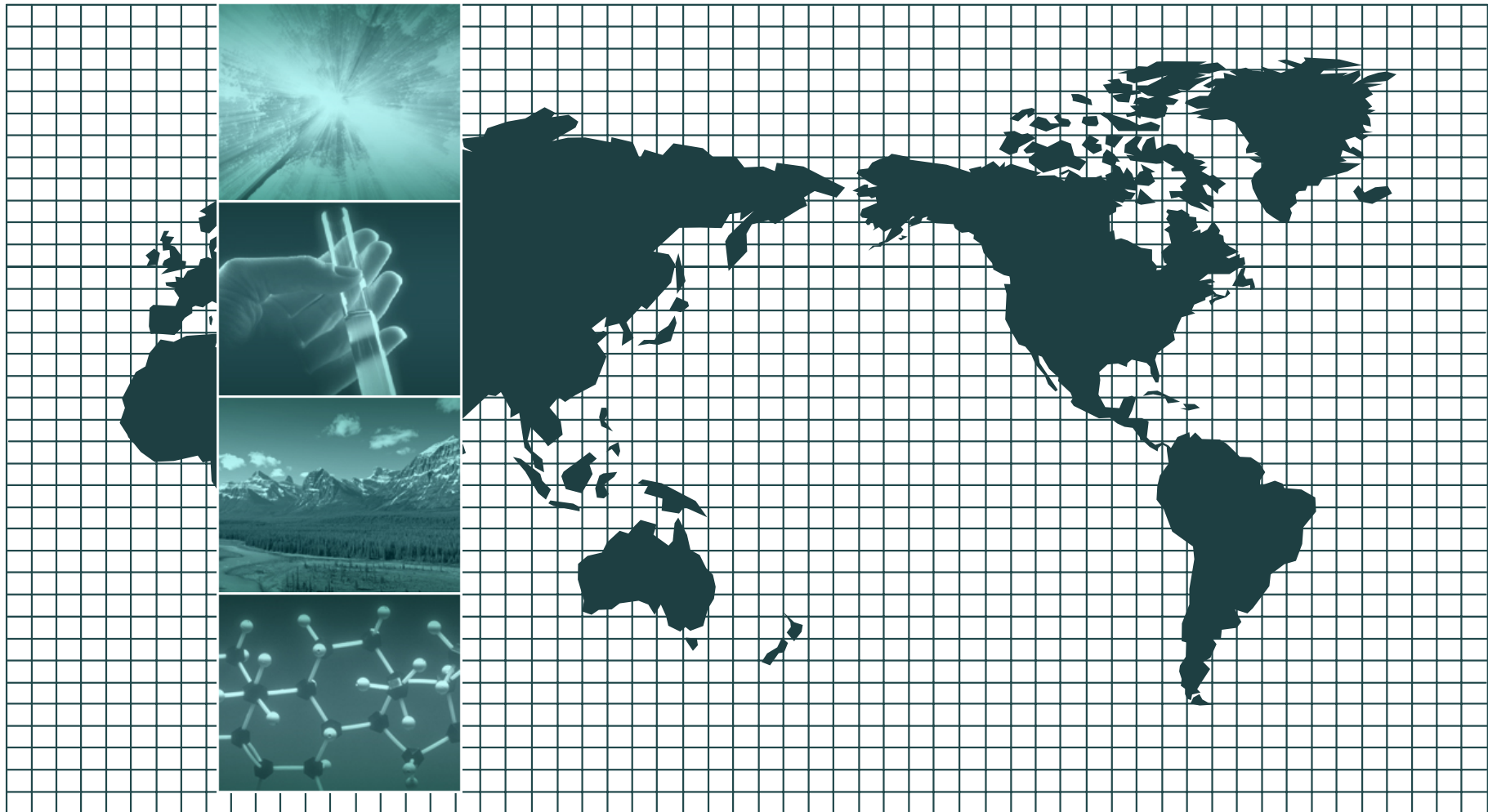


# New Pharmaceutical Containment System in Japan



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 **JGC CORPORATION**

# Our Profile



沈阳药科大学

北京事务所

日挥工程咨询(上海)有限公司



日挥株式会社

横滨

注册资金

235亿日元 (约合17.7亿人民币)

营业额 (2007 财度 )

5500亿日元

雇员

日挥集团 9,200人

(其中日本国内 4,500 + 海外

# New Pharmaceutical Containment System in Japan



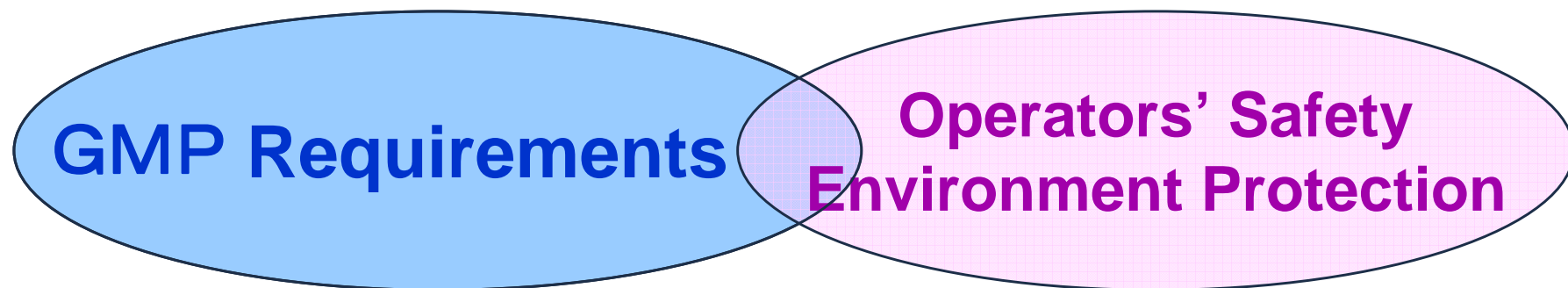
# Concept for Highly Potent Materials Handling

## ■ GMP Requirements...

- ◆ To Avoid Cross contamination

## ■ Operators Safety and Environmental Requirement...

- ◆ To Protect Operators
- ◆ To Avoid Environmental Pollution



# JGC's Approach to Containment Design

**1999, 2001**

**ISPE Amsterdam Conference**

**2001**

**PDA Japan Chapter**

**2002**

**ISPE Philadelphia Conference**

**2002**

**ISPE Berlin Conference**

**2003**

**ISPE Japan Conference**



**2002~**

**SMEPAC\* member**

**2008**

**ISPE Containment COP\*\* member**

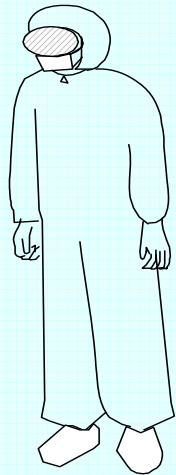
\* Standardized Measurement for Equipment Particulate Airborne Concentrations.

