FDA-EMA Aseptic Requirements

Annex 1

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Who is Richard Denk?

Who is…?

RICHARD DENK (SKAN)

ISPE CEO John Bournas and Richard Denk

… last summer – Zermatt / Switzerland

Agenda

1	**Updates on Annex 1**
2	**Highly Potent Aseptic Containment Requirements**
3	**Highly Potent Aseptic Processing. Technical Solutions for operator and product protection**
4	**Question and Answer**

New Draft Annex 1

- Draft send out December 2017
- Total 6000 Comments
- Waiting on the next release
- Reasons for the update. Quality Risk Management, New Technologies like Single Used
  Closed Systems, Disposables, Robotics……
- Operators should not have access to Grade A as they are the highest risk of Contamination

New Draft Annex 1

Barrier Technologies

- 5.15 Isolator or Restricted Access Barrier System (RABS) technologies, and the associated processes, should be designed so as to provide maximum protection of the grade A environment.

Reading the Draft Annex 1 "Barrier Technologies" are the most preferred solution to protect the sterile product from the Operator and Environment.

What are the major reasons for that!

RABS versus Isolator

RABS

- Surrounding Grade B
- Decontamination together with the surrounding room

Isolator

- Surrounding Grade D or better
- Integrated Decontamination System

Protection of Grade A Environment

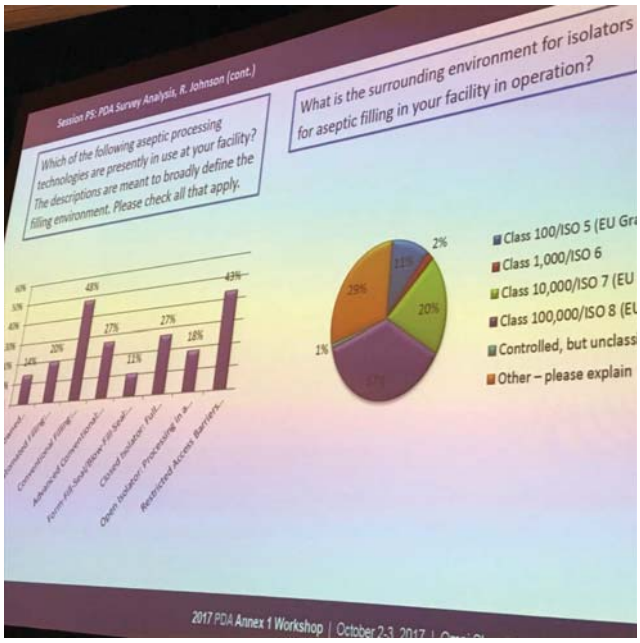
Facilities

Conventional Aseptic Processing
Highest risk of human intervention

RABS «Restricted Access Barrier System»
Reduced risk of human intervention

Isolators
Lowest risk of human intervention

Protection of Grade A Environment



PDA Survey
Introduced during the Annex 1 Workshop in Washington DC 2018

Protection of Grade A Environment

Facilities

Conventional Aseptic Processing
Highest risk of human intervention

Conventional Solution

- Operator have access to critical areas
- No Barrier
- Contamination Risk on the Curtain.
- Intensive Training and Monitoring
- Technology should be replaced to better ones.

Protection of Grade A Environment

RABS " Restricted Access Barrier System"

- Operator have access to critical areas
- Barrier but doors can be opened
- Decontamination inside of the door before closing.
- Intensive Training and Monitoring
- More and more poor designed RABS on the market.

RABS «Restricted Access Barrier System»
Reduced risk of human intervention

Protection of Grade A Environment

Serious FDA Warning Letter issued to European Manufacturer of sterile Drugs, Part 2

In case of serious violations of GMP requirements, the American FDA issues a Warning Letter to the company in question. The company must react to this within 15 working days and submit a corrective action plan to the FDA.

