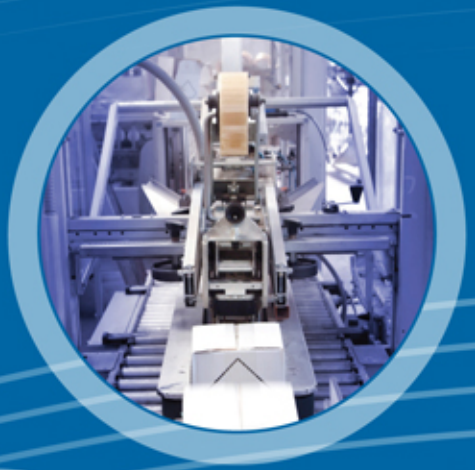
Connecting People, Science and Regulation®

Maturing Aseptic Technologies create more flexible Facilities

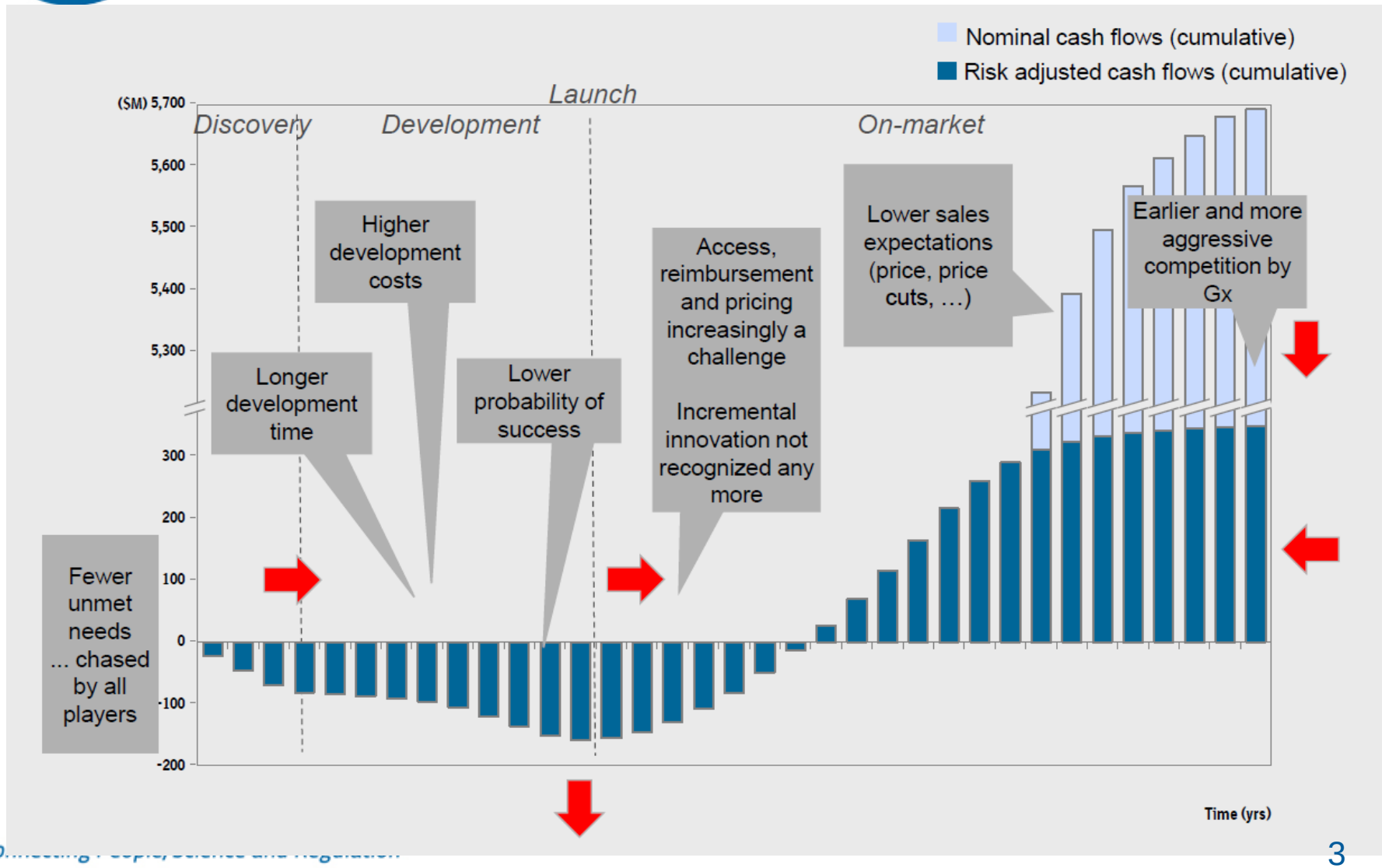


Dr. Friedrich Haefele
Boehringer Ingelheim Pharma GmbH & Co. KG

Content

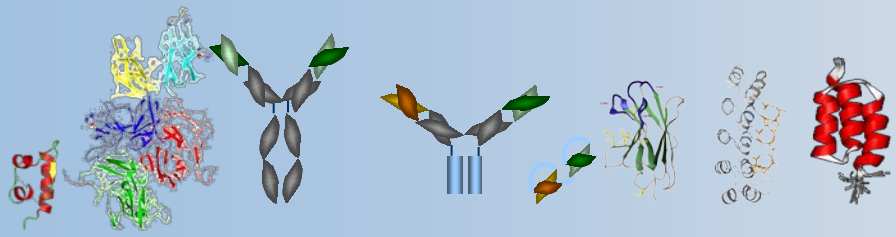
- Changing Environment for Parenteral Manufacturing
- Translation into Facility Construction
- User requirements for a flexible parenterals filling unit
- Conversion into BI´s Modular Isolator Plant…
- Comparison Modular Isolator Plant to RABS/Conventional Clean room filling (Project Execution, Running Costs)
- Summary

The PM Pharmamodel does not work anymore…



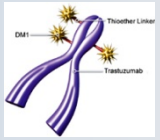
Technology Platforms API
New Molecular Entities (NBE+NCE=NME`s)

Biotechnology New Biological Entities (NBEs)	BioTech meets Chemistry	Chemistry (NCEs)
Dominant Cell Systems: Mammalian, Microbials	Conjugates: PEGylation HESylation Antibody Drug	
Major process steps: Upstream / Fermentation Downstream / Purification	Synthetic Biology Synthesis using cell-free systems	Chemical Synthesis

