

**Charlotte Enghave Fruergaard**  
**2015.10.07**

# **Advanced Aseptic Processing**

Advanced Aseptic Processing can improve the product quality  
and reduce the risk to patients

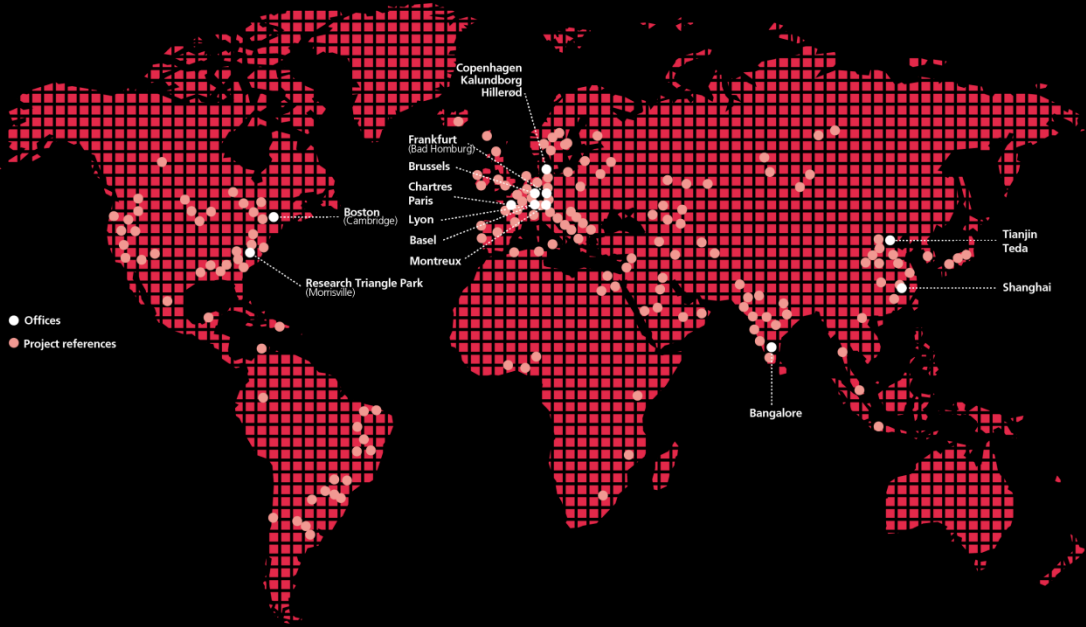
Market trends  
shows an increase  
in aseptic  
processing...

Increasing  
Regulatory  
expectations...

... forcing  
Technology  
changes

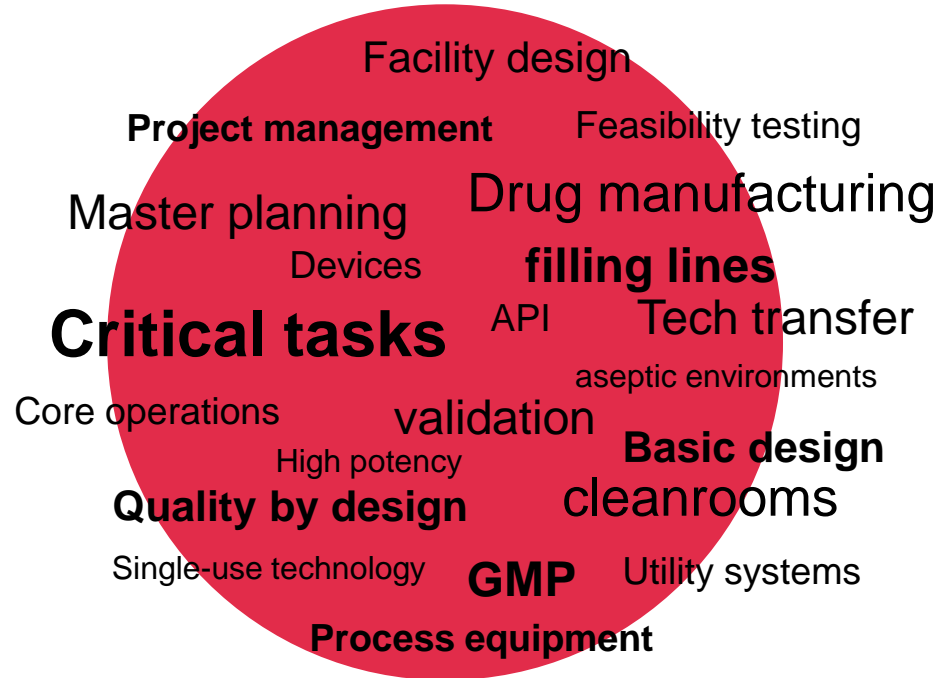
# Who are we?

- An international company specialised in pharma engineering
- Over 85 years of experience in pharma engineering
- Close to 2,000 professionals with extensive pharma project experience and technical expertise
- Around 3,000 projects per year



# We are focused on pharma engineering

- GMP, pharmaceutical process and business conditions is our daily life
- Leading experts with deep insight in pharma engineering
- Many of our engineers have been working in production or development



Advanced **Aseptic Processing** can improve the product quality and reduce the risk to patients

Market trends shows an increase in aseptic processing...

Increasing Regulatory expectations...

