Trends in Sterile Manufacturing Technologies

ISPE Thailand Annual Meeting

Charlotte Enghave Fruergaard
2013.07.18
Where we come from

1930s – Danish Novo and Nordisk Gentofte (later Novo Nordisk) employed the first engineers.

1974 – Pharmaplan was founded as part of the medical care group by Fresenius, Germany.

1991 – After functioning as in-house consultants at Novo Nordisk for years, NNE (Novo Nordisk Engineering A/S) demerged as an independent company.

2007 – Acquisition of Pharmaplan, a company similar to NNE in DNA. NNE Pharmaplan was founded.

Recent awards
2004 IChemE: “Haden Freeman Award for Engineering Excellence”
2005 ISPE Facility of the Year Award winner – Novo Nordisk’s NovoSeven (FVII) facility
2008 ISPE Company of the Year winner
2009 ISPE Facility of the Year Award winner – Facility Integration – hameln pharmaceuticals, Germany
2009 ISPE Facility of the Year Award winner – Operational Excellence – R&D division of US biotech company, Switzerland
2009 Emerson: “PlantWeb Excellence” for DeltaV application for Pronova BioPharma project (KalOmega)

With 80 years of experience we are passionate about our services to the pharma and biotech industries.
Who we are

We are the leading consulting and engineering company in the complex field of pharma and biotech.

We count close to 1,700 professionals with project experience and knowledge related to pharma and biotech.

More than 200 have hands-on development or production experience.

We executed 2,929 projects in 2012.
Optimal production processes

DEVELOP
- Process & Product development
- Project development

ESTABLISH
- Investment project CD / BD / DD / CON / C&Q

IMPROVE
- Optimisation, training, revamps, GAP analysis, operational support

Company revenue
2012
USD 294M
EUR 224M
Agenda

- Market changes forcing technology changes…
- Aseptic/Sterile processes
- Technology Trends
What is **OSD** and **Biotech**?

Small Molecules vs. Large Molecules

**Small Molecules OSD**

- Chemical Active Pharmaceutical Ingredient (API)
- Chemical Synthesis
- Drying or Granulating
- Formulation
- Tableting
- Packaging

Since “1899”

**Large Molecules Biotech**

- Biologics Active Pharmaceutical Ingredient (API)
- Fermentation or Cell Culture
- Formulation
- Aseptic Filling
- Packaging

Since “1982”

**Interferon molecule vs Aspirin**
Large Molecules grows faster
Small Molecule drugs is the big market

Shifting roles:
• The shift from small to large molecules became visible in 2003

The Economist 2005
Market changes forcing technology changes…

- **Products**
  New products are more and more classified as high potent and require both a very high level of aseptic processing and operator / environmental protection

- **Batch sizes**
  Small batch sizes of very high value. Based on better diagnostic methods, personalized treatment (1 vial = 1 batch) will increase

- **Processes**
  New products (mainly Biopharmaceuticals) are usually produced by aseptic processes

- **Primary containers**
  Pre-filled syringes and new developed devices are growing fast

- **Automation**
  Elimination of the “human factor” to avoid direct human impact for all critical process steps (class A operations) in a reproducible, validatable and documentable way
Agenda

- Market changes forcing technology changes…
- Aseptic/Sterile processes
- Technology Trends
From API to Finished Product
excl. QA/QC

Manufacturing of Sterile Products
- Wash & Sterilisation (incl. Comp. Prep.)
- Compounding (Preparation)
- Filling
- Barrier Isolator
- Lyophilizing

Assembly & Packaging
- Assembly
- Labelling
- Packaging

Logistics & Controls in Manufacturing
- Logistics
- Material Handling
- Inspection
- Controls

Filled units
Sterile Products – Definition

Sterile products are products free from living microorganisms.

**Ph. Eur. section 5.1.1. Methods of Preparation of Sterile Products**

- It is expected that the principles of good manufacturing practice will have been observed in the design of the process including, in particular, the use of
  - qualified personnel with appropriate training
  - adequate premises
  - suitable production equipment, designed for easy cleaning and sterilisation
  - adequate precautions to minimise the bio burden prior to sterilisation
  - validated procedures for all critical production steps
  - environmental monitoring and in-process testing procedures
- Sterilisation shall be done in the final container if at all possible
- Sterility Assurance Level (SAL) of minimum 1:1,000,000
Sterile or Aseptic manufacturing?

