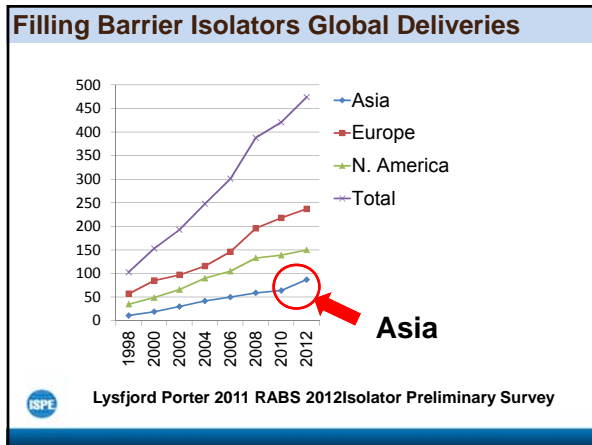


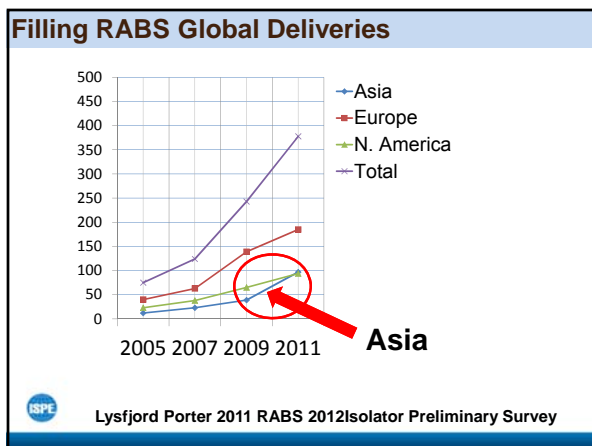
Trends of Barrier Technology in China and Japan

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 Connecting a World of
Pharmaceutical Knowledge





Trends of Barrier Technology in Asia

- ✓ The introduction of Isolators and RABSs in Asia are being now in highest gear, which driving leaders are Chinese and Japanese.
- ✓ So, both wanted to try to show you what are going on including the backgrounds.

Agenda

1. **Trends of Barrier Technology in China**
2. **Trends of Barrier Technology in Japan**
3. **Summary**




1 Trends of Barrier Technology in China

Agenda


- 1 The implementation process and opportunities of GMP in China
- 2 Application of Barrier technology in China



History of Chinese GMP




| | |
|------|---|
| 1975 | China Pharmaceutical Industry Companies propagandize GMP firstly in china |
| 1982 | CPIC formulate the front page GMP firstly in china |
| 1984 | SFDA formulate GMP and enacted by Government |
| 1988 | The ministry of health enact the first legal GMP in china |
| 1992 | The ministry of health modify GMP |
| 1998 | SFDA modify GMP again |
| 2011 | SFDA modify GMP again |


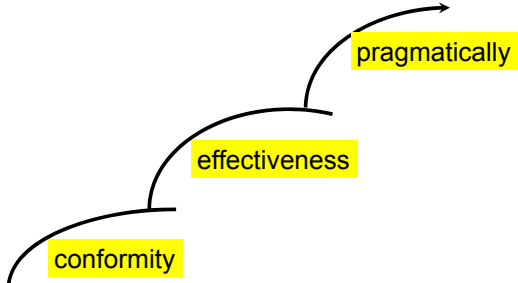


The purpose of the Chinese GMP revision


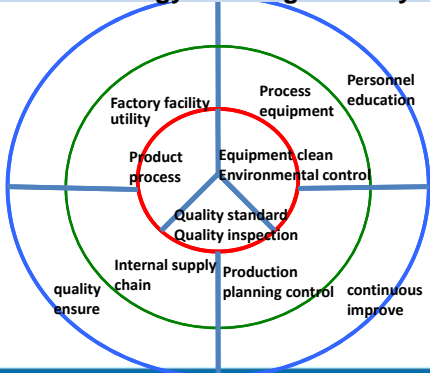
1. The change of supervision and management concept for drug
2. Raise the level of the pharmaceutical industry of China
3. Promote the development of pharmaceutical enterprise



