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ENGINEERING PHARMACEUTICAL INNOVATION

Basics of design and layout development for parenteral facilities including pros and cons for advanced containment

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NNE Pharmaplan India Limited

ISPE Hyderabad Chapter
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Thanks

for support & Guidance

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Before we begin…

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1. **Growing Market:**
   There will be higher demand of small volume parenteral facilities since the market share of biopharmaceutical products will continuously increase in the future

2. **Decreasing Batch Sizes:**
   Due to better diagnostic methods, the number and size of blockbuster products (“one size fits all”) will decrease which will require a higher flexibility for the production facilities

3. **Shifting of Production Capacities:**
   Globally, the market will disproportionately increase in countries like Brazil , Russia, India and China (BRIC) and other countries like South Korea or Taiwan

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1. **Building / Process Utilities**
   → Flexibility
   → Personnel and material flow excellence
   → Working condition excellence
   → Green technology
   → Modular facilities

2. **Process Technology**
   → Cleanroom technology
   → Ready to fill (RTF) primary containers
   → Single Use Components

3. **Some conclusions**

1. Building & Process Utilities -- Flexibility

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1. Building concept to allow max. freedom for future expansion of the production functions and required support functions and technical areas
2. Design to allow remodelling of areas while production is continuing within adjacent production areas
3. Design to allow easy building expansion while production is continuing within adjacent production areas

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1. Building & Process Utilities -- Flexibility

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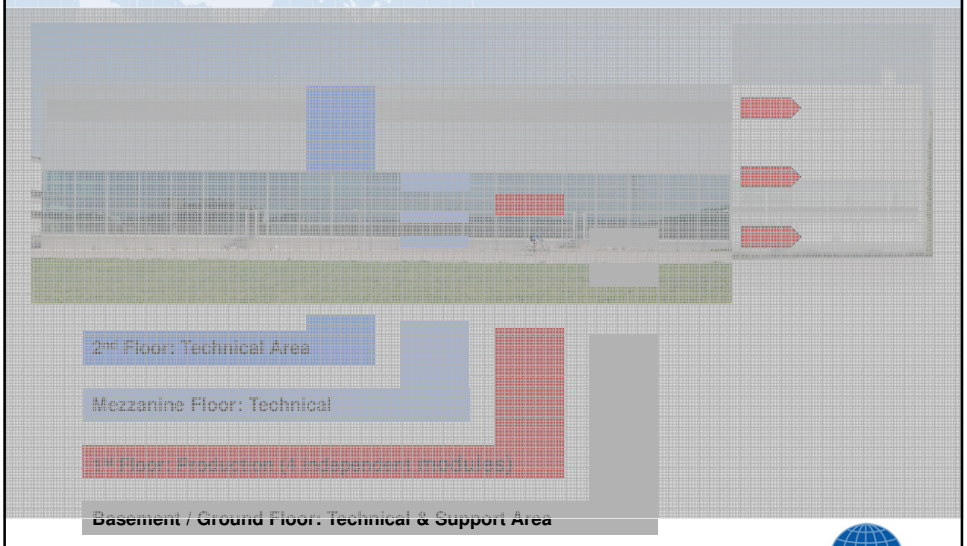

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1. Building & Process Utilities -- Flexibility

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1. Building & Process Utilities -- Flexibility