Two aspects were criticized with regard to 21 CFR 211.113: "inadequate aseptic techniques" and "mechanical faults during media fill". The inspector supported the "inadequate aseptic techniques" with a video recording of a line set-up followed by the filling. It showed the following incorrect behaviour:

- an employee handed a pen to another employee directly above the stopper bowl
- an employee was sitting on the floor during line set-up and did not change his gown afterwards
- an employee was leaning against the cleanroom wall
- an employee left the door of an RABS open for a considerable time during the filling without working in the immediate area

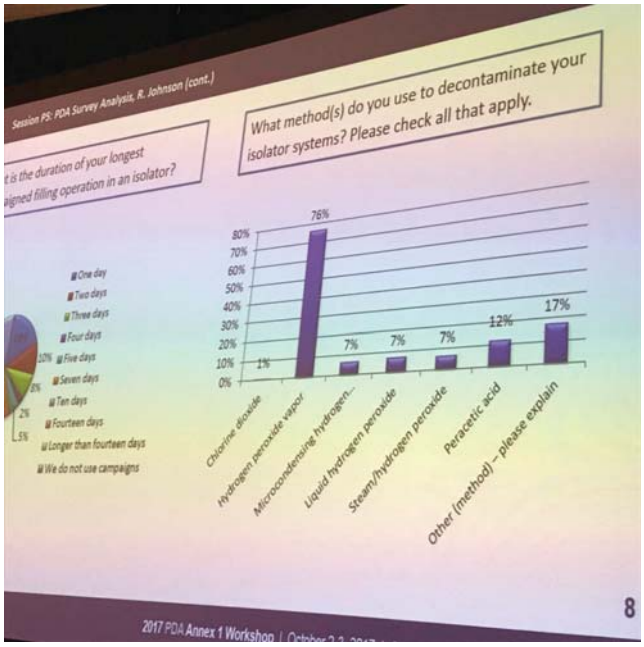
Protection of Grade A Environment

Isolators
Lowest risk of human intervention

Isolators

- Operator have no direct access to critical areas
- Validated and accepted decontamination system with
  H_2O_2
- Reduced Clean Room requirements outside of the Isolator (ISO 7/8 Class C/D)
- Less Gowning of the Operator
- More and more poor designed Isolators on the market.
  High risk to the product

Protection of Grade A Environment



PDA Survey
Introduced during the Annex 1 Workshop in Washington DC on the 2nd and 3rd of October

New Draft Annex 1

Barrier Technologies

- 5.16 The design of the RABS or isolator shall take into account all critical factors associated with these technologies, including the quality of the air inside and the surrounding area, the materials and component transfer, the decontamination, disinfection or sterilization processes and the risk factors associated with the manufacturing operations and materials, and the operations conducted within the critical zone.

Now let`s have a more detailed look on that!

