30	275	110
邻二甲苯	30	554	144

***以上滤毒盒使用寿命通过3M滤毒盒使用寿命计算软件算出，其它相关参数均设定为：温度20˚C，相对湿度65%，低劳动强度**



有机蒸气滤毒盒对不同种类的有机蒸气防护难易程度不同

其他（化学吸附）滤毒盒的特性及使用寿命

有机蒸气滤毒盒	化学吸附滤毒盒
靠分子间力吸附	靠化学反应吸附
会产生解吸附	通常不解吸附
环境湿度对使用寿命影响明显	环境湿度对使用寿命影响不明显
 	 

- 化学吸附滤毒盒使用寿命按实际接触毒物的时间计算

如：现场H_2S：100mg/m^3，20 ℃，中度体力劳动，每天接触6小时。
使用滤毒盒使用寿命计算软件估算酸性气体滤毒盒使用寿命：

相对湿度RH	6002CN使用寿命估算值（小时）	6003CN使用寿命估算值（小时）
65%	367	173
90%	367	173

用人单位呼吸保护计划

用人单位应依据GB/T 18664-2002建立呼吸保护计划：

- ✓ 危害辨识
- ✓ 工程控制
- ✓ 监测
- ✓ 选择
- ✓ 医学评价
- ✓ 发放呼吸防护用品
- ✓ 更换周期
- ✓ 保养、清洁、存放、维修和检查
- ✓ 劳动者培训
- ✓ 适合性检验
- ✓ 现场使用检查

3M可提供的服务：

- ✓ 呼吸防护用品选择指导
- ✓ 针对不同人员提供呼吸防护知识培训
- ✓ 呼吸防护用品更换周期指导
- ✓ 检验劳动者佩戴呼吸防护用品适合性的方法培训
- ✓ 其他类防护及PPE技术支持（听力、眼面、身体防化、足部、坠落防护）

Questions

PSCI Supplier Conference Shanghai

PSCI供应商会议 · 上海

Closing Comments
总结致辞

Ingrid Vande Velde Johnson and Johnson

Lamy Bao Bristol-Myers Squibb

SEPT 20 PSCI SUPPLIER CONFERENCE

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Our **VISION** is to establish and **promote responsible practices** that will continuously improve **ethics, labor, health, safety and environmentally sustainable outcomes** for our supply chains.

我们的**愿景**是建立和促进负责任的实践，不断改善供应链的道德、劳动力、健康、安全和环境可持续成果。

THE MEMBERSHIP 成员

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

30 member* companies already share the **PSCI VISION** and are committed to **continuous improvement in the supply chain**

30个公司成员*已经分享了PSCI 愿景，并致力于不断改进供应链

abbvie	Allergan	AstraZeneca	Baxter	BAYER	Biogen
Boehringer Ingelheim	Bristol-Myers Squibb	Catalent	Celgene	SINOCHEM DSM — DSM Sinochem Pharmaceuticals	ESTEVE
EVOLAN	gsk	Johnson & Johnson	LEO	Lilly	Mallinckrodt Pharmaceuticals
MERCK	NOVARTIS	novo nordisk	ORION	Pfizer	Roche
SANOFI	SHIONOGI	Shire	Takeda	TEVA	West

Full members have the following symbol: FULL MEMBER The rest are associate members.

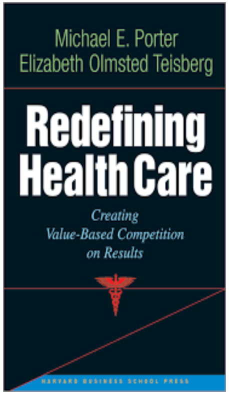

Alone we can do so little,
Together we can do so much.
团结力量大

Nordea

Sum Of + Us

International Labour Organization

SPHS
INFORMAL INTERAGENCY TASK TEAM



THE PSCI PRINCIPLES AND THE IMPLEMENTATION GUIDANCE
PSCI 原则与实施指南

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

The PSCI created **Industry Principles for Responsible Supply Chain Management**.