Can the solution tolerate heat treatment?

- **Yes**  ➔ Sterile manufacture
  - Sterilization takes place in the end of the process (= terminal sterilisation)

- **No**  ➔ Aseptic manufacture
  - The solution is sterile filtered and thereafter only comes in contact with sterilised utensils and tanks in a classified environment (grade A/ISO 5 with a grade B/ISO 7 background)
    - Filter pore size is 0.22 µm = 0.00022 mm
Why do we have GMP?

• Manufacturing of pharmaceutical products is all about “Risk for the patient”

• This is why we document, train and qualify…

• Traceability is being able to trace BACK – especially when something goes wrong (batch numbers and documentation)
Washing Process

• **Purpose of washing**
  • Secure no leftover from previous product, i.e. no cross contamination
  • Reduction of endotoxin and particles

• **Items to be washed in a utensil washer**
  • Utensils
  • Machine parts
  • Hoses

• **Typical process**
  • Rinse
  • Wash with or without detergent
  • Several rinse phases.
  • Conductivity measurement
  • Drying
Sterilization Process

• **Purpose of sterilization:**
  • Secure a product free of living microorganisms with a sterility assurance level of $10^{-6}$ or better

• **Terminal sterilization**
  • Product produced at least in grade D and sterilized in final container

• **Aseptic preparation**
  • Each primary packaging component sterilized individually
  • Solutions sterile filtered
  • All handling and filling of aseptically prepared products must be done in grade A/ISO 5 with grade B/ISO 7 background

• **Items to be sterilized**
  • All items going to grade B/ISO 7 including sanitizers and gowning
Methods of Sterilization

- **Saturated steam (Autoclave/SIP)**: 121°C, minimum 15 minutes, pressure + 0,1 bar
- **Hot water**: 121 °C, minimum F₀ 15 minutes
- **Dry heat sterilization**: 160 °C, minimum F₇₁ 38 minutes
- **Dry heat depyrogenation**: 250 °C, minimum F₇₁ 15 minutes, lead to a 3 log reduction of endotoxin
- **VHP sterilization**: Demonstrate a SAL of 10⁻⁶
- **Filtration**: Pore size ≤ 0,22 µm
- **Radiation /e-beam**: A minimum dose of 25 kGy
Liquid Compounding – Preparation

Liquid compounding of Sterile Products is mixing of

- Water for Injection (WFI)
- Active Pharmaceutical Ingredient (API)
- Other raw materials, e.g.
  - Stabilisers (physical/chemical)
  - Preservatives (if multiple use product)
  - Isotonic substances
Filling Process

- To take the sterile product from Compounding and fill it into a primary packing, which must protect the product and keep it sterile until use
  - Multiple Batch Filling: Filling more than one batch between full cleaning/decontamination of the filling line
- During filling protection against contamination from the following must be avoided:
  - The primary packing itself
  - Surroundings & People
Surroundings & People

- People are the most contaminating source for the product
**Particle generation from one person per minute**

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<td>Walking</td>
<td>5,380,000</td>
<td>1,285,000</td>
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</table>

According to:

Takasago Thermal Engineering Co - Fläkt
Surroundings & People

- People are the most contaminating source for the product

- This must be reduced by protecting the filling process:
  - Conventional Clean Room (CCR)
  - Restricted Access Barrier System (RABS)
  - Isolator
Material Input/Output

- Glass
- Washing
- Sterilization
- Filling
- Pistons
- Combi seals
- Product from Compounding

Filled and inspected Glass
What are Barrier Systems?

• A physical barrier which separates the operator from the process.