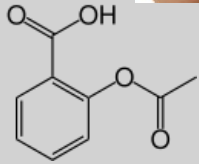
... forcing Technology changes

# OSD and Biotech

Small Molecules vs. Large Molecules

## Small Molecules OSD

Chemical  
Active Pharmaceutical Ingredient  
(API)



Chemical  
Synthesis



Drying or  
Granulating



Formulation



Tableting



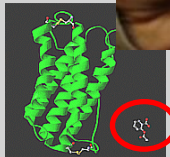
Packaging

"Tablets"  
Oral Solid Dosage Form  
(OSD)

Since  
"1899"

## Large Molecules Biotech

Biologics API



Interferon molecule  
vs Aspirin



Fermentation or  
Cell Culture



Formulation



Aseptic  
Filling



Packaging

"Injectables"  
Parenteral Dosage Form

Since  
"1982"

# Aseptic Processing





- To take the sterile product from Compounding and fill it into a sterile primary packing, which must protect the product and keep it sterile until use
- During Aseptic Processing protection against contamination from the following must be avoided:
  - The primary packing itself
  - Surroundings & People



# Why is this necessary?

**Particle generation from one person per minute**



	448,000	142,000	14,920
	4,450,000	462,000	48,600
	2,240,000	390,000	31,700
	5,380,000	1,285,000	157,000

According to:

Takasago Thermal Engineering Co – Fläkt

Advanced Aseptic Processing can improve the product quality and reduce the risk to patients

**Market trends**

shows an increase in aseptic processing...

Increasing Regulatory expectations...

... forcing Technology changes



# Market trends forcing technology changes...

- **Processes**

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

- **High Potent 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



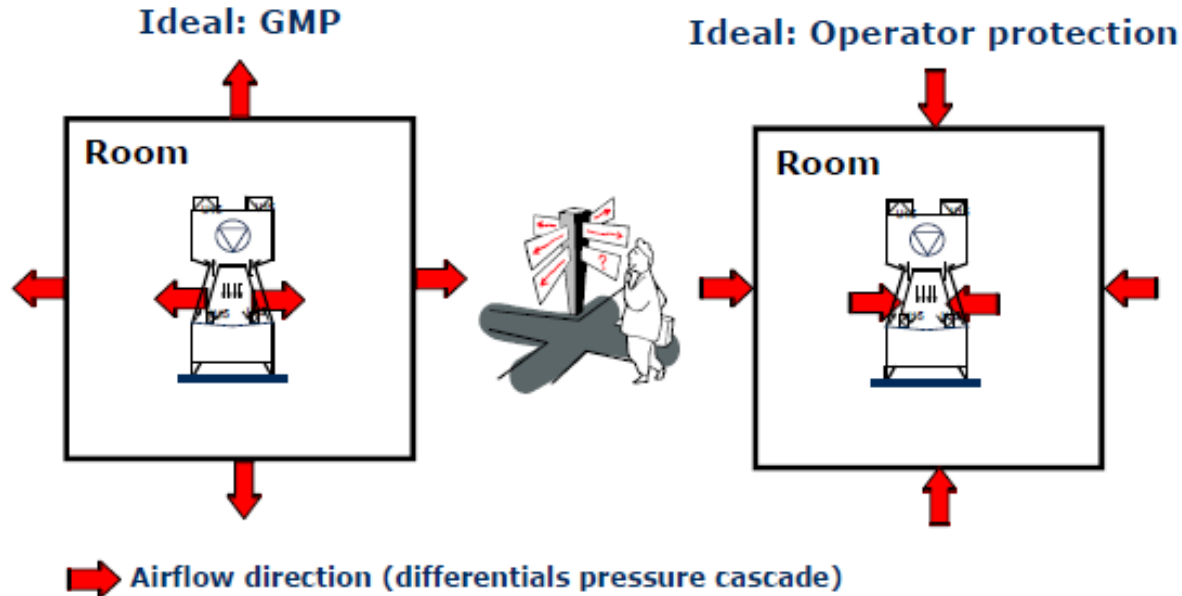
# Market trends – High Potent Drugs

1. Global market value was at around **\$ 9.1 billion** (2011)
  2. Estimated market CAGR is **9.9% per year** from 2012-2018
- The ratio of new APIs which are classified to be high potent is rising
  - 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

Source:



# Conflict of GMP vs. operator protection



# Market trends forcing technology changes...

- **Smaller Batch sizes**

Smaller batch sizes of very high value. Due to better diagnostic methods, the number and size of blockbuster products (“one size fits all”) will decrease and personalized treatment (1 vial = 1 batch) will increase. This will require a higher flexibility for the production facilities

- **Primary containers**

Pre-filled syringes and new developed devices are growing fast



# Market trends – High Value Drugs

The Product and the Disease...  
#1: AbbVie Humira for Arthritis



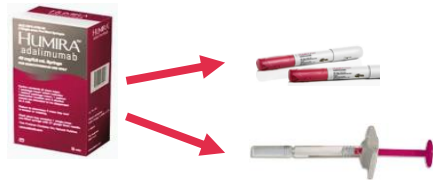
Injecting HUMIRA with the HUMIRA® Pen

See no needle...  
Fear no needle.

The HUMIRA® Pen  
The needle is never visible, not even during injection.

0.8 mL Prefilled Syringe  
0.4 mL Pediatric Prefilled Syringe

**Humira 40 Mg prefilled syringe**  
**1843 Euro**



The Product and the Disease...  
#2: Roche Avastin for Cancer



Avastin is injected into a vein through an IV.

A healthcare provider will give you this injection.

Avastin is usually given once every 2 weeks.

<http://www.drugs.com/avastin.html>

**Avastin 25 Mg/ml 400 Mg vial**  
**1668 Euro**



The Product and the Disease...  
#3: Pfizer Enbrel for Arthritis



Before I started ENBREL, the pain in my joints was intense. Now, I'm able to do many of the things I love.