\*\*Community of Practice

# Concept for Achieving Containment

Operators  
Safety

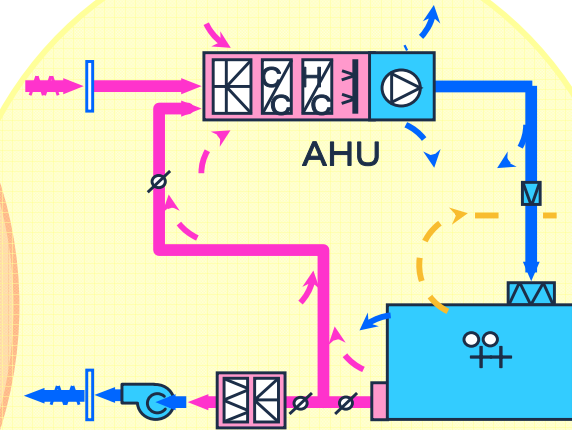
Environmental  
Protection



**Gowning**



**Equipment**



**Room Air Handling**

# Steps of Containment Design

## Design Procedure of Facilities for Highly Potent Materials

Step1: **Limit of Exposure Level of Highly Potent Materials (Potency, Toxicity, Carcinogenicity, Sensitivity)**



Step2: **Handling Status of Materials (Level 1 ~ 5)**



Step3: **Required Barrier Level**



Step4: **Find Optimum Combination of “Equipment”  
“Gowning” “Room Air Handling”**

**★ Integrated with GMP requirements  
(Clean Classification)**

Patented: PAT. No. 4263707

# Step 1. Classification of Exposure Level (PB-ECL Table)

PB-ECL Category		1	2	3	4	5
Exposure Level ( $\mu\text{g}/\text{m}^3$ )		1000~5000	100~1000	1~100	<1	NIL
1. Active	Potency (mg/day)	>100	10-100	0.1-10	<0.1	<0.1
2. Hazard	Toxicity LD50 (mg/kgR) Toxicity of Oral OSHA/HCS WHMIS(Canada) Toxic Control La Ocean Pollution Control(GESAMP)	>2000: non-toxic	500-2000: almost non toxic	50-500: slightly toxic 50-500: toxic 30-300: slightly toxic	5-50: toxic  <50: highly toxic <50: highly toxic <30: toxic	<5: highly toxic
	Toxicity of intravenous	>100: non toxic	500-2000: practically non hazardous	50-500: slightly hazardous	5-50: moderately hazardous	<5: highly hazard
				7-100: toxic		<7: highly toxic
3. Others	Carcinogenicity (IARC)	—	—	—	2A, 2B: potentially yes	1: yes
	Sensitivity	low	low-middle	middle	middle-high	high

Potency

Toxicity

Carcinogenicity

Sensitivity



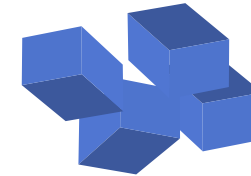
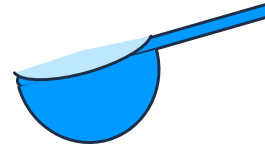
Exposure control limit : 4  
 Exposure level <  $1 \mu\text{g}/\text{m}^3$



## Step 2. Analysis of Process

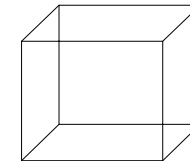
- **Status of potent compounds**

Liquid? Solid?



- **Containers, reactors, process operation**

Closed? Open?



- **Handling volume**

Large? Small?



## Step 3. Required Barrier Level

State \ PB-ECL	1	2	3	4	5
Large volume of powder	0.5	1.0	1.5	2.0	≥ 2.0
Small volume of powder				1.5	
Wet powder		0.5	1.0	1.0	
Very small amount of powder or liquid			0.5	0.5	
Powder/liquid to be contained	0	0	0	0	0.5

# Definition of Barrier Level

Barrier level 0	Man/environment <b>may not</b> be protected against potent compounds
Barrier level 0.5	Man/environment are <b>partially</b> protected against potent compounds
Barrier level 1.0	Man/environment are <b>fully</b> protected against potent compounds
Barrier level 1.5	Man/environment are <b>more fully</b> protected against potent compounds
Barrier level 2.0	Man/environment are <b>doubly</b> protected against potent compounds

# Definition of Barrier Level

## Design Criteria

### For Operator

Required Barrier Level  
for each process

$\leq$   
 $\equiv$

Equipment Containment Level

+

Protection Level by Gowning

### For Environment

Required Barrier Level  
for each process

$\leq$   
 $\equiv$

Equipment Containment Level

+

Containment Level by Facilities

# Step 4. Optimum Combination “Equipment”

Open Booth



Safety Cabinet



Glove Box



## Functional Barrier Level






0.0

0.5

1.0

# Step 4. Optimum Combination “Gowning”

## Typical Gowning Procedure & Functional Barrier Level

ISPE Definition	External	Unclassified	Pharmaceutical	Controlled	Clean / Critical
Gowning	 General	 Uniform	 Uniform + Cap	 Clean garments	 Sterile garments
		<ul style="list-style-type: none"> <li>* Shirts</li> <li>* Pants</li> <li>* Shoes</li> </ul>	<ul style="list-style-type: none"> <li>* Cap</li> <li>* Shirts</li> <li>* Pants</li> <li>* Shoes</li> </ul>	<ul style="list-style-type: none"> <li>* Cap</li> <li>* Respirator</li> <li>* Gloves</li> <li>* Coat</li> <li>* Shoe cover</li> </ul>	<ul style="list-style-type: none"> <li>* Coverall</li> <li>* Boots</li> <li>* Gloves</li> <li>* Respirator</li> <li>* Hood</li> <li>* Goggles</li> </ul>
Clean Class (In Operation)	—	—	—	Class 100,000	Class 10,000
Grade (EU-GMP)	—	—	—	Grade-D	Grade-B, C
Functional Barrier Level	<b>0</b>	<b>0</b>	<b>0</b>	<b>0.5</b>	<b>1.0</b>

