PHARMAprocess

Innovation Forum in Pharmaceutical Process

Overview of Low voltage Electron Beam sterilization system and the Benefits

Case study in the application of Low Voltage EB system
for Nest Syringe Tubs Filling Line
and Vial Filling Line as well

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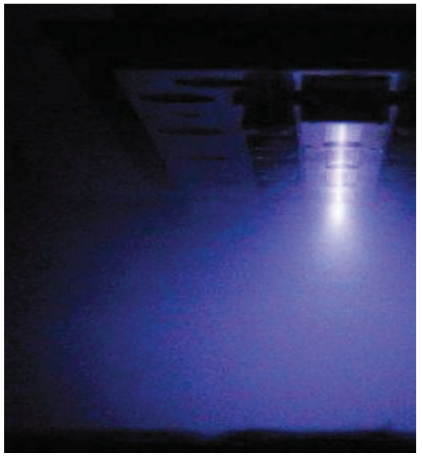
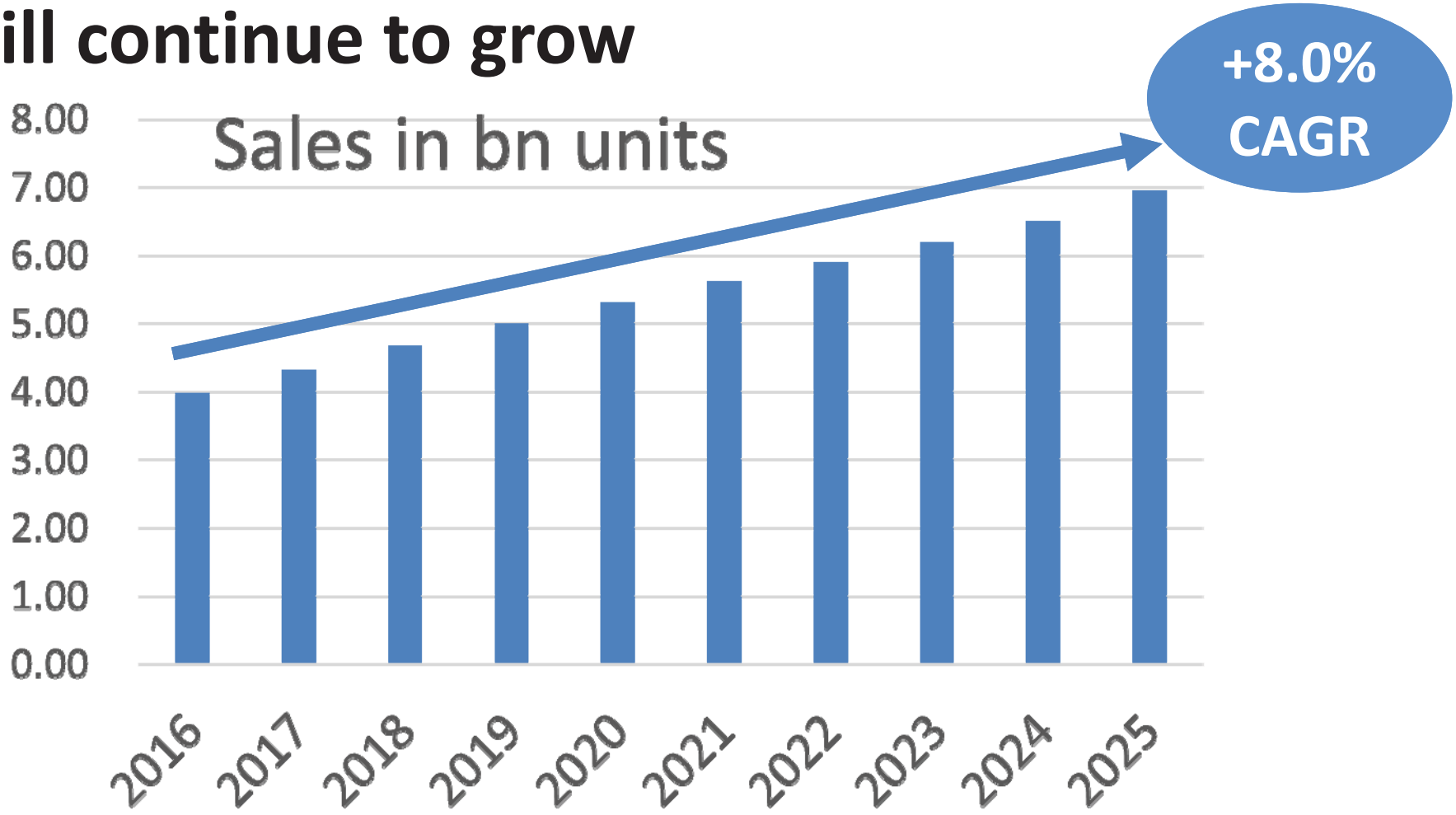
Agenda

1. Trend about prefilled syringe to be used
2. Evaluation of tub surface decontamination to introduce the tub into an aseptic filling isolator
3. A study of mouse hole
4. Overview of Electron Beam sterilization
5. Benefit of Low Voltage EB
6. Case study of the application of Low Voltage EB
   - ✓ Sterilization for Tub of Syringe Barrels
   - ✓ Sterilization for Vial Containers
7. Lesson learned
8. Summery



PFS market will continue to grow



- ✓ PFS market will grow up to >5 bio units in 2020
- ✓ One of the growth driver is the Biotech drugs

Source ; Visiongan, Prefilled syringe and Related system world market outlook 2010-2025

2013-05-21 S. Tamatsukuri, PhD.
Global D&D/GPS, TERUMO corporation

Drugs and devices for new era

Before

LMW, synthetic

Oral

Biotech

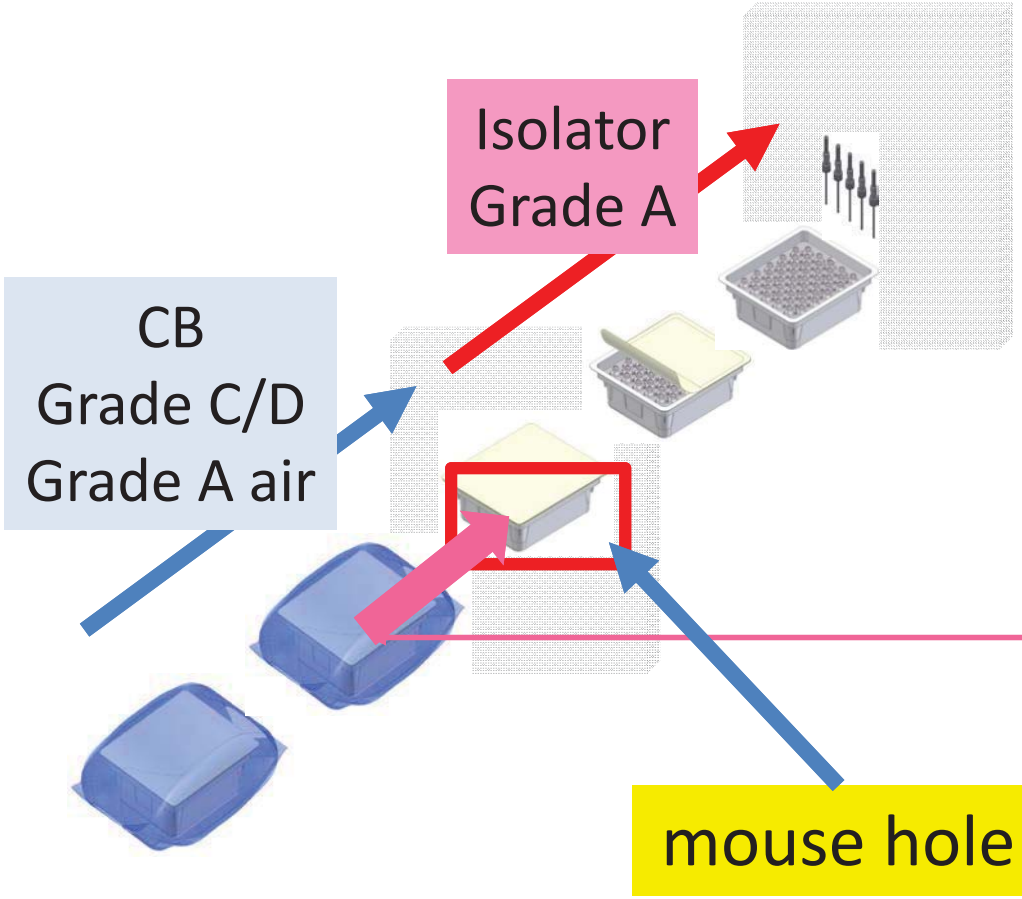
Injection

Future

Needs for PFS compatible with biologics

2013-05-21 S. Tamatsukuri, PhD.
Global D&D/GPS, TERUMO corporation

Method of tub（surface decontamination to introduce it）into an aseptic filling isolator



	Method
1	Auto-Debag
2	Alcohol
3	VHP
4	UV
5	EB

Evaluation of tab

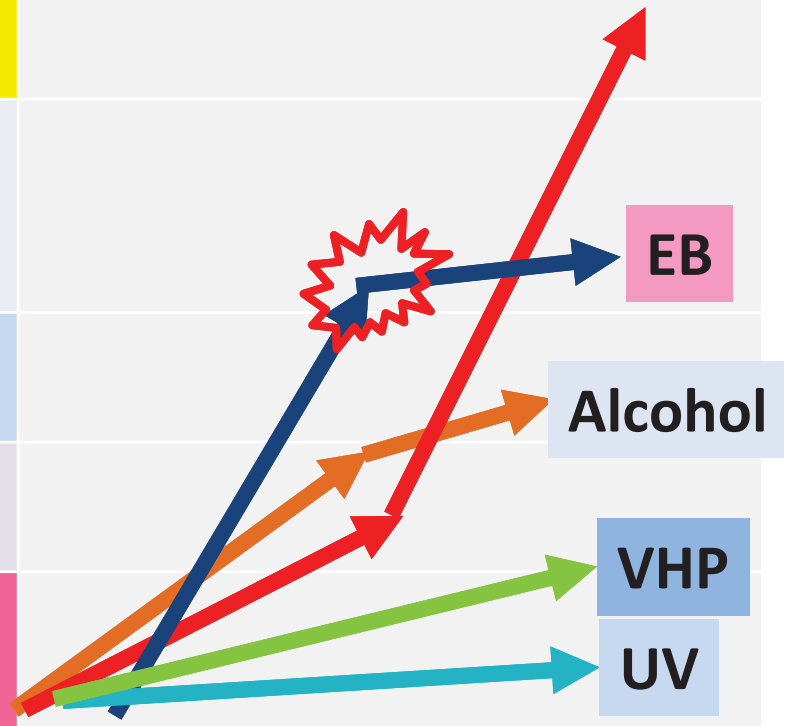
surface decontamination to introduce a aseptic filling isolator

	Method	cost	Running Cost	GMP compatibility	Validation	SAL	Residual chemicals	Cycle time	Easy or difficult to combine with isolator	Total point
1	Auto-Debag	7	10	1	1	2	10	9	9	6.1
2	Alcohol	7	9	2	2	2	7	7	7	5.6
3	VHP	4	7	7	6	7	4	2	4	4.6
4	UV	5	9	3	3	5	10	6	9	5.4
5	EB	2	9	10	9	10	9	10	9	7.0
	Weighting To point	35	5	15	10	5	5	20	5	100