These five Principles outline our **expectations for sustainable supply chains in our industry** and provide descriptions of our expectations for pharmaceutical supply chain partners:

PSCI制定了**制药工业“负责的供应链管理”原则**。

这五项原则概述了我们对行业可持续供应链的期望，并描述了我们**对药品供应链合作伙伴的期望**：

ETHICS 道德

LABOR 劳工

HEALTH & SAFETY 健康与安全

ENVIRONMENT 环境

MANAGEMENT SYSTEMS 管理系统

To put these into practice simply, our comprehensive Implementation Guidance provides 为了便于将这些付诸实践，我们提供全面的实施指南:

- ✓ **Clarity** about the Principles in each of the five areas 清楚地了解五个领域中的每一个原则
- ✓ A **framework** for improvement 一个改进的框架
- ✓ **Examples** of how to meet the PSCI expectations 如何满足PSCI期望的示例

THE PSCI STRATEGY 2018 -2020
2018-2020 策略

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

VISION & PURPOSE

Our **VISION** is to establish and promote responsible practices that will continuously improve ethics, labor, health, safety and environmentally sustainable outcomes for our supply chains.

The **PURPOSE** of the initiative is to bring together members to define, implement, and champion responsible supply chain practices; fair and safe work places, responsible business practices, environmental sustainability and efficiency of resources and improved supplier capability.

PRIORITY AREAS 优先领域

FAIR AND SAFE WORK PLACES

- Worker protection
- Process safety
- Fair treatment
- Wages, benefits and working hours
- Freely chosen employment

RESPONSIBLE BUSINESS PRACTICE

- Business integrity and fair competition
- Bribery and corruption
- Data privacy
- Data security

ENVIRONMENTAL SUSTAINABILITY AND EFFICIENCY OF RESOURCES

- Water use and management
- Waste management
- Pharmaceuticals in the Environment
- Anti-Microbial Resistance
- Energy use and carbon footprint

SUPPLIER CAPABILITY

- Sustainable sourcing and traceability
- Transparency and disclosure
- Business resilience
- Management capability and systems

STRATEGIC PILLARS AND OBJECTIVES 策略和目标

1. LEADERSHIP

1.1 Promote the PSCI Principles, audit and methodology to define the industry's expectations

1.2 Secure a higher profile for PSCI within member companies

1.3 Lay the foundations for becoming the one-stop-shop for responsible procurement in Pharma

2. A COMMUNITY OF IMPROVING SUPPLIERS

2.1 Deliver excellence in supplier capability building

2.2 Enhance collaboration among members and suppliers

2.3 Explore a supplier recognition model

3. PARTNERING

3.1 Build external partnerships

3.2 Build PSCI's external profile and visibility

3.3 Offer PSCI as the delivery partner for other sustainability objectives

GOVERNING WITH TRANSPARENCY AND MANAGING WITH ACCOUNTABILITY

G.1 Allow greater diversity of members

G.2 Be a healthy, growing, trusted organization

G.3 Develop ways to measure PSCI's impact

- **A common voice for our industry.**
- **Set standards** for ethics, labour, health & safety, environment, management systems (The Principles & Implementation Guidance)
- **Build supplier capability**
  - Conferences
  - Resource library
  - Webinars
- Define common **supplier assessment tools** (e.g. Audit framework, SAQ, audit protocols).
- **Audit and promote audit sharing** to reduce burden on the industry and drive continuous improvement

- **我们行业的共同声音**
- **制定**道德，劳工，健康与安全，环境，管理体系**标准**（原则与实施指南）
- **建立供应商能力**
  - **会议**
  - **资源库**
  - **网络研讨会**
- 定义通用**供应商评估工具**（例如审计框架，SAQ，审计协议）。
- **审核和促进审核共享**，以减轻行业负担并推动持续改进

PSCI SUPPLIER CONFERENCE

A REFLECTION ON LAST TWO DAYS
我们对这两天的建议

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

This is your conference……这是你们的会议

- Prompt response on invitation - immediately fully booked
- 4 case study sessions
- Presentations = topics submitted by you
- First time also suppliers presenting = a success!
- Not only presenters but all of you talking & networking
- 2 days = new journey of continuous improvement
- **Tell us how we can best support you so that we can continue to improve our conferences and support programs**
- 迅速回馈 - 很快报名满员
- 4个案例分享主题
- 演讲主题来自于集体智慧
- 第一次有供应商代表与我们分享您的经验
- 是所有人一起分享交流
- 这两天是又一次持续提高的崭新旅程
- 告诉我们如何最好地为您提供支持，以便我们能够继续改进我们的会议和支持计划

CONTACT US
联系我们

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PSCI

@PSCInitiative

Look forward to see you soon!

Feed Back Survey
反馈调查问卷

- 请扫描二维码填写反馈调查后，方可离场
- 离场时归还名牌，并领取演讲资料USB