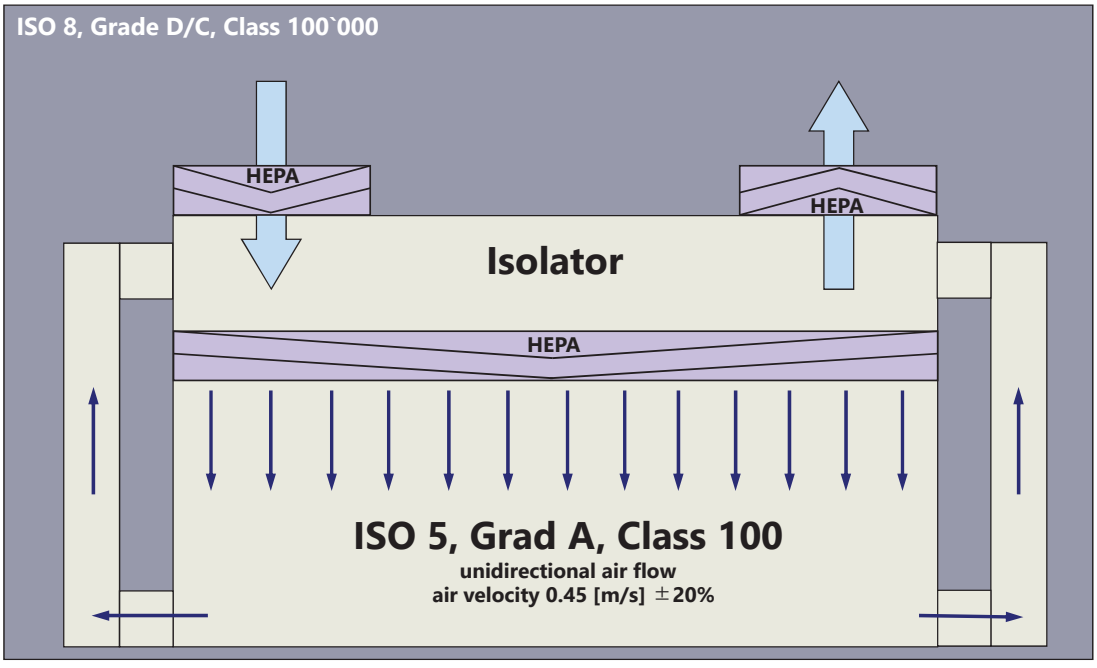
New Draft Annex 1

Barrier Technologies

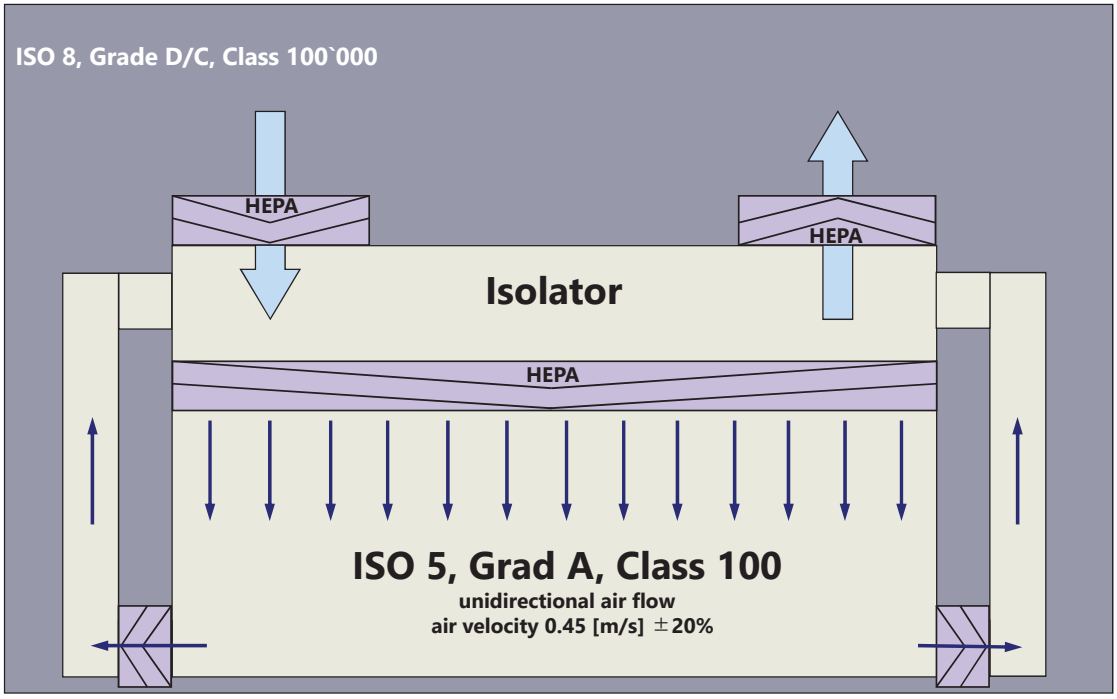
- 5.17 The critical zone of the RABS or isolator used for aseptic processes should meet grade A with unidirectional air flow. Under certain circumstances turbulent airflow may be justified in a closed isolator when proven to have no negative impact on the product. The design of the RABS and open isolators should ensure a positive airflow from the critical zones to the surrounding areas.

What does this mean!