Base data is Oliver Vogt : Case Study: Utilizing Electron Beam Surface Decontamination to Transfer Sterile Syringe Barrels into an Isolated Aseptic Syringe Filling Line (Pharma engineering)（Jan.2010）

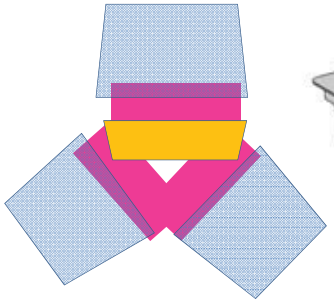
Evaluation of tub
Surface Decontamination to introduce into an aseptic filling isolator

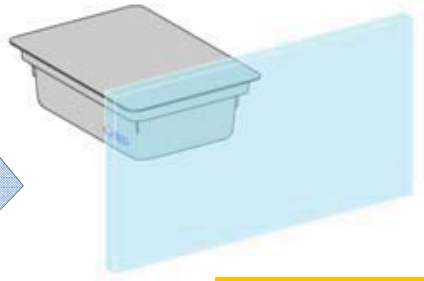
	Methods	issues	Trend images
1	Auto-Debagging	Is it possible to debag with No contamination in the process? Is it allowed to put it into an isolator through a mouse hole?	
2	Alcohol	Not effective decontamination can be made. Potential to catch fire in the next process.	
3	VHP	Longer cycle time. Concern of VHP's residue	
4	UV	Disinfection effectiveness on the shadow area	
5	EB	X-ray,Ozone, panicle generation, Higher cost, Lower life time	



Problem of EB tab sterilization

the problem of the EB was found out by long-time actual operation





BD

Un-uniform dose

High X-ray

High Ozone generation

Problem of supplier

Particle generation

Short life time

Auto-Debagging

EB

Alcohol

VHP

UV

Auto-Debagging Method

- ✓ Is it possible to debag with No contamination in the process?
- ✓ Is it allowed to put it into an isolator through a mouse hole?

Auto-Debagging Method

Controlled area

Warehouse receipt

Control supply chain

Remove outer packing to limit particle & micro transfer

Transfer corridor Grade D

Tubs are introduced through the Mouse hole into the isolator(Grade A aseptic area)

Grade D

Grade C

Disinfect– Protect

Isolator Grade A

Filling satirized container

Surround environmen Grade C

De-Bag1 Transfer hatch

No touch transfer zone Grade B

Non-intervention De-bag 2

mouse hole

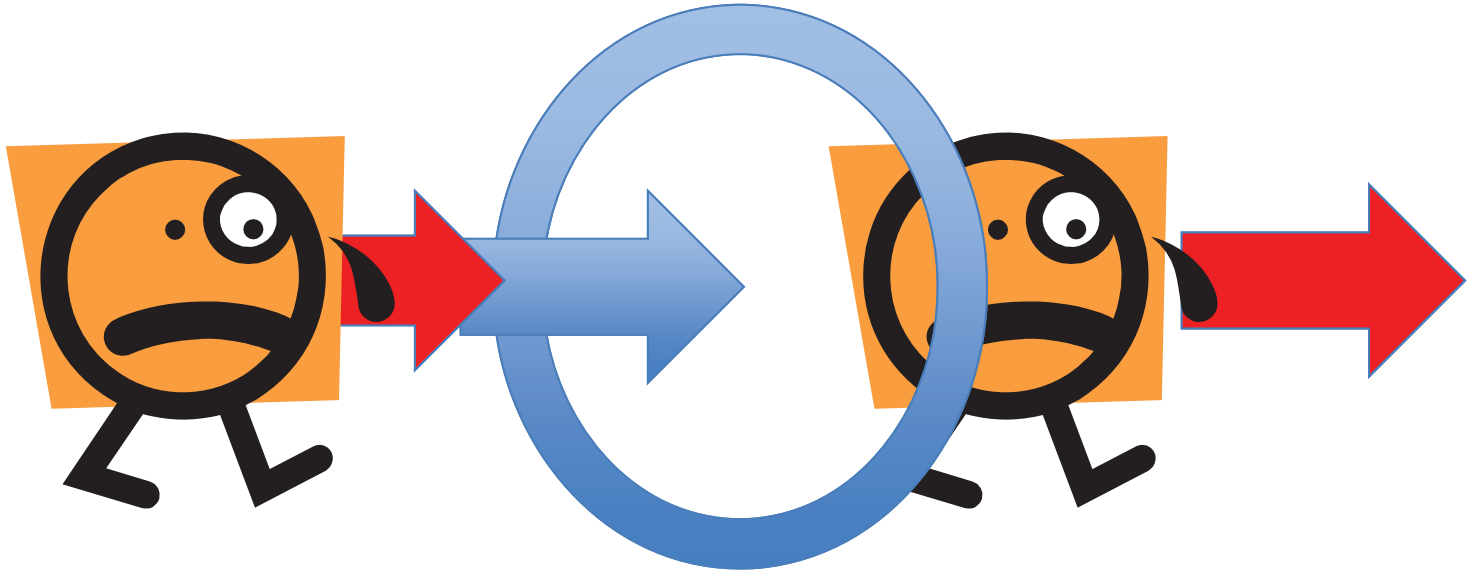
△P=20~25Pa

Air velocity is 6~10m/s

Isolator Grade A

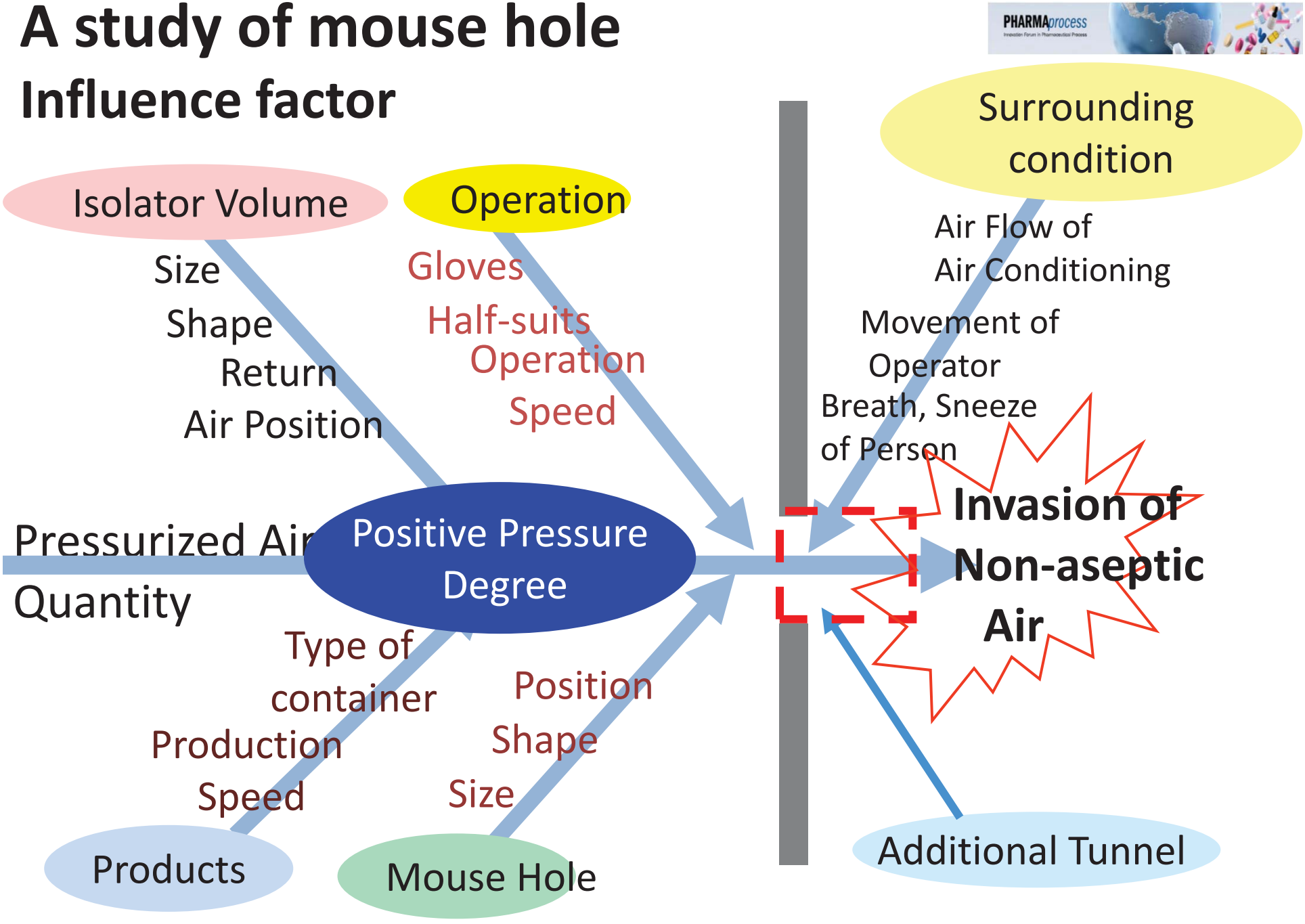
A study of mouse hole

A Mouse hole is typically used for taking out finished sealed products from the isolator.



