ISOLATOR TECHNOLOGY MANUFACTURING

Design…Qualification…Experience

Complimentary WEBINAR
Wednesday, December 12, 2007

This webinar presents the methods used at Baxter's Halle, Germany facility for the design and validation/qualification of isolators used for the aseptic production of sterile drug products.

Featured Speakers:
Frank Generotzky
Corinna Schneider

Speakers

Frank Generotzky

Director of Technology and Engineering

Mr. Frank Generotzky is recognized as an expert in the field of aseptic manufacturing of parenteral products, and is a frequent presenter at several European Conferences and ISPE Meetings for Sterile Drug Manufacturing. He earned his Diploma for Pharmaceutical Engineering from the University of Applied Science Lippe / Höxter in Germany.

Since 1996 Frank has designed and installed several production-lines in standard Cleanroom Technology as well as in Isolator Technology at Baxter's facility in Halle, Germany. Starting in 2001 Frank headed the production department for sterile cytotoxic drugs (liquid, powders and lyophilisates).

In his present role, Frank is responsible for the strategic development of Pharmaceutical Technology in Halle. He is leading a team of 13 engineers, who design, plan and realize the investment projects in Halle according to customer and market requirements.

Corinna Schneider

QA Specialist GMP Compliance

Ms. Corinna Schneider, is recognized as an expert in the field of sterile drug products produced by aseptic processing. She developed and implemented a complex VHP sterilization process for isolators and equipment parts in Halle/Germany and presented this method at pharmaceutical conferences and workshops in Europe and in the US. She trained local regulatory inspectors in VHP cycle development and presented her concept several times to the FDA. Ms. Schneider earned her Diploma for Pharmaceutical Engineering from the University of Applied Science Lippe / Höxter in Germany.

From 1995 to 2000 she headed the Microbiological Quality Control Lab and focused on environmental monitoring, validation of aseptic processing, and microbial identification. In her current position in Quality Assurance she is responsible for GMP compliance, internal and external auditing, and several compliance projects to improve the effectiveness of the quality management system.

Topics

Isolator Design Criteria

- Different Isolator Applications
- Process Development

Qualification of “critical” Design Features

- Airflow Investigation Near Mouseholes
- Isolator Integrity
- VHP Sterilization

Isolator Technology versus Conventional Cleanroom

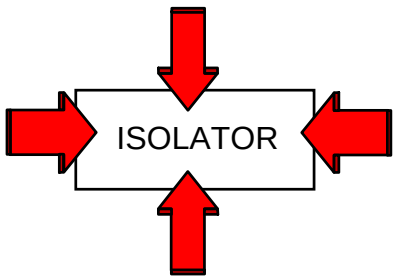
Designing Isolators

Different Isolator Applications

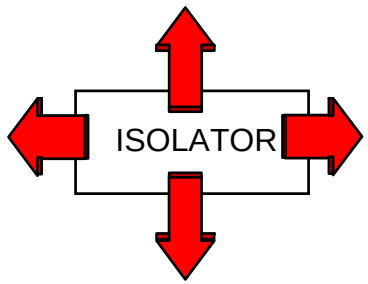
- Isolators for compounding and handling of toxic powder

Sterilizable isolators for aseptic processing

- Negative pressure isolators (-50 Pa to -150 Pa)



Positive pressure isolators (25 Pa to 100 Pa)



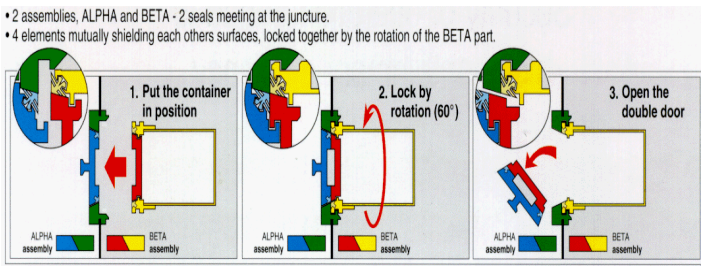
- Isolator for manual sterile operations
  => “Closed Isolators”

Isolators on automatic filling machines
=> “Open Isolators”

Different Isolator Applications
Requirements on Containment Isolators

- Generally operated under negative pressure to ensure max. operator safety
- Typically classified as ISO 7 (Class 10,000 at rest, Grade C)
- They must not exchange air with the surrounding environment (except through a HEPA filter)
- Equipped with nitrogen supply if required
- All materials exiting the isolator must be cleaned or contained
- They must be cleanable in a reproducible and quantifiable manner; swab-tests and tracer substances should be used during qualification

Different Isolator Applications
Containment Isolator for Compounding



- negative pressure of -100 Pa, electronically controlled
- interlocked isolator door after start of operation
- visual display indicates permanent status of the isolator
- radii in the isolator chamber >15 mm, chamber and fittings require gradient of 2 %
- tightness test before each process
- glove test prior to manufacturing
- “push – push” system for exhaust air filters
- integrated rapid transfer ports (RTP) for loading and discharging without compromising the surrounding