# Step 4. Optimum Combination “Gowning”

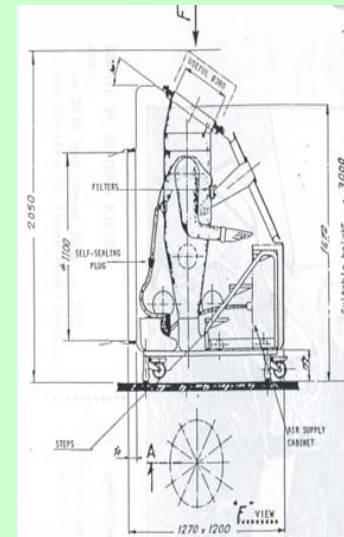
## Gowning for Protection Against Extremely Hazardous Materials

### Aeration Suite



Functional Barrier Level  
**1.5**

### Space Suite

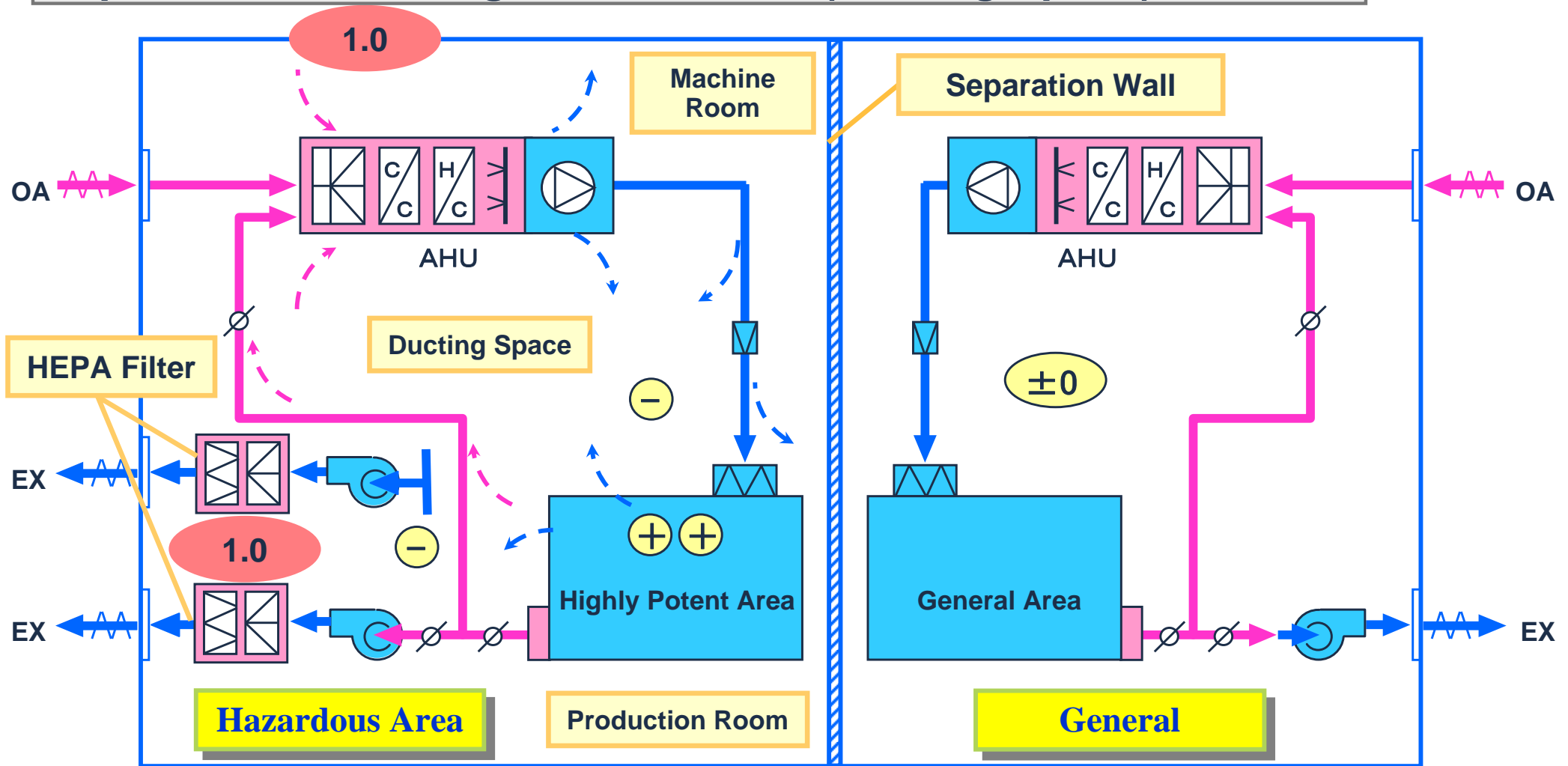


® La Calhène

Functional Barrier Level  
**2.0**

# Optimum Combination “Room Air Handling”

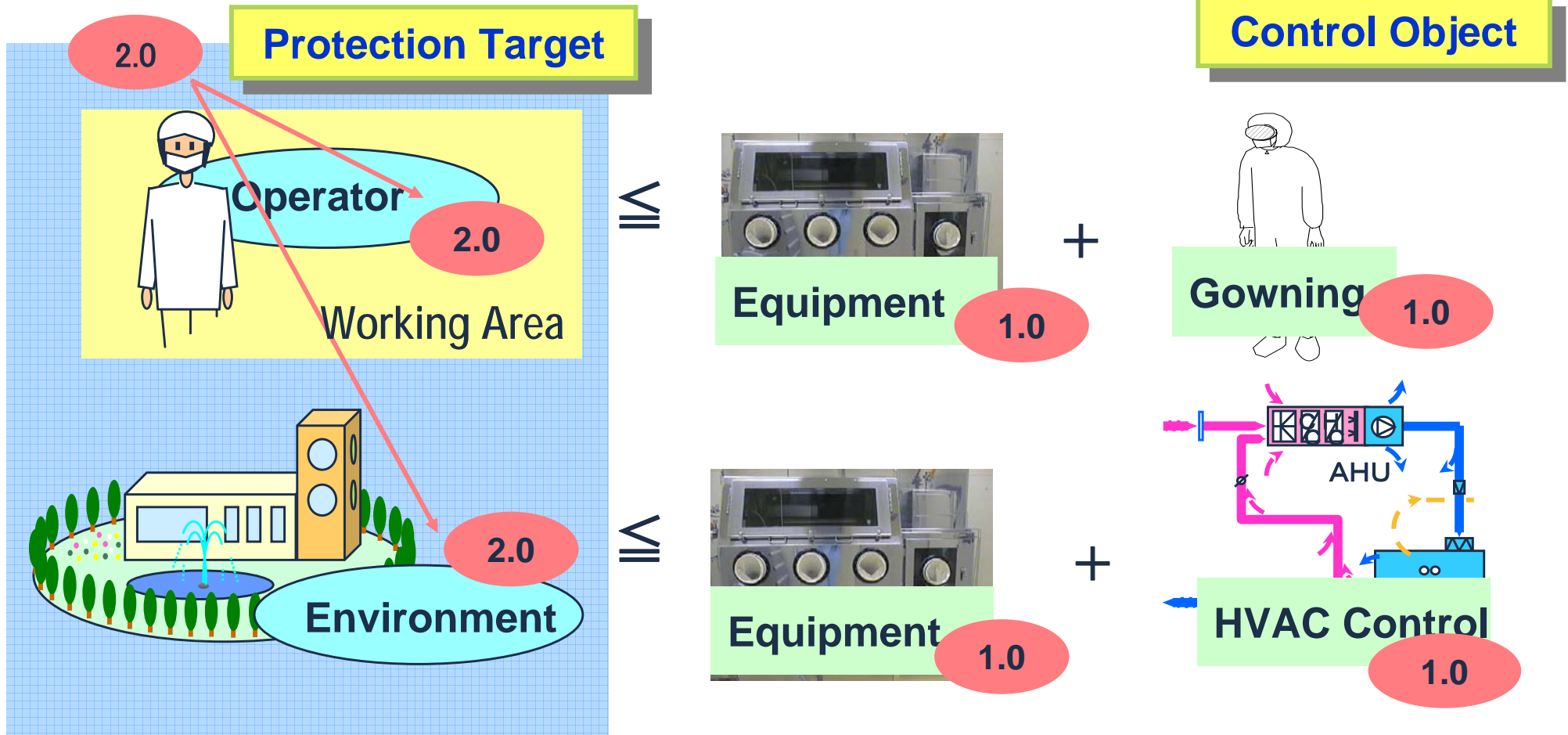
Separation Wall + Negative Pressure (Ducting Space) FBL : 1.0