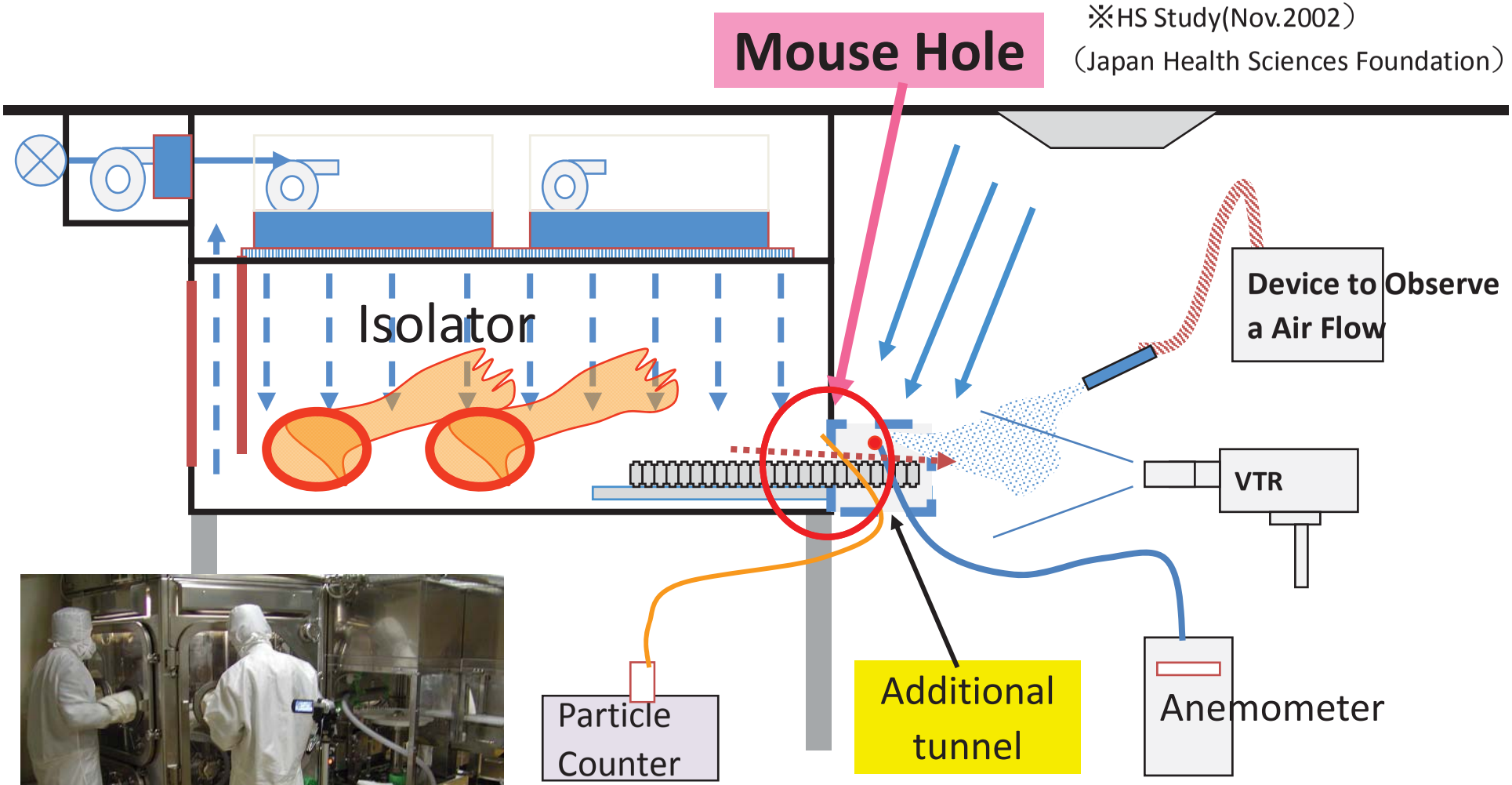
A study of mouse hole

Influence factor



A study of mouse hole
Summary of experiment

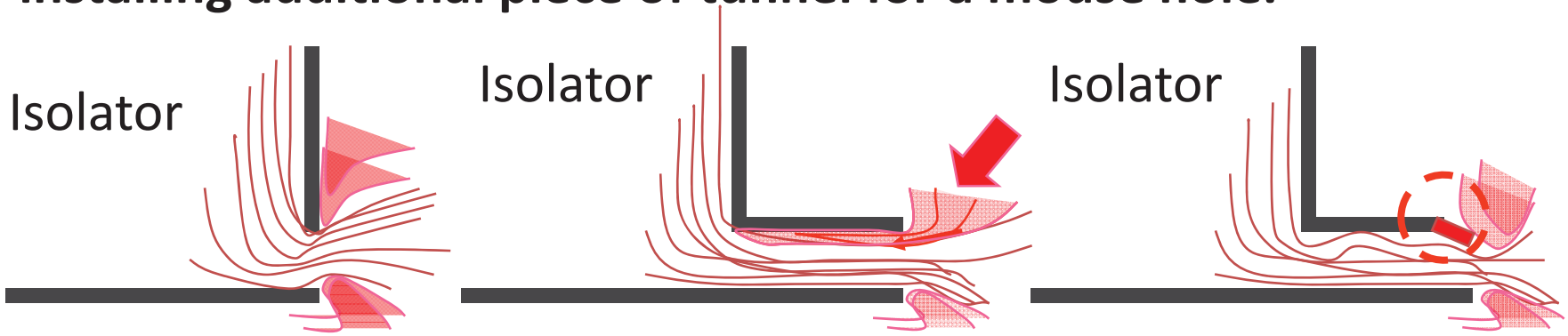
DAIICHI Pharm.: Kojima, Yamuchi
JGC; Watanabe ,Sagara, Ono
※HS Study(Nov.2002）
（Japan Health Sciences Foundation）



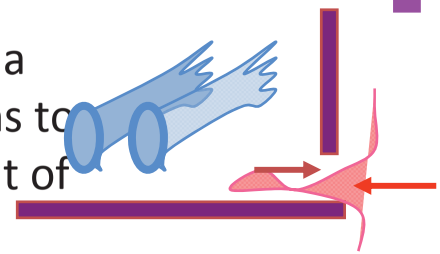
A Study of Mouse Hole

Topics

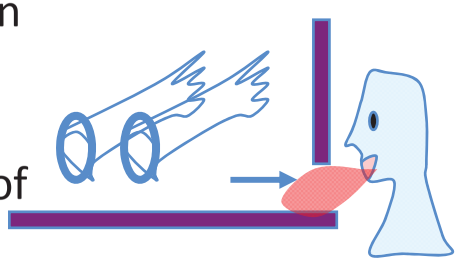
- ✓ **There might be an invasion of air surrounding isolator even if installing additional piece of tunnel for a mouse hole.**



- A little air rate of positive pressure from isolator by a small mouse hole happens to cause a reversal of current of air by radical glove operation.



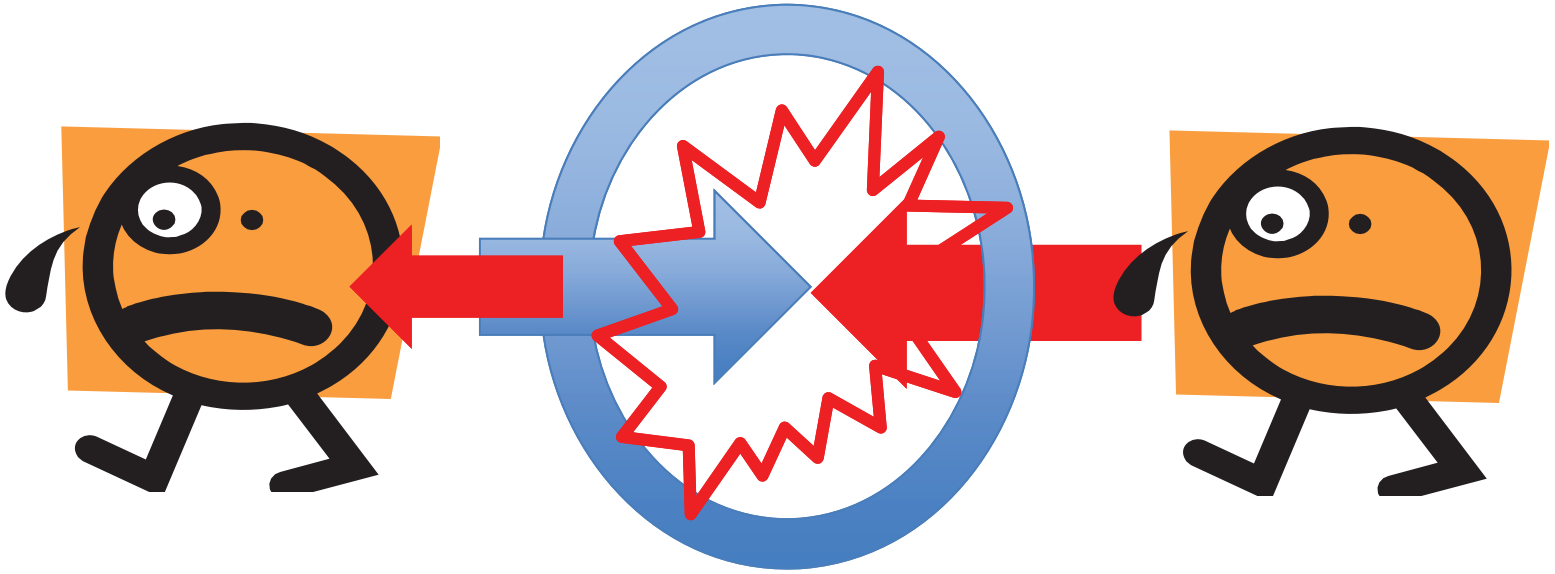
- An invasion of pollution air was confirmed in a mouse hole by expiration in the case of 40 Pa of internal pressure.



- ✓ **Possibility of an unexpected problem**
- ✓ **A plan such as shape of isolator, a size characteristic, setting of internal pressure in consideration of use and shape of a mouse hole are important.**

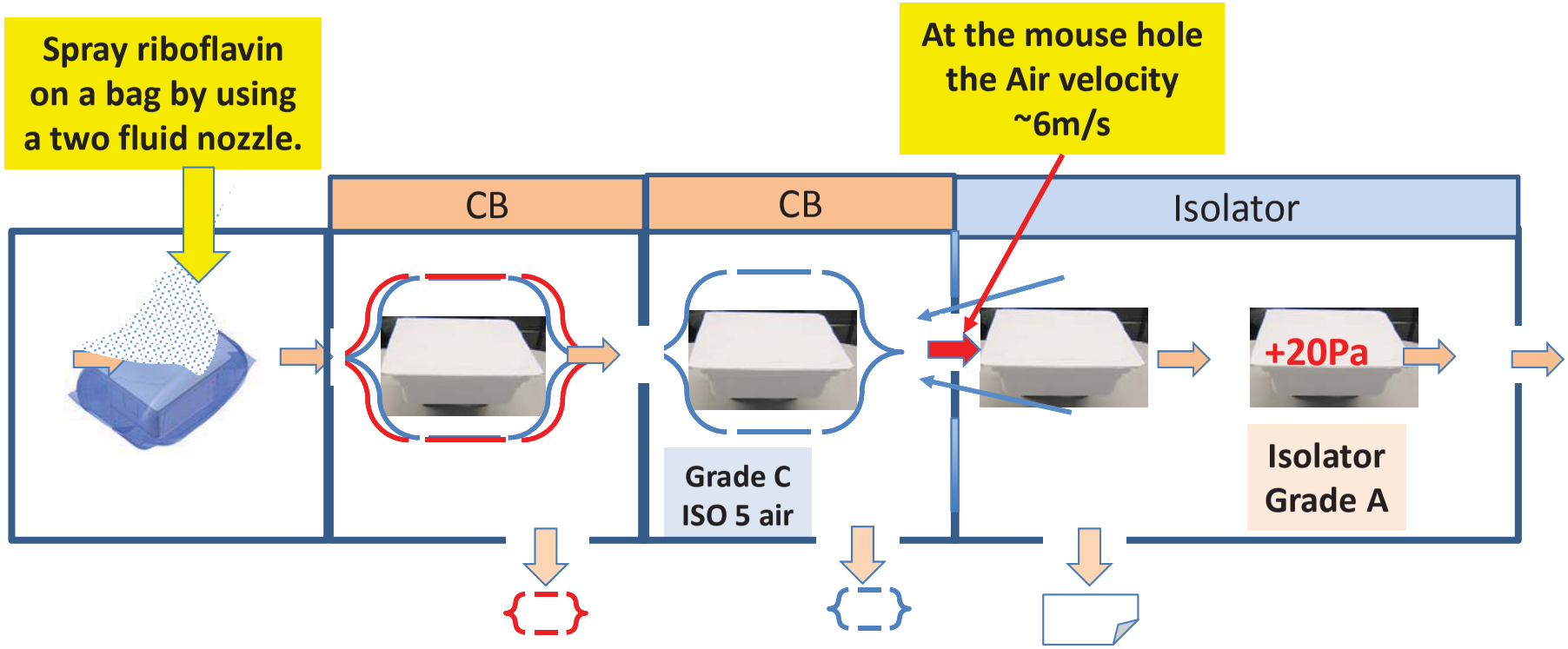
A study of mouse hole on Auto-Debagging Method

Is it feasible to introduce any items aseptically through the Mouse hole into the isolator?