Different Isolator Applications
Requirements on Isolators for Aseptic Processing

- They must not exchange air with the surrounding environment except when that air passes though a HEPA filter
- Typically classified as ISO 5 (Class 100, Grade A)
- These units are typically operated under positive pressure and are subject to sterilization procedures prior to use
- They must be sterilized in a reproducible manner (VHP)
- All materials that enter the isolator must be sterilized and must enter either directly through a decontaminating or sterilizing system or via a rapid transfer port

Different Isolator Applications
„Closed Isolator“ for Aseptic Operations

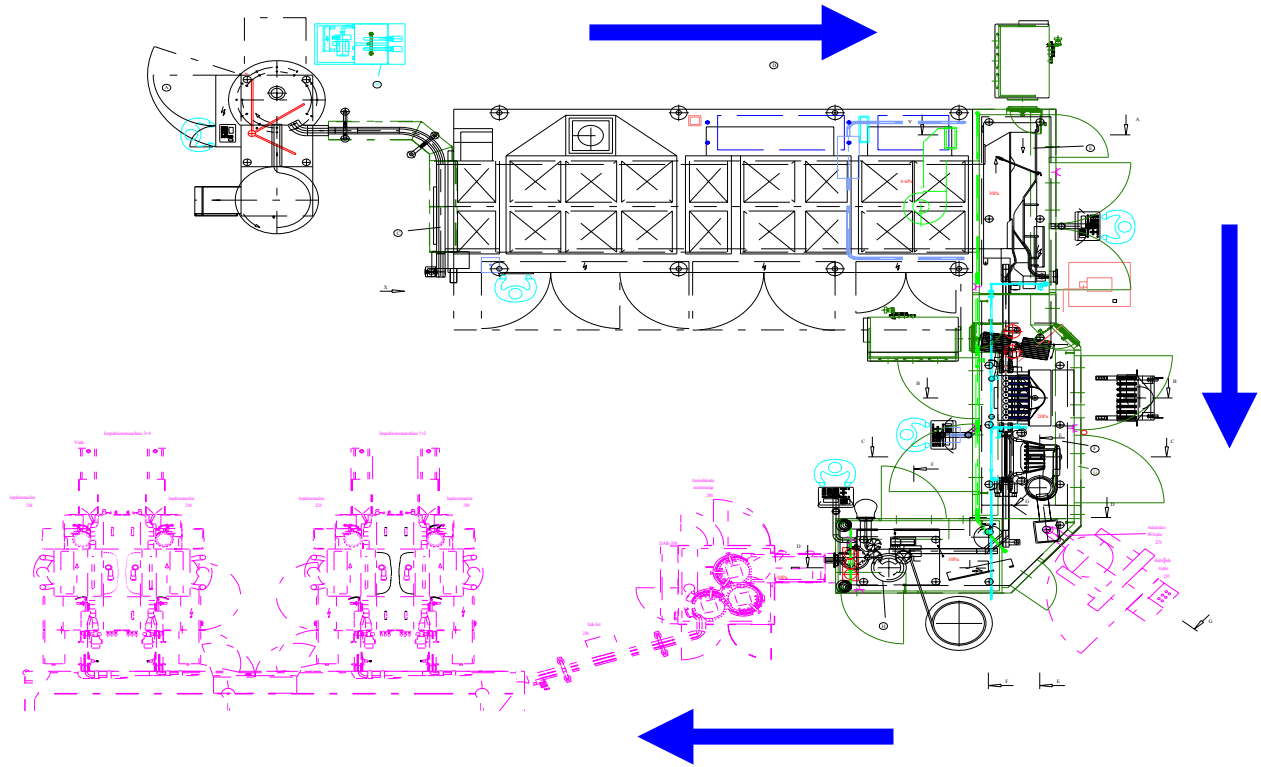
- “Closed Box” with HEPA filter H14
- discontinuously loading and discharging
- all transfer processes are conducted via aseptic connections (RTP, SIP)

Example: Isolator for Aseptic Filling

- Isolator:
  - Grade A, (ISO 5)
  - VHP sterilization
  - positive pressure (+ 100Pa)
- “Double Door” port-system for aseptic discharging of the isolator