**4 x Enbrel 50 Mg prefilled syringe**  
**1764 Euro**



<http://www.medipreis.de/>

# Market trends – **Smaller Batch Sizes**

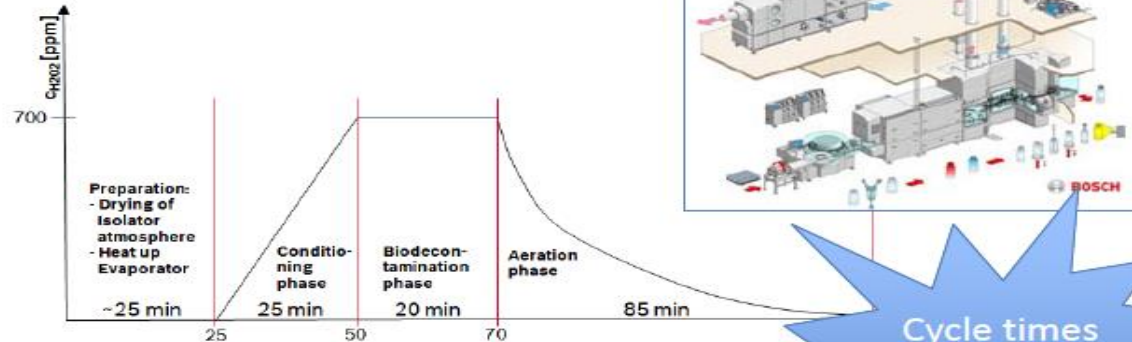
- **Flexible equipment** with shorter batch change-over time needed
- Fast and safe **material transfer** in and out of the Barrier system during production
- **Transfer airlocks** with very short VHP cycles (app. 15 min) available on the market
- **Shorter decontamination cycles** (down to 2-3 hours) for isolators today
- **Optimization** of all relevant batch change-over steps needed, e.g. parallel glove testing with multiple wireless units



# Market trends – Smaller Batch Sizes

## Cycle Time – Customer Example

- US-Customer



- Real life values from cycle development of a Vial Filling
- Total cycle time for reaching <1 ppm: 2h 35min
- Aeration with standard fresh air rate of 40%, no special measures for Aeration

Cycle times  
<2h possible



ISPE Aseptic Conference Baltimore, February 2015  
Matthias Angelmaier, Bosch Packaging Pharma Liquid

# Market trends forcing technology changes...

- **Dealing with Contract Manufactures**

More and more are using CMO's but would like to know their product and process better before handing their product to a CMO

- **Automation**

Trend to automate GMP processes in order to eliminate the “human factor” for all critical process steps (class A operations) in a reproducible, validatable and documentable way



# Market trends forcing technology changes...

- **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

- **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



Advanced Aseptic Processing can improve the product quality and reduce the risk to patients

Market trends shows an increase in aseptic processing...

Increasing **Regulatory expectations**...

... forcing **Technology changes**



# Regulatory – Guidelines

- **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

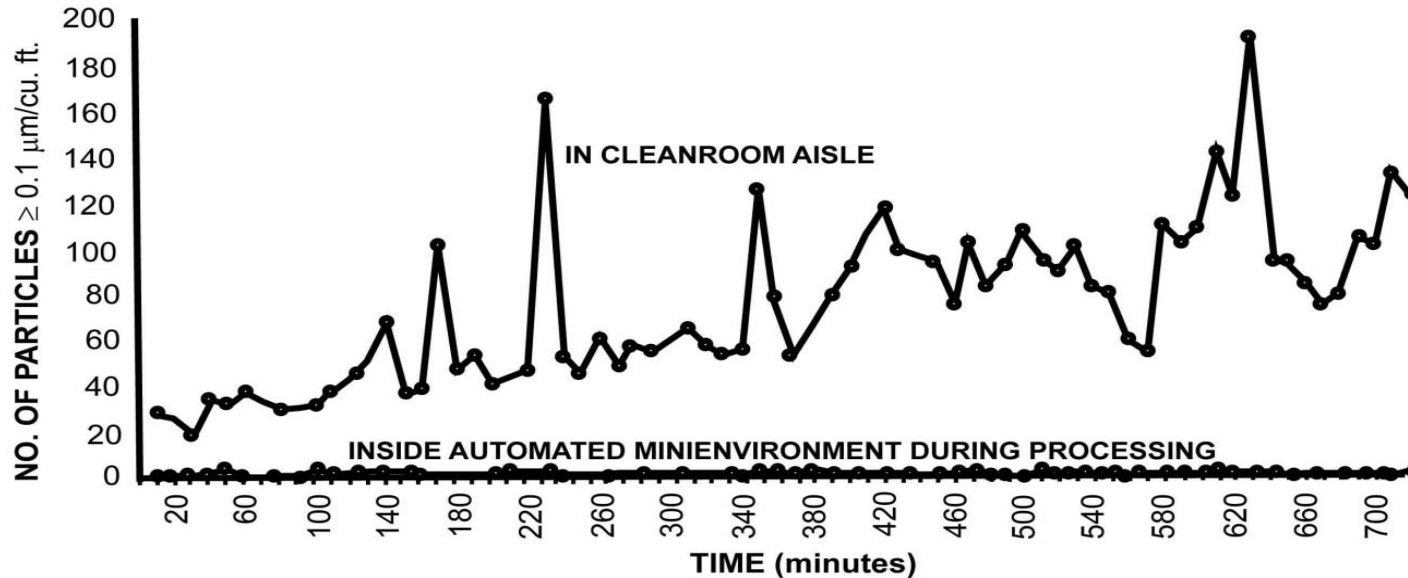
- **FDA Guidance „Sterile Drug Products Produced by Aseptic Processing“, Published version September 2004:**

- **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 – Expectations

**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”**



*ISPE Aseptic Conference Baltimore, March 2013*  
*Rick Friedman, Associate Director, OMPQ, FDA*

# Regulatory – Expectations

## 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 uses.”



*ISPE Barrier Isolation Technology Conference Berlin, September 2007*  
*Presentation by Ian Thrussell, MHRA*



Advanced Aseptic Processing can improve the product quality and reduce the risk to patients

Market trends shows an increase in aseptic processing...

Increasing Regulatory expectations...

