PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
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2023 PSCI China Supplier Conference
PSCI 中国供应商大会（成都）

活性药物管控策略——供应商案例分享

Potent Compounds and Control Strategy – Supplier Case Study

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嘉宾介绍 Speaker Bio

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- 背景：
- 30制药行业工作经验，药学专业背景；
- 执业药师；
- 先后服务于多家制剂和原料药、医药中间体生产企业；
- 在制药企业先后担任技术员、建设项目工艺主管、设备部经理、项目经理、工程总监、总工程师等职位。

议程 Agenda

高活性化合物的定义
Definition of High Potent Compound

OEL & PDE的确定
Determination of OEL & PDE

暴露风险定性评估
Qualitative Assessment of Exposure Risk

高活项目的设计交付文件
Typical Engineering Deliverables for High Potent Compound Project

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您对高活性化合物的定义

1. OEL小于1μg/m³;
2. OEL小于10μg/m³;
3. PDE小于10μg/d

投票选项:

A：1

B：2

C：3

D：1和3

E：2和3

F: 不知道

观众互动环节：请扫描左上方二维码参与现场问答

（问答将以匿名形式进行）

高活性化合物的定义
Definition of High Potent Compound

来源：ISPE Baseline Volume 7: Risk-Based Manufacture of Pharmaceutical Products-A Guide to Managing Risks Associated with Cross-Contamination

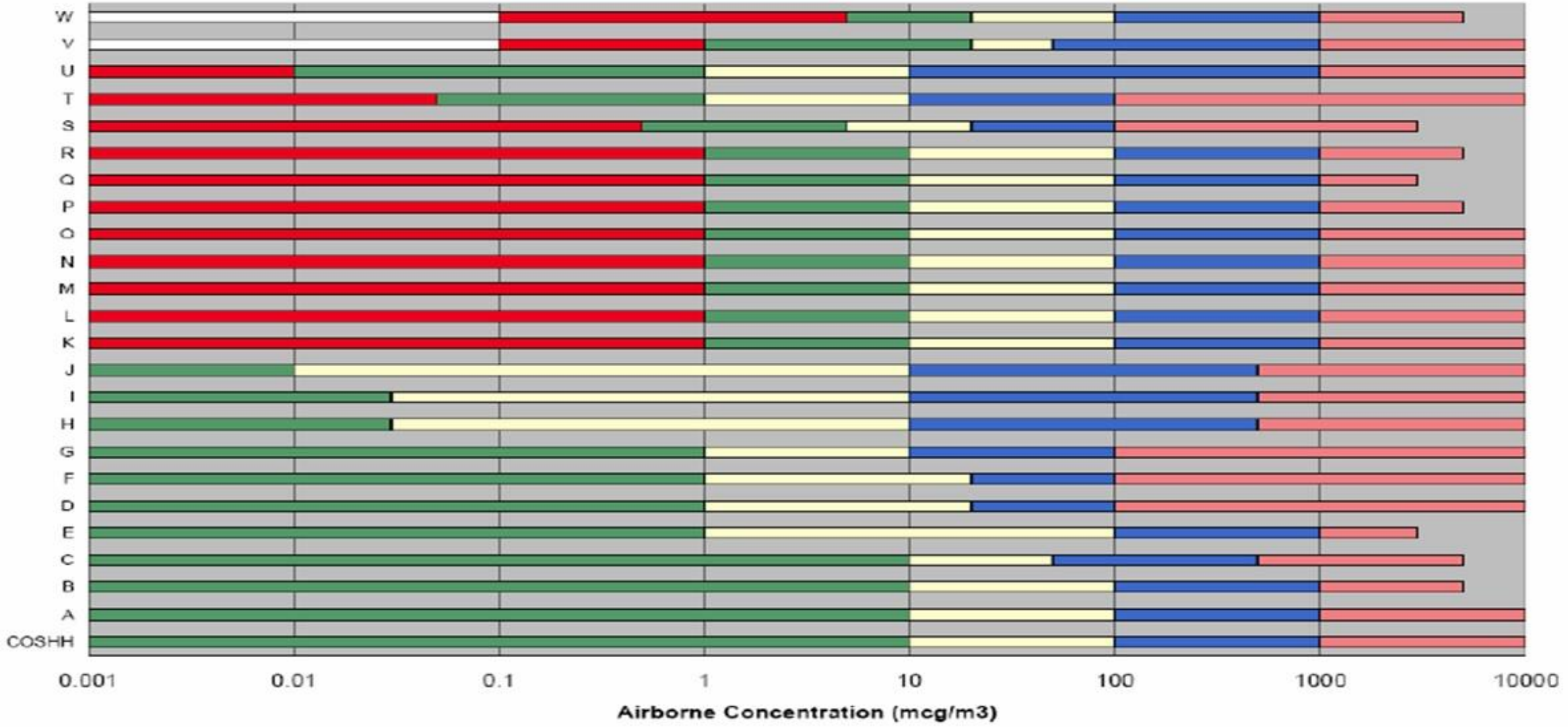
从GMP角度，高活性药品的定义应该使用ADE或PDE，而不是使用OEB

Table 2.1: Summary of Differences for IH and cGMP Considerations

Perspective	Industrial Hygiene	Quality (cGMP)
WHO/WHAT Exposed Population Variables (Age, Immunology, Fitness)	**Worker** Usually healthy	**Product** Introducing risk to Patient via the product
Route of Entry	**Inhalation** Dermal Transmucosal Membranes Ingestion	**Product Cross-Contamination** by settled powder or retained product X into/onto Product Y **Patient Ingestion, IV**
Primary Exposure Mechanism(s) or How exposure/cross-contamination occurs	- **Inhalation** (Settled dust can be re-suspended to be breathed at another time) - **Skin Absorption** contact, via wounds - **Mucous Membranes** Contaminated worker touches mucous membranes - **Ingestion**	- **Mix-Up** wrong materials - **Retention** inadequate cleaning - **Mechanical Transfer** moving residue from one thing to another - **Airborne Transfer** powder available in air and contacts product, equipment
Basis of Standards for Risk Assessment	**Occupational Exposure Limit (OEL)** expressed by an AIRBORNE concentration (mass per cubic meter of air) to address primary route of entry for exposure: Inhalation	**Acceptable Daily Exposure (ADE)** expressed as mg/day **Cleaning Limit** expressed as mg/swab or mg/l to address primary route of exposure: Ingestion, IV