Different Isolator Applications

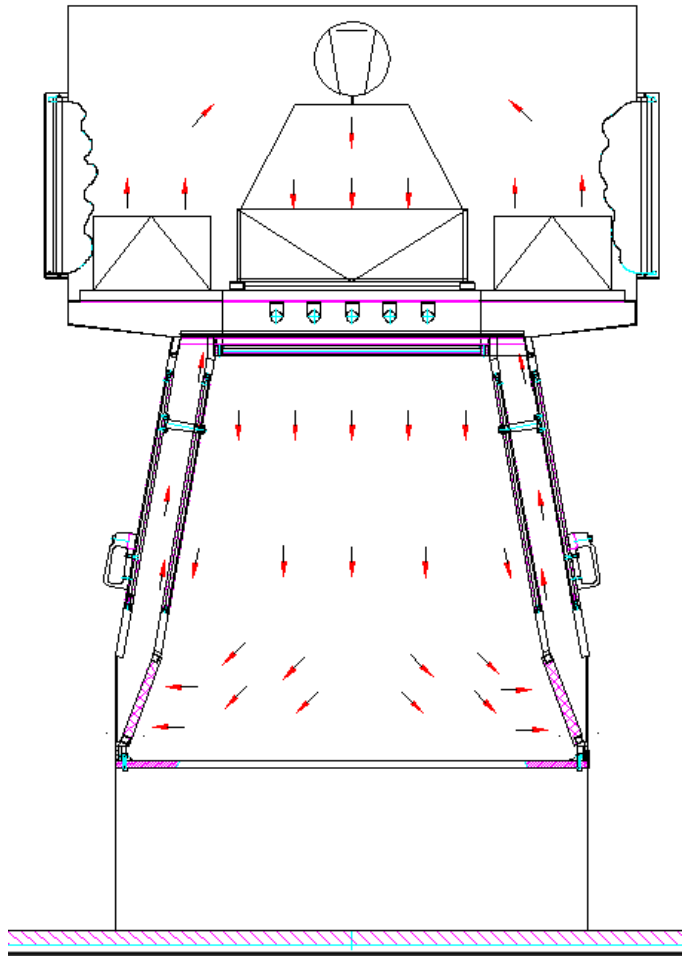
„Open Isolators“ for continuous Aseptic Operations



Different Isolator Applications

„Open Isolators“ for continuous Aseptic Operations

- Continuous supply with materials during operation, while maintaining Grad A ISO 5
- Unidirectional airflow of 0.45 m/s (+/- 0.1m/s)
- Safety features:
  - double wall design
  - filtration of recirculated air
  - pneumatic gaskets (controlled and alarmed)
  - CIP for containment and air ducts
  - emergency mode including pressure reversal



Different Isolator Applications

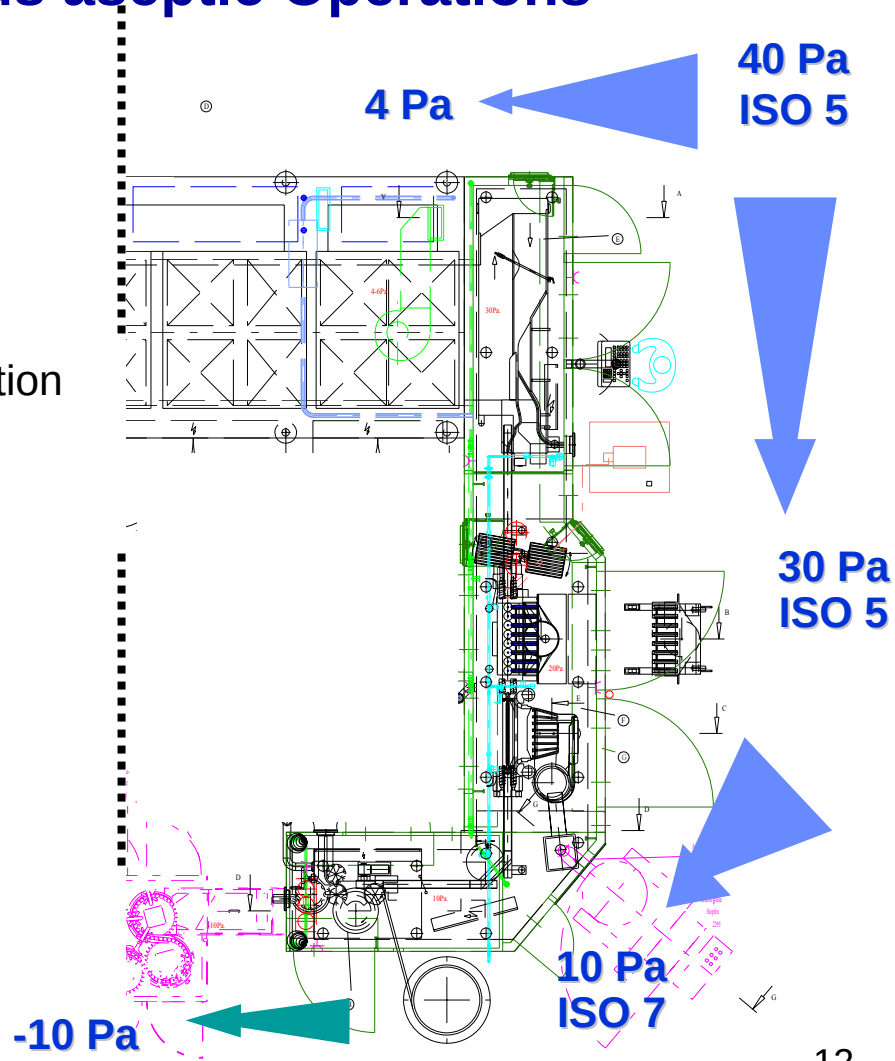
„Open Isolators“ for continuous aseptic Operations