... forcing **Technology changes**



# Technology changes...

... forcing  
Technology  
changes

- Advanced Cleanroom Technology – Barrier Systems
- Robotic Systems
- Ready to Use Technology
- Disposable Systems
- PAT

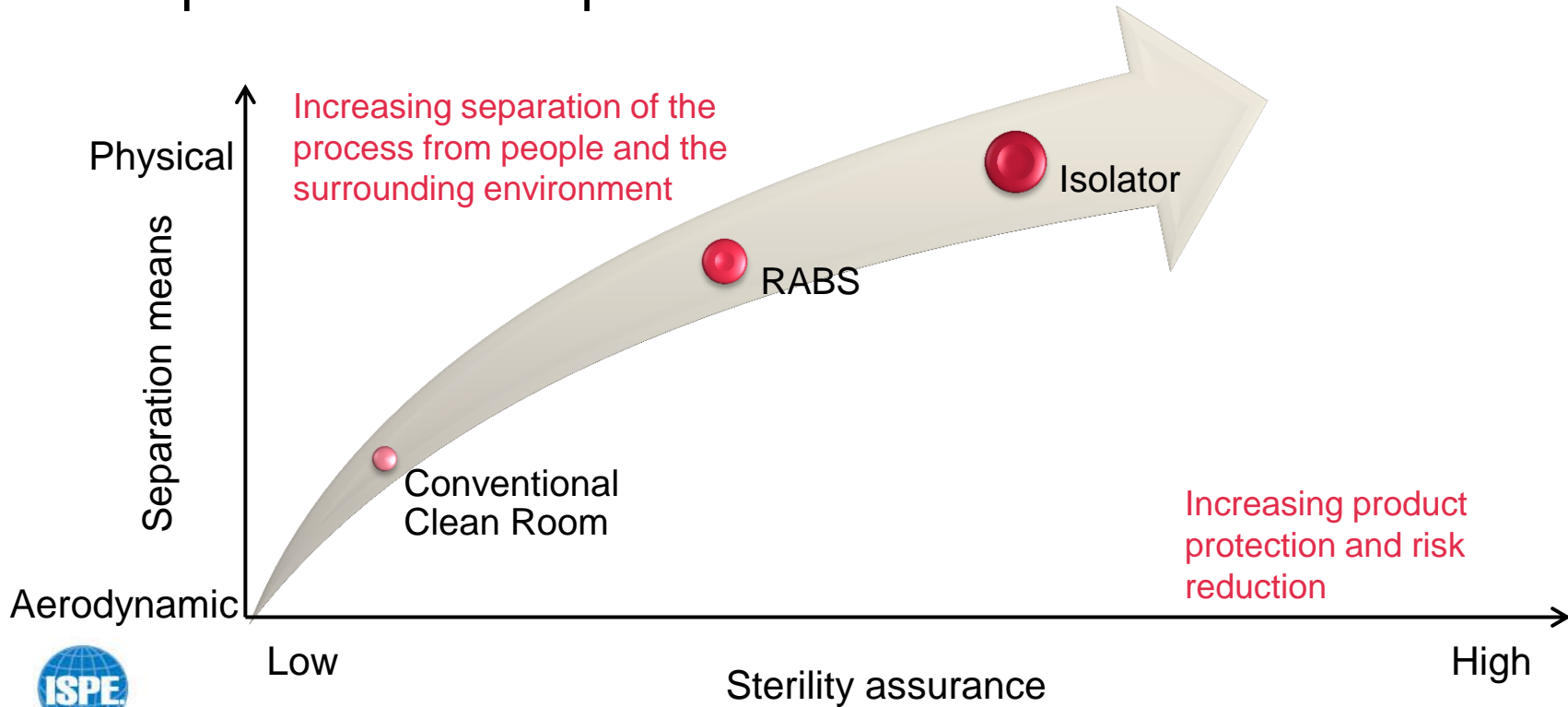


# What are Barrier Systems?

- 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**”



# Separation Concept

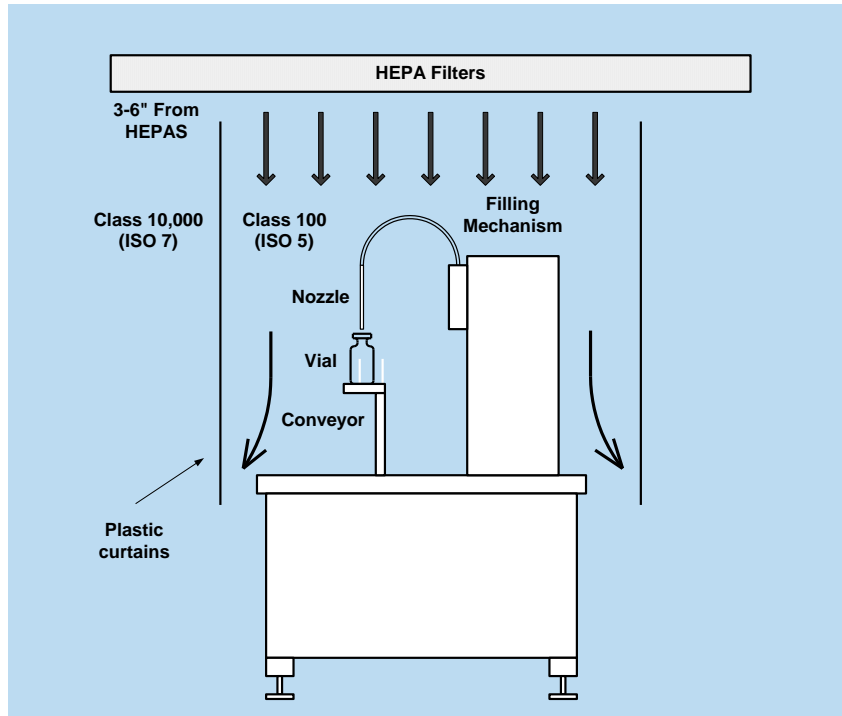


# Definitions – Conventional Clean Room

- Conventional Clean Room (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 – Conventional Clean Room