高活性化合物的定义
Definition of High Potent Compound

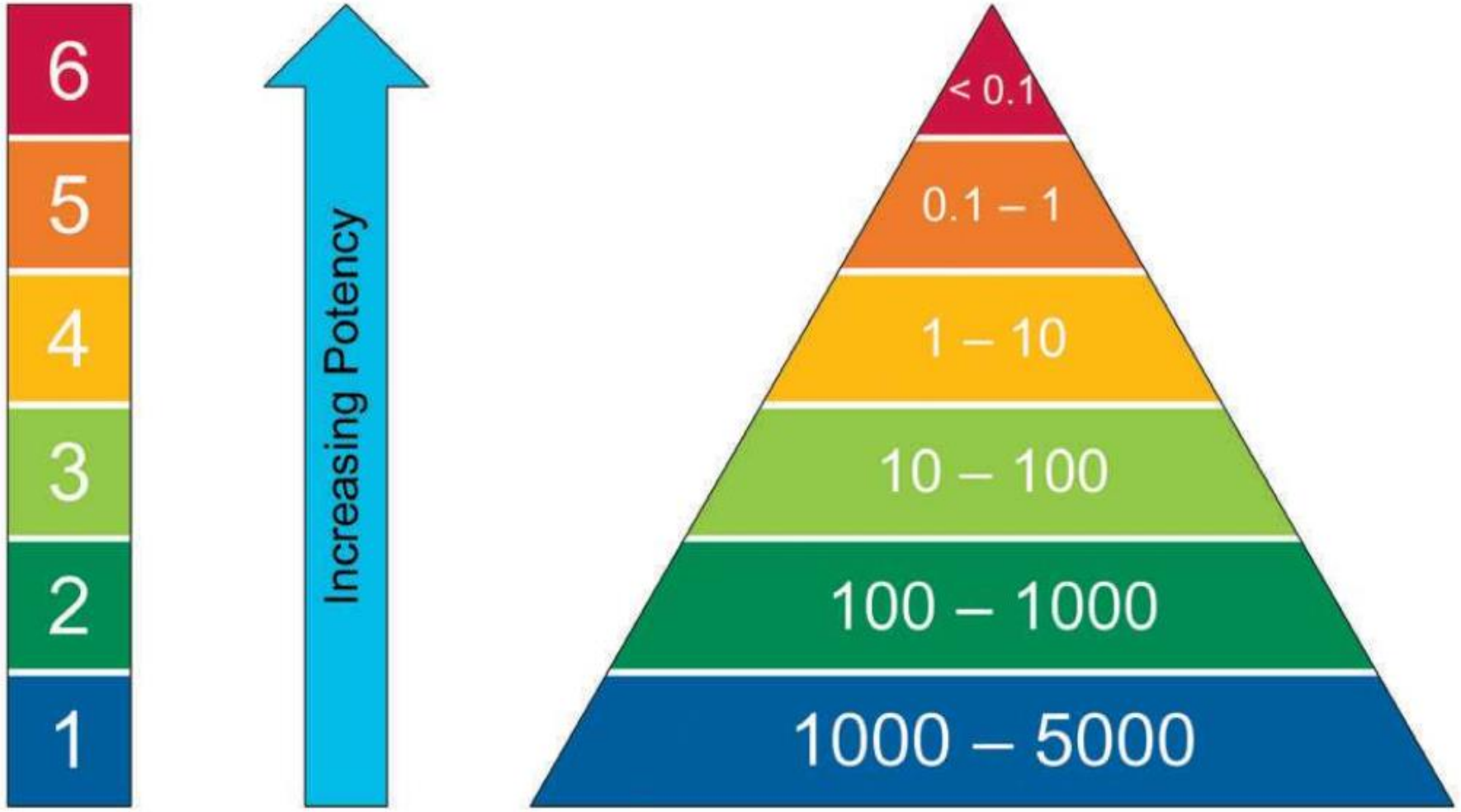
这个是不同公司对于OEB的定义，
每个公司都有一些区别，有6个等级的，也有4个等级的



高活性化合物的定义
Definition of High Potent Compound

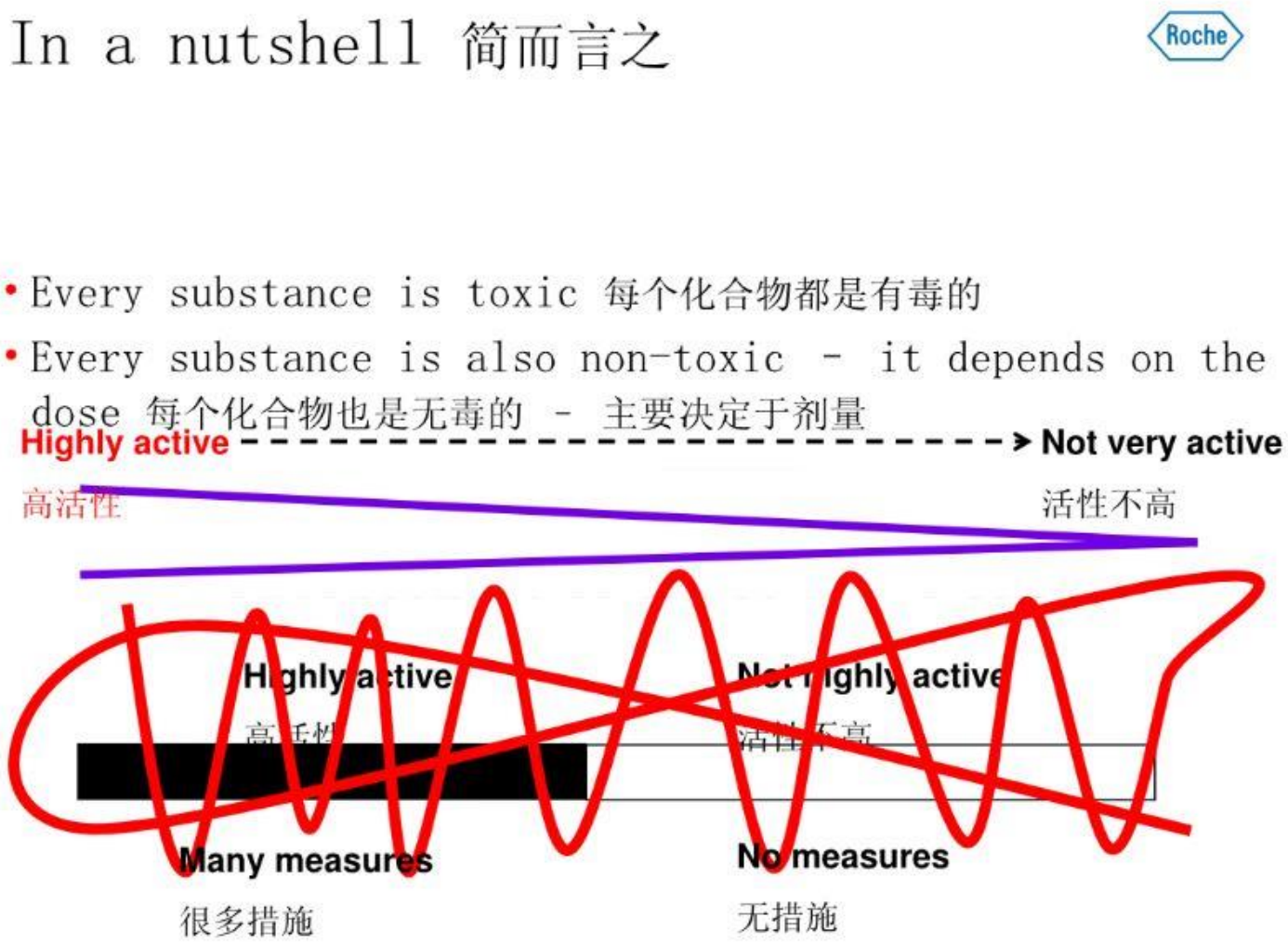
ISPE Good Practice Guide:
Containment for Potent Compounds