- Classifications:
  Filling: ISO 5 / Grade A
  Capping: ISO 7 / Grade C
  Support Area: ISO 8 / Grade D

- VHP sterilization for ISO 5 / Grade A
  - stopper bowls included in VHP sterilization
  - CIP / SIP for filling equipment

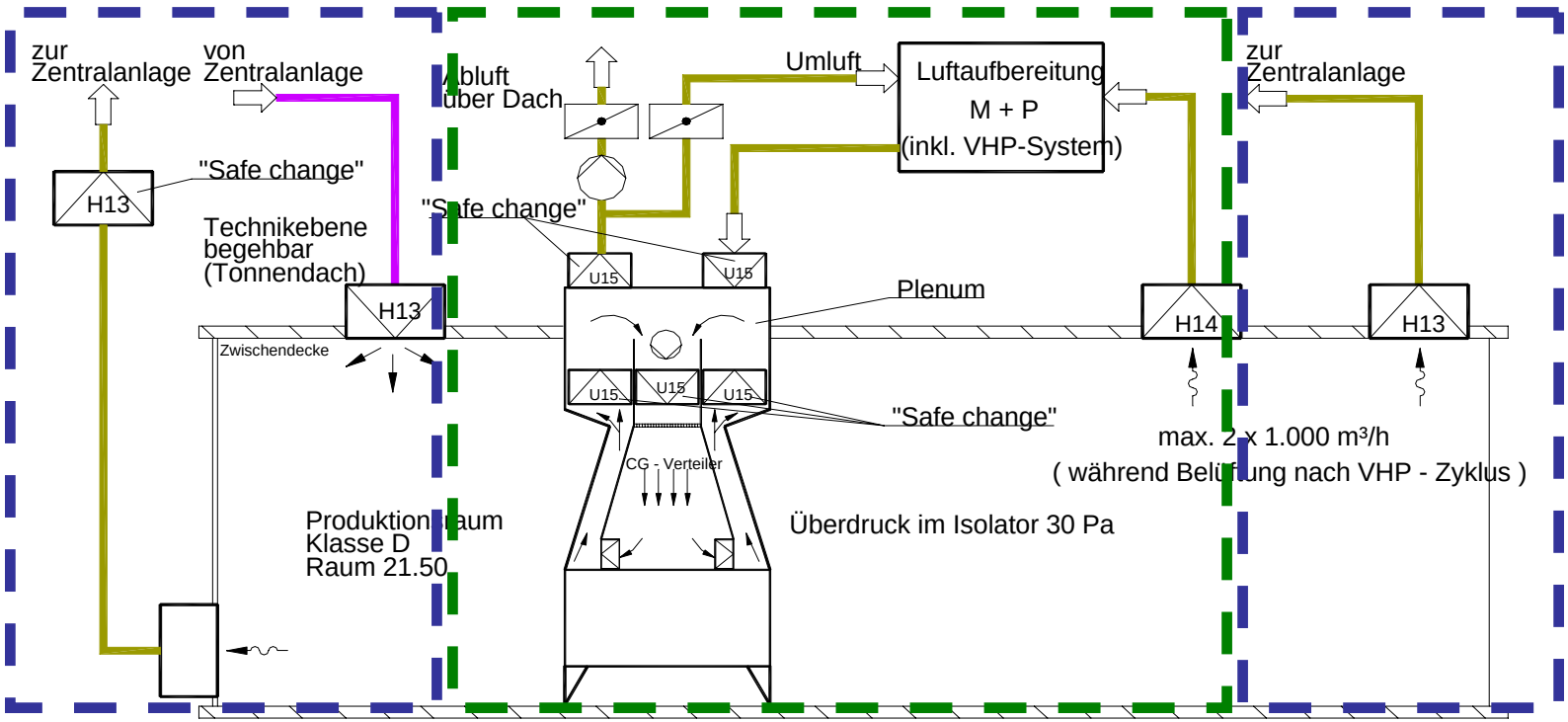
- Caps and capping equipment:
  - no sterilisation
  - controlled disinfection

- Environmental Monitoring:
  - particles 0.5µm, 5.0µm
  - viable air monitoring
  - surfaces (RODAC)
  - Temp, diff. pressure, relative humidity