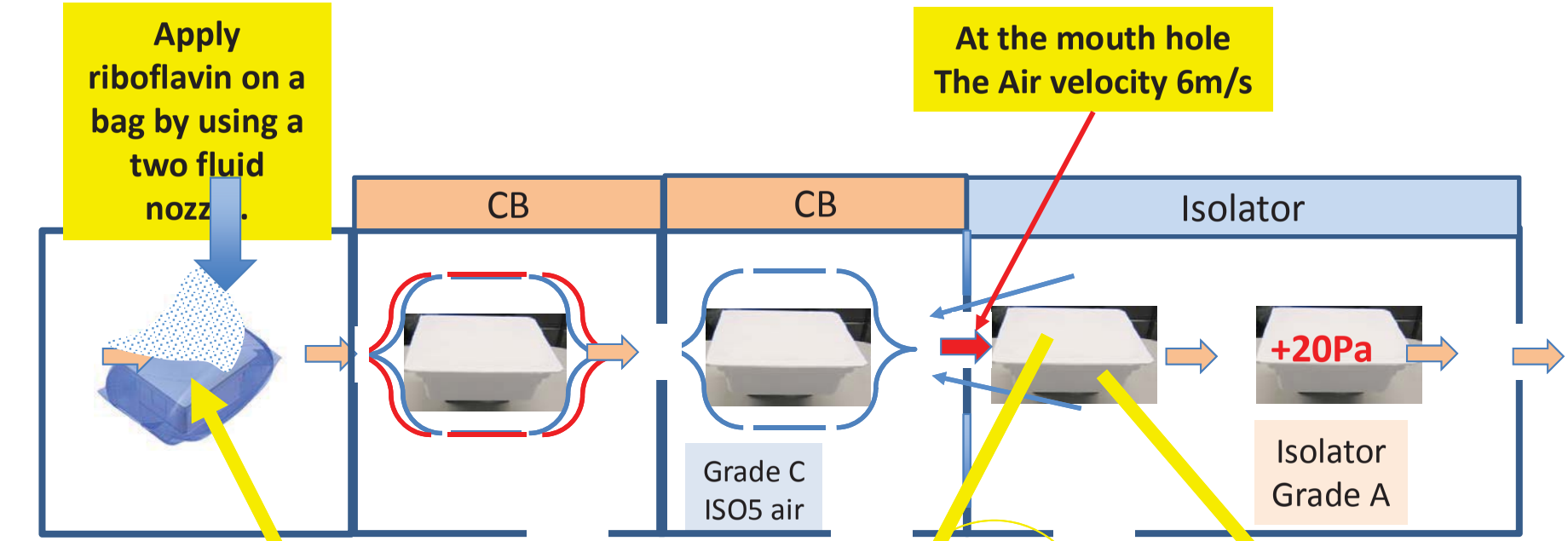
Test procedure

1. Spray riboflavin on a bag by using a two fluid nozzle
2. removing the double bag sheets one by one carefully by hand
3. verify to check a traces of the riboflavin on the tub

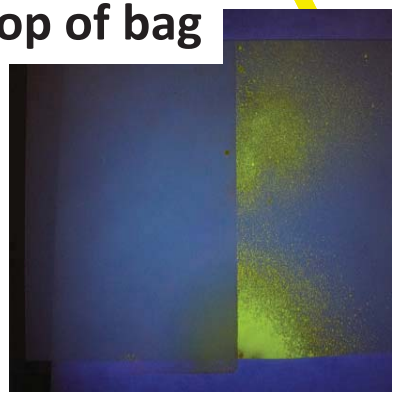


Test result

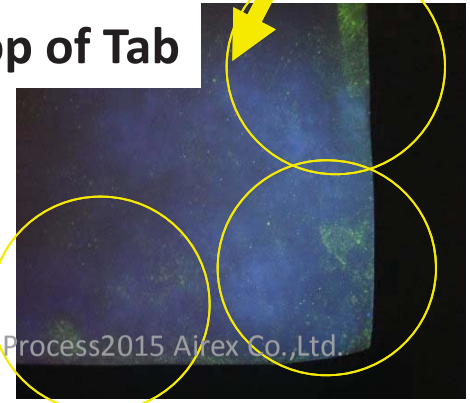
We found the trace of the riboflavin on the tub

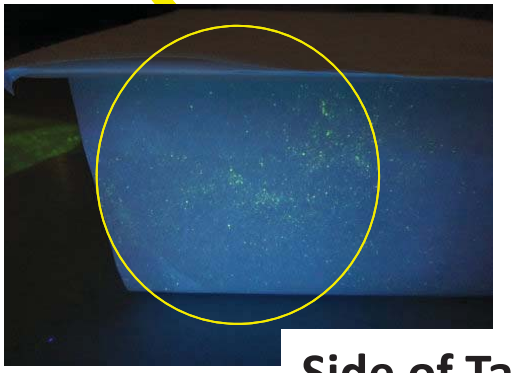


Top of bag



Top of Tab

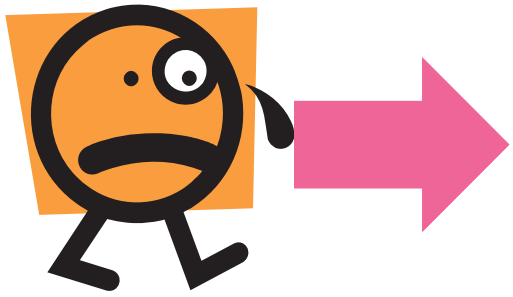




Side of Tab

Is it feasible to introduce any items aseptically through the Mouse hole into the isolator?

- ✓ It has a higher Risk to intoduce a tub into an isolator through a Mouth hole aseptically with removing the unstable shape bag (debagging).
- ✓ The risk goes much higher especially in case of a filling with larger amount and higher speed.



Electron Beam striation Method

X-ray, Ozone, panicle generation,
Higher cost, Lower life time

Traditional Electron Beam

- Around for >50 years, **well known sterilization technology**
- Benefits for pharmaceutical and medical device manufacturer

✓ Large, expensive, high maintenance, profound cover

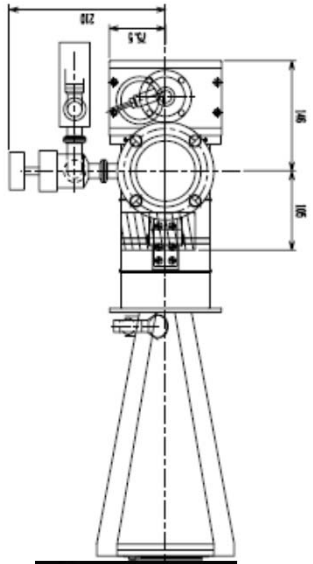
✓ **Severe management is required**

✓ **Off-line process**

New Electron Beam Smart EB© System

Smart EB
Airex

1. **Always being kept to be evacuated by using vacuum pump.**
2. **Low voltage system (Max70KV,4mA)**
3. **At the time of the electron window damaged, only need to replace the window**