SFDA supervisory and administrative idea transformation of Pharmaceutical



China GMP system of the 2010 version
=Product technology + Management system



The essence of the GMP management

1. Reduce the contaminate caused by Process loss
2. Optimize the allocation of resources to reduce the product cost
3. Improve the production efficiency
4. Continuous improvement to reduce the cost of the process control



《Pharmaceutical industry "twelfth five-year" development plan》 (Abstract)

- ✓ Constantly improve the quality standards
- ✓ Improve the “Chinese pharmacopoeia” which is the core of the national drug standards system
- ✓ Strengthen the standard scientific nature, rationality and operability, improve the standard of authority and seriousness.



New opportunities: Key pharmaceutical process equipment manufacturing

- ✓ Key process equipment, development and manufacturing of the system
 - the development and application of technology, such as Online control, on-line detection, Aseptic connection, CIP, SIP, **barrier system**






New opportunities: Design and construction of pharmaceutical engineering

- ✓ **System, scientific and practical pharmaceutical facility design**
 - The integration of process, equipment, utilities, building structure and production operation
 - Systematic facilities planning ideas and methods
- ✓ **The science of engineering construction management**
 - Scientific of project management
 - Based on the scientific risk analysis and validation plan





2 Application of Barrier technology in China

- ✓ **Aseptic Processing Lines**
Filling, Freeze drying ,
Capping, etc.
- ✓ **Aseptic or/and Potent API**
Weighing, Charging,
Filter Dryer, Dispensing, Sampling
- ✓ **Lab Application**
Sterile Test Isolator



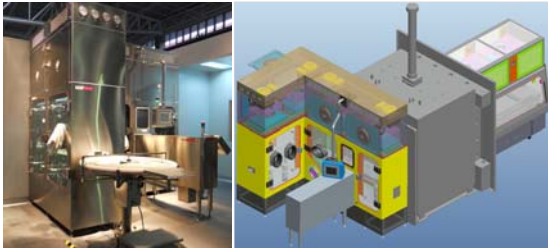
Application1 Closed RABS



Application2 Isolator front of freeze dryer



Application3—Isolator for freeze dryer





Applications- Aseptic Processing Lines

1. Isolator is integrated with the Automated Loading System in front of the freeze dryer
2. Isolator is supposed to maintain an Grade A environment
3. Rigid wall enclosure provides full physical separation of the aseptic processing operations from operators



Characteristics of Barrier


1. Double windows are designed for air return
2. Inflatable gaskets are used for windows sealing
3. Safety switches to detect the opening of doors




Safety light curtain and safety switches are installed to quick response to miss-operations during the production.

ISPE

Application5 Aseptic or/and Potent API



Pass box is used to pre-cleaned containers and valves with filtered compressed air.



Isolator is designed for the process to open the inner covers of the API containers and to assemble with the butterfly valves.

ISPE


Introduction Status of Barrier system in China

1. Barrier systems are being introduced in China with highly rapid way
2. Because of being strongly impacted by the China GMP's revision
3. In China, RABS have been mainly introduced

ISPE

Introduction Status of Barrier system in China

- 4. Aseptic isolators are the minority
- 5. But it can be assumed that the number of the isolators will be on the increase gradually
- 6. Containment isolators and Sterility testing isolators are developing in the introductions as well




2 Trends of Barrier Technology in Japan

Agenda

2-1 Trend of Isolator and RABS in Japan

2-2 Topics

- A) Development of a RABS integrated with decontamination box as an formulation line
- B) Development of a new HEPA Cart for transferring to/from RABSs
- C) Study how to validate decontamination of gloves