• As important as the barrier itself are the linked features and processes such as:
  • Properly designed equipment (ergonomics) and HVAC system
  • Material transfer procedures
  • Working procedures and training of the operators
  • Procedures in terms of intervention and accidents

• That’s why it is called a “system”
Definitions – CCR

- Conventional Clean Rooms (CCR)
  - ISO 5 (class A) surrounded by ISO 7 (class B) room
  - Pressure difference (15 Pa) between the clean room classes
  - Critical operations with open sensitive products are carried out under Unidirectional Airflow (class A protection)
  - Manipulations (i.e. trouble shooting, change of format parts) are done directly by opening of the machine cladding
  - Operator gets directly in contact with critical surfaces (class A area)
  - Gowning of the operator according to class B requirements
  - Material transition to class B (autoclave, pass box, dry heat oven)
  - Regular wipe sanitization
  - Heavy routine viable monitoring
  - Periodical room sanitization
  - Machine parts pre-sterilized or disinfected in situ
Definitions – RABS

- **Restricted Access Barrier System (RABS)**
- Surrounding clean room class B for the filling operation
- Pressure difference (15 Pa) between the clean room classes
- All manipulations during production are done via gloves of the RABS
- Ergonomic designed system for the process inside (Mock-up studies)
- Transfer of format parts via Rapid Transfer Port (RTP)
- Material transfer via Rapid Transfer Port (RTP) or material locks
- Gowning of the operator according class B requirements
- Conventional cleaning and disinfection
- Same viable monitoring as CCR
- Locked doors (barrier) during operation

*Sterility Assurance Level (SAL)*
Definitions – Isolators

- Isolators
  - ISO 5 (class A) inside isolator
  - Surrounding clean room ISO 8 (class D or C) for the filling operation
  - Positive pressure difference towards the filling room
  - Ergonomic designed system for the process inside (Mock-up studies)
  - Complete closed system with Vaporized Hydrogen Peroxide (VHP) decontamination of all surfaces
  - Complete independent HVAC unit
  - All manipulations during production are done via gloves
  - Gowning of the operator according class C or D requirements
  - Material transfer via Rapid Transfer Port (RTP) or material locks
  - Area to be monitored is very limited
  - Very high SAL
The Technologies

Clean Room
- Environment: B/A
- Complexity: Low
- Comfort: Low, due to clean room garment
- Aseptic quality: Low SAL~3 (*)
- Campaigning unusual

Open RABS (active or passive)
- Environment: B
- No overpressure to surroundings
- Complexity: High, due to transfer techniques and restricted access by gloves
- Comfort: Even lower, due to clean room garment and restricted access
- Aseptic quality: Slightly improved SAL~4
- Several days campaign unusual

Closed RABS
- Environment: D
- Overpressure
- Complexity: Highest, due to transfer techniques and biodecontamination
- Comfort: Medium, no clean room garment, but some restrictions
- Aseptic quality: Highest SAL~6 log
- Week(s) campaign possible

Isolator

(*) Sterility Assurance Level
The Technologies

Clean Room

Conventional Clean Room

Currently most installed aseptic production lines are based on this technology. For new projects not anymore “state-of-the-art“.

RABS

Open RABS (active or passive)

Rather new technology, with large increase in terms of installations within the past years.

Closed RABS

Barrier Systems

Isolator

Closed RABS

Since more than ten years developing quite fast, first in Europe, then also USA and Japan. First choice technology for handling of high potent APIs.

Isolator

(\textit{*}) Sterility Assurance Level
Conflict of GMP vs. operator protection

Airflow direction (differentials pressure cascade)
## Pro and Cons

<table>
<thead>
<tr>
<th></th>
<th>CCR</th>
<th>RABS</th>
<th>Isolator</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Validation, start-up risk</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Complex isolator validation</td>
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<td>Necessity of experts</td>
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<td>Medium</td>
<td>High</td>
<td>Aseptic behavior needed in all 3</td>
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<td>Suitability for campaigning</td>
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<td>Medium</td>
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<td>Higher productivity with campaigning</td>
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<td>Sterility Assurance Level (SAL)</td>
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<td>Regulatory scrutiny</td>
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<td>Low</td>
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<td>Risk – SAL – Media Fill</td>
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<tr>
<td>Microbial Sampling</td>
<td>Normal</td>
<td>Normal</td>
<td>Less</td>
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<tr>
<td>Suitability for processing potent drugs</td>
<td>Not given</td>
<td>Limited</td>
<td>Very good</td>
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<tr>
<td>Maintenance complexity</td>
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<td>Medium</td>
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<tr>
<td>Access for service</td>
<td>Easy</td>
<td>Restricted</td>
<td>Restricted</td>
<td>Better for isolator due to garment</td>
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<tr>
<td>Realization time</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
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</table>
Considerations – Product