HEPA Filter FBL : 1.0



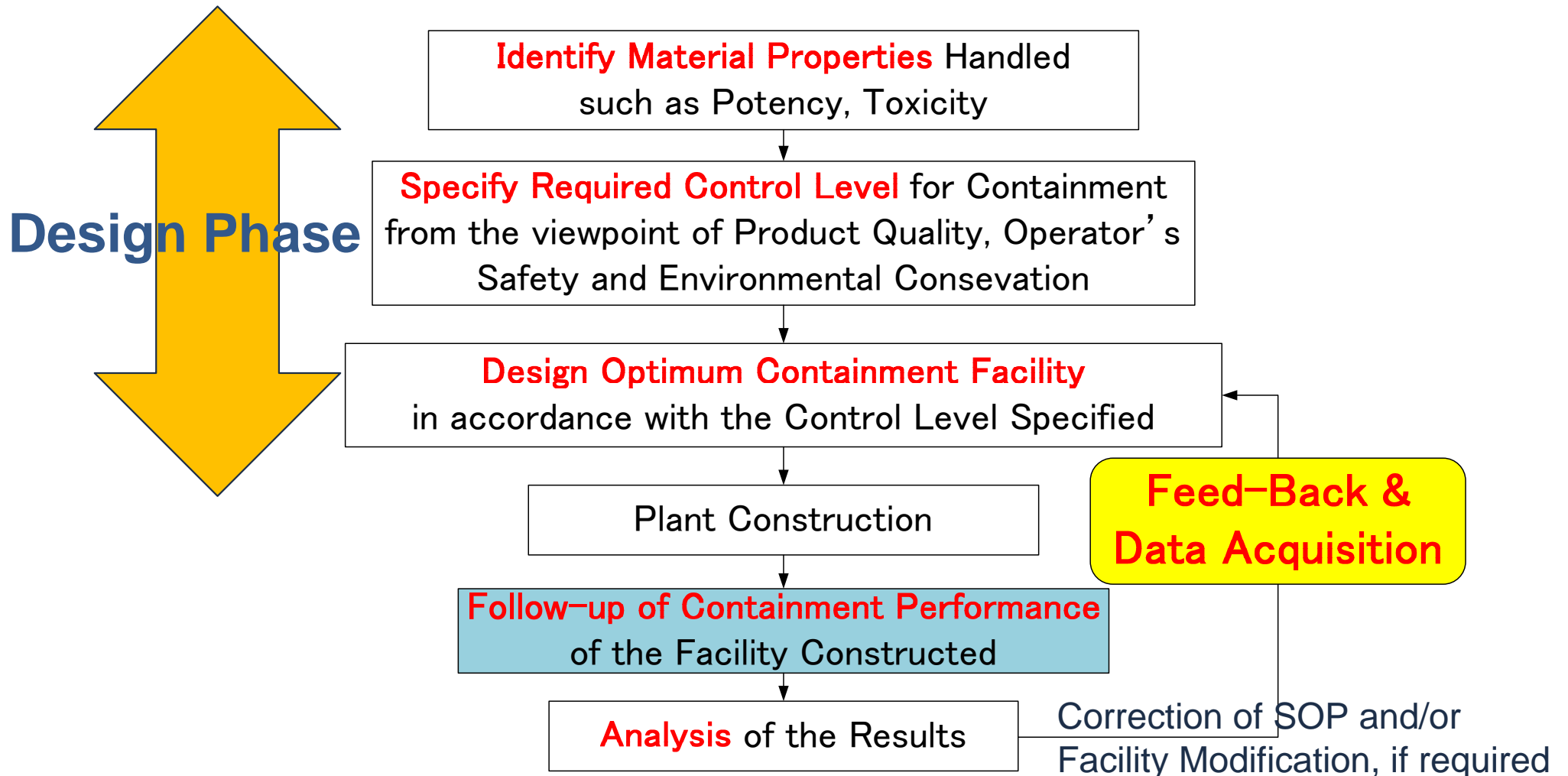
# Design Conclusion



**Operators / Environment will be properly protected against hazardous materials**

# Follow-up Activity

**Follow-up Activity is Very Important !**



# Procedure for Follow-up

## Method

- **Air sampling for working environment**  
: Closed face type head by constant flow pump
- **Surface monitoring**  
: Swabbing interior and/or exterior surface of equipment, and floors of working places
- **Chemical analysis to determine concentration of chemical hazards**  
: Established method by client

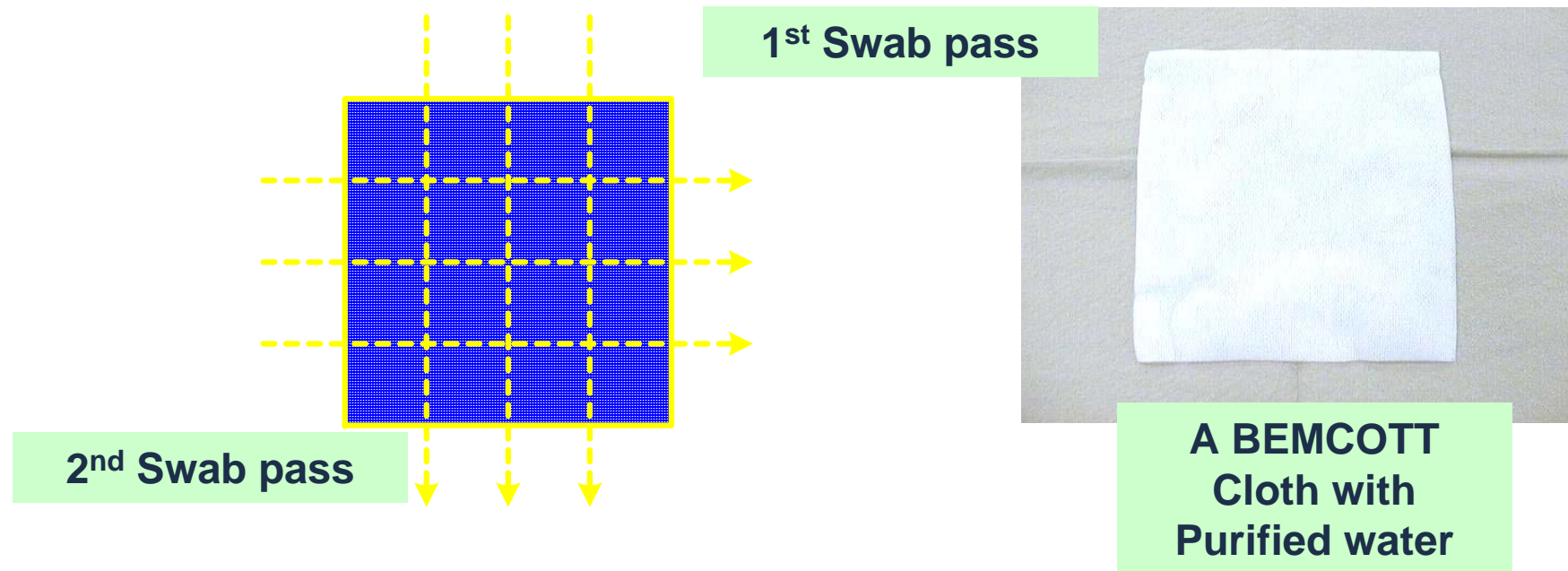
# Air Sampling

- Calibrated constant flow air sampling with 3 L/min
- Cassette type closed head with a PTFE 0.45  $\mu$  m pore size filter