Figure 2.1: Compound Classification



高活性化合物的定义
Definition of High Potent Compound

- 来源：上海罗氏制药有限公司 沈晴 在CCFDIE-ISPE秋季大会 “ADE的概念及其在清洁验证和共线生产风险评估中的运用”



高活性化合物的定义
Definition of High Potent Compound

Draft

- Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to support assessment of products to determine whether they may be highly hazardous?
- A: Yes. Extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours).
- Additional adjustment factors
  - target population (worker vs patient)
  - route of exposure etc.
- If the resulting PDE value is 10 µg/day or lower the product should be considered as highly hazardous.

来源：EMA指南：

Questions and answers on implementation of risk based prevention of cross contamination in production and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (EMA/CHMP/CVMP/SWP/169430/2012)

高活性化合物的定义
Definition of High Potent Compound

Final release version

Q2. Is there a framework that could be used to define the significance of the Health-Based Exposure Limit (HBEL) such that there can be broad guidance on the extent of Quality Risk Management (QRM) and control measures required?

A: Firstly, it should be recognised that hazard varies on a continuum scale and that there are no firm cut off points, risk should be controlled on a proportionate basis. However, as a broad hypothetical model the following figure could be considered to show the increasing level of hazard (red being highest hazard) presented by products and there should be a commensurate increase in the level of control to prevent potential cross contamination in a shared facility. Actual HBEL values should be used in QRM studies to determine the actual controls required.

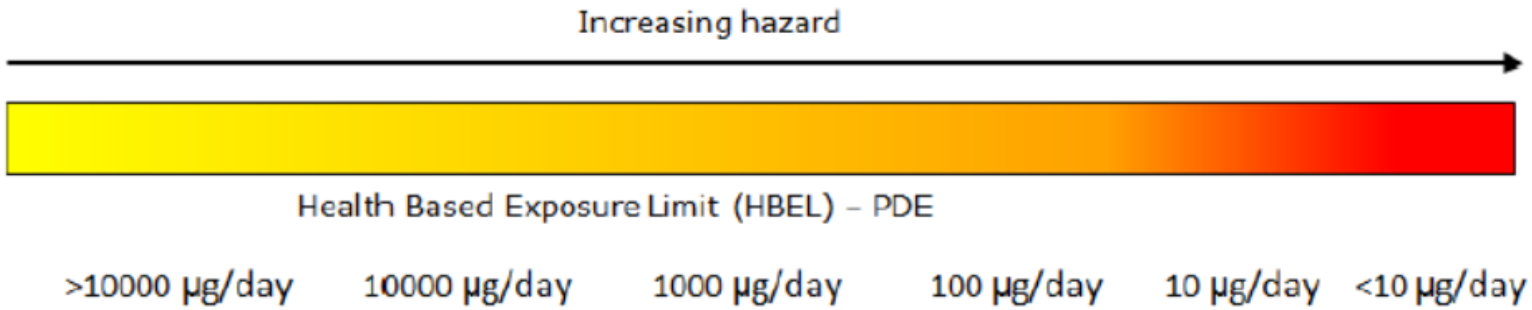


Diagram developed from an original concept published by ISPE. Source: ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products, International Society for Pharmaceutical Engineering (ISPE), Second Edition, July 2017.

- 从欧盟的法规角度，在草案中，定义了“highly hazardous”,但在正式发布版本取消了“highly hazardous”的定义，要求所有产品都应该根据PDE来评估清洁验证的残留限度，这个观点与职业卫生角度是相同的。

高活性化合物的定义
Definition of High Potent Compound

- 尽管从IH风险控制角度，以及从GMP的交叉污染控制角度，划分高活性和非高活性是不合理的，但是从实践角度，还是会给高活性化合物进行定义：
- 通常CDMO公司从两个维度定义高活性化合物：
  - 从IH角度，通常是定义OEB5为高活性化合物，也就是OEL值小于1μg/m³；
  - 从GMP角度，通常是定义PDE小于10μg/d为高活性化合物；
- Big Pharma对风险控制更严格，通常把OEB4和OEB5都定义为高活性化合物，也就是OEL值小于10μg/m³ 。

OEL & PDE的确定
Determination of OEL & PDE

- GBZ 2.1 - 2019 工作场所有害因素职业接触限值 第1部分 化学有害因素)
- OEL：职业接触限值(Occupational Exposure Limit，OEL)定义：
  - 长期反复接触，绝大多数接触者
- From: ISPE Baseline Volume 7: Risk-Based Manufacture of Pharmaceutical Products
- Occupational Exposure limit (OEL)定义
  - 40 hours a week over a working lifetime.
- (From: EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
- Permitted Daily Exposure 定义：
  - every day for a lifetime.