- Multi product production
- One product
- No of individual preparations per Year
- Containment
- Preservatives?
- Explosion proof
- Batch sizes – Multiple batch filling
- Protein – $\text{H}_2\text{O}_2$ sensitivity
- Price of product
Considerations – Process

- Complexity of process
  - Ampoules → Vials → Syringes → Cartridge
  - Powder?
  - Freeze Drying
- Material Transfer
  - Transfer door/lock
  - α/β-ports
- Gloves
  - Sterile mounting
  - Integrity testing
  - Replacement period
- Leak testing
- H₂O₂-decontamination
Considerations – Working Environment

• Product and Operator Safety (positive or negative Δ pressure)
• Working procedures and training of users
• Procedures in terms of intervention and accidents
• Surrounding room environment (operator comfort)
• Energy saving
Main Challenges

• Vaporised Hydrogen Peroxide sensors (VHP-sensors)
  • Inaccurate
• Biological Indicators
  • BI’s are biological
  • D-value determination
  • Needed Log-value
• VHP as a sterilising agent
  • Surface decontamination
  • Parts with in-direct product contact
  • Harmful to proteins
• Gloves
  • Integrity testing
Technology Evaluation

• Technology ready!
  • But still some inexpedient issues ~ VHP sensors, biological indicators, gloves. Challenges for experts, not obstacles.

• Suppliers ready!
  • All major suppliers are of high standard.
  • Filling line, isolator/RABS and facility designed together.

• Knowledge ready!
  • It seems as the use of properly chosen consultants/experts can minimize both the change over time and the time for and risk of validation.

• Isolators call for experts
  • Goal/level setting, process development, decision of acceptance criteria, validation and interpretation of results.

• RABS may be a solution
Regulatory requirements

The regulatory authorities are demanding more and more barrier systems to eliminate direct operator impact to critical processes:

• There is no doubt that the operator is biggest risk of a potential particulate and microbiological contamination for the production of pharmaceuticals

• US-FDA – Rick Friedman comments in March 2013:
  • "Conventional cleanrooms are on the borderline of compliance"
Regulatory – Guidelines

The regulatory authorities are demanding more and more barrier systems to eliminate direct operator impact to critical processes:

• EU GMP Guideline (New Annex 1):
  ‘Manufacture of Medicinal Products‘, Section ‘Isolator Technology‘
  • 21. The utilization of isolator technology to minimize human interventions in processing areas may result in a **significant decrease in the risk of microbiological contamination** of aseptically manufactured products from the environment…
  • 122. Restricted access barriers and isolators may be **beneficial in assuring the required conditions and minimising direct human interventions** into the capping operation.
Regulatory – Guidelines

- FDA Guidance „Sterile Drug Products Produced by Aseptic Processing“, Published version September 2004:

- ASEPTIC PROCESSING ISOLATORS (Appendix 1)
  Aseptic processing using isolation systems minimizes the extent of personnel involvement and separates the external cleanroom environment from the aseptic processing line. A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages* over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems. Manufacturers should also be aware of the need to establish new procedures addressing issues unique to isolators.
Regulatory – Why

Airborne Particle Counts vs. Time Inside a Barrier Enclosure in a Cleanroom and Inside the Same Cleanroom
(Abuzeid, Microcontamination July, 1993)
Regulatory – EU Statement

• What is the general position on the use of isolators and restricted access barriers vs. old conventional thinking?
  • “The transfer of materials into the aseptic processing zone and the role of people in the process are key concerns.”
  • “Robust material transfer strategies together with automation and enhanced product protection (from people) are therefore key to minimising risk.”
  • “Use of isolators for aseptic processing is therefore to be supported but ultimately it is for industry to select and justify the technologies it used.”
Regulatory – FDA Statement

• “The FDA would not tell a manufacturer that they must use a specific single technology to assure adherence to aseptic processing requirements. The FDA does indicate its general preference for isolators and provides corresponding regulatory incentives for them. A sound RABS concept also can provide added protection versus traditional processing approaches.”
Why consider Isolator Technology

- **Authorities** – Less scrutiny
- **Industry** – “State of Art”
- **Economical** – Cheaper per unit produced (with comparable SAL)
- **Manning** – Less microbiological sampling/testing
- **Risk** – No scrap of product due to sterility issues or failure in Media fills
- **Environmental** – Eliminating high class cleanroom environment, less space
- **Cost** – Reduction of running costs
- **Operator** – Protection with potent products
Why consider Isolator Technology