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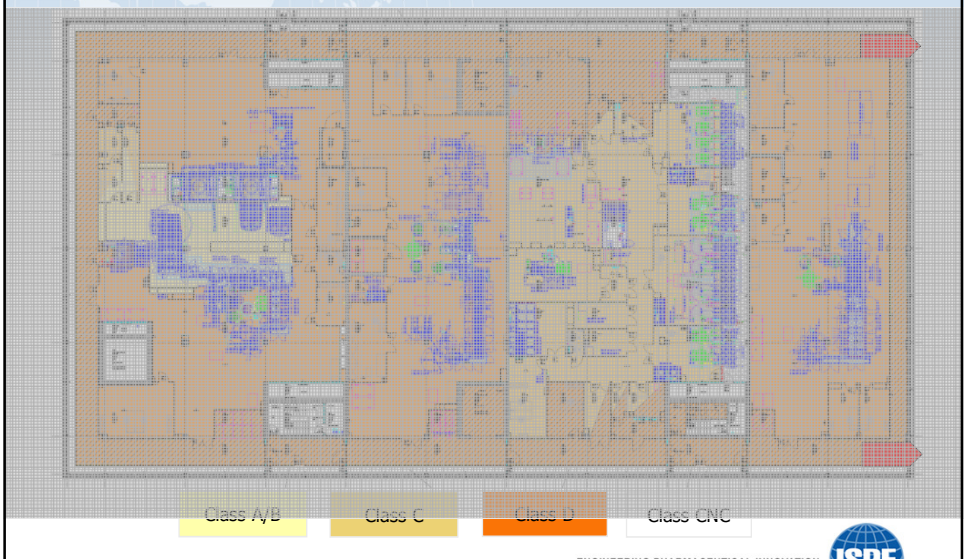

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1. Building & Process Utilities --
Personnel & Material Flow Excellence

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1. **Minimizing manual material flow distances**

2. **Unidirectional material flow:**
   Avoiding of any cross contamination by separating material flows by dedication of the corridors
   - Corridor 1 : Raw material, primary packaging material, clean equipment
   - Corridor 2 : Semi finished goods, dirty equipment

3. **Gowning concepts which are simplifying / minimizing the gowning procedures and distances from the change rooms to the work places**

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1. Building & Process Utilities --
Personnel & Material Flow Excellence

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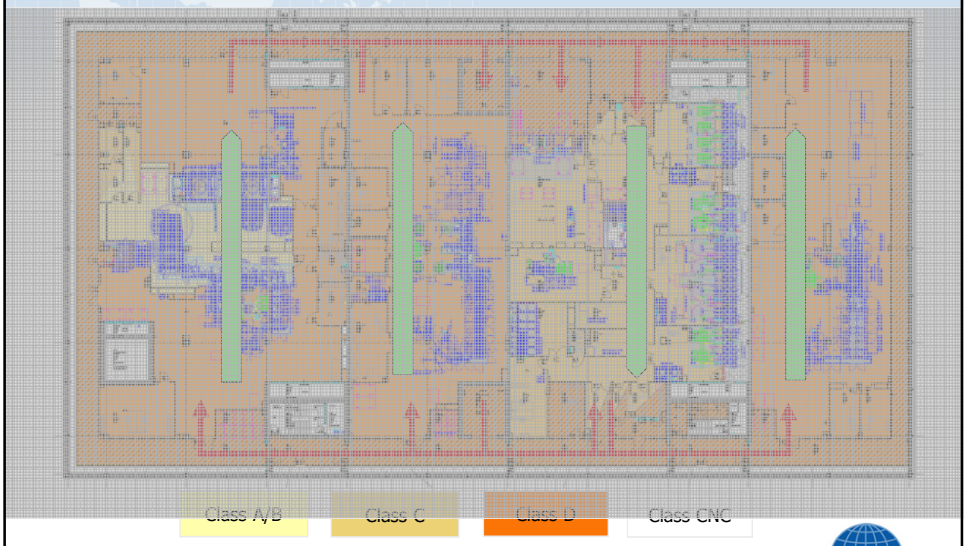