OEL & PDE的确定

Determination of OEL & PDE

影响因素	OEL	PDE	备注
Critical effects			主要与给药途径相关，OEL评估主要是吸入方式进入全身血液系统的作用，以及肺部的直接作用。
Route of Entry	Inhalation	Based on the next drug product	通过生物利用度和药代动力学调整因子减少两者的差异
Population Variables	generally healthy individuals	children or elderly, have at least one active medical condition.	由于OEL是针对特定的健康人群，相比较患者来说，可以接受更高的暴露量。

- Intravenously静脉注射给药是最差状态，药物100%进入血液系统，而且没有吸收过程；
- 吸入的方式，通常会按照更保守的100%生物利用度来考虑。
- 通常情况下，患者至少有一种疾病，OEL计算的暴露量，应该比PDE计算的暴露量稍微高一些；对于一些特殊情况，比如青霉素，由于PDE是针对一些不特定的患者群体，OEL是针对特定的健康群体，因此有可能OEL计算的暴露量会比PDE计算的暴露量高出几个数量级。

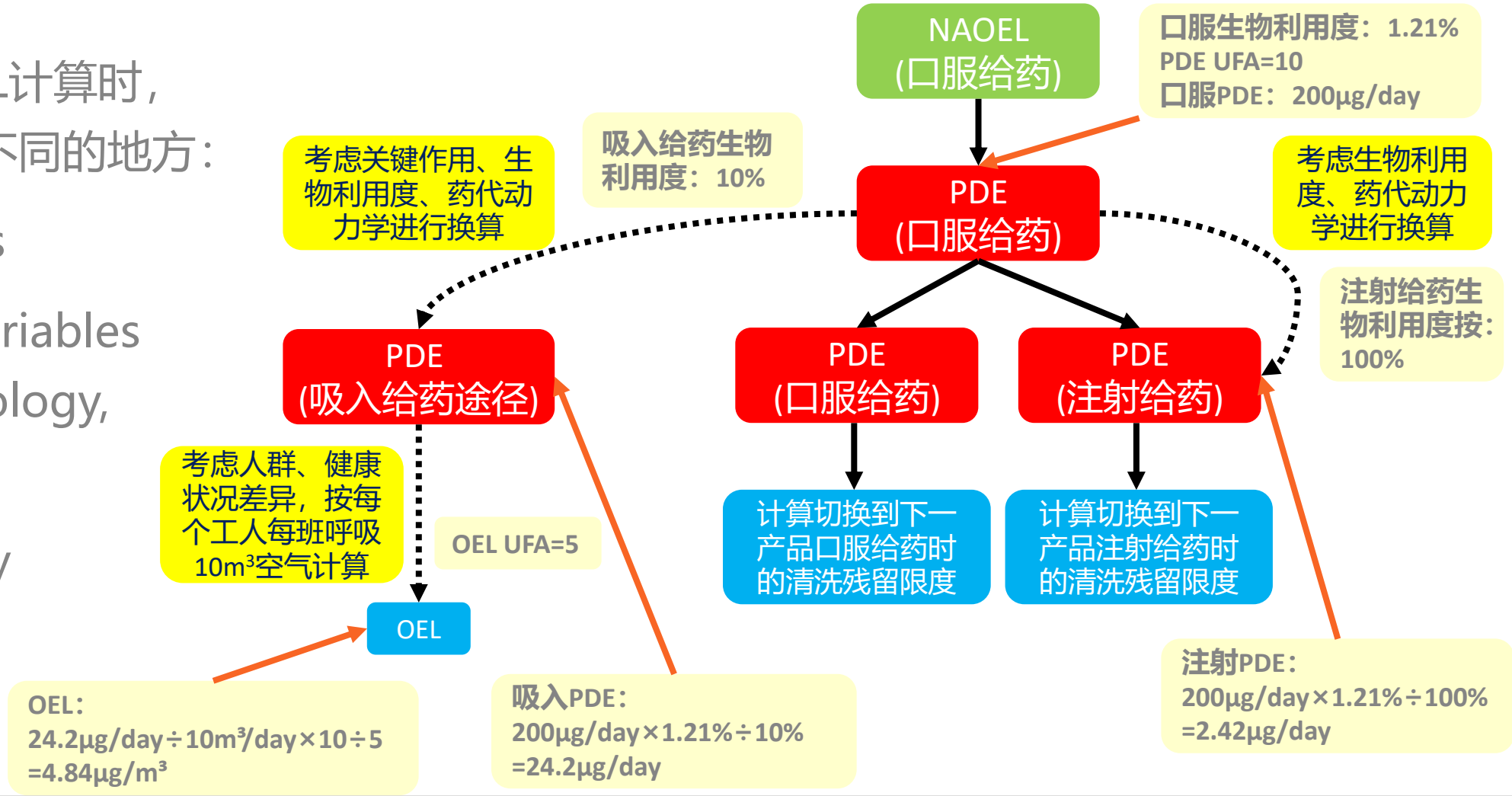
OEL & PDE的确定
Determination of OEL & PDE

Compound	Method	Entry route	Dose / Concentration	Species	Duration	POD	Calculated Oral PDE (µg/day)	F1-F5 (body weight is 50kg)	Calculated OEL (µg/m^3)	UFc (body weight is 50kg)
	Embryo-fetal development study	Intravenous	0.02, 0.08, 0.16, 0.32 and 0.00008, 0.0004, 0.002 mg/kg/day	Rat	Throughout the period of organogenesis	0.002 mg/kg/day (NOAEL)	200	F1 = 5 from rat to human; F2 = 10 for variability between individuals; F3 = 1 for whole period of organogenesis; F4 = 1 for maternal toxicity; F5 = 1 for NOAEL; Bioavailability correction factor = 0.0121 for intravenous to oral (oral bioavailability is 1.21%)	4	UF_H = 5 from rat to human; UF_A = 5 for variability between health adult worker; UFs = 1 for whole period of organogenesis; UF_L = 1 for NOAEL; UF_D = 1 for complete database; α = 0.1 from intravenous to inhalation (inhalation bioavailability is 10%); MF = 1 for maternal toxicity

OEL & PDE的确定

Determination of OEL & PDE

- PDE计算与OEL计算时，需要考虑两者不同的地方：
- Critical effects
- Population Variables (Age, Immunology, Fitness)
- Route of Entry