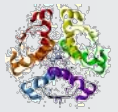


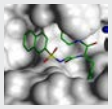
Natural structures

Designed natural structures



Fusions/Conjugates

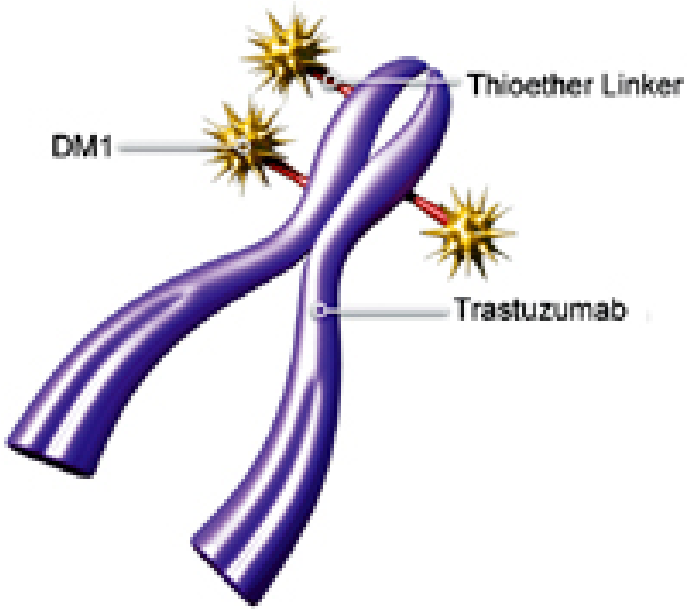




Synthetic molecules

Innovative therapeutic approaches ...

ADCs and Therapeutic Vaccines



Genentech
T-DM1 combines Genentech's blockbuster antibody Herceptin and the antimitotic cytotoxic DM1 using ImmunoGen's linker technology.

Sarah Webb, Nature Biotechnology 29, 297–298 (2011)
Published online 08 April 2011

...require new

Regulatory Considerations for

- Assay Development in Product Characterization &Quality Control

and set new technological challenges for

- Production of toxins
- Conjugation of toxin to Mab
- Fill & Finish services
  - aseptic processing
  - cross contamination
  - operators safety

Biopharmaceuticals = Parenterals
at present no real alternatives (transdermal, oral….)

„Biopharma meets Medical Devices“

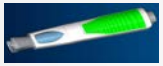
liquid

Ampoule →

Vials → Combination Products

Cartridges → Pens

Prefilled Syringes → Autoinjectors



Lyo

Vial →

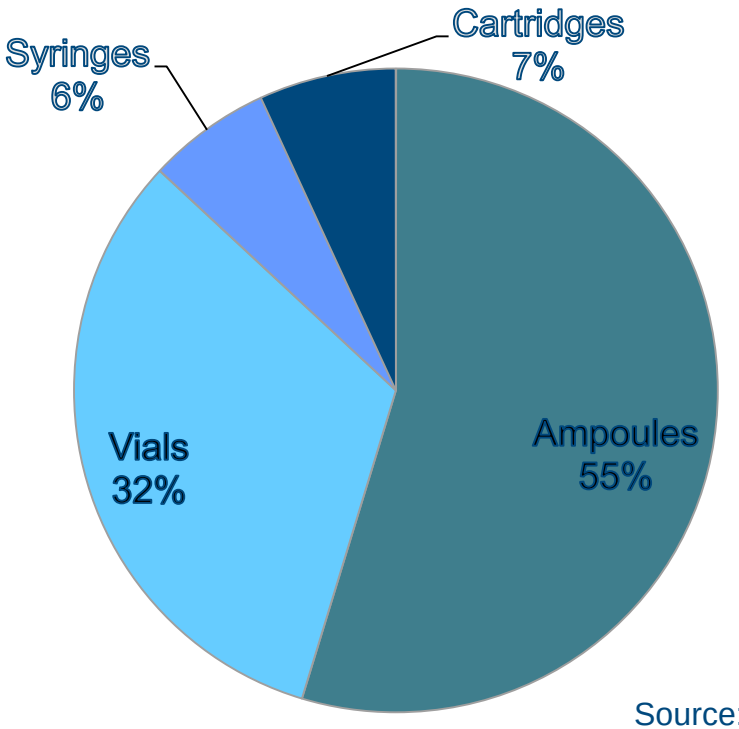
Doublechamber Cartridges →

Pens

Connectors to mobile systems

Global Market Estimation 2012
Small Volume Parenterals (up to 50 mL)

SVP 2012: Total 29 bn units



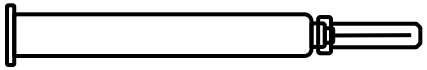
Source: IMS Data

Global Market Growth Estimation 2013 - 2018
Small Volume Parenterals (up to 50 mL)

UNITS

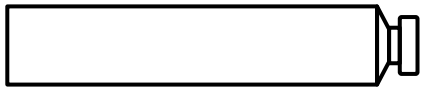
+4-5%

- Anti-Diabetics
- High Value Drugs in Valuable Markets
- Rare Deseases
- Vaccines in Emerging Markets



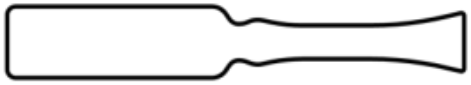
+5-8%

- Anti-coagulants
- Vaccines
- Anti-infectives
- Anti-inflammatory agents
- Haematological agents
- MS treatments
- Human growth hormones
- Obstetric agents
- Cancer therapies
- Pain relievers



+8-10%

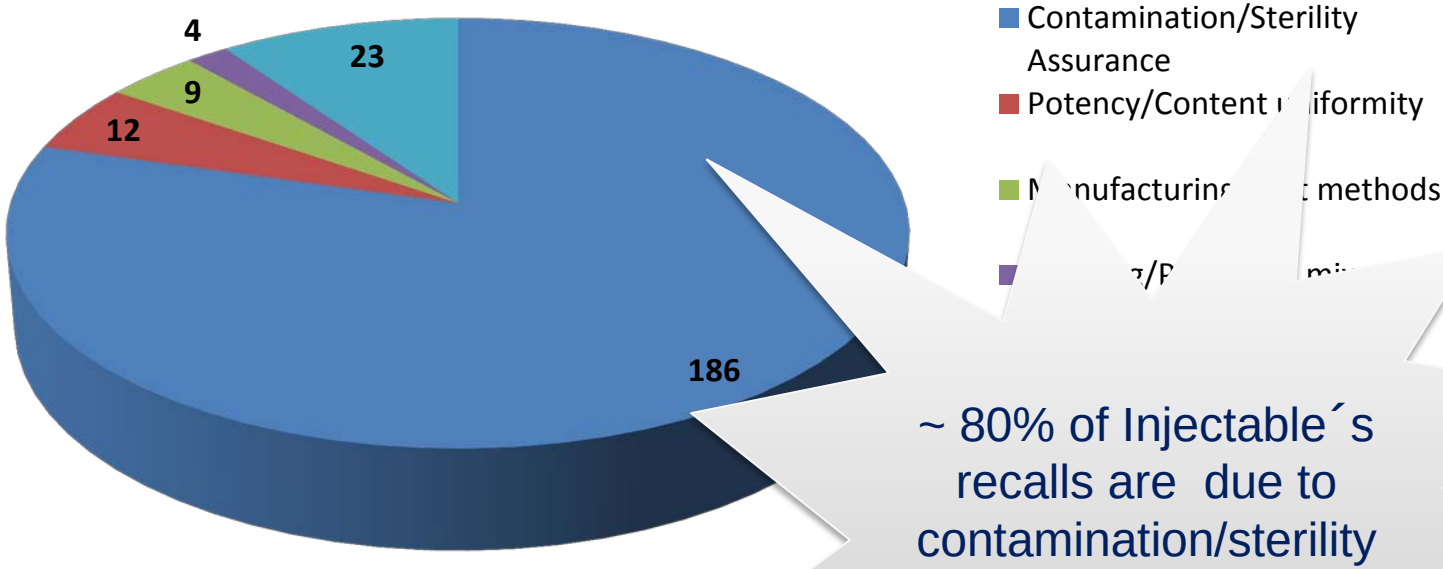
- Anti-Diabetics
- Self-Injections
- MS treatments
- Human growth hormones