2-1 Trend of Isolator and RABS in Japan

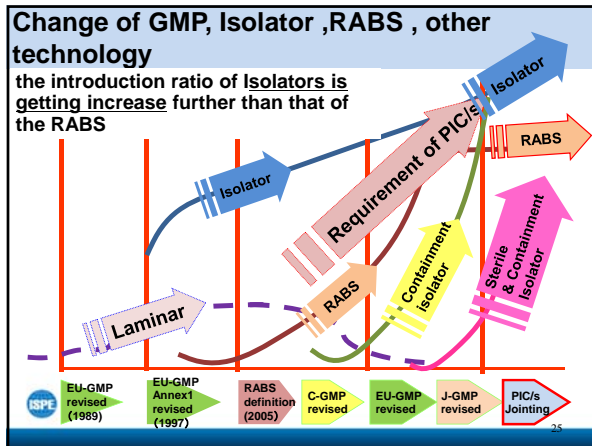
- ✓ GMP inspection system is now on the process of revision heading toward joining PIC/S

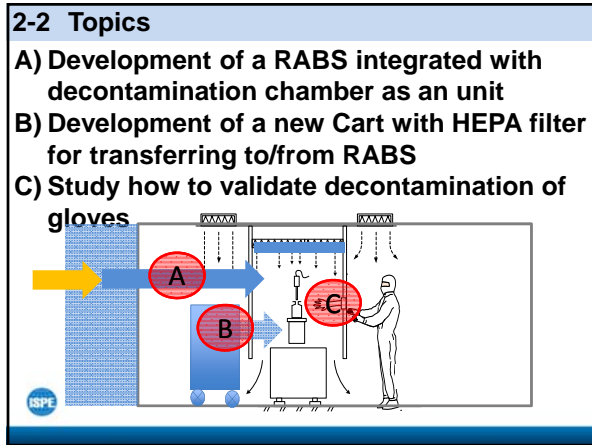
2012 Revision of GMP (Utilization of PIC/s)
2013 Notice of enforcement of the revised GMP
Local evaluation in Japan by the PIC/s
→ delegation
Awaiting the Member authorization

The GMP's revised points toward joining PIC/S

- 1. Global perspectives
- 2. Quality Assurance
- ✓ Introduction of Risk management concept
- ✓ Complete revision of Validation criteria









RABS Layout of Ophthalmic filling line

- ✓ Integration of a decontamination chamber and a RABS
- ✓ Enabling to carry materials by using conveyers
- ✓ Possible to decontaminate areas partially

Decontamination Chamber Box

- ✓ Automatic conveying of the hung bags in the decontamination chamber possible
- ✓ Automatic removing of the bags at the outlet part

Decontamination using HPG

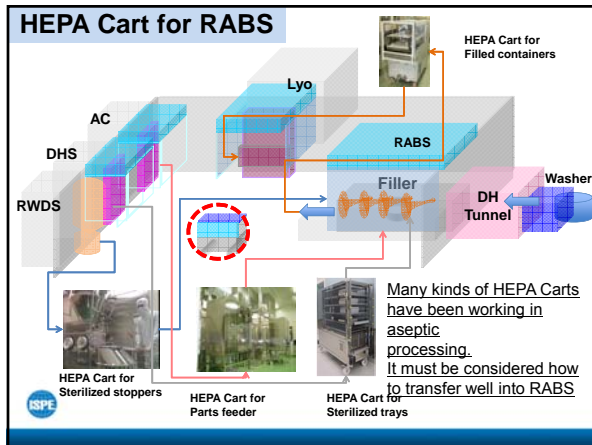
Partial decontamination Possible

RABS inside view

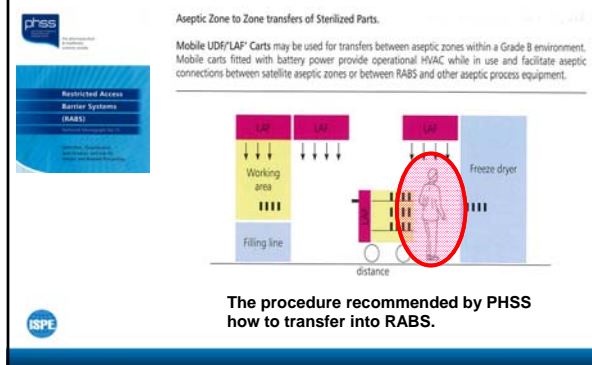
B) Development of a new HEPA Cart for transferring to/from RABSs