暴露风险定性评估
Qualitative Assessment of Exposure Risk

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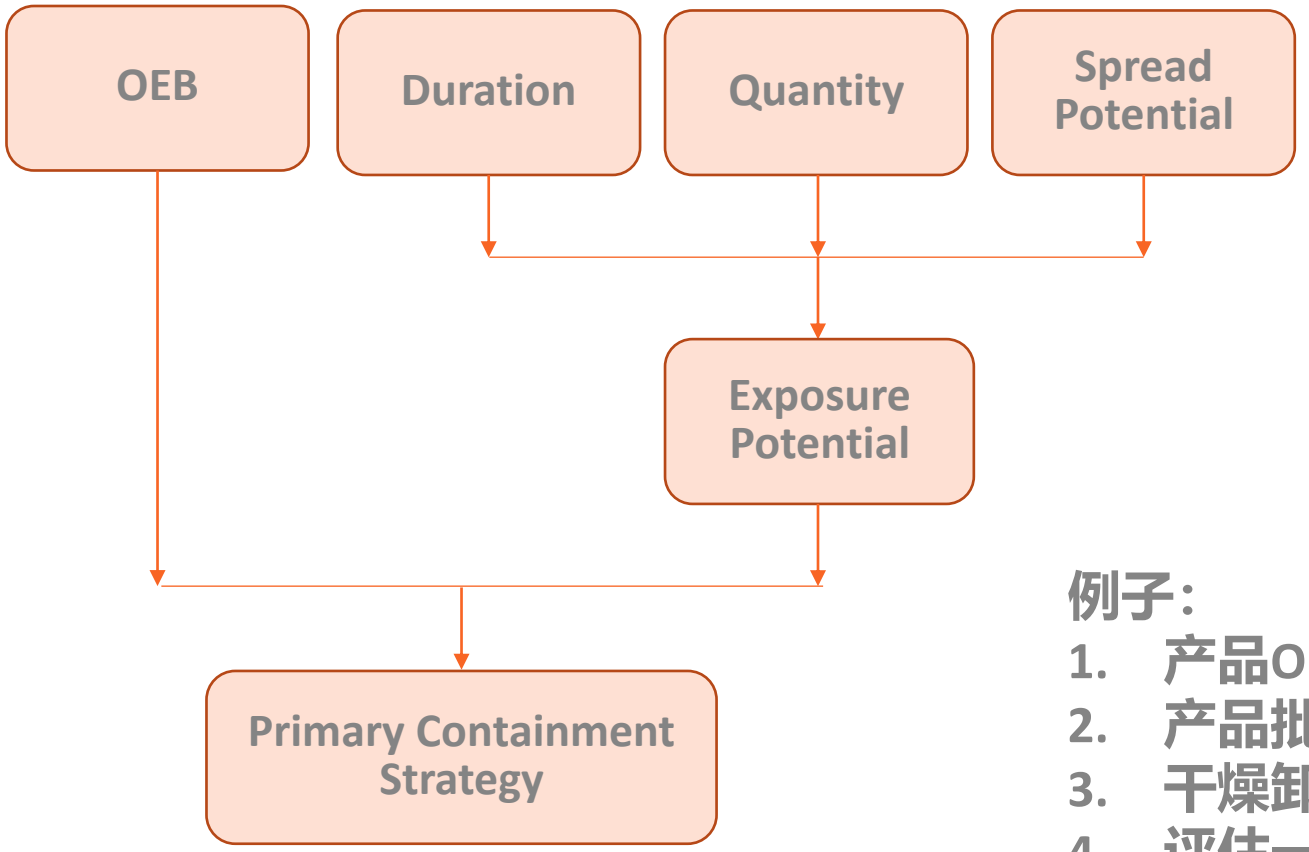
Containment for Potent Compounds

一级密闭措施评估方法：



例子：

1. 产品OEL：5微克/m^3，属于OEB 4；
2. 产品批量：60kg/批；
3. 干燥卸料操作时间：60min
4. 评估一级密闭要求和二级密闭要求

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Table 3.3: Spread Potential Related to Potential Exposure (Primary Containment)

Spread Potential			
Minimal	**Low**	**Medium**	**High**
	Low Volatility NBP > 250°C	Volatile NBP > 120°C	Highly Volatile NBP < 120°C
	Granules without fine dust OEL > 10 µg/m³	Moderately dusty, low fine dust content OEL > 10 µg/m³	Very dusty, electrostatically charging fine dust OEL < 10 µg/m³
Low Concentration in Aqueous Solution	In Solution/Suspension (Solid in Liquid)	Dilution Active Substance/ Excipient (Solid in Solid)	Pure Potent Material

Note that some nominally "wet" materials such as centrifuged solids can be dusty if effective solid/liquid separation is achieved, and the residual liquid content in the solid is correspondingly low. Treat all potent materials with nominal OELs less than 10 µg/m³ as "high" spread potential regardless of physical solid form.

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Containment for Potent Compounds

Table 3.4: Exposure Potential (Primary Containment)

	Spread Potential			
Quantity	**Low**	**Medium**	**High**	**Length of Time**
Smallest (< 10 mg)	EP 0	EP 1	EP 1	Short < 15 min
	EP 0	EP 1	EP 1	Long > 15 min
Small (< 500 g)	EP 1	EP 1	EP 2	Short < 15 min
	EP 1	EP 2	EP 3	Long > 15 min
Medium (0.5–200 kg)	EP 1	EP 2	EP 3	Short < 15 min
	EP 2	EP 3	EP 4	Long > 15 min
Large (> 200 kg)	EP 2	EP 3	EP 4	Short < 15 min
	EP 3	EP 4	EP 4	Long > 15 min

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Containment for Potent Compounds

Table 3.5: Primary Containment Strategy

	Exposure Potential (EP)				
OEB Range	**0**	**1**	**2**	**3**	**4**
OEB-6 (< 100 ng/m³)	PCS 2	PCS 3	PCS 4	PCS 4/5	PCS 4/5
OEB-5 (0.1–1 µg/m³)	PCS 2	PCS 2	PCS 3	PCS 4	PCS 4/5
OEB-4 (1–10 µg/m³)	PCS 1	PCS 2	PCS 2	PCS 3	PCS 4
OEB-3 (10–100 µg/m³)	PCS 1	PCS 2	PCS 2	PCS 2	PCS 3
OEB-2 (0.1–1 mg/m³)	PCS 1	PCS 1	PCS 1	PCS 2	PCS 2
OEB-1 (> 1 mg/m³)	PCS 1	PCS 1	PCS 1	PCS 2	PCS 2

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Table 3.1: Primary Containment Strategy (PCS)

Primary Containment Strategy (PCS)	PCS 1	PCS 2	PCS 3	PCS 4	PCS 5
# of Physical Barriers*	0	0	1	2	No operator present
General	No Open Handling of Solids or Liquids				
Description of Generic Approach	Effective Room Ventilation (min 6–8 AC/h)	Extract-based Systems	Barrier-based Containment	Enhanced Barrier-based Containment	Automated or Robotic Processes within Barrier-based Containment

* Number represents the nominal number of physical barriers between the exposure source and the worker.