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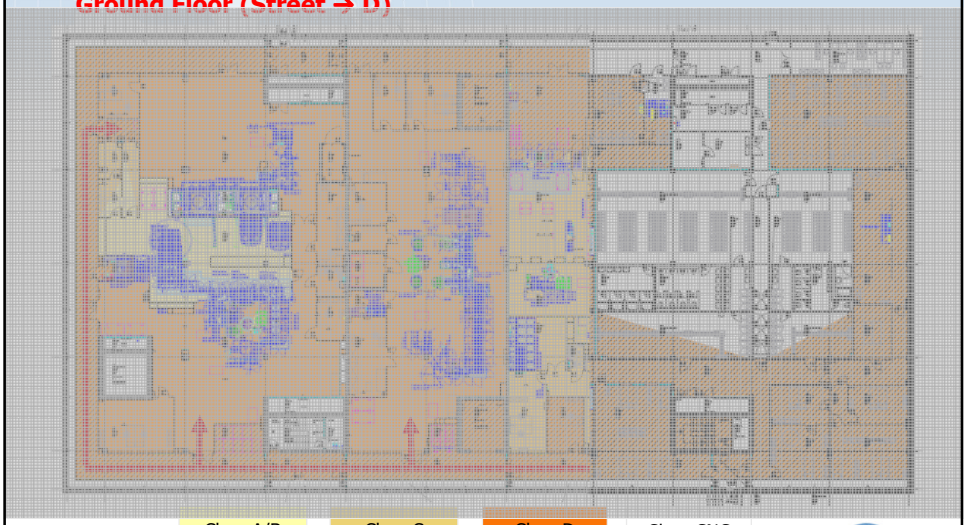
1. Building & Process Utilities --
Personnel & Material Flow Excellence

Ground Floor (Street → D)



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1. Building & Process Utilities --
Working Condition Excellence

1. Maximize daylight visibility for all permanent work places, including the possibility to control it in order to avoid negative impacts, e. g. ingress of heat or glazing (RABS & isolator)
2. Minimize noise emission for all permanent work places
3. Provide contemporary social rooms in short distance to the work places (change rooms, canteen, cafeteria)
4. Better working conditions
   Higher staff motivation
   Better product quality

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1. Building & Process Utilities --
Working Condition Excellence

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Noise insulation installed on a vial washing machine

Maximize natural illumination within production areas

Possibility to protect heat ingress by using shades and double glass walls with ventilation

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1. Building & Process Utilities --
Working Condition Excellence

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3. Provide contemporary social rooms in short distances to the work places (change rooms, canteen, cafeteria)

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1. Building & Process Utilities -- Green Technology

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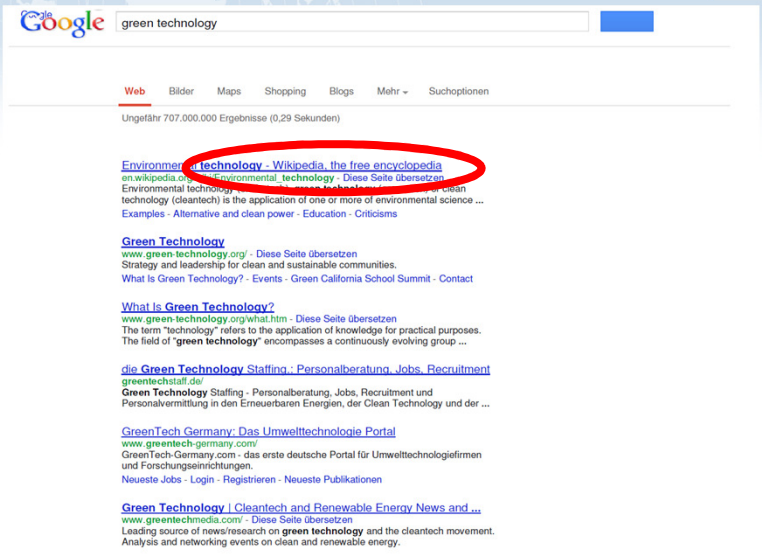

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1. Building & Process Utilities -- Energy Effeciency

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- **US Green Building Council**
  LEED (Leadership in Energy and Environmental Design) Rating:
  Certified: 40-49 points
  Silver: 50-59 points
  Gold: 60-79 points
  Platinum: 80-110 points

- Score system to measure the sustainability of a new building or a building after a major renovation in terms of the following aspects:
  - Site selection
  - Water consumption
  - Energy consumption
  - Protection of the earth atmosphere-
  - Choice of construction material

- Most frequent used (outside of the USA) in Asia

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1. Building & Process Utilities -- Green Technology

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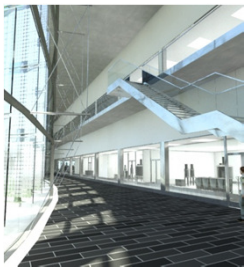
1. Typical Measures used in Pharmaceutical Facilities are :