• Increasing amount of high potent APIs
• The protection of the operator as well as the environment for the production of pharmaceutical products becomes more and more important because of the following reasons:
  • The ratio of new APIs which are classified to be high potent is rising continuously:
    1990: approx. 5%
    2002: approx. 30%
    2015: ?
  • Existing APIs which were originally classified as not high potent are re-classified to be high potent
  • The importance of operator and environment protection is constantly growing in our society with the result of stricter laws and regulations
Summary – Isolator

• Isolator benefits:
  ✓ Higher product quality (e.g. SAL 6 log), reduced risk
  ✓ Better protection of personnel (containment)
  ✓ More comfort for personnel
  ✓ Lower facility cost and running costs (Class C or D)

• Isolator appropriate for:
  ✓ High output machines
  ✓ Long filling campaigns
  ✓ Expensive products
  ✓ Aseptic and potent drug
Conclusion / Recommendation

• Barrier systems are important to improve the product quality, and if required to provide an operator and environmental protection

• For new facilities the use of barrier technology is almost mandatory

• Barrier systems which are using gloves for manipulations have to be designed very well in order to give the operator good ergonomics for all required manipulations

• In order to avoid gloves and manual handling operations the trend go to a fully automized process

• An evaluation based on the products and processes about the kind of barrier systems should be done in an early project phase, because this has a huge impact in the overall facility design.

• The technology is a mature, ready to use, but experts are necessary to secure the right solution and to educate.
Agenda

• Market changes forcing technology changes…
• Aseptic/Sterile processes
• Technology Trends
Industry Trends – Overall

• **Avoiding of aseptic handling**
  Trend to avoid any manual aseptic handling of pre-sterilized components. If it cannot be avoided the use of a barrier system is almost mandatory

• **Automation**
  Trend to automize GMP critical processes in order to eliminate the “human factor” at all

• **Energy efficiency**
  Trend to save energy because it becomes more and more a significant cost factor

• **PAT (Process Analytical Technology)**
  Biopharmaceutical products are becoming more and more expensive, therefore PAT becomes more and more importance to decrease / avoid product loses
Technology Trends
Equipment cleaning

- Automation / Validation
  Clear industry trend to avoid any manual handling steps. Very difficult to achieve reproducible cleaning result by performing cleaning processes of critical equipment parts manually.

Picture courtesy Belimed Sauter AG
Technology Trends
Stopper treatment

- Automation
  Clear industry trend to avoid any manual handling steps, especially after sterilization

- Aseptic transfer (Use of Barrier Technology)
  Charging of stoppers into the stopper hopper of a filling machine equipped with a RABS or an isolator is more time consuming compared to a filling line in conventional design. As higher the filling machine speed, and / or as larger the rubber stopper size is, as more relevant this issue gets.

- Process control
  A closed automated process combining all or partly the following process steps in one unit provides better process control:
  - Washing (with or without detergents)
  - Siliconization
  - Sterilisation
  - Drying
Technology Trends
Stopper treatment

Lifecycle process:

Receiving: Unclassified area

Treatment & Transfer: Cleanroom D or C

Connection: Rapid Transfer Port

Cleanroom A/B or Isolator

* Picture courtesy ATEC Steritec GmbH
** Picture courtesy GETINGE-LA CALHENE
Technology Trends
Stopper treatment

Aseptic stopper transfer:
Technology Trends
Sterilisation technology
VHP Passbox:

Picture courtesy Metall + Plastic GmbH
Technology Trends
Sterilisation technology

E-Beam:
• E-Beam is the only continuous sterilization method to supply high speed pre-filled syringe filling machines
• Lifetime of the emitters are not satisfying for some suppliers, nevertheless it will become the standard sterilization method for tub sterilization
• A DIN/ISO standard for tubs of pre-filled syringes is currently under examination
Technology Trends
Sterilisation technology

E-Beam:

Picture courtesy Metall + Plastic GmbH
Technology Trends
Disposable Systems

1. Coupling for bag or vessel connection
2. Peristaltic pump when delivery container is not pressurized
3. Bioburden sample bag
4. Sterilizing grade product filter
5. Vent bag
6. Intermediate reservoir bag
7. Disposable manifold
8. Peristaltic dosing pumps
9. Beta-Bag
10. Isolator/RABS wall towards filling
11. Filling needles
Technology Trends
Single Use Technology