+5%

- Vaccines
- 1° Healthcare

2012 US Drug Recall Analysis for Injectables by Problem area



Source: „The Gold Sheet“, Vol.47, No.5, May

~ 80% of Injectable´s recalls are due to contamination/sterility assurance issues

For parenteral facility construction this translates into…

- Provide options for all relevant dosage forms
- Be prepared for high potent drug processing
- Consider a high variability of products with small batch size
- Delay decision point for project kick off
- Less upfront capital expenditure
- Shorten timelines for project execution
- Shorten timelines for equipment qualification
- Quick process transfer and validation
- Low running costs
- Comply with increasing quality standards- especially for aseptic processing

User requirements
for a flexible parenterals filling unit

User requirements -1-
for a flexible parenterals filling unit…

- Construction in Isolator technology ISO5/A in ISO7/C

  => simple Gowning Concept

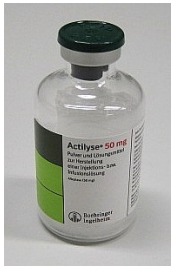
  => flexible Personnel utilisation
- automatic, reproducible, well documented system for Bio- Decontamination

  => significant increase of SAL relative to Conventional Cleanrooms and open - RABS Systems
- reduced Microbiological Monitoring

  => less risk for false positives

User requirements -2-
for a flexible parenterals filling unit…

Vials (lyophilisate)



Vials (liquid)

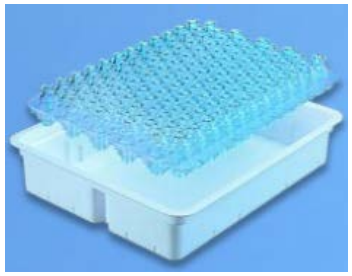
Pre-filled Syringes

Single and Double Chamber Cartridges

Aseptic filling			
Vial size		Size	
Vial type	Diameter	pilot scale, clinic	
		liquid	lyo
2 R	16 mm	10,000	6,500
6 R	22 mm	8,000	3,350
10 R	24 mm	7,000	na
20 R	30 mm	5,000	1,750
50 mL	40 mm	2,200	na
100 mL	47 mm	2,000	na
Capacity p.a.		1Mio 20R Vials (liquid)	
Syringe:	1 mL long	Lot size: 10,000	
Capacity p.a.		1 Mio syringes	
Cartridge	1 mL – 3 mL	Lot size: 8,000	
Capacity p.a.		800K cartridges	
Double Chamber Cartridge (DKK):	1 mL – 3 mL	Lot size: 4,000	
Capacity p.a.		150K DKK	

User requirements -3-
for a flexible parenterals filling unit…

Utilization of Ready to Use Components…



Nuova Ompi
glass division
Stevanato Group

BD

Boehringer Ingelheim

…or do it your self!

SCHOTT
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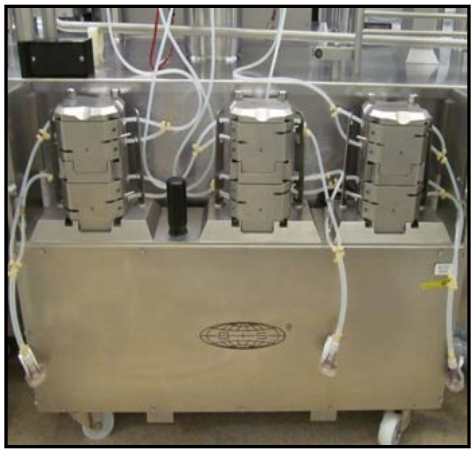
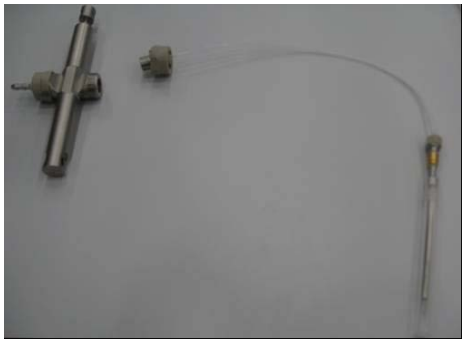
User requirements -4-
for a flexible parenterals filling unit…

- Sartorius IDC Port ID 105 mm
- CRL Autoclavable SS Beta Container for 190 mm RPT port
- Getinge 190mm DPTE® Container



- Peristaltic pumps
- Rotary piston pumps



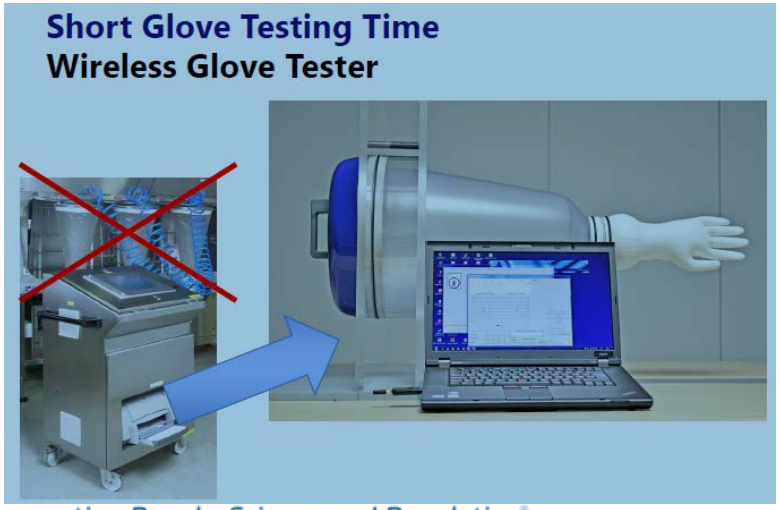
Customized disposible
Filling set

DPTE® transfer system =
Double Door Transfer Port
(Getinge La Calhène)