- Possibility of using renewable energies
- High efficient energy recovery for HVAC units
- Re-use of waste heat, mainly for pre-heating purposes
- Re-use of "clean" water (e. g. water from final rinse processes)
- Wind energy
- Photovoltaic System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1. Building & Process Utilities -- Modular Facilities

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NNE Pharmaplan standerdized modular facility :

1. Pre-engineered production facility to decrease the timeline for implementation but allows customer specific configuration
2. Capable of being implemented as a new building or within an existing building
3. Build in flexibility with scale up possibility (clinical (500 l reactor), launch (1000 l reactor or market supply (up to 2000 l reactor)
4. Freedom to choose a variety of brands based on customer standards
5. Consequent use of single use technology, isolator technology and RTU components for fill & finish

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   - → Ready to fill (RTF) primary containers
   - → Single Use Components

3. Some conclusions

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2. Process Technology -- Cleanroom Technology

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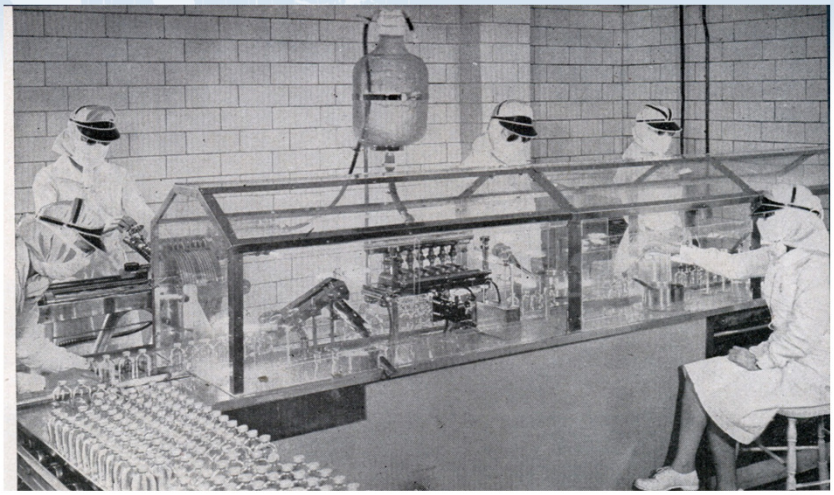
State of the art 60 years ago…



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2. Process Technology -- Cleanroom Technology

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State of the art today (RABS)…

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2. Process Technology -- Cleanroom Technology

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State of the art today (Isolator)…

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2. Process Technology -- Cleanroom Technology

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State of the art 2050…

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2. Process Technology -- Cleanroom Technology

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Main comparison criteria for "RABS / isolator :

Criteria	RABS	Isolator	Remarks
Sterility Assurance Level	+ to ++*	++	*if room sterilistation installed
Operator protection	- to +*	++	*for closed RABS
Material and Personnel flow	-	+	
Investment costs	o	-	
Running costs	-	+	
Productivity	o to ++	-- to ++	depending on prod. portfolio
Regulatory compliance	+	+	
Industry trend	+	+	
Realization time	-	--	

•-- = very bad (very high) - = bad (high) o = fair + = good (low) ++ = very good (very low)

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2. Process Technology -- Cleanroom Technology

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Investment Costs:

- The number of manufacturers for class A isolators has increased in the past, it is not the usual three anymore… It is very likely that the competition will even increase in the future.
- The design of RABS is getting more and more sophisticated. Today RABS filling machines are placed in rooms which are capable of being VHP decontaminated which increases the investment significantly.
- Higher investment costs are often justified by lower running costs showing lower TCO.