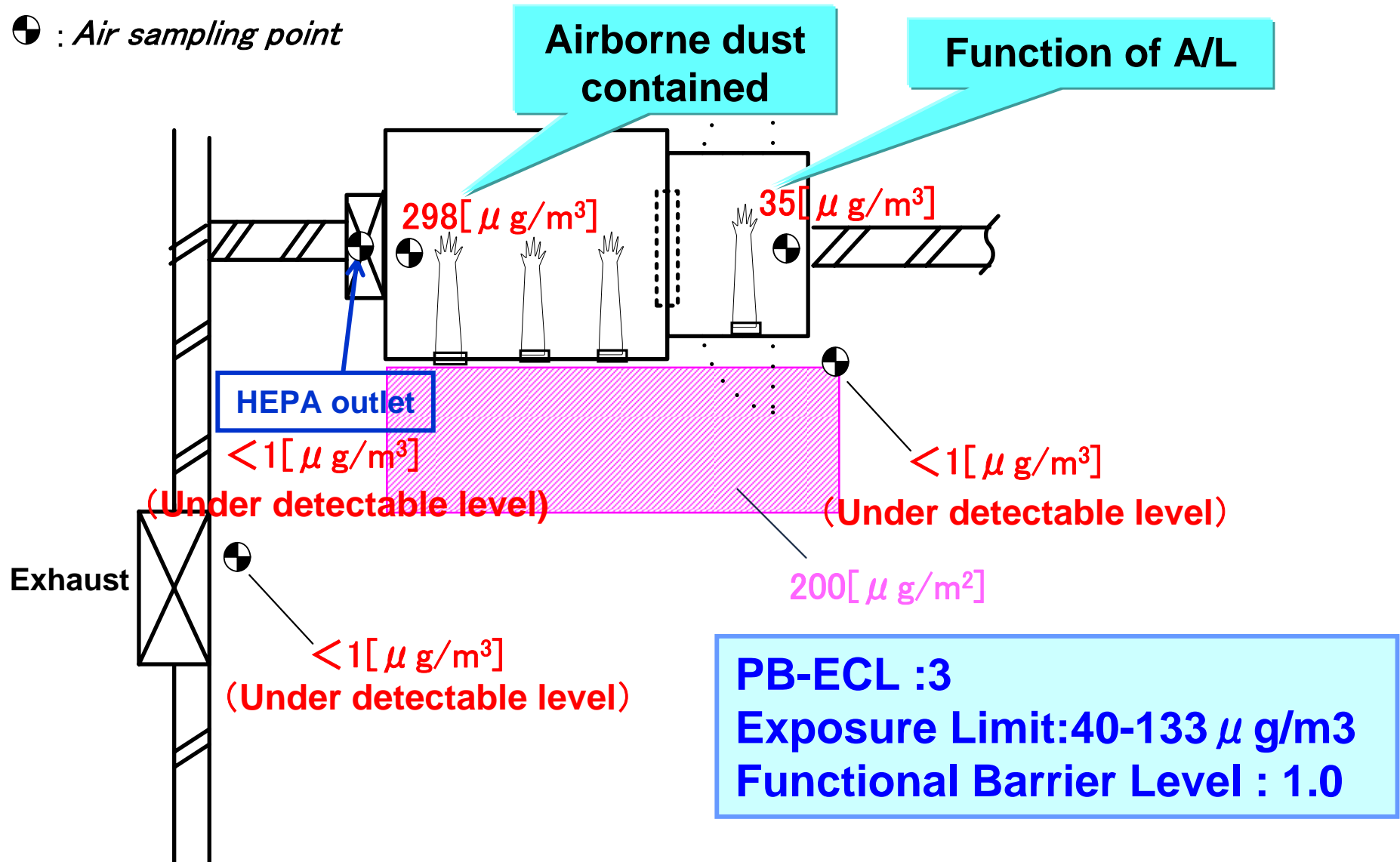
# Surface monitoring

- **Standardised swab procedure previously reported**  
:Cocker N., Extract Technology Ltd., presented in 1999 Continuing Education Amsterdam Conference
- **Swab with a cloth wet by purified water**