User requirements -5-
for a flexible parenterals filling unit…

The LYOVAC™ GT 10-P

Provide option for Lyophilizer integration

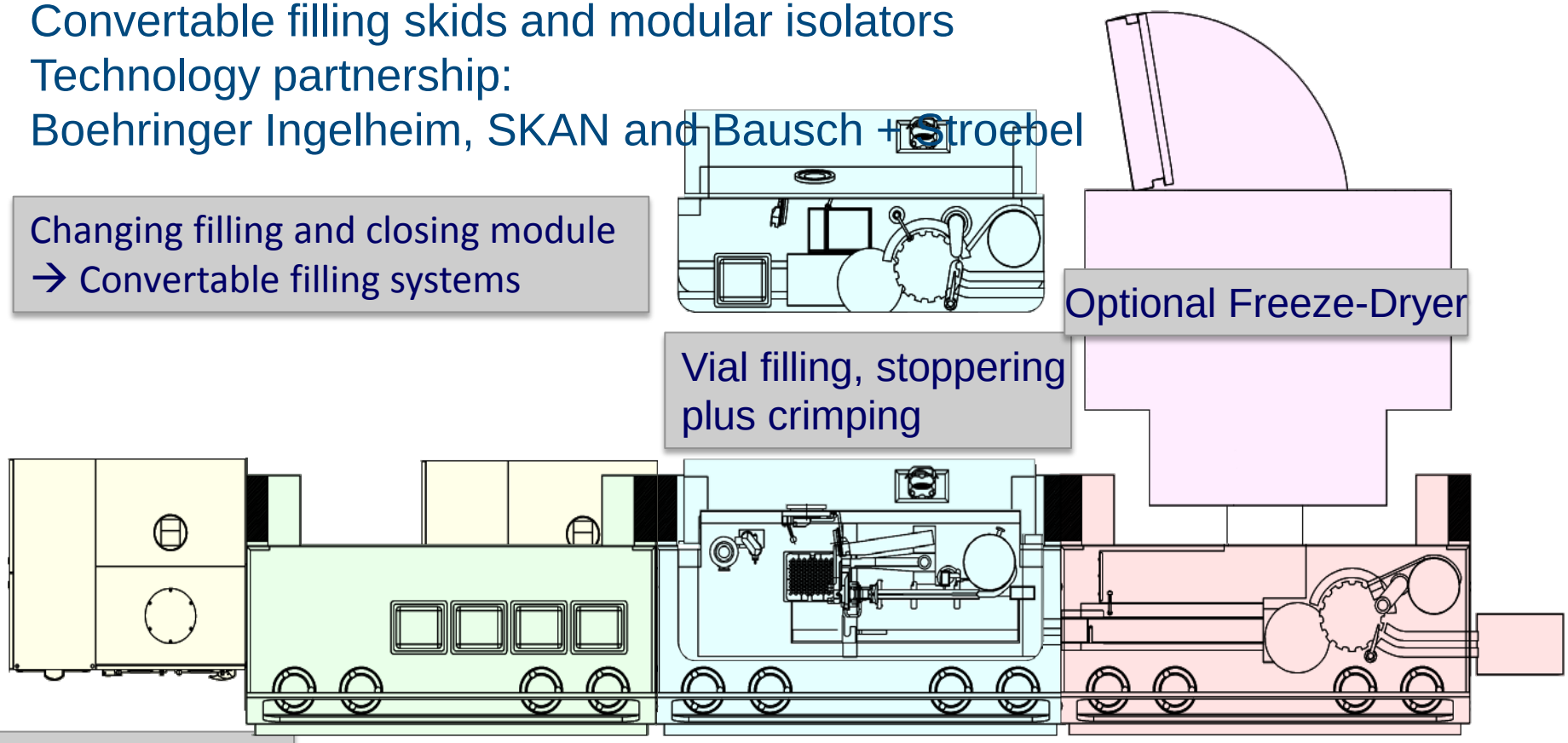


Conversion
into BI´s Modular Isolator Plant…

Conversion
into BI´s Modular Isolator Plant…

Convertable filling skids and modular isolators
Technology partnership:
Boehringer Ingelheim, SKAN and Bausch + Ströbel

Changing filling and closing module
→ Convertable filling systems



Optional Freeze-Dryer

Vial filling, stoppering plus crimping

Quick H_2O_2 Airlock

Empty modules e.g. decontaminating tubs/ pre-fill staging

Syringe filling and closing

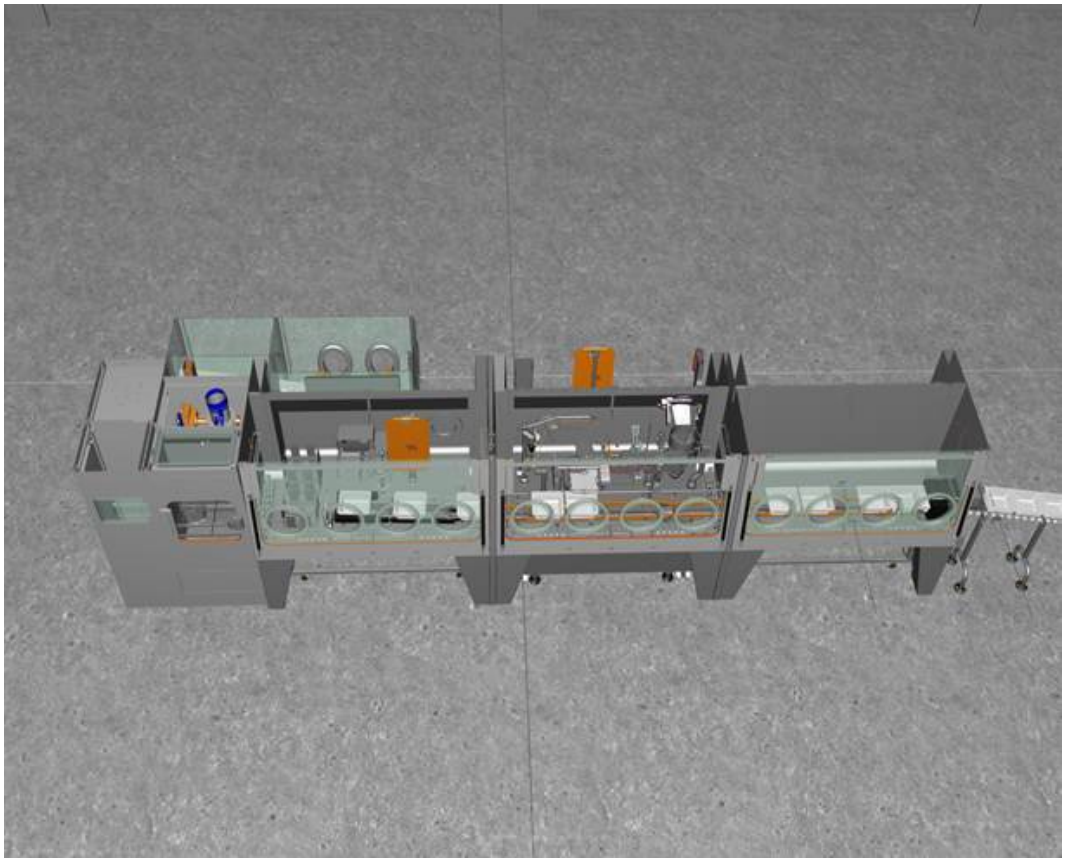
Vial lyo crimping

Conversion into BI´s Modular Isolator Plant…

Specially designed „mouseholes“ allow docking of:

- „SARA“ quick airlock (~20 minute cycle)

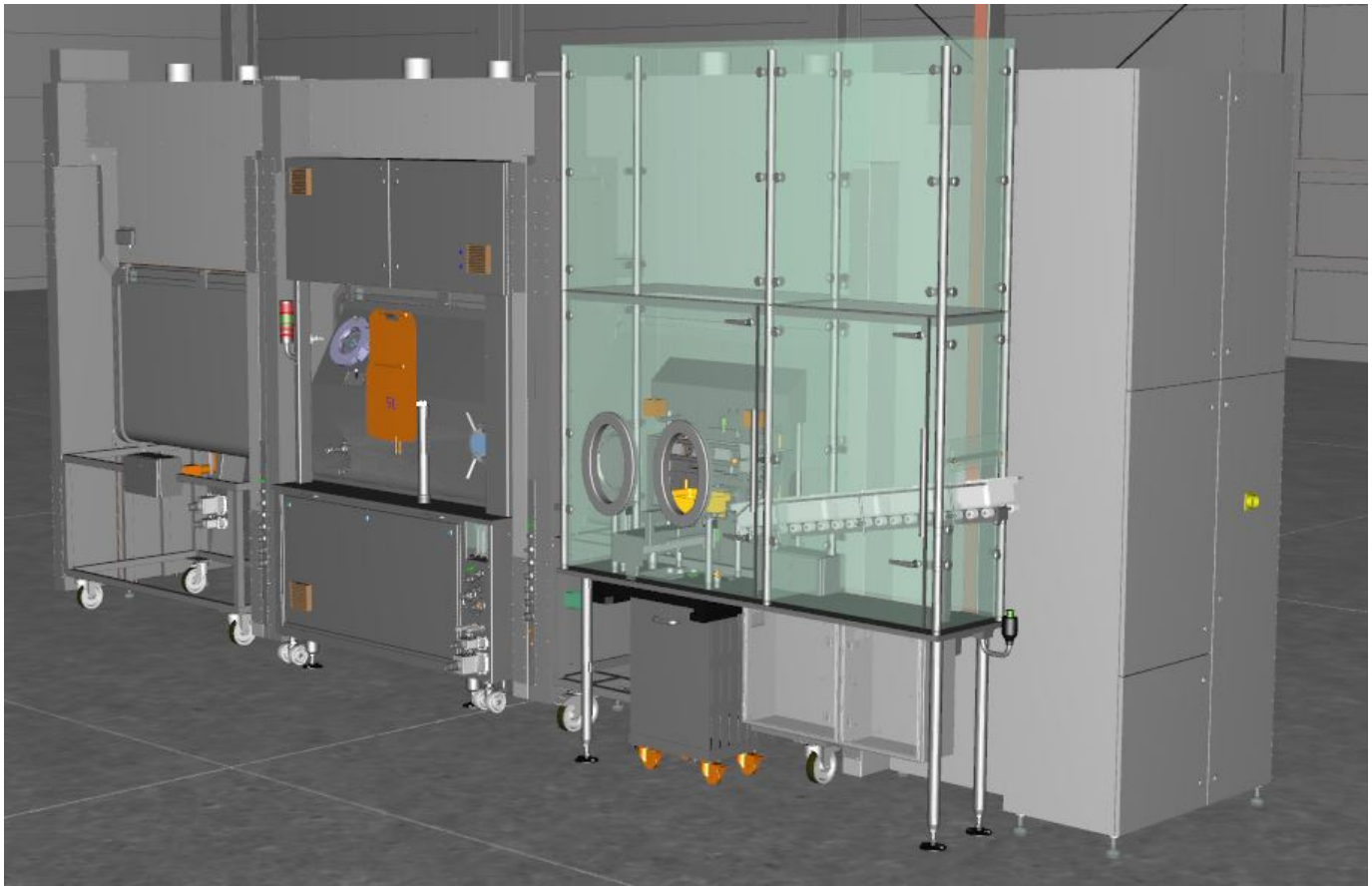
- Separate „Standard“ Isolators (~3.5 hrs cycle) for



- Unpacking…
- Filling…
- Sealing…

Conversion
into BI´s Modular Isolator Plant…

Conversion into BI´s Modular Isolator Plant…



Automated Tub Unpacking Machine (TUM)

allows

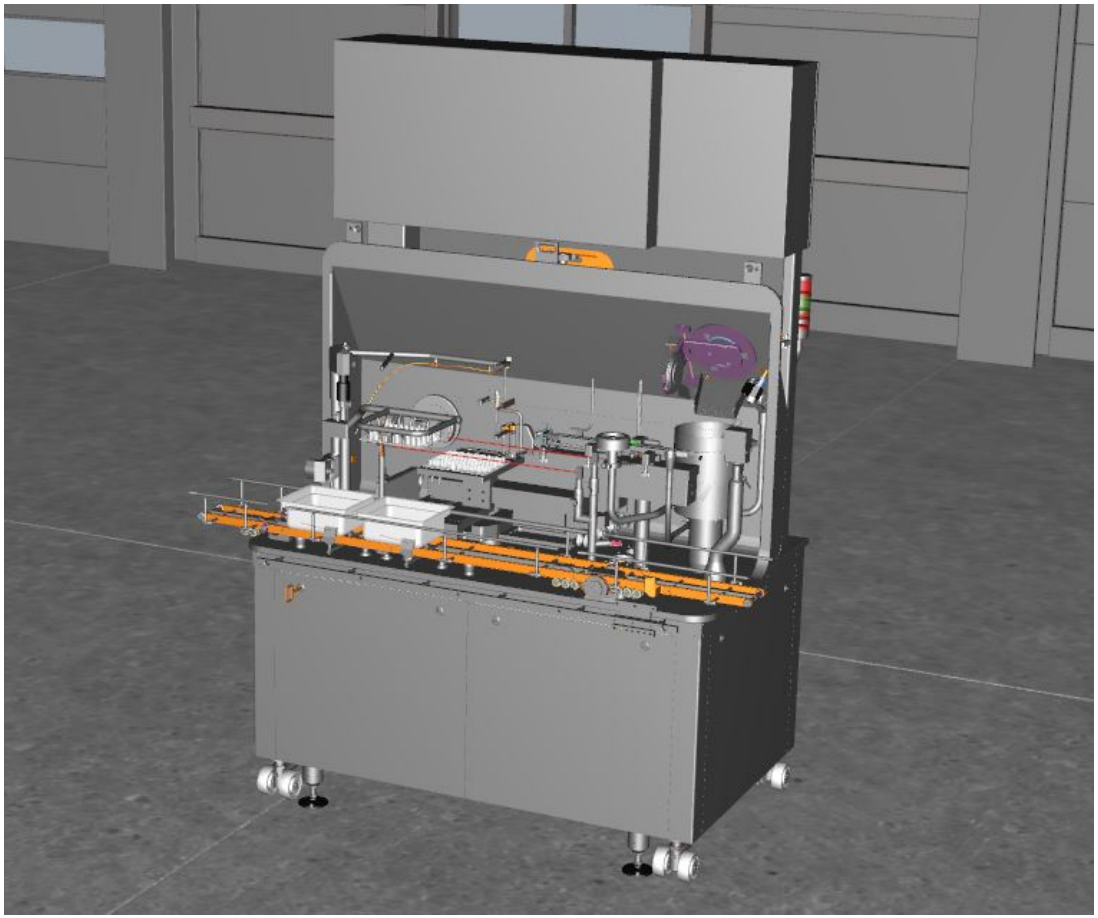
efficient Transfer of nested Ready to Use (RTU) Components