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Investment costs (Example: Filling line for vials: Isolator vs. open RABS)

Description	Unit Price [Mio €]	Unit	RABS [amount]	Isolator [amount]	RABS [Mio €]	Isolator [Mio €]
Class D area	0,004	m²	620	650	2,5	2,6
Class A/B area	0,008	m²	60	0	0,5	0,0
Isolator class A	2,9	pcs	0	1	0,0	2,9
RABS system	0,4	pcs	1	0	0,4	0,0
Filling line	-	pcs	1	1	4,5	4,6
VHP passthrough	0,7	pcs	1	0	0,7	0,0
VHP room decontamination	0,9	pcs	1	0	0,9	0,0
Steam sterilizer	1,0	pcs	1	1	0,4	0,4
TOTAL					**9,9**	**10,5**

2. Process Technology -- Cleanroom Technology

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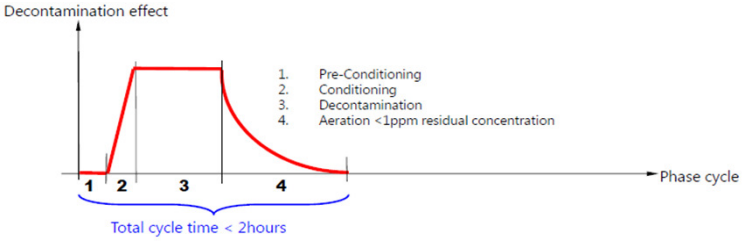
Productivity:

- **Isolators did always have the advantage in terms of productivity for big batches. A batch duration of 5 days for example is common practice.**
- **Isolators did always have the disadvantage if batch sizes are small and frequent format changes requiring an opening of the isolator with a time consuming VHP cycle.**
  Today the situation has changed:



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2. Process Technology -- Cleanroom Technology

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Regulatory Compliance:

- **In the past the US FDA was more doubtful rather than supporting isolator technology. Since a couple of years the picture has changed completely. The FDA favors isolator technology:**

  Rick Friedman:
  (Director, Division of Manufacturing & Product Quality, CDER, *FDA)*
  Comments in 6/2009
  "He would not put in conventional cleanrooms but in isolators and perhaps RABS (Restricted Access Barrier Systems)"

- **Many multinational companies already have internal guidelines in place saying that isolator technology is the company standard for processes requiring class A.**
  Any exception has to be specifically justified.

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2. Process Technology -- Cleanroom Technology

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Summary:

- Isolator technology has improved a lot during the recent past years and there is still a huge potential to develop further particularly in combination with the following 3 upcoming technologies:

  1. Single use filling systems
  2. RTF primary containers and RTU closures (syringes and vials)
  3. Robotic technology

It will become more and more unlikely in the future not to decide for an isolator system compared to RABS setup, which brings me back to the question…

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State of the art for aseptic /fill & finish by 2025…

?

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2. Process Technology -- RTF Primary Containers

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1. Currently already a standard for liquid syringes
2. First supplier on the market which can deliver also RTF vials, others are already in the process of building up production capacities for this product and will introduce the product soon to the market.
3. The design / size of the RTF vials is very similar to the RTF syringes which will soon offer a new dimension of flexibility to the pharmaceutical manufacturers
4. Soon there will be Tray filling machines on the market which are able to fill and close syringes and vials (liquid & lyophilized) on a day to day routine without major format change

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2. Process Technology -- RTF Primary Containers

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Already available from Ompi (see below), others will follow soon…

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2. Process Technology -- RTF Primary Containers

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Advantages RTF Process

- **Product Quality**
  No glass to glass contact during vial transport, de-pyrogenation & freeze drying
- **Investment Costs**
  No washing machine, tunnel required, less complex equipment for loading and unloading of a freeze dryer required and smaller cleanroom required
- **Flexibility**
  Possibility to process different primary container types and/or sizes on the same equipment with very short change over times

Disadvantages RTF Process:

- **Costs per Unit of the Primary Packaging Material**
  Significant higher costs (vials / syringes)
- **Supply to the Market, Number of Suppliers**
  Supply to market just started for vials, machines for dual use in the development phase
- **Equipment Utilization**
  Approx. 30% less utilization within a freeze dryer

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2. Process Technology -- Cleanroom Technology

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vanrx PharmaSystems Inc.

SA25 RAPTOR Aseptic Filling Workcell

SA25 RAPTOR Aseptic Filling Workcell is a fully integrated and isolated filling system for the production of sterile injectables.