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Enhanced Barrier-based Containment

从指南的要求来看，连续袋只能作为PCS3 的措施，而这个例子要求的是 PCS4的措施。因此只通过连续袋来做一级密闭是不被接受的，需要在连续袋的基础上再增加其它密闭措施。

左侧图片为三合一的卸料装置照片：
比如采用图片中的方式，连续袋外面再增加隔离器。

1. Continuous liner : Barrier – based Containment
2. Isolator : Enhanced

暴露风险定性评估

Qualitative Assessment of Exposure Risk

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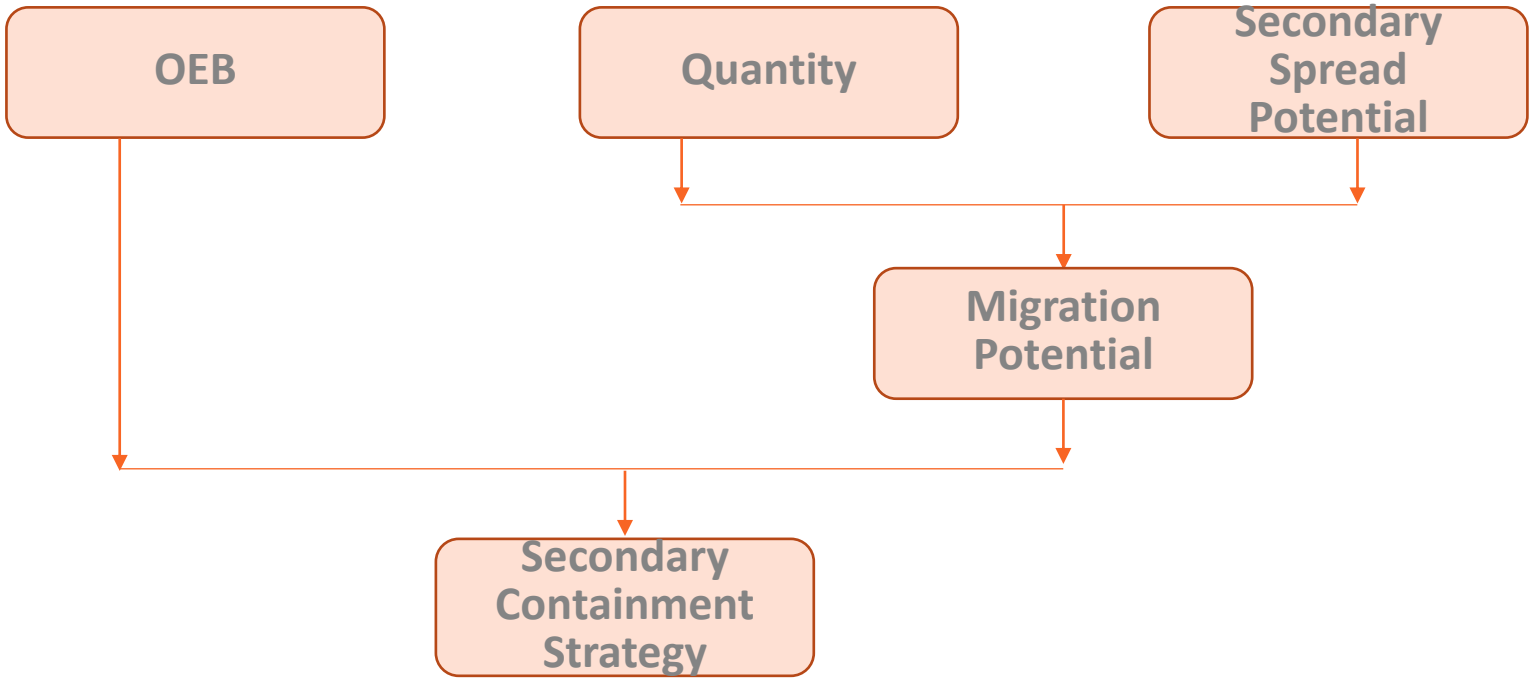
Containment for Potent Compounds

二级密闭措施评估方法：



暴露风险定性评估
Qualitative Assessment of Exposure Risk

ISPE Good Practice Guide:
Containment for Potent Compounds

Table 3.6: Spread Potential Related to Potential Carryover and Cleanability (Secondary Containment)

Secondary Spread Potential (SSP)			
Minimal	**Low**	**Medium**	**High**
	Highly Volatile, BP < 120°C	Volatile, BP > 120°C	Low Volatile, BP > 250°C
	Granules without fine dust and OEL > 10 µg /m^3	Moderately dusty, low fine dust content and OEL > 10 µg/m^3	Very dusty, electrostatically charged and fine dusts all materials with OEL < 10 µg/m^3
Aqueous Solutions and Low Concentration	In Solution/Suspension (Solid in Liquid)	Dilution Active Substance/ Excipient (Solid in Solid)	Solid/Pure Potent Substance

The order of solvent BP relates to cleaning where high BP solvents, e.g., sticky oils, can be difficult to remove and so have poor cleanability, and so present an enhanced exposure risk. In the case of solids, the particle size and the electrostatic chargeability are important, again determining a degree of material "dustiness." It should be noted that potent materials with a nominal OEL of 10 µg/m^3 are considered as having a "high" SSP regardless of form based on the experience of the team that developed the model.

暴露风险定性评估
Qualitative Assessment of Exposure Risk

ISPE Good Practice Guide:
Containment for Potent Compounds

Table 3.7: Carryover Potential (Secondary Containment)

	Secondary Spread Potential (SSP)			
Amount	**Minimal**	**Low**	**Medium**	**High**
Smallest (< 10 mg)	MP 0	MP 0	MP 1	MP 1
Small (10 mg–500 g)	MP 0	MP 1	MP 2	MP 3
Medium (0.5–200 kg)	MP 1	MP 2	MP 3	MP 4
Large (> 200 kg)	MP 2	MP 3	MP 4	MP 4

暴露风险定性评估
Qualitative Assessment of Exposure Risk

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Containment for Potent Compounds

Table 3.8: Secondary Containment Strategy

		Migration Potential (MP)				
OEB Range		MP 0	MP 1	MP 2	MP 3	MP 4
OEB-6	< 100 ng/m³	SCS 1	SCS 2	SCS 3	SCS 4	SCS 4
OEB-5	0.1–1 µg/m³	SCS 1	SCS 1	SCS 2	SCS 3	SCS 4
OEB-4	1–10 µg/m³	SCS 1	SCS 1	SCS 2	SCS 3	SCS 4
OEB-3	10–100 µg/m³	SCS 1	SCS 1	SCS 1	SCS 2	SCS 3
OEB-2	0.1–1 mg/m³	SCS 1	SCS 1	SCS 1	SCS 1	SCS 1
OEB-1	> 1 mg/m³	SCS 1	SCS 1	SCS 1	SCS 1	SCS 1