Conversion
into BI´s Modular Isolator Plant…

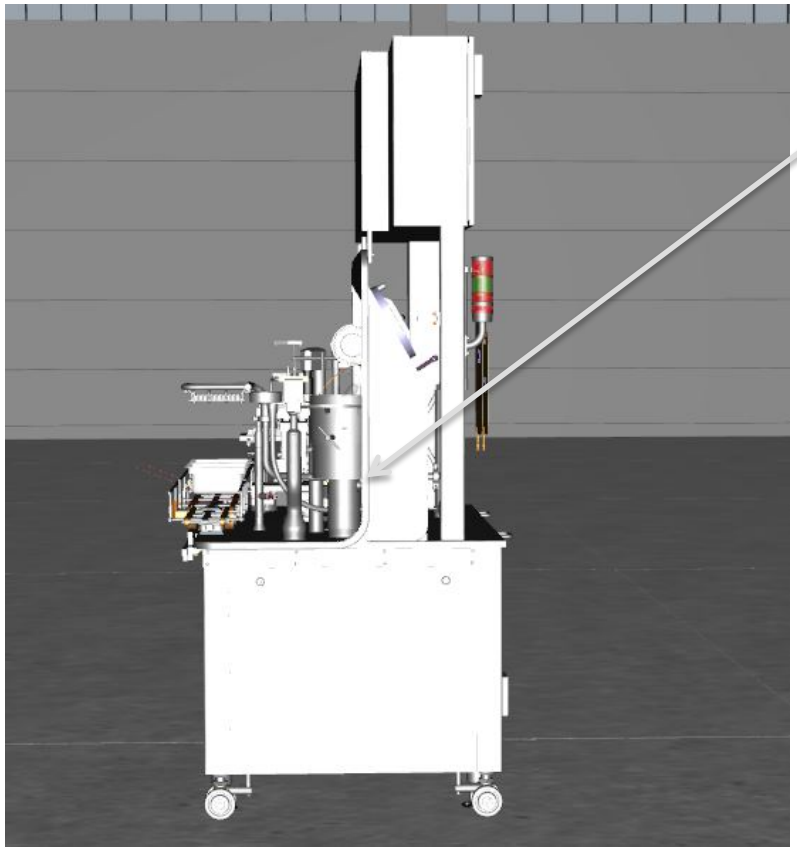
Flexible „L-flanges“
allow
docking of
various filling
principles

- Syringes
- Cartridges
- Vials

to a
„Standard“ Isolator



Conversion into BI´s Modular Isolator Plant…



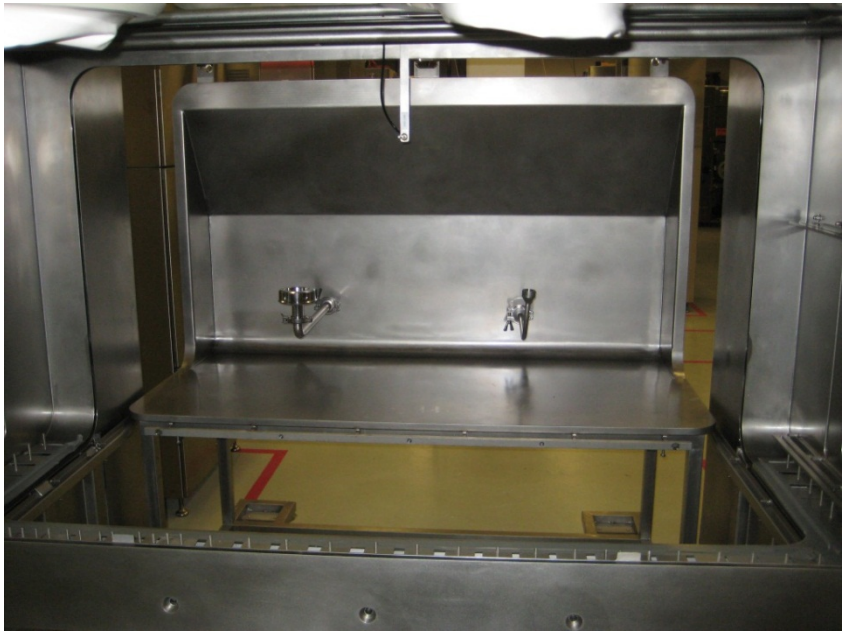
Filler and Isolator Interface

Filler L flange skid

Isolator pneumatic seal

Conversion
into BI´s Modular Isolator Plant…

L-flange Design enables Conversion for Vial and Syringe Operation



Conversion
into BI´s Modular Isolator Plant…

- Syringe Filling

Syringe Filling Isolator Layout (Top View)