"Zero Intervention" ensures product integrity by eliminating aseptic interventions and aseptic assembly.

Designed for clinical & small batch operations, the SA25 RAPTOR is ideal for potent compounds, biologics, vaccines and personalized medicine.

Specifications

Speed	25upm (3mL)
Accuracy	±1.0%
Interior Classification	ISO 5
Exterior Classification	ISO 8
Space Requirements	< 55m² (600ft²)

Features

Full 316L Stainless Interior & Robotics
No Change Parts**
Washdown & CIP Ready
Vapor Peroxide and ClO_2 Gas Compatible
Zero Intervention Technology
Disposable Fill Path
Automated EM Monitoring

* Pictures courtesy Vanrx PharamSystems Inc.

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2. Process Technology -- RTF Primary Containers

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Case Study:
Small Scale Production Equipment for a Company in Malaysia

- **Liquid and freeze dried vials**
- **Performance up to 1.000 units per hour**
- **Design capable of handling products up to a OEB 1-20µg/m³**
- **Investment for the following equipment less than 4 Mio Euro (5 Mio. US $)**
  - 2 Isolators (Grade A)
  - 1 VHP pass box
  - 1 FD (5m² shelf area)
  - 1 Filling and closing equipment
  - 1 Capping machine
  - 1 Isolator (Grade C)
  - 1 Outside washing machine

→ A bulk vial line would be min. 6 Mio. Euro (7.5 Mio US $)

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2. Process Technology -- RTF Primary Containers

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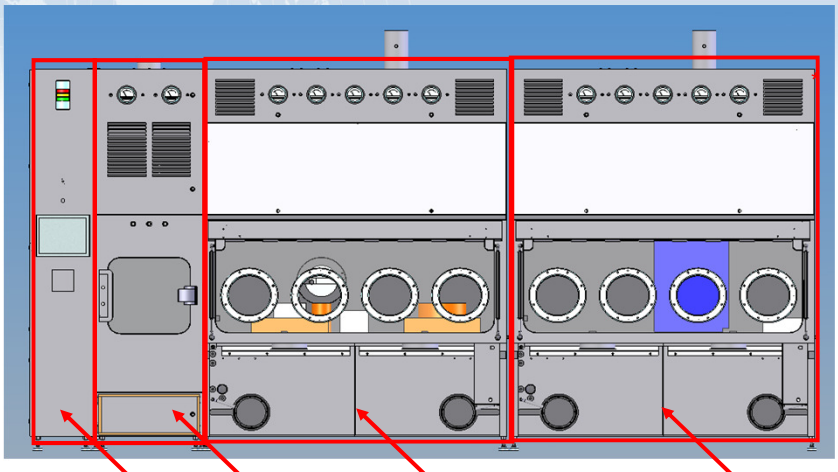

* Pictures courtesy Skan AG

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2. Process Technology -- RTF Primary Containers

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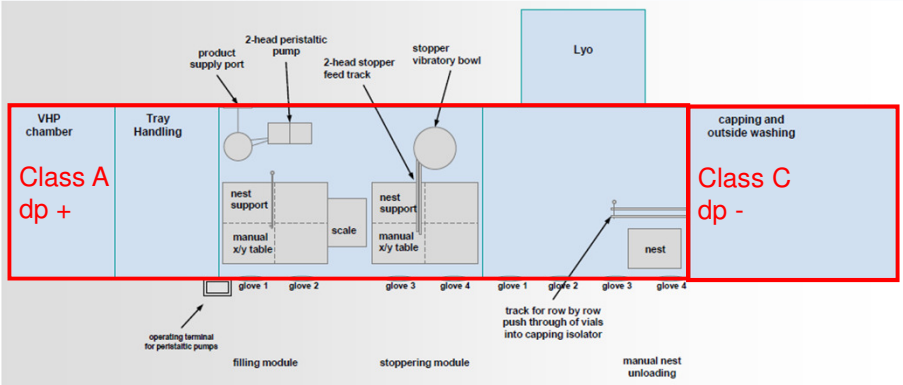

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2. Process Technology -- RTF Primary Containers