暴露风险定性评估
Qualitative Assessment of Exposure Risk

ISPE Good Practice Guide:
Containment for Potent Compounds

Table 3.2: Secondary Containment Strategy (SCS)

Secondary Containment Strategy (SCS)	SCS 1	SCS 2	SCS 3	SCS 4
Number of Barriers to Surroundings	0	1	1/2	2
Operations Scale		Separate Room	Separate Room Maintained under Negative Pressure with or without Air Lock Access	Separate Room with Pressure Controlled Air Locks Separate Material and Personnel Access
Laboratory	Standard Laboratory Layout	Separate Laboratory or Room	Separate Laboratory Maintained under Negative Pressure	Separate Laboratory with Access Air Locks Maintained under Pressure Differential Control

暴露风险定性评估

Qualitative Assessment of Exposure Risk

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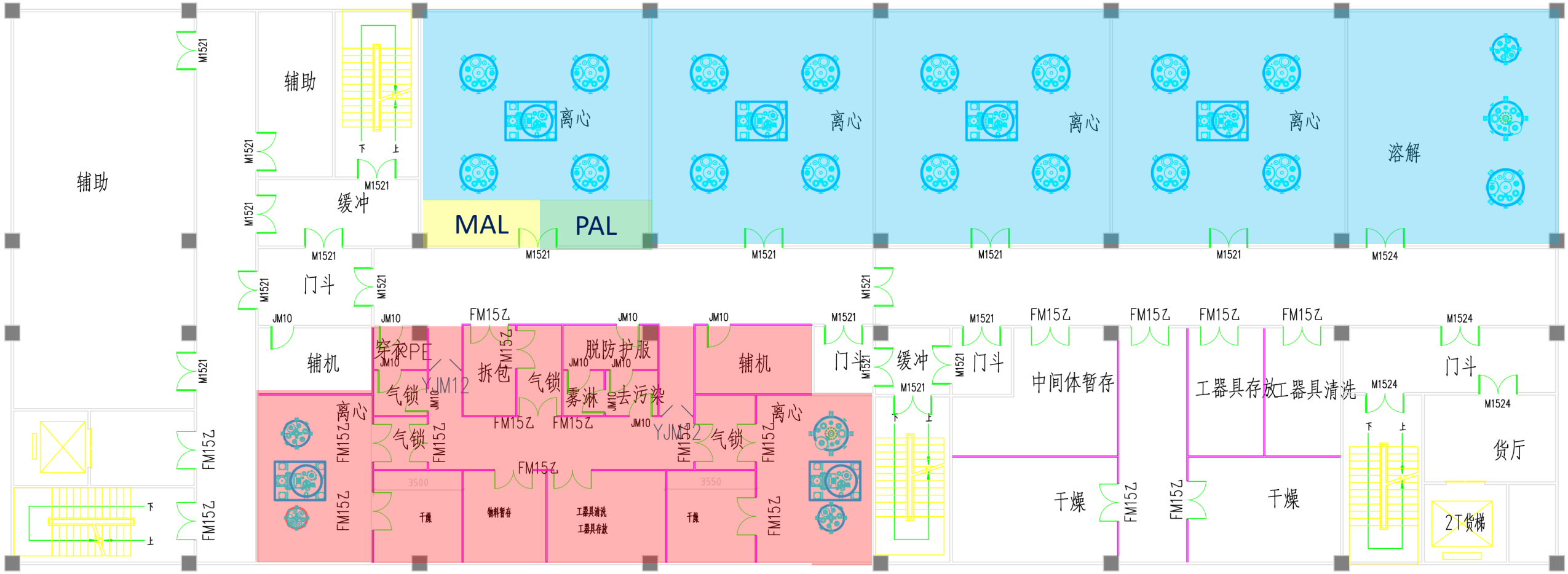
Containment for Potent Compounds

OEB 5 生产区

OEB 4 生产区



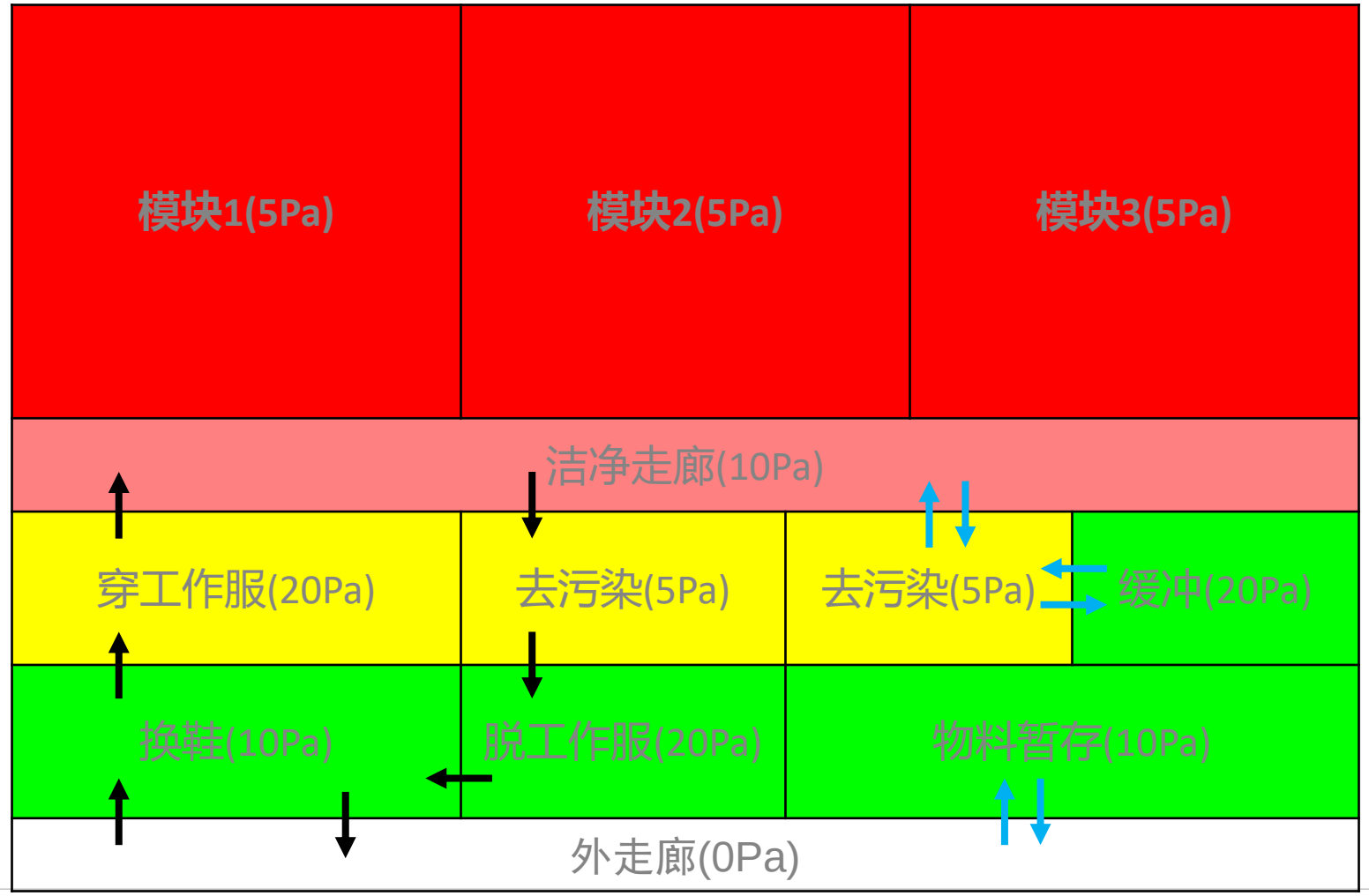
OEB 4生产区只是单独隔离的房间，及时空调系统控制房间在负压状态下，也只能满足SCS 3的要求，而这个例子要求的是 SCS 4，因此只有在原方案的基础上，增加人流气闸和物流气闸才能满足SCS 4的要求（如最左侧例子）。