Ratings

EB Irradiation Unit

Input voltage：Max.70KV, Single phase 100V (50/6

Power consumption：**less than500W**

EB Control panel

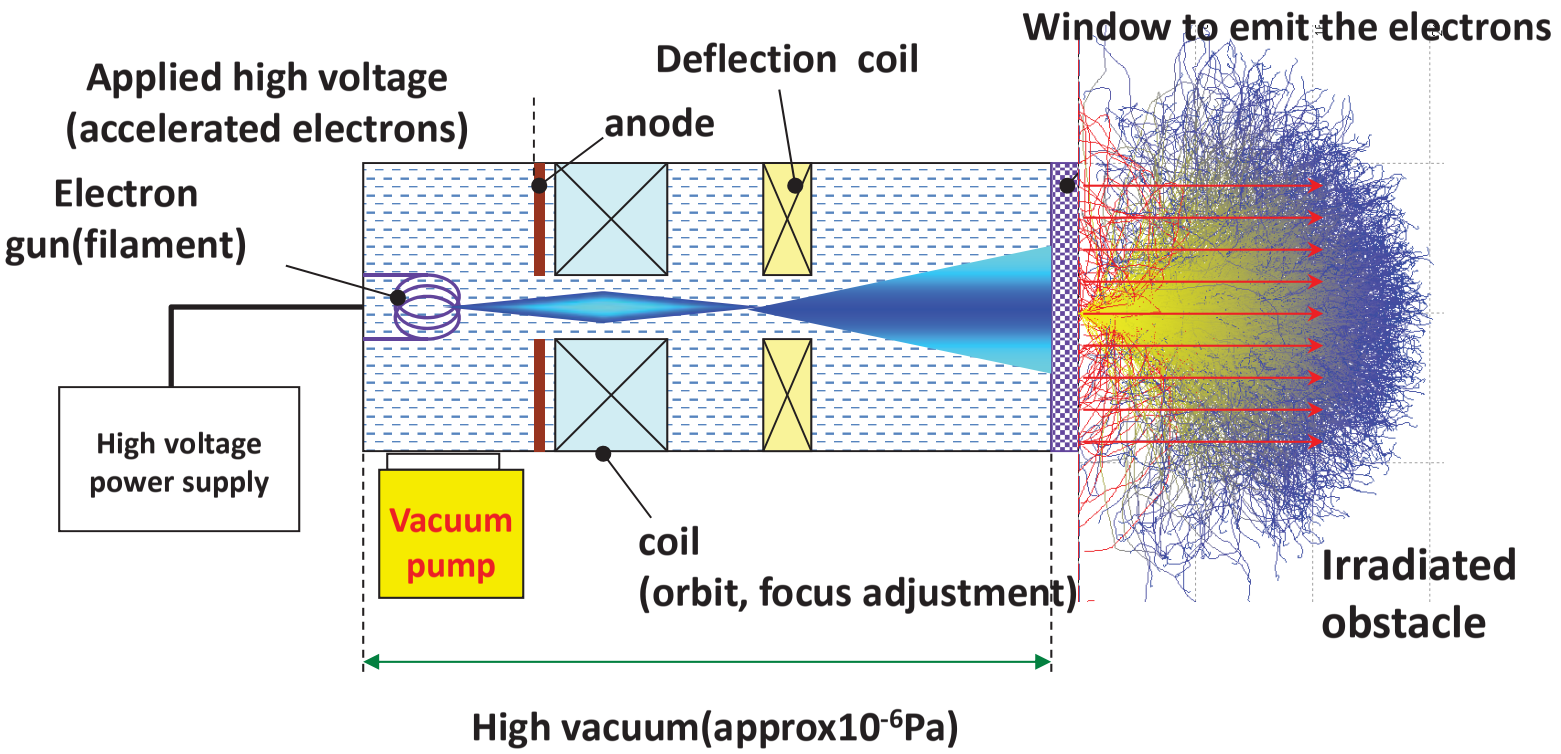
Power consumption：**less than 800W**

Rotary pump

Power consumption：**less than 250W**

Hamamatsu Photonics

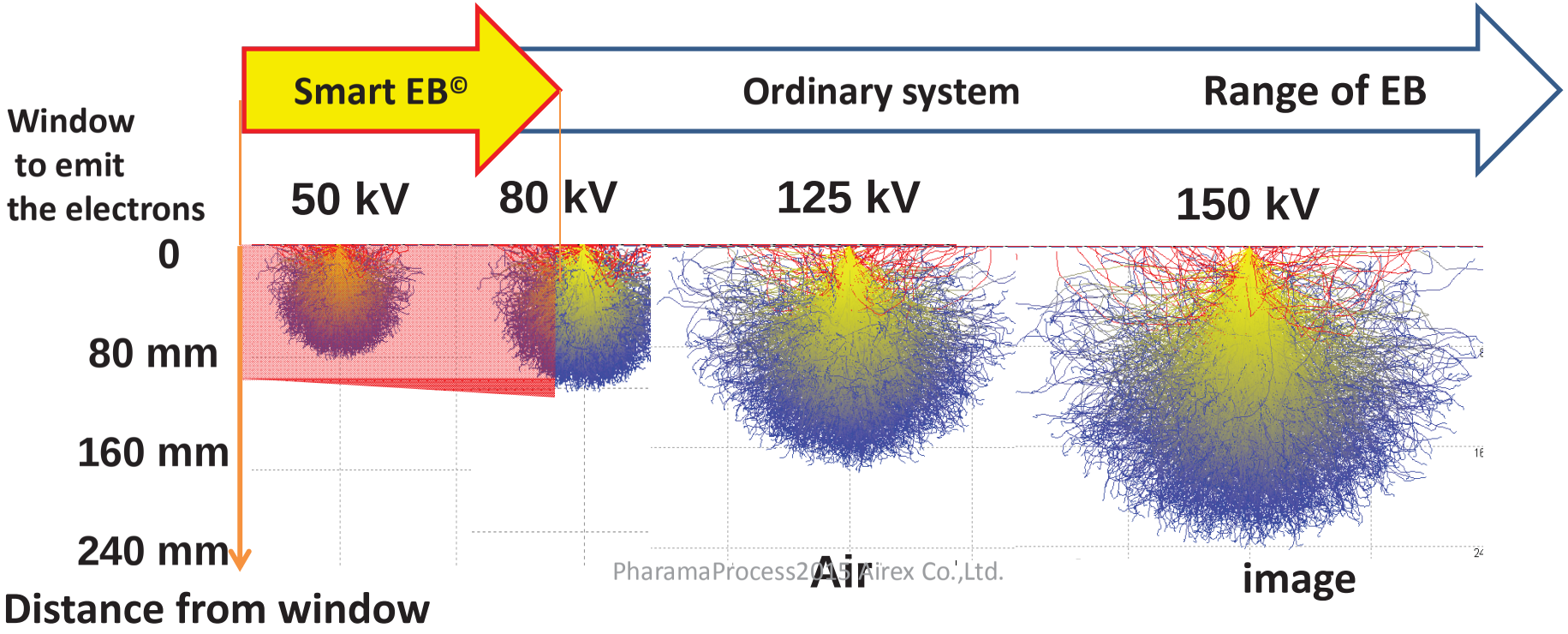
Overview of the Low Voltage Electron Beam System



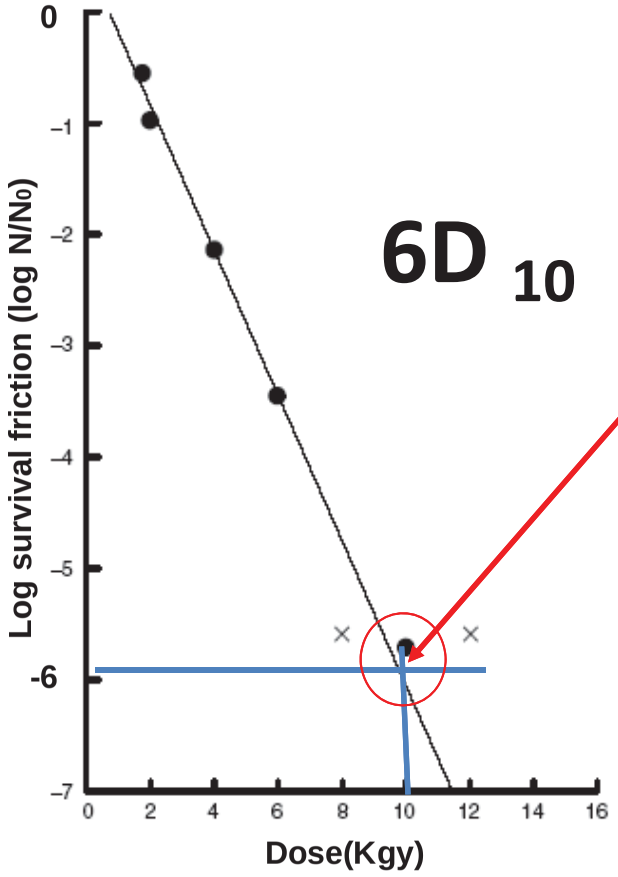
- ✓Electrons are emitted as thermions from an electron gun
- ✓Accelerated in between electrodes applied high voltage
- ✓Vacuum pump always sucks the air into the vacuum chamber
- ✓Emit electrons to outside passing through the window

Low voltage EB scattering

- ✓ Electrons make an entry into atmosphere and interact with the air molecules then going to become dispersed with losing their energy
- ✓ Traveling length in the air for electron beam, to be depending on accelerating voltage.



EB is Effective on Microorganisms



$6D_{10} = 10.2$ kGy

Fig. 4 Dose response of *Bacillus pumilus* spores (ATCC 27142) treated on the inner bottom sidewall of 0.47 HDPE bottles.

Source: Cleghorn, Dunn, Nablo. "Sterilization of plastic containers using electron beam irradiation directed through the opening." Journal of Applied Microbiology, Volume 93 Page 937 - December 2002

Control Dose level of Surface Sterilization

EB Effectiveness on D-Value

Bacillus Pumilus Spores ATCC # 27142 (E601)

D_{10} = 1.7 kGy

$6D_{10}$ = 10.2 kGy

Minimum dose = 15 ~ 25 kGy>

It is Magic figure, no real rational, but to consider safety margin etc.

Dose level at any point on the container's surface（Gy）>15~25kgy

Reference:From "Electron Beam Sensitivities in the Spores of Bacillus pumilus E601 Strain" J. Antibact. Antifung. Agents Vol.17, No.7, 1989 by Y. Watanabe, H. Ito and I. Ishigaki, and "In-Line Electron sterilization and Its Application to Aseptic Packaging" March 1985 by P.M. Fletcher, J. Aaronson and S.V. Nablo

Benefit of Low Voltage EB

- ✓Dry and Low temperature process
- ✓Quite low Ozone generation
- ✓Quite low impact to objectives
- ✓Comparatively low energy consumption
- ✓Easy maintenance at site
- ✓Stainless steel plate cover is enough to cut x-ray
- ✓Unnecessary of the special license
- ✓Low operating cost

↓

- ✓In-line and in-house process
- ✓Continuous treatment with monitoring and recording for GMP parameters

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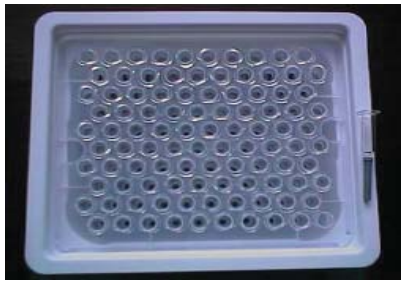
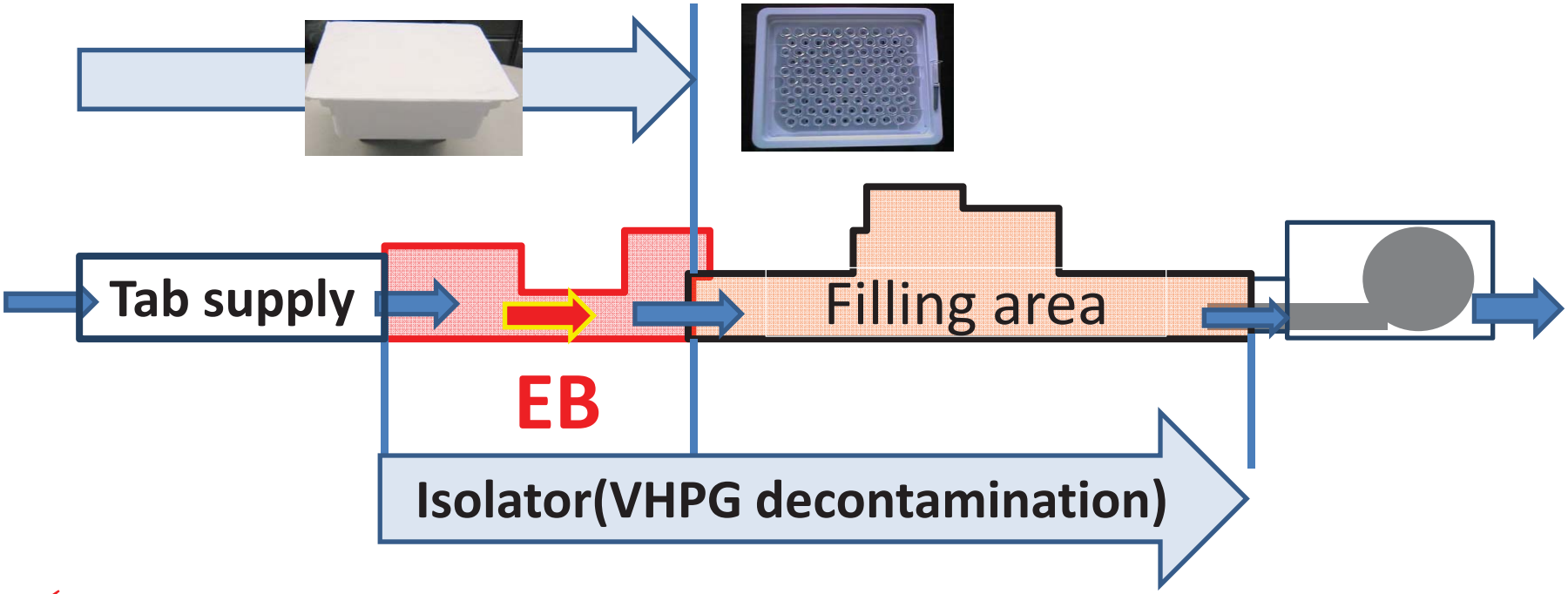
- ✓**Basically surface or core sterilization**

Case study of application of Low Voltage EB

Utilizing EB Sterilization for Tub of Syringe Barrels Introduced into an Isolated Aseptic Filling Line



Layout of syringe tab filling process combined with EB tub sterilization



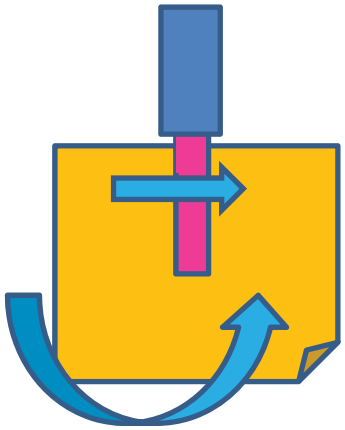
- ✓ EB tunnel is installed before the filling process.
- ✓ Surface of tabs are sterilized by the E-beam
- ✓ Filled with the liquid product, then will be conveyed to the next process

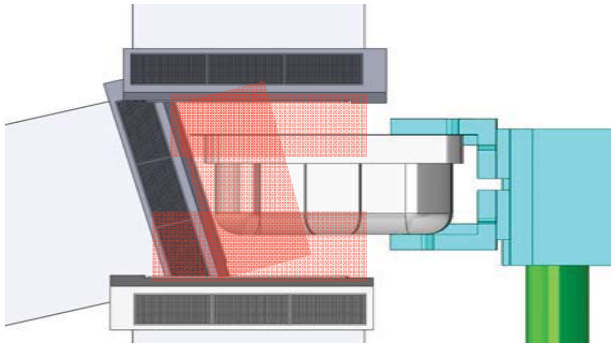
Smart EB©

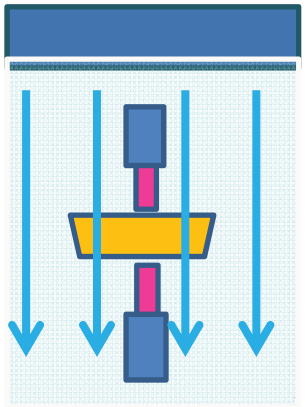
Concept of new EB Sterilization for surface decontamination of tub of syringe barrels