Different Isolator Applications
Example: Design HVAC

- Isolators should be equipped with independent HVAC systems



Configuration of an Isolator

Mock-Up and Risk Analysis

Process	IPC / Monitoring	Qualification / Validation
Cleaning	CIP Reinigung Isolatoren und produktb. Teile	Temperatur, Druck Reinigungszeit Rückstände	Reinigungseffizienz
Changeover	Abfüllmaschine Justage Initiatoren Handschuhtest Beladen Isolatoren	SOP´s reproduzierbare Positionierung Beladung Grenzwerte f. Dichtigkeit	Validierung Beladung Grenzwert Druckabf. Sterilisation von: - Stopfen - produktberühr. Teile - VHP Isolator
Testrun	Justierung Kalibrierung Filtertest	SOP´s Grenzwerte IPK Waage	Formatbezogene Vorgaben zur Ma- schineneinstellung
Leak tightness	Integrität Isolator Dichtigkeit SIP	Grenzwert Druckabfall Zeit	Qualifizierung der zul. Dichtigkeit
Sanitization **Sterilization**	Abfüllmaschine (SIP) Isolator (VHP)	Temperatur , Druck, Menge, Zeit, Differenz- druck	Validierung der VHP Sterilisation und SIP
Set-up **before start**	Abfüllmaschine Ausrüstung IPK	MA Qualifizierung	Qualifizierung Reinraums
Manufacturing		Füllmenge Monitoring (physik. /mikrobiologisch) v (Luft) p (diff.), T (Luft) rel. Feuchte (Luft), 100% Inspektion	Qualifizierung der Transfersysteme

Validation of aeptic processing and Cleaning Validation

Process Development
Mock-up Study (Model Scale 1:1)

- determination of the size; use 1:1 drawings of all machines in the isolator
- simulate loading (tools, agar, probes …)
- determine positions for particle counting and viable air monitoring
- determine ports for validation purpose (t, p, rel. humidity, NIR, filter integrity …)
- determine position for gloves carefully
- define interfaces for HVAC, media, computer-systems, supplier of filling-machine …
- use CIP / SIP where ever possible, reduce manual handling

Simulation of all operations in the isolator

- change of product contacting parts
- simulate monitoring
- adjustment of sensors or leadings
- solve technical problems (jam of vials or stoppers ..)

Qualification of an Isolator

Qualification of “critical” Design Features

Isolators require a high level of qualification and validation with focus on:

- **Airflow Investigation Near Mouseholes**
- **Isolator Integrity**
- **Vaporised Hydrogen Peroxid (VHP) Sterilization**

Inspectional Findings: Isolator Qualification
(R. Friedmann & J. Agalloco*)

- **Dynamic filling line conditions not evaluated**. Filling line was not in operation during smoke studies.

- **Smoke studies did not evaluate the pressure changes** caused by introducing a glove into the isolator, or retrieving the glove from the isolator.

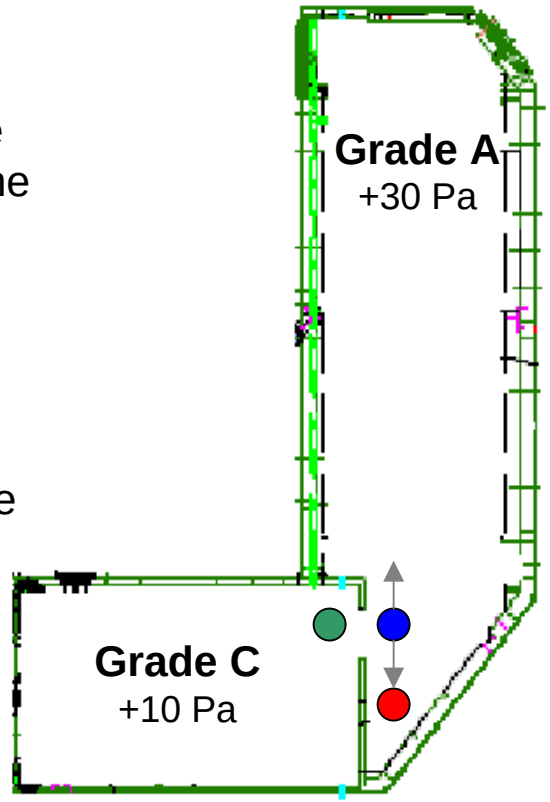
- There was no data documenting isolator airflow parameters, such as **air pressurization and velocities**, during smoke studies. The acceptability of the lower air pressure limit was not evaluated.

* Presentation by R. Friedman & J. Agalloco; Agallaco & Ass., NJ 2004

Qualification of Isolator Integrity near Mouseholes

PDA TR 34 Appendix B L-R Method

- In this test a **concentration of particles** with a mean size of approximately 0.5 µm is generated within 5-10 cm of the isolator opening.
- The particle concentration should be in the range of 100,000-1,000,000 per m^3.
- An **electronic particle counter** calibrated to the 0.5µm particulate size is used to scan the opening from inside the isolator. The particle counts observed on the isolator side of the opening should not be significantly different from the **background count** at the same location.



In the measuring location (critical region) the number of particles per unit volume should be less than 0.01% of the initial challenge level to assure absence of airborne microbial contamination under routine operational conditions.

Isolator Integrity
Leak-Testing

- Pressure Hold Test
  - positive pressure isolators
  - Test pressure: operating pressure x 2
  - less than 0.5% of the total volume of the isolator per hour is acceptable
- Pressure Drop Test
  - negative pressure isolators
  - Test pressure: -200Pa
  - max. 50 Pa rise of pressure 6 min is acceptable
- Gloves (Hypalon 0.8 mm):
  - Test pressure: 500 Pa after “stressing” the glove
  - less than 50 Pa in 4 min
  - supported by physical / microbial qualifications and trend analysis

VHP Sterilization

Examples of Inspectional FDA Findings (R. Friedmann & J. Agalloco)

- "Decontamination validation cycle study **did not evaluate the actual commercial cycle**. Validation runs were conducted at levels which often exceeded the proposed hydrogen peroxide decontamination concentration setpoint of *** mg/l by as much as 30 - 90%."