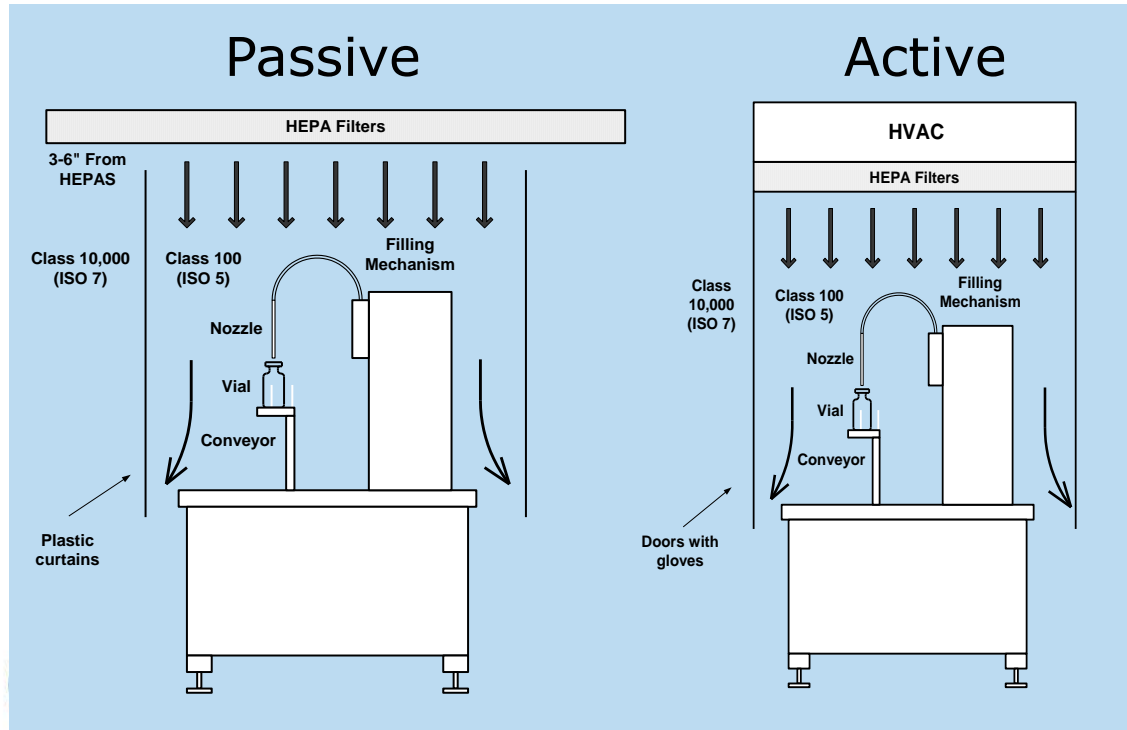


# Definitions – RABS

- 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
  - The system isolates the operator from the critical areas to increase Sterility Assurance Level (SAL)



# Definitions – RABS

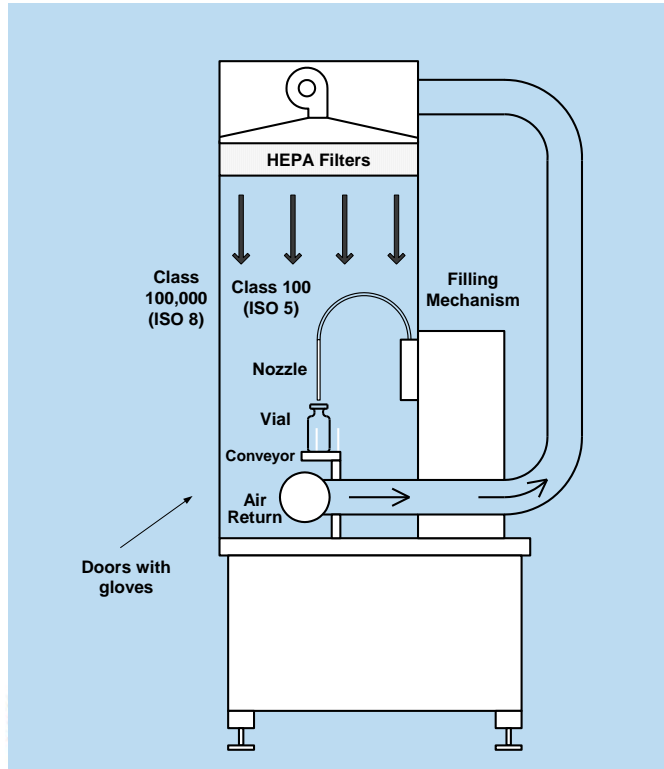


# Definitions – Isolators

- 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



# Definitions – Isolators



# Barrier Systems

## Clean Room



**Conventional Clean Room**

## RABS Restricted Access Barrier Systems



**Open RABS  
(active or passive)**



**Closed RABS**

## Isolator



**Isolator**

- Environment: B/A
- Complexity: Low
- Comfort: Low, due to clean room garment
- Aseptic quality: Low SAL~10<sup>-3</sup> (\*)
- Multiple Batch filling unusual

- 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~10<sup>-4</sup>
- Several days Multiple Batch filling unusual

- Environment: D
- Overpressure
- Complexity: Highest, due to transfer techniques and biodecontamination
- Comfort: Medium, no clean room garment, but some restrictions
- Aseptic quality: Highest SAL~10<sup>-6</sup>
- Week(s) Multiple Batch filling possible