高活项目的设计交付文件
Typical Engineering Deliverables for High Potent Compound Project

- 暴露定性风险评估及一级密闭和二级密闭工程控制措施选择
- 一级密闭和二级密闭控制策略
- 高活性平面布置图
- 高活性平面分区图(红区、黄区、绿区)
- 人流、物流图
- 空调分区图(送风、排风、回风)
- 空调压差图
- 空调系统图(包括送风过滤、回风、排风过滤等)

高活项目的设计交付文件
Typical Engineering Deliverables for High Potent Compound Project

- 高活洁净区空调压差图



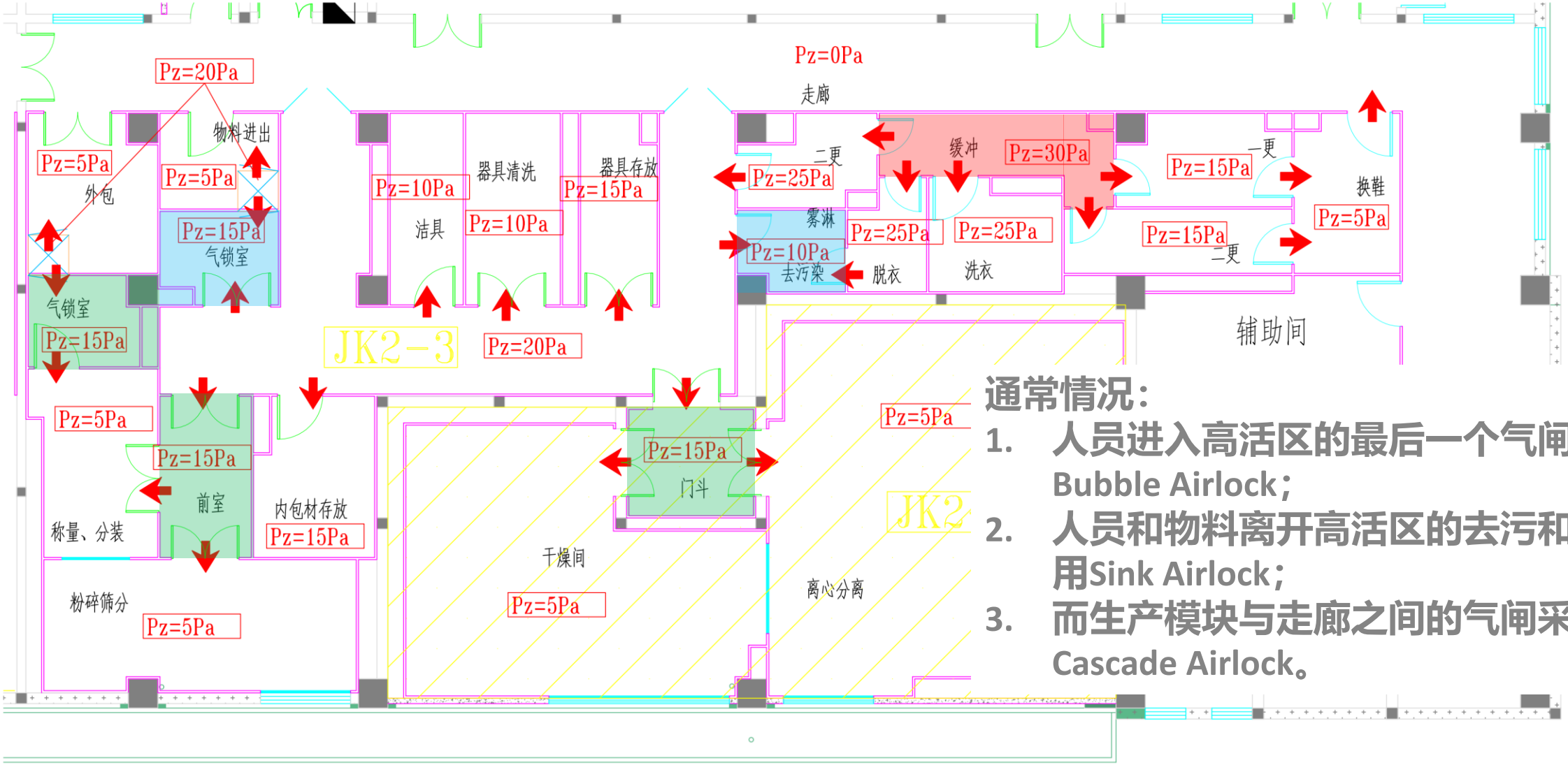
WHO Technical Report Series, No. 961, 2011

4.7.11 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figures 19–21):
- **Cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;**
- **Sink airlock: lower pressure inside the airlock and higher pressure on both outer sides;**
- **Bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.**

高活项目的设计交付文件
Typical Engineering Deliverables for High Potent Compound Project

Bubble Airlock
Sink Airlock
Cascade Airlock

- 高活洁净区空调压差图



通常情况：

1. **人员进入高活区的最后一个气闸采用Bubble Airlock；**
2. **人员和物料离开高活区的去污和雾淋采用Sink Airlock；**
3. **而生产模块与走廊之间的气闸采用Cascade Airlock。**

提问环节 Q&A