- "**No actual measurements of concentration of sterilant that circulated within the expansive isolator**. Only indirect measurements (e.g., internal VHP 1001 generator results for flow rate and H2O2 mg/l) to monitor VHP concentration."

- "**The VHP decontamination studies for the isolator did not provide an adequate challenge of the cycle to determine the weak points of VHP distribution/ penetration** (i.e., where air flow is most variable or potentially compromised)."

* Presentation by R. Friedman & J. Agalloco; Agallaco & Ass., NJ 2004

VHP Sterilization

Examples of Inspectional FDA Findings (R. Friedmann & J. Agalloco)

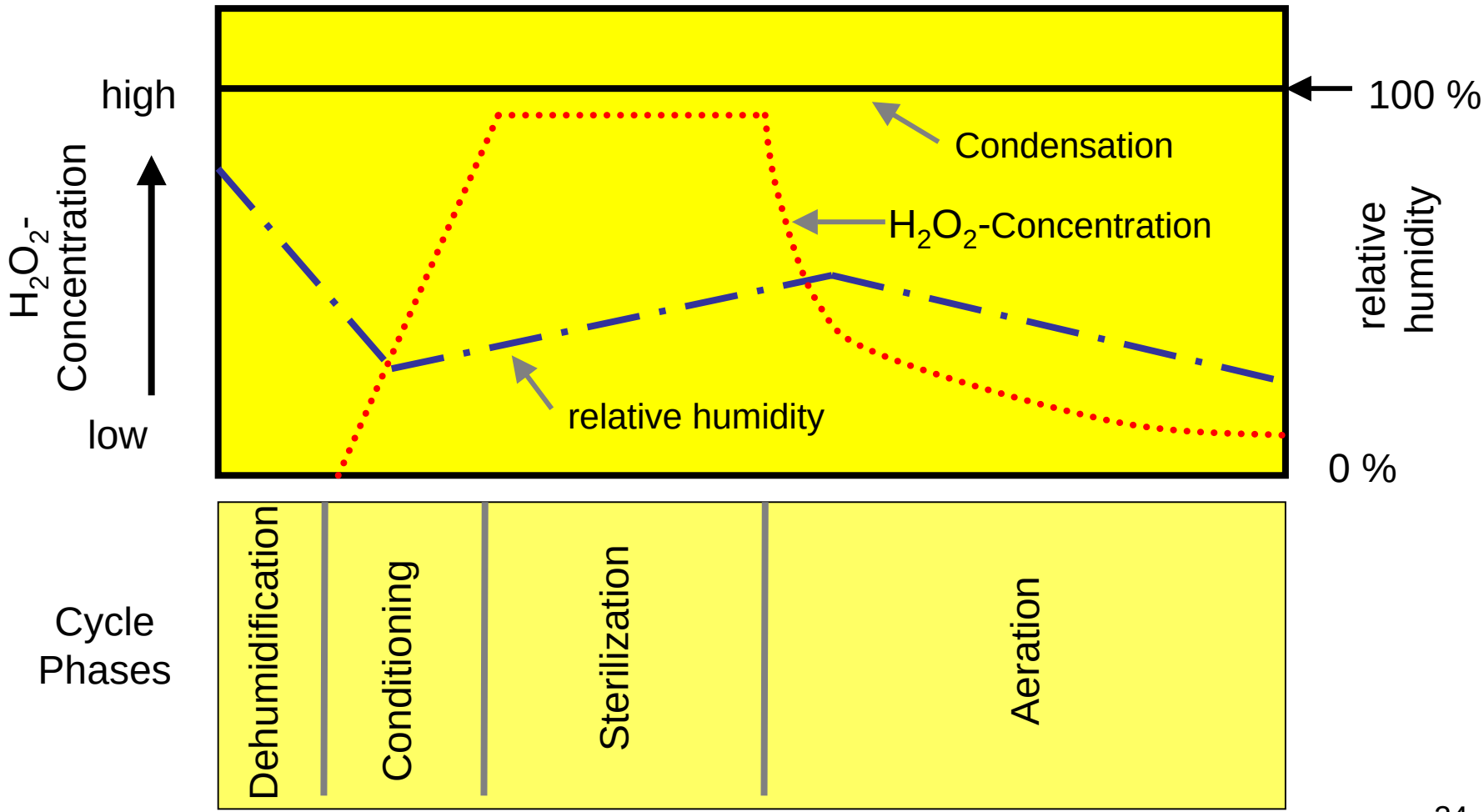
- **"Many worst-case locations were not evaluated**. Some examples:
  - Between fingers of installed isolator gloves. Four of nineteen filling isolator gloves were evaluated, and only at the outside of the cuff
  - Occluded surface created by folding the glove into its gauntlet (sleeve) during the VHP cycle
  - the stopper bowl locations of most concern (e.g., low point in the bowl)"

- **"VHP study inappropriately applied fraction negative mathematics** to the vaporized hydrogen peroxide process. The fraction negative mathematical approach is fundamentally premised on essentially **uniform distribution of the sterilant, and use of replicates**."