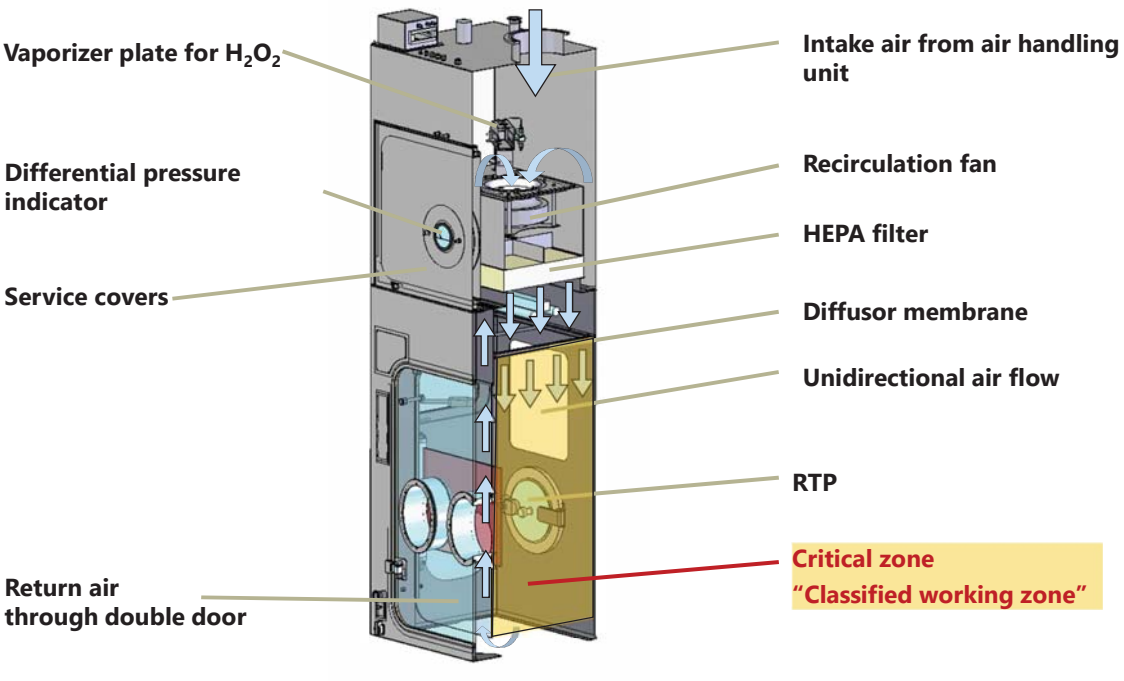
Grade A Unidirectional Air Flow



Grade A Unidirectional Air Flow (Aseptic Critical Zone)



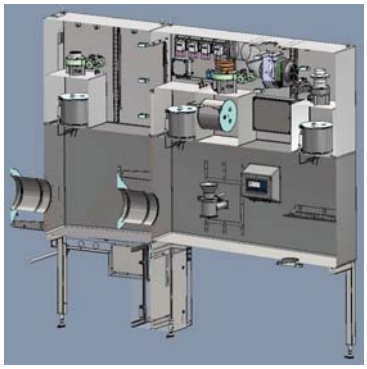
Grade A Unidirectional Air Flow (Aseptic Critical Zone)



Grade A Unidirectional Air Flow (Aseptic Critical Zone Filling Line)

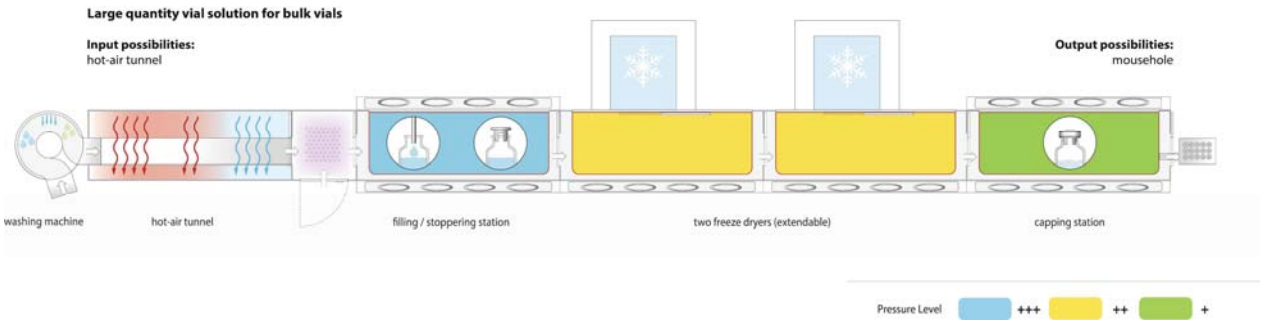
- Unidirectional airflow shall not be disturbed above open container like vials, syringes etc.
- Air should not return from areas below to the filling zone or open containers.