VTR

1. Three EB emitters to be used
2. Irradiation shall be done with moving and turning a tub
3. To keep always the distance almost equal between the irradiation window and the obstacle to be sterilized
4. To keep unidirectional air flow during sterilizing



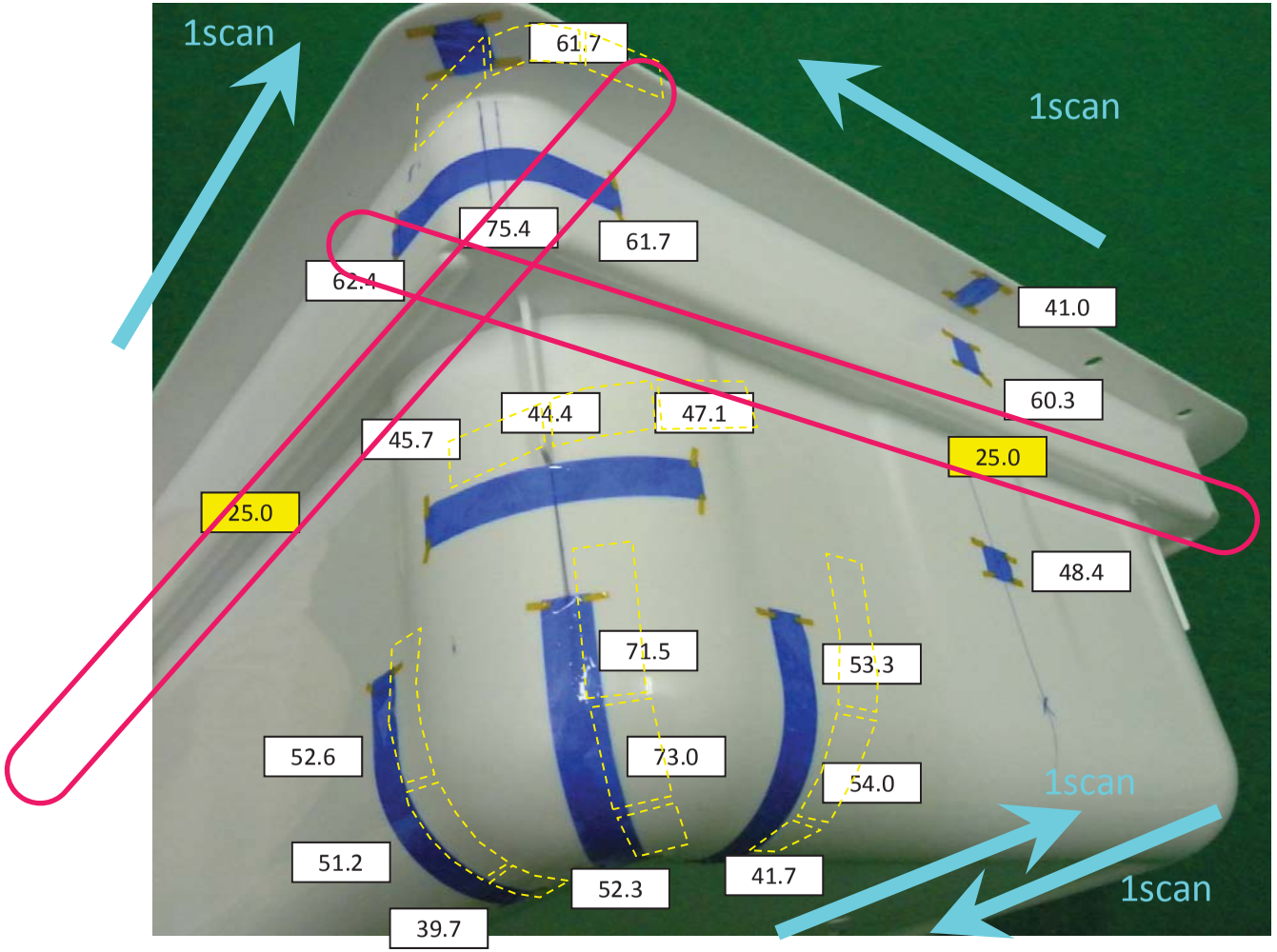




Verification of E-beam Validation

1. E-beam dose mapping on tub surface of outside and inside
2. Residual Ozone gas analysis inside tubs
3. Temperature rise in the tubs
4. Influence of the E-beam to tabs and syringes
5. Air flow analysis inside of unit
6. Performance of the tubs conveying

Dose mapping
on the Side irradiation test (4 time scan)



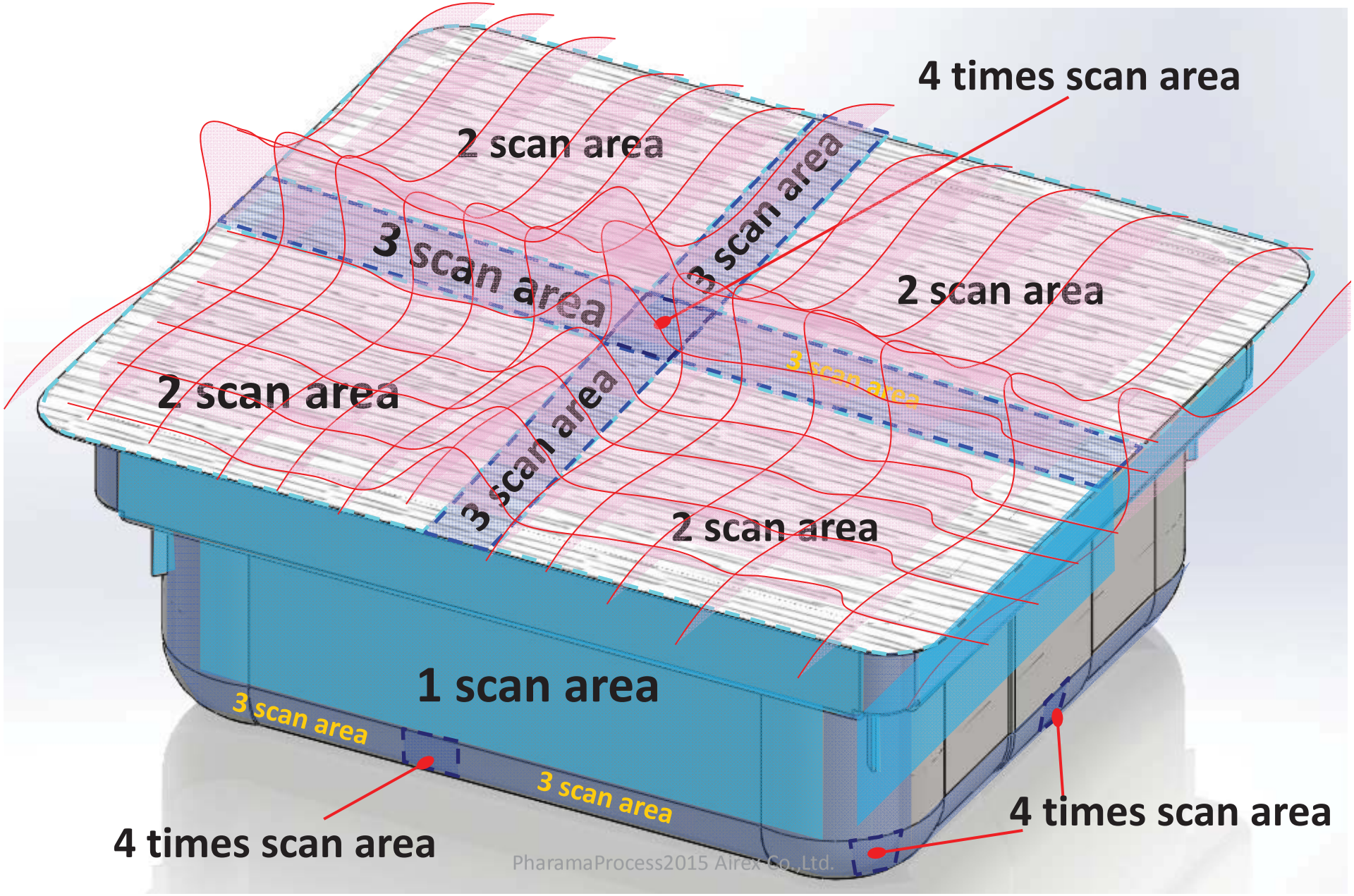
VTR

Cold Spot

[kGy]

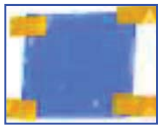
E-beam dose can obtain 25kGy> at every where

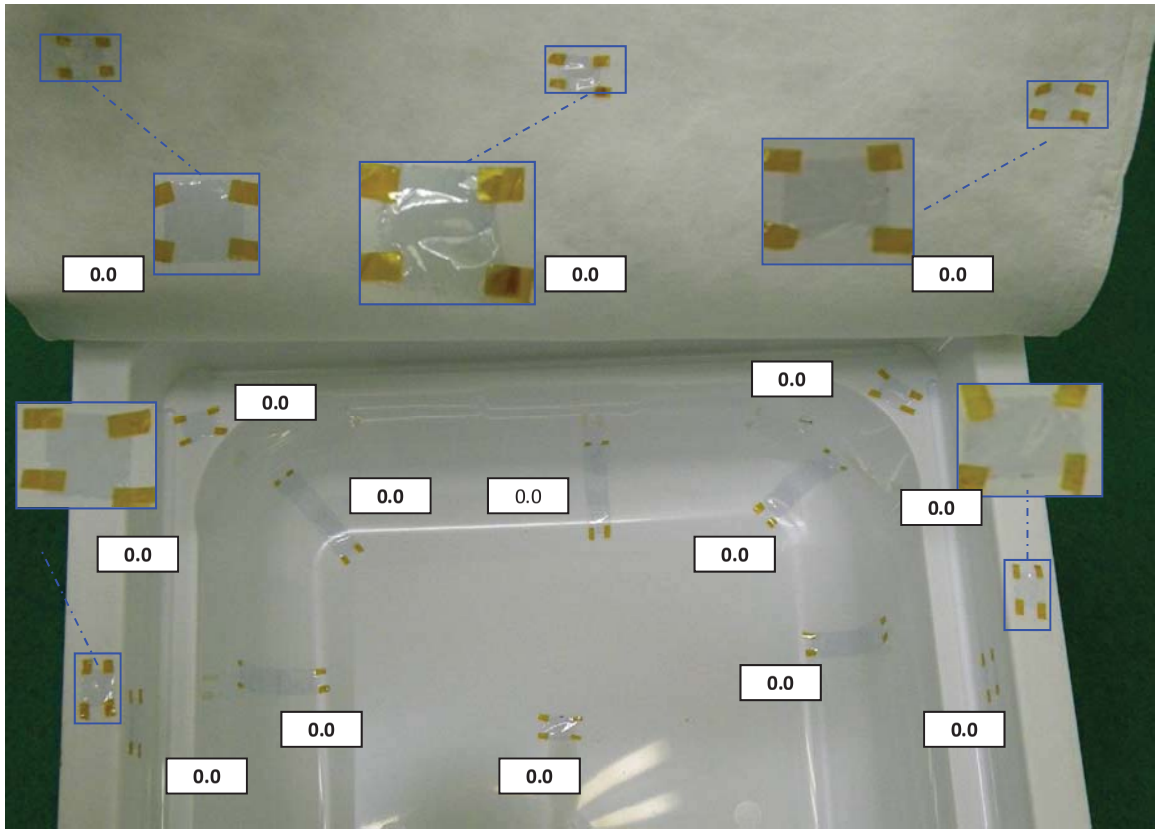
Dose image mapping



Dose mapping
<u>inside</u> tubs (4 times scan)