* Presentation by R. Friedman & J. Agalloco; Agallaco & Ass., NJ 2004

VHP Sterilization

VHP Process



VHP Sterilization

VHP Cycle Development

Sterilization Target:
12-log-Reduction = overkill Process

- Measurement of Process Parameters
- Use of Biological Indicators
- Determination of D-Value

VHP Sterilization
Process Parameters

Temperature
- Determination of temperature differences in the Isolator
- Reproducibility of temperature profiles

Relative Humidity
- Development of conditioning phase:
  Determination of time to reach max. relative humidity
- Reproducibility of RH-profile

VHP-Concentration
- Development of conditioning phase:
  Determination of time to reach max. VHP concentration
- Reproducible run of concentration curve
- Definition of “worst case” environmental conditions:
  low gas concentration at low temperatures in the isolator

VHP-Distribution
- Uniform distribution of VHP with chemical indicators

VHP-Flow
- Unidirectional/turbulent VHP Flow, airflow pattern

VHP Sterilization
Biological Indicator

Type

- *Geobacillus stearothermophilus* ATCC 12980, 10^6 spores on stainless steel carrier

Locations

- 5 - 10 BIs per m^3
- Masked locations like fingers or crinkles of gloves or rails for stoppers
- Documented rationale for each BI location
- Short cycles for identification of **worst case locations** => non-sterile BIs

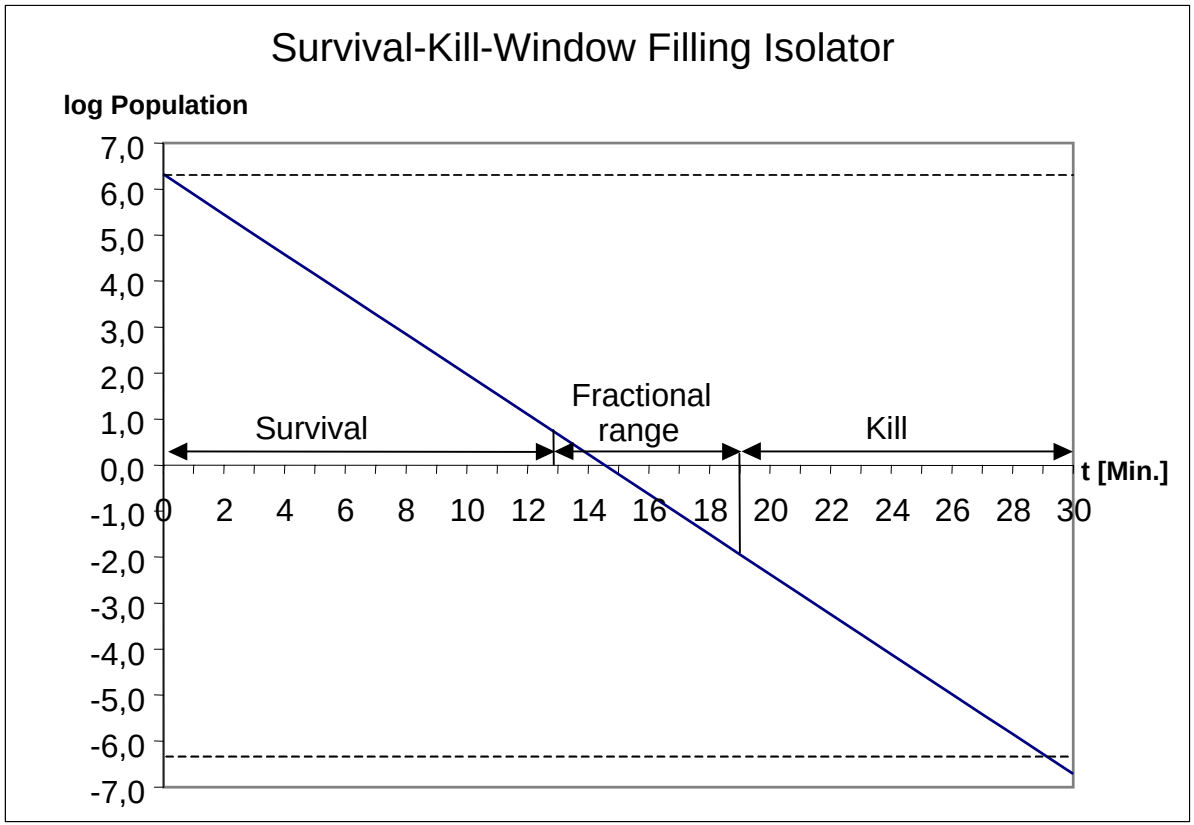
VHP Sterilization
Biological Indicator

No correlation between process parameters and results of BIs !