Grade A - Air Flow (Aseptic Critical Zone Dispensing API)



- Weighing and Dispensing of Aseptic Powders (API)

Positive Air Flow



- Positive air flow from the critical zone to surrounding areas inside the isolator
- Positive air flow from inside the isolator to surrounding areas.

New Draft Annex 1

Barrier Technologies

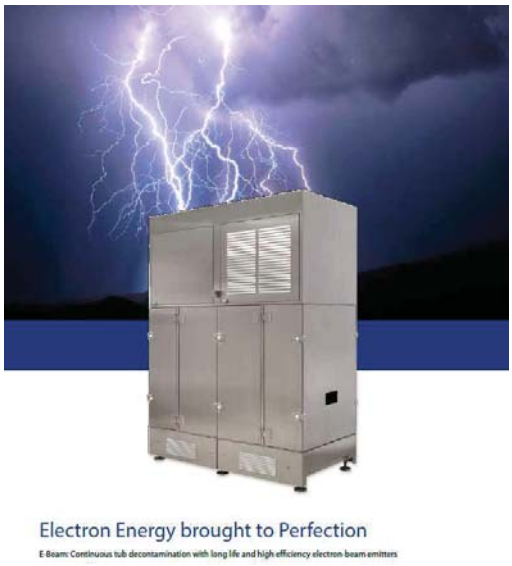
- 5.16 The design of the RABS or isolator shall take into account all critical factors associated with these technologies, including the quality of the air inside and the surrounding area, the materials and component transfer, the decontamination, disinfection or sterilization processes and the risk factors associated with the manufacturing operations and materials, and the operations conducted within the critical zone.

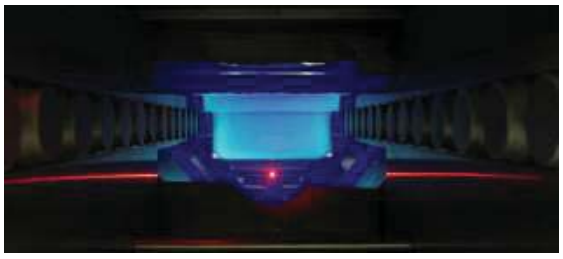
Now let`s have a more detailed look on that!

Materials and Component Transfer

- Dry heat Tunnel (automated/validated)

Materials and Component Transfer





- E-Beam Tunnel (automated/validated)

Materials and Component Transfer

- H_2O_2 Material Air Lock (validated)
- Rapid Transfer Port (validated)

Materials and Component Transfer

- Stopper Processor/Transfer

There will be a PDA Technical Report by the End of the Year.