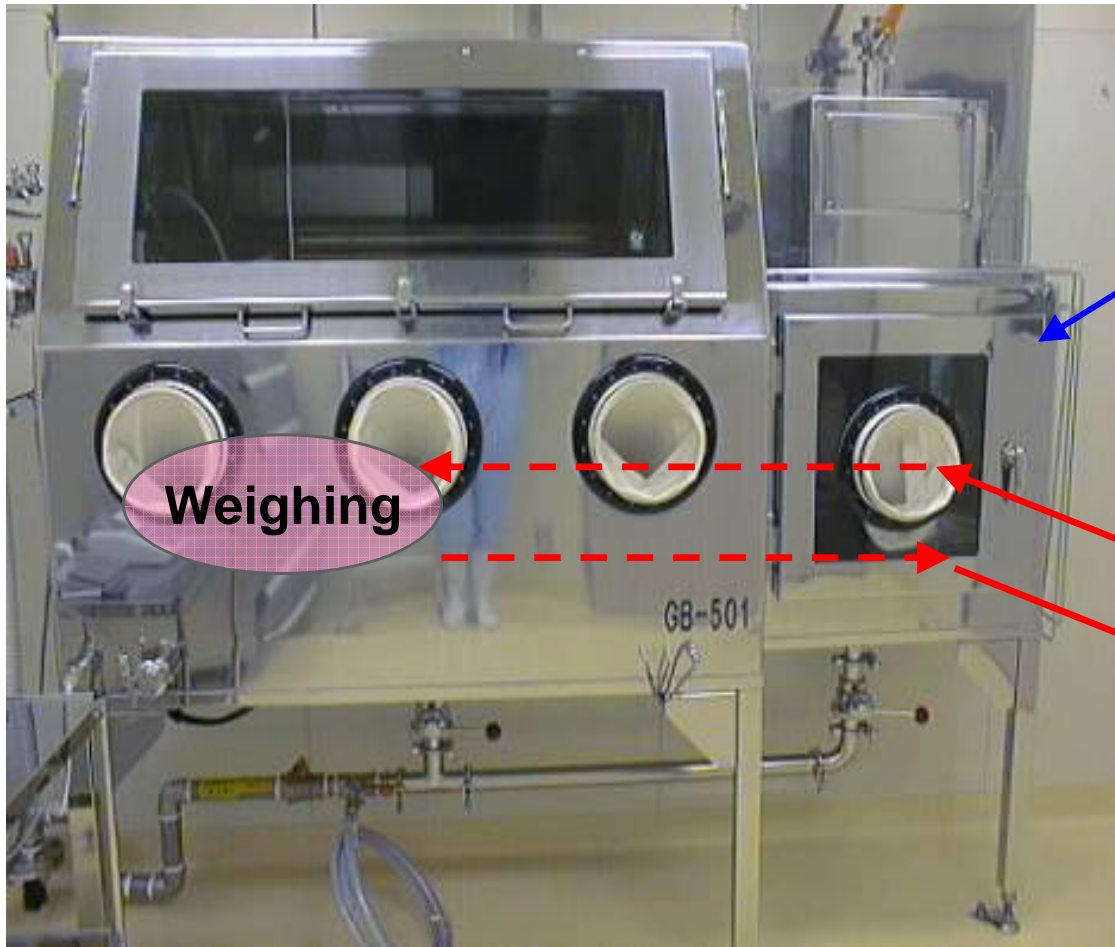


# Evaluation of Weighing Glove Box

⊕ : Air sampling point



# Weighing Glove Box



Pass box

Weighing

Raw material

# Evaluation of Reactor Charging

## Reactor Charging

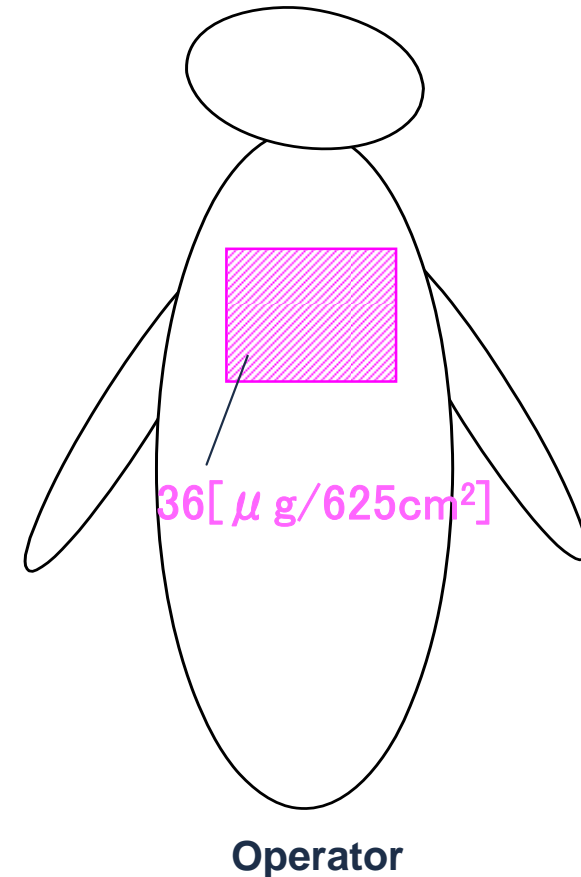
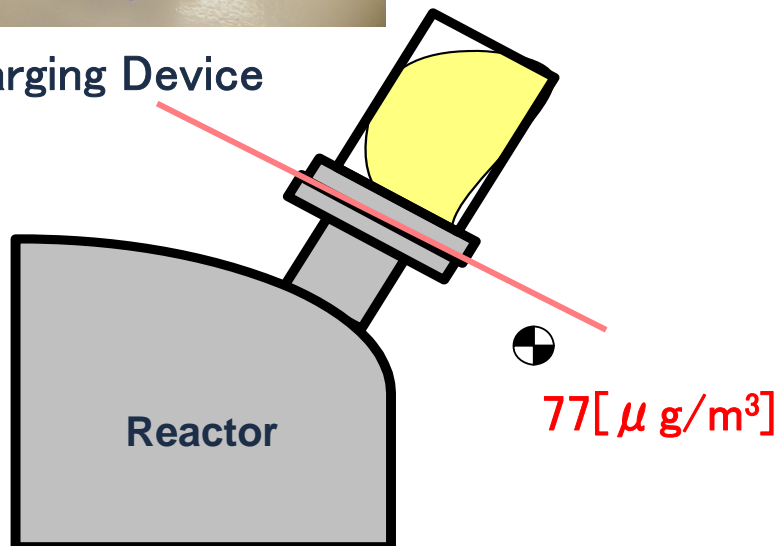
⊕ : Air sampling point