ISPE



Recommendation how to dock HEPA Cart with RABS by the PHSS



Example of HEPA Cart for Sterilized stoppers

- ✓ Grade A can be maintained
- ✓ Stoppers can be fed into parts feeder without manual handling

HEPA Cart with Reversing device.

RABS

Grade A

Grade A

Example: HEPA Cart for Sterilized stoppers

- ✓ Products can be always maintained in Grade A at the Support A area to be opened gradually
- ✓ Vials can be transferred into Lyo without manual handlings.

Support A area

Grade A

Grade A

Design, Validation and Utilization of The HEPA Carts.

- ✓ To establish a chain of many Grade A areas sequentially
- ✓ To plan no operator interfering into Grade A area directly
- ✓ To discuss of equipping Automation devices
- ✓ To consider to install Gloves on the Cart
- ✓ To transfer products into Grade A area through the Support area A
- ✓ To ensure positive air flow during connection or door opening
- ✓ To design enabling decontamination inside the Cart

**C) Study how to validate
decontamination of gloves**



**Consideration Necessity of Gloves
decontamination.**

1. Gloves decontamination is a must for Isolators and RABS
2. Although many tests were done for several materials about the decontamination impacts; D-values,
3. Not so many studies about influence of shapes to be subjected to decontamination
4. Gloves, in particularly, are complicated in the shapes, and the reproducibility of decontamination is uncertain
5. Consideration about proper BIs placing methods in the validation for Gloves decontamination has not been done

Purpose of this study

1. To study the right BIs placing positions in Glove decontamination
2. To discuss whether the reproducibility of Gloves decontamination is OK or not.



To find the adequate BIs placing positions
 How and where are suitable for BIs placing?

Type A
 To place BIs in between fingers (Bridge)

Type B
 To wrap BIs around fingers (Around)

Type C
 To place a BIs in a bent Glove

Test items

I Basic assessment

- To estimate D-value for each material
- To check the impact based on the BI placing positions

II Assessment with Gloves

- To check the impact according to the BIs placing positions
- To check the influence of air velocity

III To find where and how to place BIs during decontaminating Gloves.

I -1 Comparison study and results in Material D-value estimation

Specification of BI to be applied

- ✓ Manufacturer : Mesa Labo
- ✓ Spore : *Geobacillus stearothermophilus*
- ✓ Applied quantity : 1.35 CFU/5µl
- ✓ LHSKP method

| Velocity (m/s) | BI Applied material | D-Value(min) |
|----------------|---------------------|--------------|
| 0.3 | SUS304 | 2.0 |
| | Hypalon | 0.3 |

- The D value of Hypalon is lower than that of SUS304
- For the test BIs with the carrier of SUS304 were used for convenience, the test can has enough margin compared with actual cases.

I -2 Checking impacts of BI placing on a finger tip

- ① BI location ; Top, Side, Bottom
- ② Distance from finger neck (L)
- ③ Gap between fingers (G)
- ④ Air velocity (m/s)

Air velocity = 0.3 and 0.5 m/s

ISPE

I -2 Test results(D-value)

| velocity | Gap G | 5mm | 10mm | 15mm | 20mm |
|----------|--------|-----|------|------|------|
| 0.3m/s | Top | 2.1 | 1.6 | 1.7 | 1.9 |
| | Side | 1.9 | 1.8 | 1.7 | 1.8 |
| | Bottom | 1.8 | 1.9 | 2.0 | 1.8 |
| 0.5m/s | Top | 2.1 | 1.5 | 1.5 | 1.5 |
| | Side | 1.7 | 1.7 | 1.6 | 1.5 |
| | Bottom | 1.6 | 1.8 | 1.6 | 1.6 |