(\*) *Sterility Assurance Level*

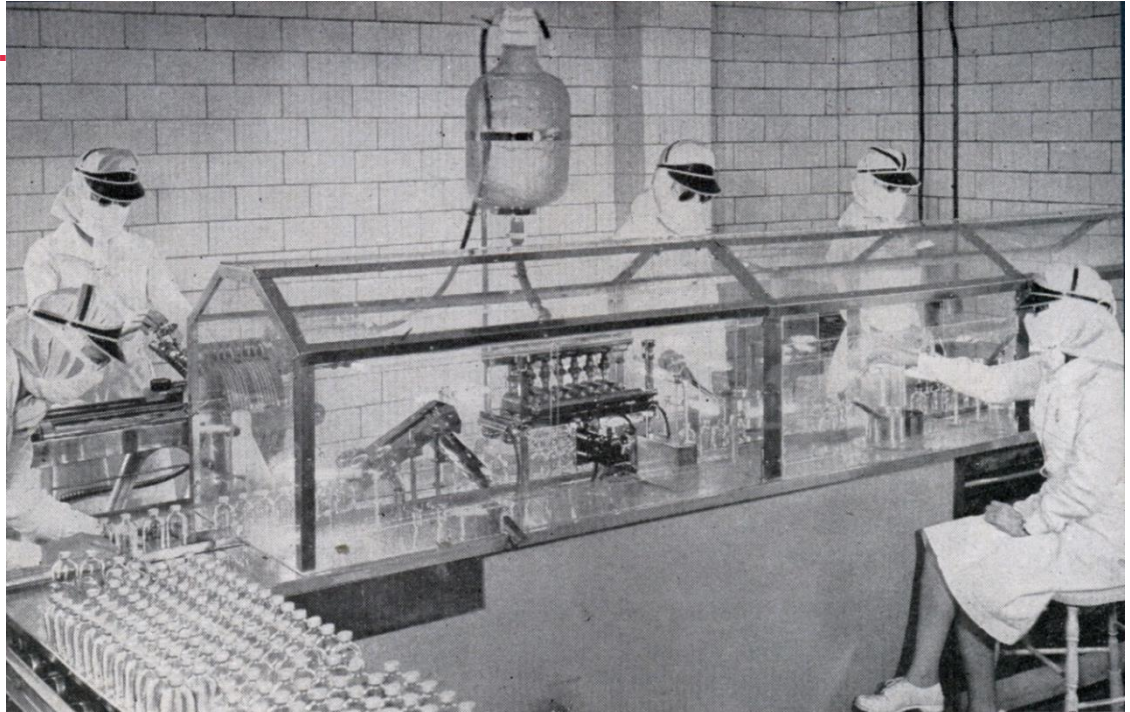
# Why consider Isolator Technology

- Authorities
  - Less scrutiny
- Industry
  - “State of Art”
- Sterility
  - Automatic, reproducible, well documented system for decontamination of all critical machine parts in situ
- Manning
  - Less microbiological sampling/testing, less time for gowning
- Risk
  - No scrap of product due to sterility issues or failure in Media fills
- Environmental
  - Eliminating high class cleanroom environment, less space
- Cost
  - Overall reduction of operational costs
- Operator
  - Protection with potent products



# Barrier Systems

State of the art 60 years ago...



# Barrier Systems – RABS

State of the art today...



# Barrier Systems – Isolator

State of the art today...



# Robotic Systems

- Robot / Handling systems:
  - More and more “semi-automatic” systems, but human intervention are still necessary or possible
  - Robotic systems are necessary for Advanced Aseptic Systems
  - Robots works better and more efficient
  - Individual positive transport
  - Avoidance of glass to glass contact
  - Minimizing rejects and glass breakage rate and very flexible
  - Fast format change
  - GOAL: 100% Automation of GMP critical processes



# Robotic Systems

## Vanrx – Workcell



*Video courtesy Vanrx Pharmsystems Inc.*

# Ready to Use Technology

## Syringes Bulk Process

De-nesting



Washing



Sterilization



Filling/Closing



Re-nesting



# Ready to Use Technology

## RTU Syringe Process

### Tub Sterilization



### Filling/Closing



# Ready to Use Technology

## RTU Vials

Tubular Glass

GERRESHEIMER

New Gx MultiShell® plastic parenteral vials  
Improved barrier properties for sensitive drugs

- 1
- 2
- 3
- 4
- 5



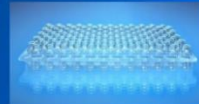
### PRODUCT PACKAGING AND FINISH DESCRIPTION

Specification	MultiShell® Standard	MultiShell® RTS	MultiShell® RTU
Production environment	ISO 7	•	•
Packaging processing	Fully automated	•	•
Packaging environment	ISO 7	•	•
Packaging materials in direct contact with vials	Produced in ISO 7	•	•
Dimensions	Accord. to standard specification	•	•
Defects	Accord. to standard specification	•	•
Cleanliness	Accord. to standard specification	•	•
Endotoxin	Certified per batch; limit: 0.06 EU/ml	•	•
Particles	Certified per batch	•	•
Bioburden	Certified per batch; limit: 10 CFU/ml	•	•
Gamma radiation	Validated sterilisation dose	•	•
Sterilisation	Certified per batch / parametric release	•	•
Endotoxin test post sterilisation	Certified per batch	•	•



Nuova Ompi  
glass division  
Stevanato Group

### Material Specifications



NEST (PP)

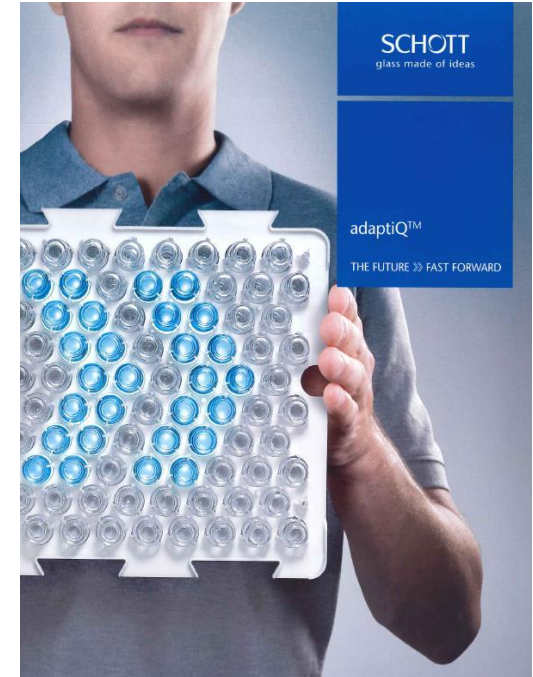


TUB (PP)