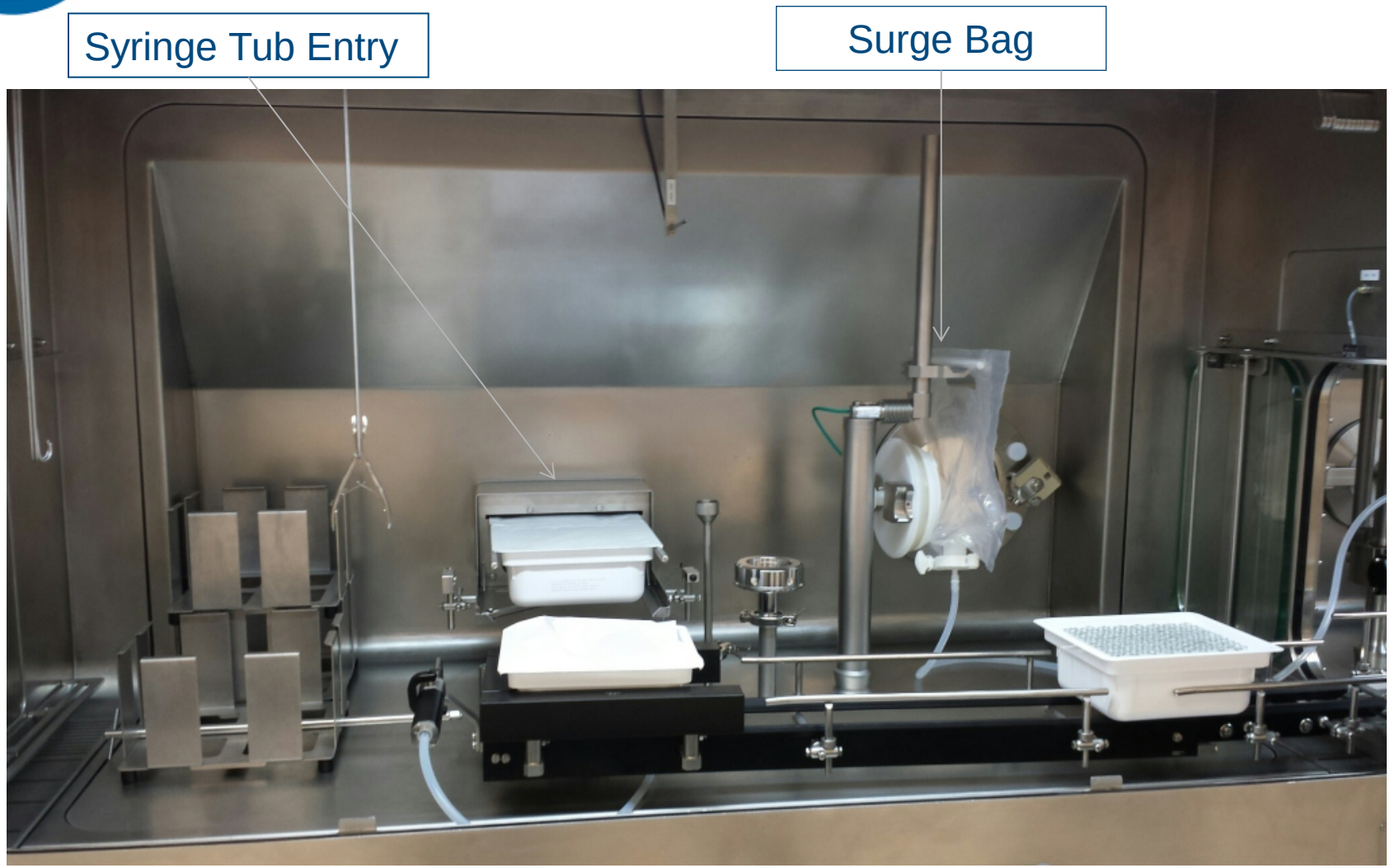
Rear of Isolator: Entry of Ready to Use Components