Air velocity = 0.3 and 0.5 m/s

D=24mm

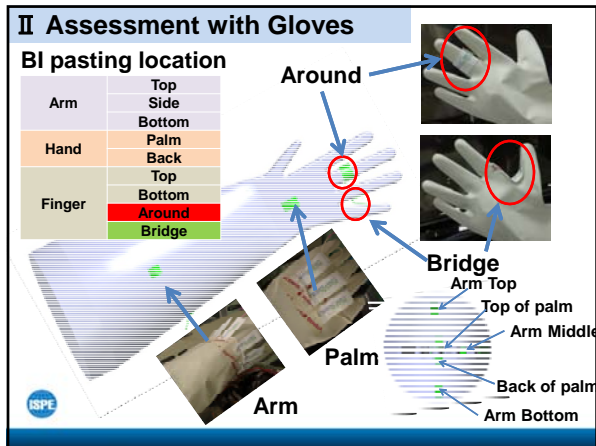
ISPE Air velocity = 0.3m/s

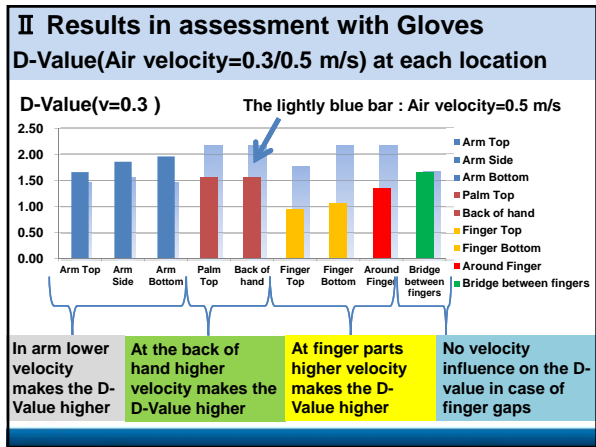
ISPE Air velocity = 0.5m/s

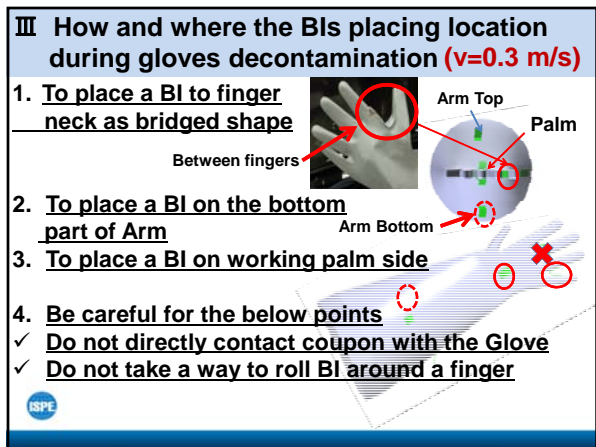
I -2 Test results(D-value)

1. Differences of D-value in Top, Side and Bottom of a finger are less than 25%
2. Side parts D-value differences are little when the gaps are between 5 to 20mm
3. D-values difference between Top and Bottom of finger are small
4. D-value differences are small when air velocity between 0.3 and 0.5m/s
5. If air velocity comes to higher, the D-values have tendencies to decrease

ISPE








3 Summary; Perspective of ISO/RABS in China and Japan

1. Barrier system are being introduced in China with highly rapid way
2. RABS, however, have been mainly introduced , but it is sure that Isolators will be on the increase gradually
3. In Japan, the introduction ratio of Isolators is getting increase further than that of the RABS
4. But, several technological developments on RABS are proceeding as well
5. There are still some issues in the decontamination etc., it must be continued to study



Thank you very much for all of your attention



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