Determination of worst case locations exclusively based on kill-pattern of BIs !

VHP Sterilization

Determination of D-value



Sterilization Time for a 12-log-Reduction (worst case location):

Sterilization Time$_{(\text{worst case})}$ = D$_{\text{worst case}}$-Value x 12 = X min

VHP Sterilization
Validation of VHP Sterilization

Requirements for Starting Validation

- Completion of all IQ/OQ activities
- Completion of cycle development

Validation

- 3 runs
- Worst case = non operating isolator for min of 12h

Acceptance Criteria

- All BIs sterile
- Defined H_2O_2 consumption
- Color change of chemical indicator
- Room conditions within limits (T, RH)

VHP Sterilization
Lessons learned

- **Efficiency and reproducibility of VHP sterilization can only be ascertained and verified using a microbiological system**

- **Individual D-Value determination is required for each isolator based on the “worst case” BI location**

Isolator Technology vs Conventional Cleanroom

Isolator Technology vs Conventional Cleanroom

Experiences gathered during Manufacturing

Quality of the aseptic environment in the Isolator

Isolator Technology	Cleanroom Technology	Result
- VHP sterilization acts sporicidal and validation is possible	- Sanitization with Isopropanol / WFI : 70/30 does not act sporicidal, validation is not possible	Sterility can be maintained more reliable in an reduced aseptic environment with a controlled sterilization method
- VHP is effective on all accessible surfaces	- Spraying of a disinfectant is less effective	**=> pro Isolator**

Isolator Technology vs Conventional Cleanroom

Experiences Gathered during Manufacturing

Quality of the "Conventional Cleanroom versus Isolators":

Isolator Technology	Cleanroom Technology	Result
- Main source of micro organism excluded: the operators - Process is protected by a solid barrier	- Personnel necessary to run the process - Process is protected by aseptic techniques and unidirectional air-flow	- Conventional cleanroom technology is more sensitive to human failures **=> pro Isolator**

Isolator Technology vs Conventional Cleanroom

Experiences gathered during Manufacturing

Results after 5 years Monitoring

- **Viable Air Monitoring:**
  Exceeded limits in Grade 100 (ISO 5) Isolators: = 0
  Exceeded limits in Grade 100 (ISO 5) sterile core area: = 0

- **Particles (continuous monitoring 0.5µm / 5.0µm):**
  Exceeded limits in Grade 100 (ISO 5) Isolators < 0.001%
  Exceeded limits in Grade 100 (ISO 5) sterile core area: > 0.01%

- **Glove, Sleeve, Overall Monitoring:**
  Exceeded limits in Grade 100 (ISO 5) Isolators : = 0
  Exceeded limits in Grade 100 (ISO 5) sterile core area: > 0.1%

- **Surface Monitoring:**
  Exceeded limits in Grade 100 (ISO 5) Isolators: = 0
  Exceeded limits in Grade 100 (ISO 5) sterile core area: > 0.1%

Isolator Technology vs Conventional Cleanroom

Experiences gathered during Manufacturing

Flexibility

Isolator Technology	Cleanroom Technology	Result
- inflexible processes - poor accessibility - limited feasibility for handling and transfers	- process design flexible - accessibility not limited - process design can be adapted to different requirements	Isolator Technology is limited suited for flexible processes with manual handling **=> pro Cleanroom**

Isolator Technology vs Conventional Cleanroom

Experiences gathered during Manufacturing

Economic Efficiency

Isolator Technology	Cleanroom Technology	Result
Mechanical trouble leads to termination of processes	More flexibility regarding troubleshooting	Risk of losing batches is lower in a conv. cleanroom **=> pro Cleanroom**
Reduction of costs for environmental monitoring and gowning possible	High costs for energy, environmental monitoring and gowning	Reduced costs for maintaining Class 100 **=> Isolator**
Operating in three shifts is possible	Daily disinfection and recovery time is required.	Increased overall time for operations **=> Isolator**

Isolator Technology vs Conventional Cleanroom

"Lessons Learned" Efficiency

1. Changeover / Conversion:

Sterile Core Area:	Changeover, test-run, disinfection **Sum: 3 h to 4 h**
Isolator:	7 h VHP sterilization + venting to limit 1 ppm 7.5 h cleaning + change over + test-run **Sum: 15.50 h**

2. Termination of Manufacturing Process:

Isolator 2003: Sterile Core Area :	ca. 2.5 % 0
Isolator 2004: Sterile Core Area :	ca. 1.5 % 0
Isolator 2005: Sterile Core Area :	ca. 1.2 % 0

Summary …

…after five years experience with Isolator Technology designed and build for the supply of the world wide market with cytostatics

Would we choose Isolator Technology again ?

Yes regarding maximum achievable product quality

Yes regarding operator safety (EHS)

Yes regarding process complexity and process stability

Yes regarding economic efficiency

Is the isolator basically the best concept for aseptic processing ?

Not always ... **but more and more!**

http://www.baxterbiopharmasolutions.com/contract_manufacturing/facilities_equipment/halle_germany.html