Outside Surface 58.9kGy





Inside dose are **<u>0 kGy</u>**

Ozone gas analysis inside tubs

＜Ozone tester's Specification＞

- ✓ Manufacturer：Thermo Fisher SCIENTIFIC
- ✓ Model：49i
- ✓ Method：Ultraviolet absorption spectrometry
- ✓ Gas sampling volume：2.0L/min
- ✓ Transportation speed:75mm/sec

＜Measurement procedure＞

①Irradiation→ ②Taking the tub out→ ③Measurement

＜Result＞

Residual Ozone conc.(ppm)			
N1	N2	N3	AVE.
0.004	0.006	0.009	0.006

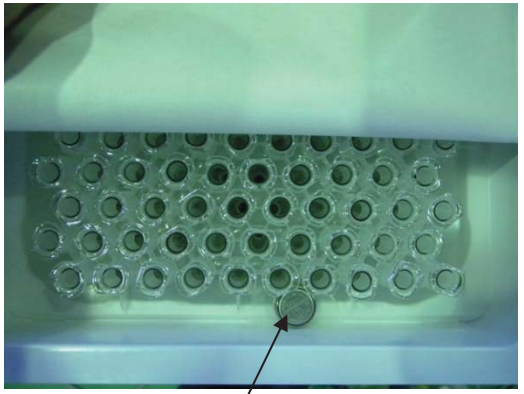
Temperature rise in the tubs

＜Measurement procedure＞

①Prepare thermocouple→

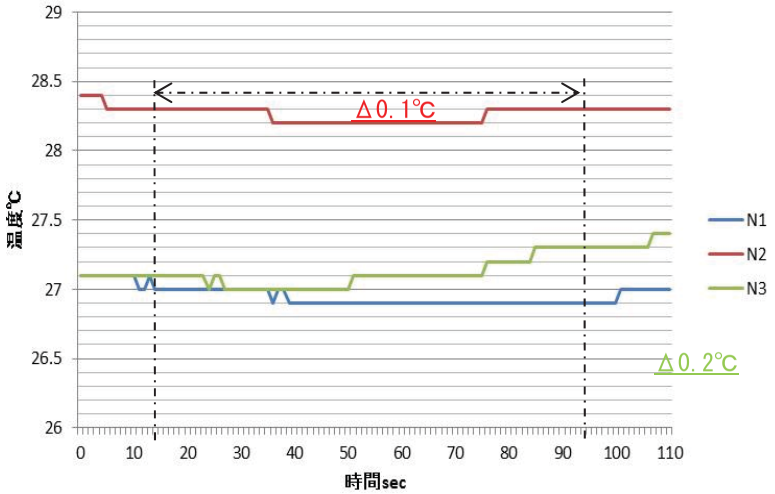
②Irradiation→

③Measurement



Thermo couple

Temperature change(℃)			
P1	P2	P3	AVE.
Δ0.1	Δ0.1	Δ0.2	Δ0.1

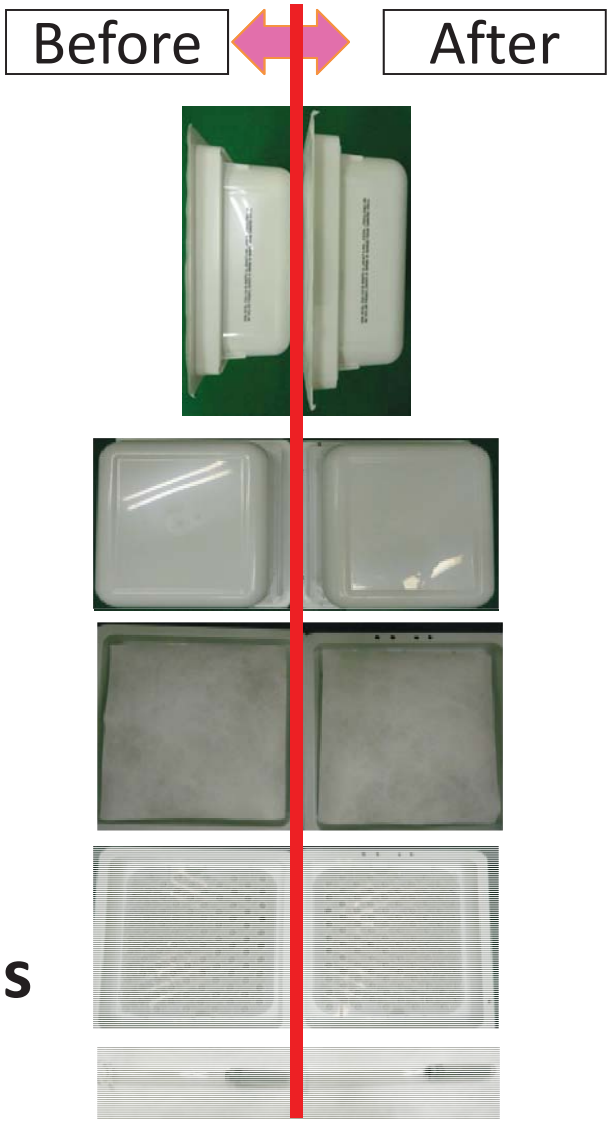


Influence of the E-beam to tabs and syringes

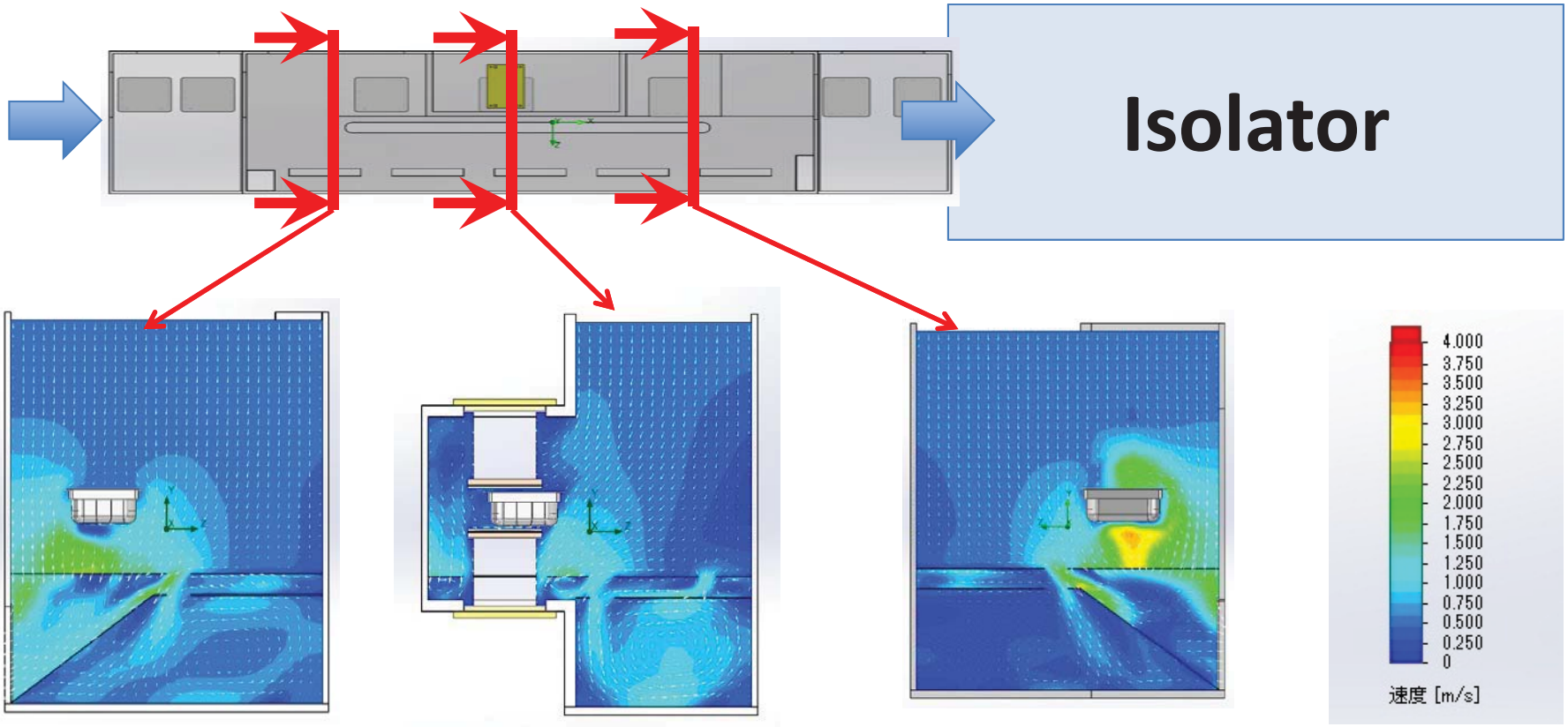
1. Perform E-beam scanning the tubs

2. Compare the surface on the tub and the appearance of the syringe for the tested sample before & after the irradiation, and check whether the E-beam has given any impact on there.

3. Result
→Any Color changes or Deformations



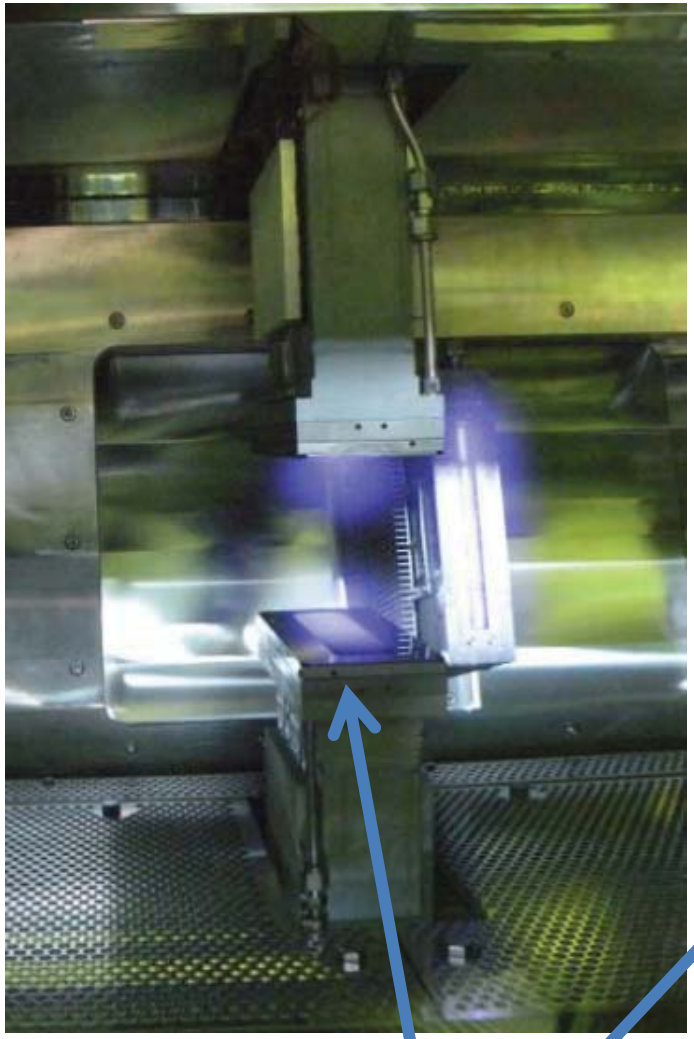
Air flow analysis inside of unit



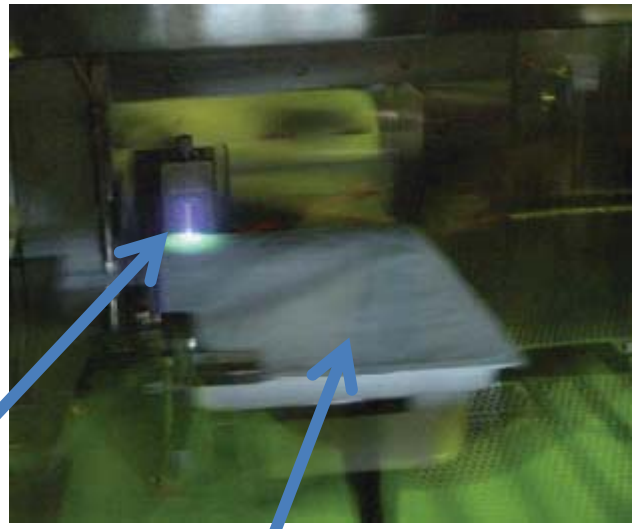
✓ To keep unidirectional air flow during sterilizing