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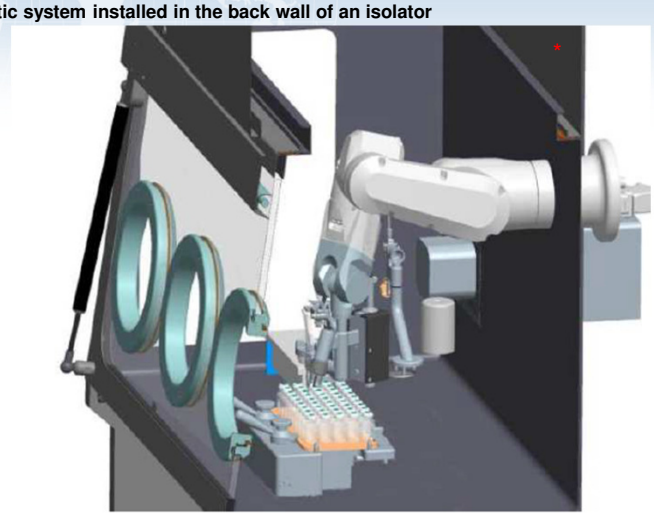
Robotic system installed in the back wall of an isolator



* Pictures courtesy Skan AG

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2. Process Technology -- Single Use Components

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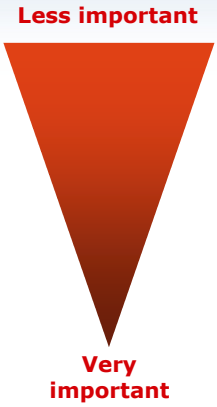
General Advantages

- Saving utilities (CIP/SIP)
- Saving investment costs
- Avoiding 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



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2. Process Technology -- Single Use Components

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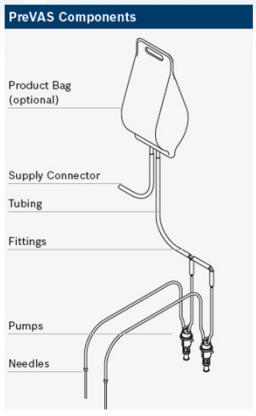
Rolling diaphragm pump or peristaltic pump



* Pictures courtesy Robert Bosch GmbH

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2. Process Technology -- Single Use Components

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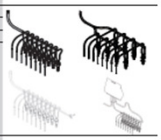
Component	Options	Picture
System Connector	Quick Disconnect Tri-Clamp Adamptar Sterile Connector Other	
Bag Assembly	None 2 Liter 5 Liter 10 Liter	
Manifold Configuration	Inline Split Line Bleed Valve Recirculation Loop	
Number of Pumps/Needles	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	
Pumping System Type	Peristaltic Dual Line 6cc RDP 50cc RDP	
Needles (Inside Diameter)	1.2mm 1.5mm 2.1mm 3.0mm 3.8mm 4.6mm 5.2mm	
Packaging Requirements	Double Bagged Tripple Bagged RTP Port for Isolator/RABS	

Advantages:

- Pre qualified construction kit which reduces costs and timelines for the user
- Reduced costs due to standardization
- Better regulatory acceptance

Disadvantages:

- Tailor made for Bosch filling machines
- Dependent on one supplier
- Customer specific changes in the system will be very limited

* Picture courtesy Robert Bosch GmbH

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3. Some conclusions

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3. Some Conclusions -- For further Questions

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- **Isolator Technology**
  Will develop further in the future and will dominate the aseptic fill & finish industry in the future
- **Single Use Filling Systems**
  Peristaltic pump systems are often the preferred system for Biopharmaceuticals, standardized (pre-validated) single use filling systems are entering the market more and more
- **Flexibility**
  Next generation of RTF filling machine will be able to process syringes **and** vials with very short downtime for change over
- **Robots / Handling systems**
  Individual positive transport, avoidance of glass to glass contact, minimizing rejects and glass breakage rate and very flexible (fast) format change

The combination of all 4 topics as a package provides significant advantages in terms of product quality, productivity and flexibility !

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Thankyou for Your Attention

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