• Now available from all well known filling machine suppliers
Costs are between 600 – 6.000 Euro per set

Picture courtesy Robert Bosch GmbH
Technology Trends
Disposable Systems

Design Trends:

Less important

• Saving of utilities (CIP/SIP)
• Saving of investment costs
• Avoiding of cleaning validation
• Faster filling machine set up between two batches/products (less filling machine downtime, especially in combination with an isolator)
• Less product loss at batch end

Very important
Technology Trends

Filling equipment

• Filling system
  Peristaltic pump systems are often the preferred system for Biopharmaceuticals and/or Disposable systems

• Robot / Handling systems
  Individual positive transport, avoidance of glass to glass contact, minimizing rejects and glass breakage rate and very flexible (fast) format change

• Performance
  • High speed filling equipment for pre-filled syringes up to 1.000 units/min.
  • Low speed filling for very small batches with fast format/product change

• Process Analytical Technology (PAT)
  • 100% check of filling volume
  • Camera inspection for stopper and cap placement
Technology Trends

Filling equipment

- Filling machine with handling systems and check weighing:
Technology Trends

Barrier Technology

History (1947):

*Popular Science* Monthly

**Bottling Machine Defies Bacteria.** Faced with a growing demand for Par-enamine, an amino-acid solution used for injections, engineers of Frederick Stearns & Co. designed this sterile filling machine to eliminate laborious hand work. The entire apparatus is enclosed by a Plexiglas hood and is subjected to a constant flood of bactericidal ultraviolet rays. The machine can fill 2,000 bottles an hour.
Industry Trends – Isolators

Barrier Isolator Filling Line – Deliveries by Year

World-wide increase in filling line isolators continue
Process technology
RABS – Pictures
Technology Trends
Freeze Dryer Loading & Unloading Technology

• Automation
  Clear industry trend to avoid any manual handling steps, especially during the freeze dryer loading

• Use of Barrier Technology
  Loading: Mainly to fulfil GMP purposes
  Unloading: Mainly to fulfil operator safety requirements

• Pass-through freeze dryer configuration
  Increases the overall performance especially when freeze drying cycle is short and number of freeze dryer connected to a filling line is 2 or more

• Vertical execution
  Technical area as well as condenser below chamber to create a maintenance access through unclassified areas
Technology Trends
Freeze Dryer Loading & Unloading Technology

Mobile automated cart for freeze dryer loading:
Summary

Future developments (subjective)

• **Filling Equipment**
  • The technical development will go in the direction of handling / robot systems which do not require a direct human intervention
    
    “...the emergence of the robotics industry, which is developing in much the same way that the computer business did 30 years ago. Think of the manufacturing robots currently used on automobile assembly lines as the equivalent of yesterday's mainframes.”
    
    – Bill Gates; A Robot in Every Home; Sci Am; 2006

• **RABS**
  • RABS technology is on the long-term not a succeeding technology
    
    “Conventional aseptic filling should become passé soon.”
    
    – Rick Friedman, Director, Div. of Mfg and Quality, FDA-CDER
  • The regulatory requirements for RABS systems will become more strict

• **Isolator**
  • Technology of the future
  • Gloves as a weak point of the isolator will more and more disappear
  • The VHP cycle times will become significantly shorter

• **Disposable technology**
  • Will increase significantly in the near future
ISPE Member Benefits

• Guidelines

• COP’s
  • Sterile Products Processing COP
  • Containment COP
  • Biotech COP

• Webpage www.ispe.org
Contact Info

Charlotte Enghave Fruergaard, PhD
Director
Chairman ISPE Board of Directors

nne pharmaPlan®
Nybrovej 80, 2820 Gentofte, Denmark
Mobile: +45 3079 7208

cen@nnepharmaPlan.com
www.nnepharmaPlan.com
Abbreviations

- CCR   Conventional Clean Room
- RABS  Restricted Access Barrier System
- UDF   Unidirectional Airflow
- SAL   Sterility Assurance Level
- VHP   Vaporized Hydrogen Peroxide
- RTP   Rapid Transfer Port
- BI    Biological Indicators