TRAY (PP)

- According to market standard
- Produced under clean room condition (ISO 7 / GMP C)
- Dry cavity injection moulds
- Inner bag produced in clean room (ISO 7 / GMP C)



SCHOTT  
glass made of Ideas

adaptIQ™

THE FUTURE >>> FAST FORWARD

# Ready to Use Technology

## RTU Vial Process



# Disposable Systems



- 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

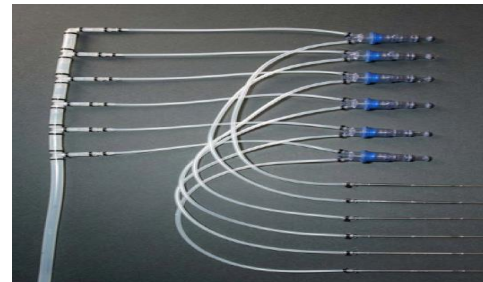


# Disposable Systems

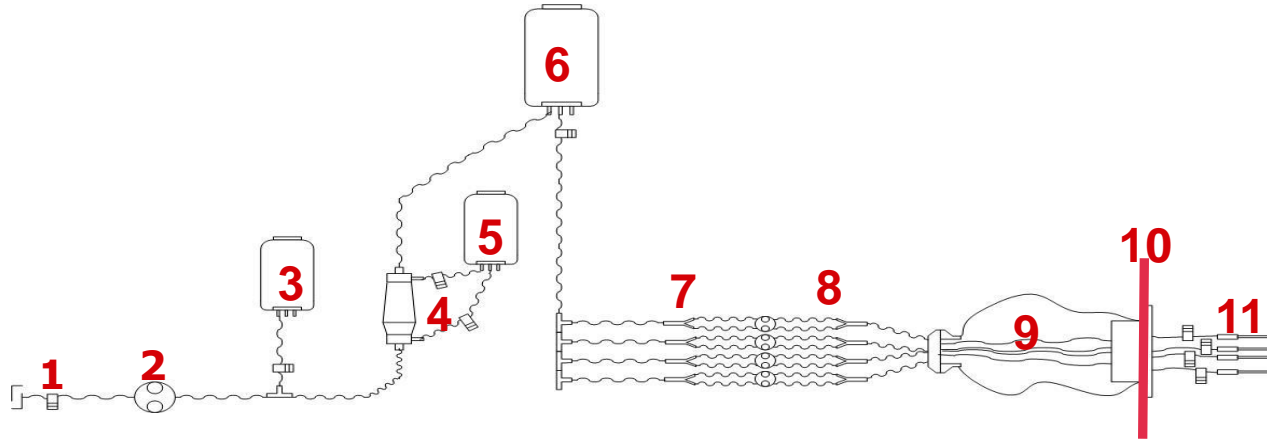
- Now available from all well known filling machine suppliers  
Costs are between 600 – 6.000 Euro per set



*Picture courtesy Bosch*



# Disposable Systems

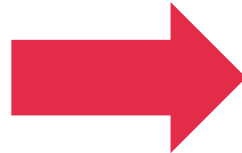


1. Coupling for bag or vessel connection
2. Peristaltic pump when delivery container is not pressurized
3. Bioburden sample bag
4. Sterilizing grade product filter
5. Vent bag

6. Intermediate reservoir bag
7. Disposable manifold
8. Peristaltic dosing pumps
9. Beta-Bag
10. Isolator/RABS wall towards filling
11. Filling needles

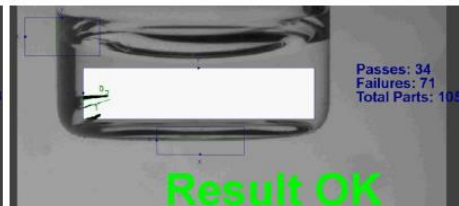
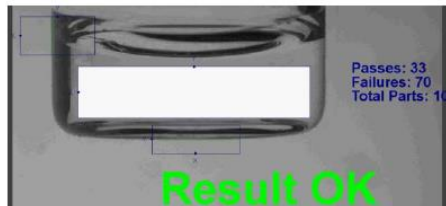
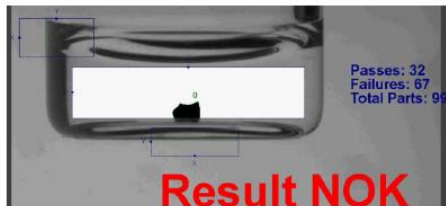
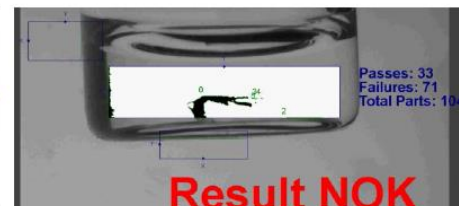
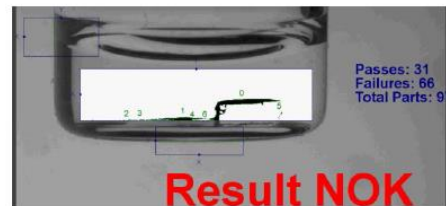
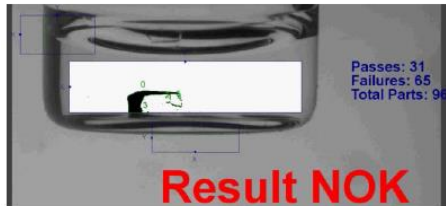
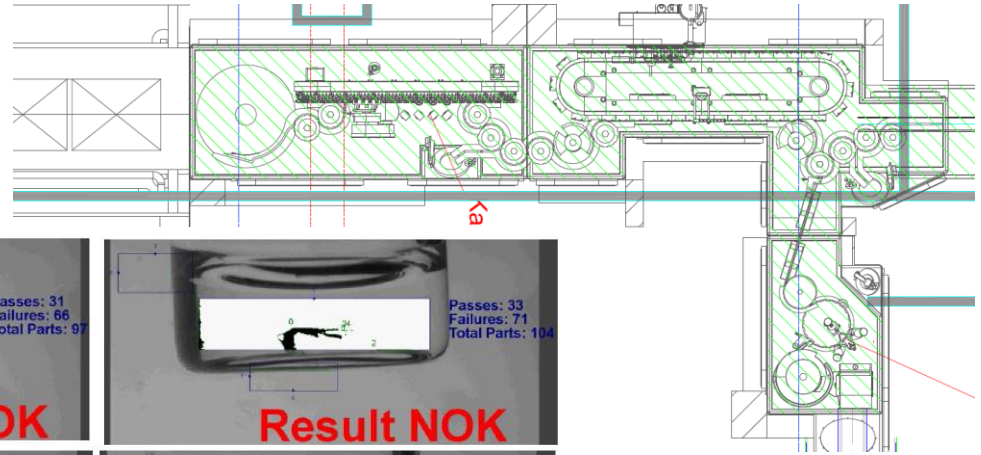