Disinfection and Decontamination

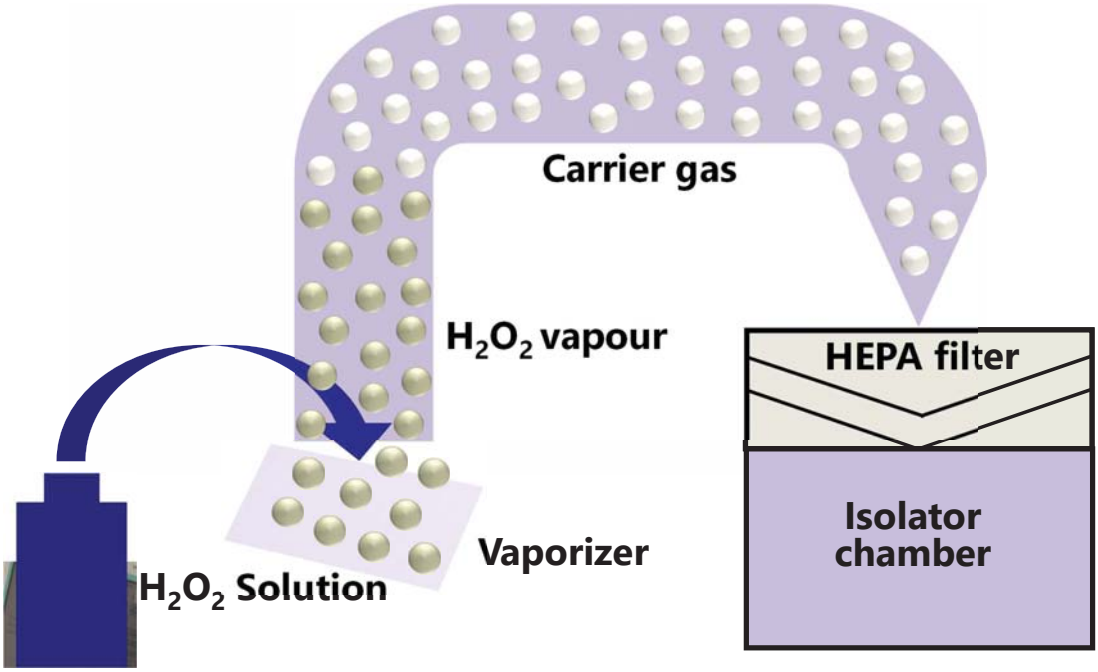
Cleaning/Disinfection

- Requirements get higher in aseptic processing
- Validation of Cleaning and Disinfection

H_2O_2 Decontamination

- Process well established
- Isolator Technology
- Vaporized Hydrogen Peroxid vH_2O_2

Disinfection and Decontamination



Disinfection and Decontamination

- **FDA: ASEPTIC GUIDELINE**

„ Cycles should be developed with an appropriate margin of extra kill to provide confidence in robustness of the decontamination processes. Normally, a four- to six-log reduction can be justified depending on the application. The specific BI spore titer used and the selection of BI placement sites should be justified."

→ …has to be understood as a total kill of BI inoculated at 10^4 to 10^6 spores / carrier

Disinfection and Decontamination

RESEARCH ARTICLE

Effect of Carrier Materials on the Resistance of Spores of *Bacillus stearothermophilus* to Gaseous Hydrogen Peroxide

A Potent and Safe H_2O_2 Fumigation Approach

- **FDA: ASEPTIC GUIDELINE**

P46

APPENDIX 1: ASEPTIC PROCESSING ISOLATORS

D. Decontamination

2. Efficacy

The decontamination method should render the inner surfaces of the isolator free of viable microorganisms. Multiple available vaporized agents are suitable for achieving decontamination. Process development and validation studies should include a thorough determination of cycle capability. The characteristics of these agents generally preclude the reliable use of statistical methods (e.g., fraction negative) to determine process lethality (Ref. 13).

P.54 References

13. Sigwarth, V. and A. Stark, "Effect of Carrier Materials on the Resistance of Spores of Bacillus stearothermophilus to Gaseous Hydrogen Peroxide," PDA Journal of Pharmaceutical Science and Technology, Vol. 57, No. 1, January/February 2003.

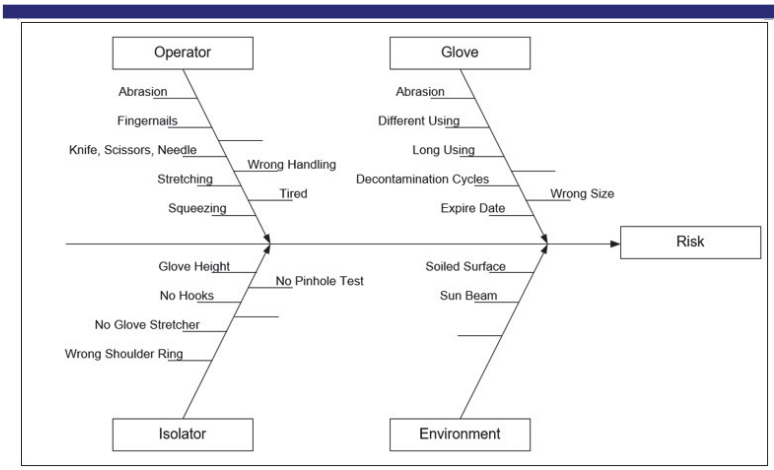
New Draft Annex 1

Barrier Technologies

- 5.21 Glove systems, as well as other parts of an isolator, are constructed of various materials that can be prone to puncture and leakage. The materials used shall be demonstrated to have good mechanical and chemical resistance. Integrity testing of the barrier systems and leak testing of the isolator and the glove system should be performed using visual, mechanical and physical methods. They should be performed at defined periods, at a minimum of the beginning and end of each batch, and following any intervention that may affect the integrity of the unit.

Now let`s have a more detailed look on gloves!

Gloves



There will be a PDA Paper about Quality Risk Management for Gloves by the End of the Year.