▨ Swabbing Area



4~5 [ $\mu\text{g}/\text{m}^3$ ] (8h TWA)  
Operating Time :26min

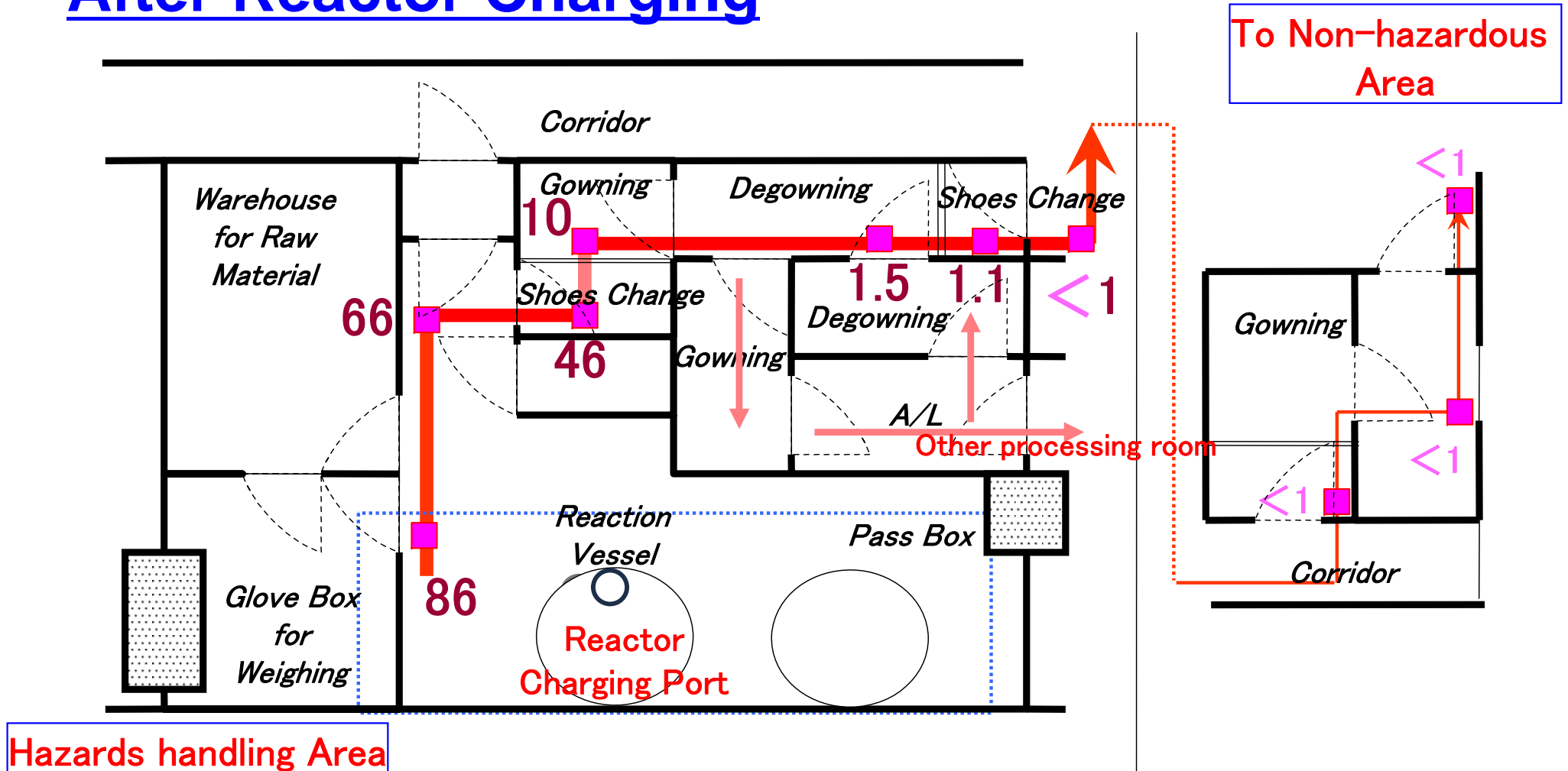
Charging Device





# Carry-over

## After Reactor Charging



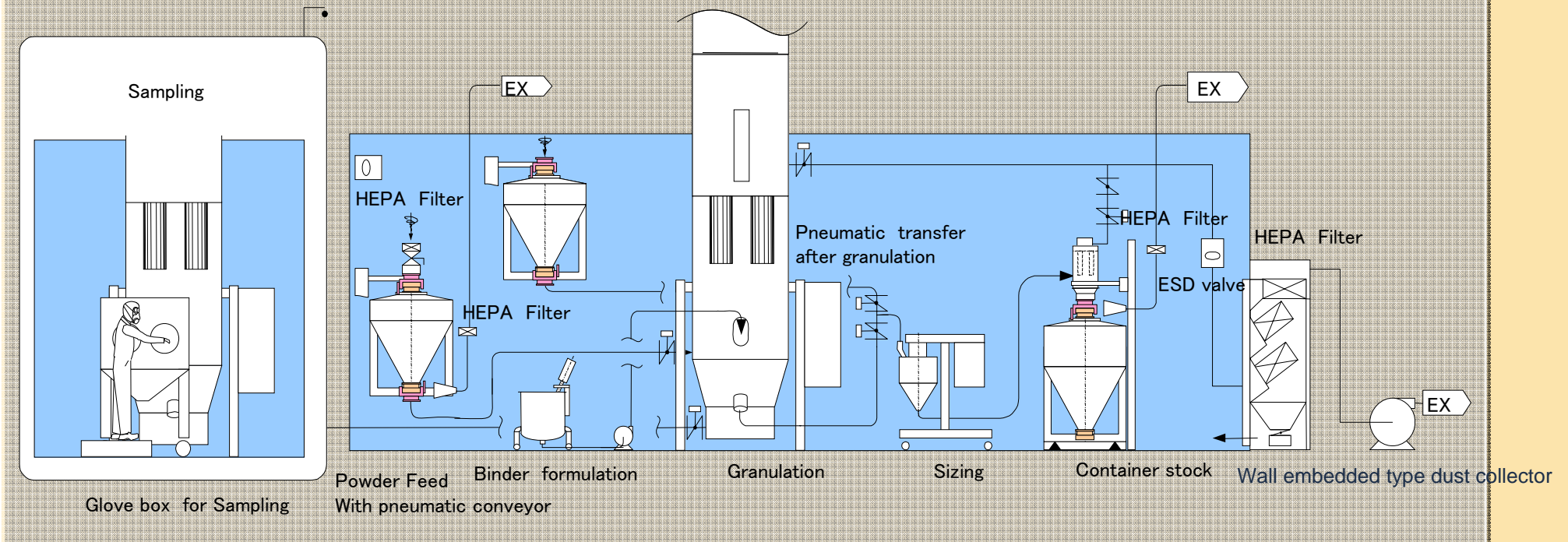
Solids Setting on Floor [ $\mu\text{g}/0.25\text{m}^2$ ]

# Process Flow: Fluid bed Granulator

## Design provision for Containment

- Enclosed powder transfer system
- Split butterfly Valve for container feed/discharge
- Globe box for sampling
- In-line sizing after granulation
- Pressure tight granulator

- Emergency shut-off Valve in dust exhausting line of Granulator
- Bag-in/out type filter bag replacement
- HEPA filter after dust collector
- Collected dust recovery from process room side



# Application (1)

## Dust collector for processing machines



HEPA filter after dust collector



Recovery of dust from process room side

Embedded dust collector in the wall of processing room

# Application (2)

## Granulation and Drying

### Fluid-bed Granulator



Glove Box for sampling

### Mixing Granulator



Globe Box for heel recovery

# Summary of Presentation

## **Hazardous Material Handling Facility should be designed ...**

- **Based on Quantitative Method**
- **Considering the Optimum Combination With Primary Enclosure, Building Facility and Gowning Procedure**

## **JGC has the unique evaluation procedure for containment performance of pharmaceutical factory ...**

Verification and Follow-up of the containment performance after construction are also very important !

Thank you for your attention

谢谢！

**For further contact ....**

**Chen Kaidong (陈凯东) ---JGC Corporation**

**Tel.:+81-45-6828518 Fax.:+81-45-6828854**

**E-mail: [chen.kaidong@jgc.co.jp](mailto:chen.kaidong@jgc.co.jp)**

**李月阳, 余敏---沈阳药科大学 日挥GMP研究室**

**电话 & 传真: 024-23986372**

**E-mail: [li.yueyang@jgc.co.jp](mailto:li.yueyang@jgc.co.jp) , [yu.min@jgc.co.jp](mailto:yu.min@jgc.co.jp)**

# Bag in/out dust collector



1. Set the filter to be replaced in the plastic bag at the outlet port.
2. Pull out the used filter into the plastic bag.
3. Sealed used filter in the bag.
4. Installed new filter in a closed manner.