Actual site view

Inside of EB unit



VTR



Tub

EB emitters

Summery of the results

surface decontamination of tub of syringe barrels

1. Smart EB^{TM} system can guarantee the dose rate level of “≧25kGy”
2. EB dose has not penetrated into the inside of the tub
3. Residual ozone concentration in the tubs were “＜0.01ppm (Max) ”
4. Temperature rise in the tubs were conformed “<0.1℃”
5. Any influence of the E-Beam irradiation to the tabs, and to the barrels
6. To keep unidirectional air flow during sterilizing

PHARMAprocess
Innovation Forum in Pharmaceutical Process

Case study of application of Low Voltage EB

Utilizing EB Sterilization for Vial Container into an Isolated Aseptic Filling Line

EB Sterilization for plastic vial containers

- ✓Examples of the surface EB sterilization for syringe containers are rare now
- ✓**No results so far has been found in that of the vial containers**

Effects in the solution

- ✓**Complete In-Line process**
- ✓Quality assurance to be increased.(More effective compared with Off-Line configuration in the management aspect.)
- ✓Easy to perform the sterility validation.

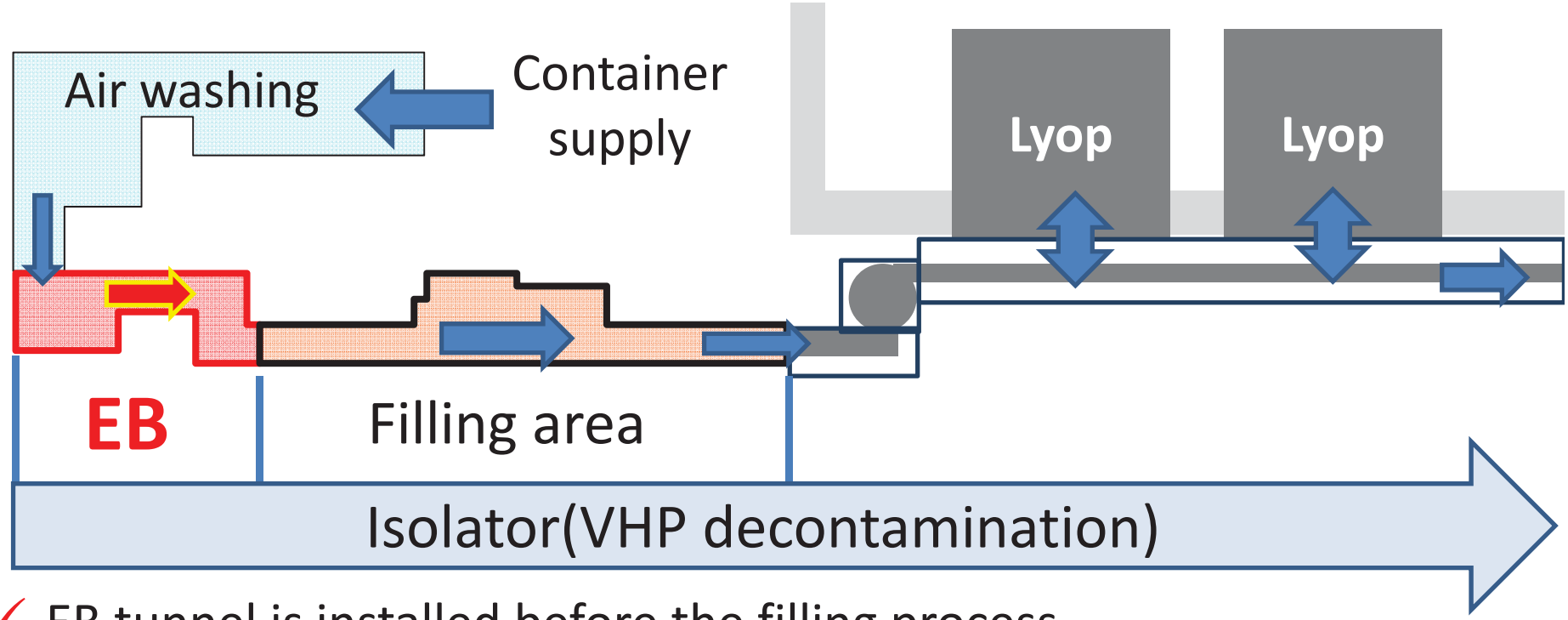
Required Kill rate

- ✓To achieve the Kill rate **25 kGy on whole surfaces**

Issues

- ✓Stabilization of the conveying process
- ✓Establishing of sterility validation
- ✓Deterioration of the containers ?
- ✓Product's change in the nature ?

Layout of vial filling process combined with EB sterilization



- ✓ EB tunnel is installed before the filling process.
- ✓ Vials cleaned by air spray for being transferred to EB
- ✓ Vials are directly sterilized by the 3units E-beams
- ✓ Filled with the liquid product, then will be conveyed to the lyophilizer

Out view of filling process combined with vial EB sterilization

Summery of the results
Utilizing EB Sterilization for Vial Containers

1. System can guarantee the dose rate level of "≧25kGy" on whole surface of vial containers
2. Any influence of the E-Beam irradiation to the vial containers
3. To keep Grade A during sterilizing
4. Speed of vial sterilization is 200 vials/min
5. FDA approved

Lessons Learned

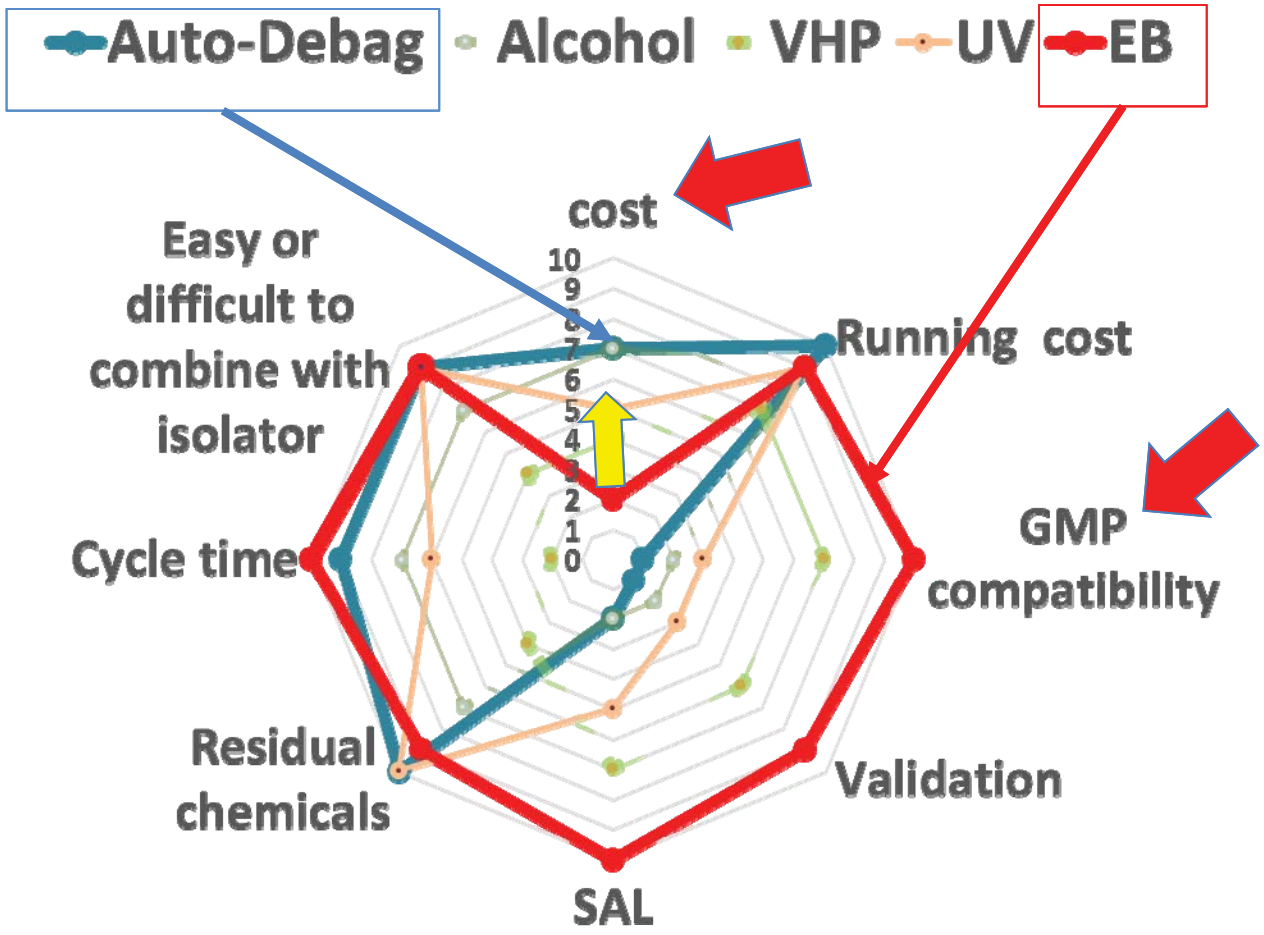
1. The parameters to control the EB dose is simply shown as in below

- ✓Eelectron accelerating voltage
- ✓Eelectron tube current
- ✓Obstacle's moving speed
- ✓Obstacle's distance

2. Low voltage and low current EB has many advantages as in below

- ✓In line process is developed
- ✓Uniform dose mapping
- ✓Low Ozone generation
- ✓Easy keep unidirectional flow and Grade A
- ✓Lead cover is unnecessary

Evaluation of tub surface decontamination to introduce it into an aseptic filling isolator



Summary 1

1. These PFS productions can be expected to grow up in the future
2. It is a crucial issue how to introduce nest syringe tubs into an isolator
3. It has been clear now that contamination risk is involved in if introducing the tubs through mouse hole into the isolator with de-bagging, Then , you need to take a really careful attention in using this method.
4. On the other hand, the best solution for introducing tubs into an isolator would be to use the Low voltage E-beam sterilization system that can perfectly disinfect the outer surface of the tubs.

Summary 2

5. The low voltage E-beam sterilization system can easily shield X-ray, and additionally that has lots of advantages such as the price and the life time.
6. In these days, this E-beam system has been initiated to apply for the sterilization of containers such as for **vials**, In addition, new applications of this system for new technologies like **Regenerative medicine, Nano-film and Microneedles** are started, it would become a key technology for the pharmaceutical manufacturing in the future.

Paradigm shift

Thank you very much for your attention

If you have any questions, please contact me by e-mail

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AiREX