# PAT – Inspection



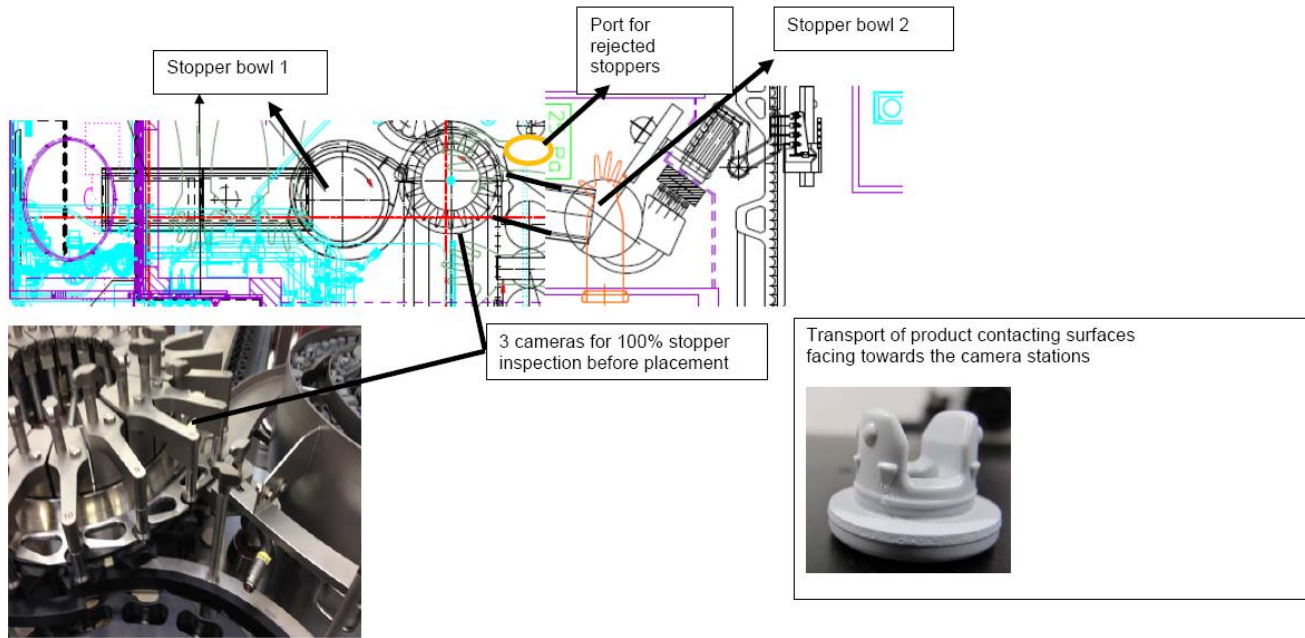
# PAT – Inspection

100% glass inspection integrated within a vial filling machine



# PAT – Inspection

## 100% stopper inspection integrated within a vial filling machine



# PAT – Filling

## Filling machine with check weighing



*Video courtesy Bosch*



# Summary

- Production facilities will gain more flexibility, decrease the investment costs and increase their productivity for smaller batch sizes (format change, cleaning, sterilization, maintenance, qualification etc.) by using a combination of the following technologies:



... this will improve the product quality and reduce the risk to patients



# Future Developments – (subjective)

- **Filling**

- 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
- Pre-sterilized/ready-to-use containers will become the choice of container when using isolator technology

- **Disposable technology and Ready-to-use**

- Will increase significantly in the near future

# Want to know more...

- Guidelines
  - Baseline® Guide: [Sterile Product Manufacturing Facilities](#) (Second Edition)
- ISPE COP's
  - [Sterile Products Processing COP](#)
  - [Disposables COP](#)
  - [Containment COP](#)
  - [Biotech COP](#)



# Contact Info

**Charlotte Enghave Fruergaard, PhD**  
Partner – Process Consulting  
Past Chairman ISPE Board of Directors

nne pharmaplan®

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

[cen@nnepharmaplan.com](mailto:cen@nnepharmaplan.com)  
[www.nnepharmaplan.com](http://www.nnepharmaplan.com)



# Questions?

*Every great and deep difficulty bears in itself its own **solution**.*

*It forces us to **change** our thinking in order to find it.*

Niels Bohr

*Everybody wants **Progress** – nobody wants **Change!***

Søren Kierkegaard