Plungers

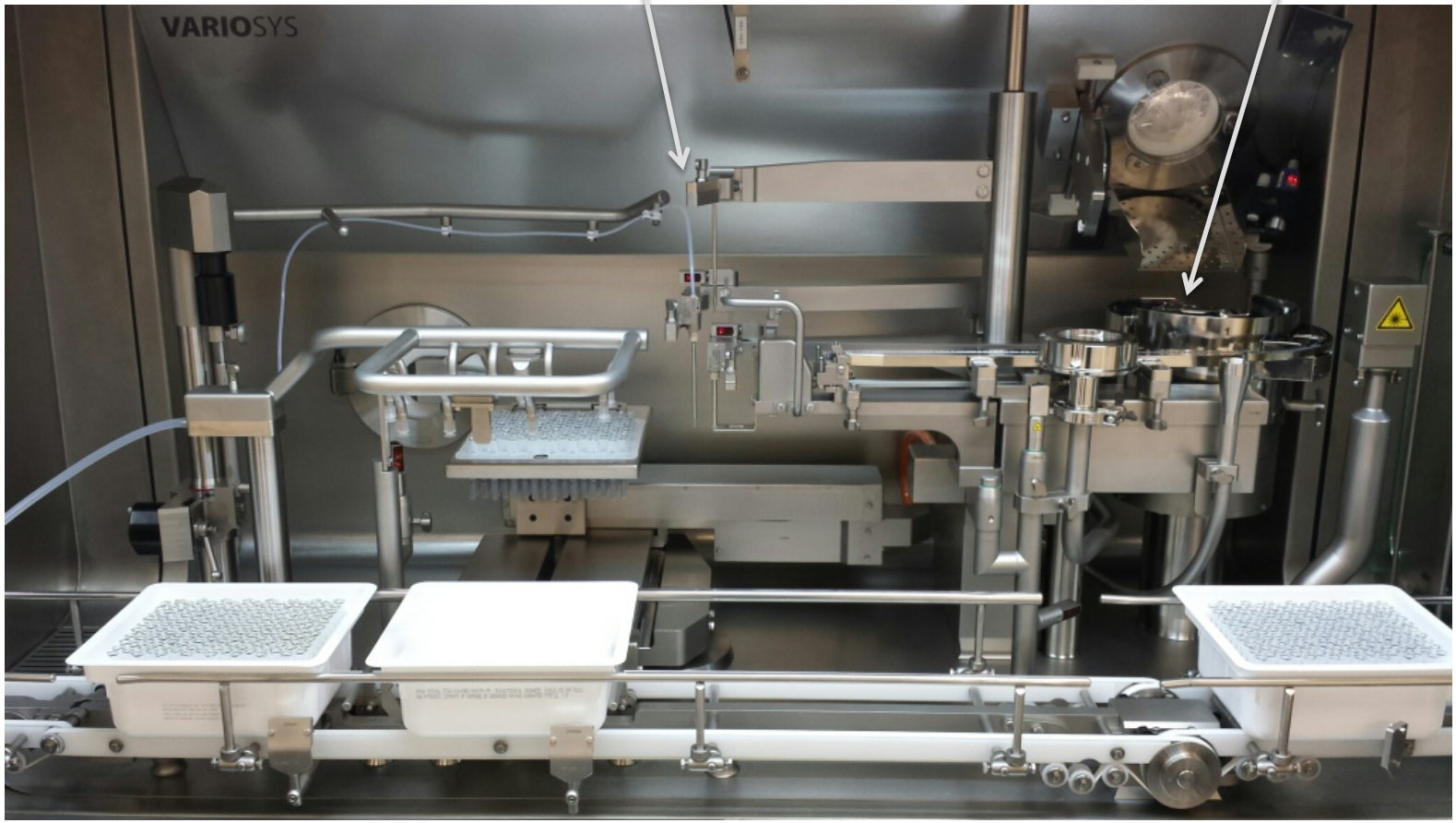
Syringe and Vial tubs

Single Use Filtration Assembly

Syringe Filler Chamber 1: Tub Entry and Surge Bag



Syringe Filler Chamber 2: Filling and Plunger Placement



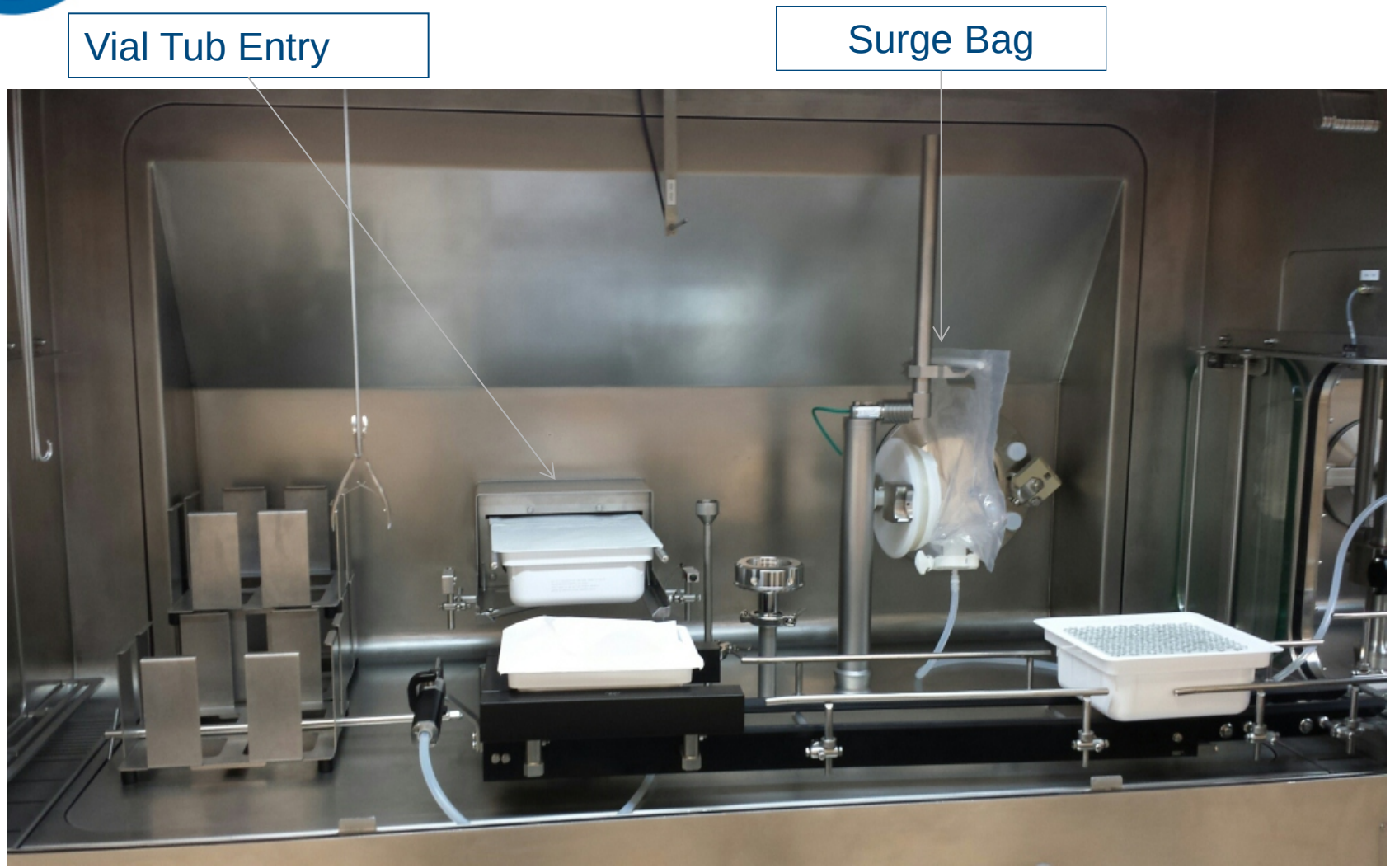
Conversion
into BI´s Modular Isolator Plant…

- Vial Filling

Vial Filling Isolator

Rapid Transfer Airock
Chamber 1 = Preparation Isolator with connected Tub Unpacking Machine
Chamber 2 = Vial Filler and Stopper Setting
Chamber 3 = Vial Capper

Vial Filling Chamber 1: Vial Introduction



Vial Filling Chamber 2: Filling and Stoppering

Vial Filling Chamber 3: Capping

Comparison Modular Isolator Plant to RABS/Conventional Clean room filling

Comparison Modular Isolator Plant to RABS/conventional Clean room filling (I)

	RABS/Conventional cleanroom (A in B) • bulk components • 1x integrated Syringe/cartridge filling line • 1x integrated vial filling line • 2x autoclave • 2x VHP deco • 2x parts washer		Modular isolator (A in C) • RTU components • 3x Standard isolators, • 4x L-flange (tub unpacking, syringe filling, vial filling, vial capping) • Quick VHP airlock • Autoclave ; parts washer	
Project Execution				
CAPEX (equipment)	12 Mio €		4.5 Mio €	- 2x Washer - 1x Siliconisation - 2x Depyro tunnel
Cleanroom footprint ; HVAC + utilities	A(ISO 5) : 2x 15m² B(ISO 5 at rest) : 2x 100m² C(ISO 7) : 2x 250m² Others : 2x 100m² Airlocks : 2x 200m² 2x 665m² = 1.330m² = 17.3mio€,		A(ISO 5) : 5m² B(ISO 5 at rest) : n.a. C(ISO 7) : 250m² Others : 60m² Airlocks : 100m² 415m² = 5.4mio€	6.500.- € - 13.000.-€ per 1m² cleanroom; HVAC + utilities
Batch size 12hrs	120.000 PFS 1mL and 120.000 2R Vials		40.000 PFS 1mL or 40.000 2R Vials	
Capacity p.a.	22 Mio PFS 1mL and 22 Mio 2R Vials		7.2 Mio PFS 1mL or 7.2 Mio 2R Vials	4 batches/week 45 weeks/a
Timeline	2 x 36 months; 2 project teams		1 x 30 months; 1 project team	Delivery/ Installation/ Qualification
Smoke studies	A(ISO 5) B(ISO 5 at rest)		A(ISO 5) n.a.	
Qualification, Validation	+ 2x Washer + 1x Siliconisation + 2x Depyro tunnel		+ VHP Deco Cycle	

Comparison Modular Isolator Plant to RABS/conventional Clean room filling (II)

Running Costs	RABS/Conventional cleanroom (A in B) • bulk components • 1x integrated Syringe/cartridge filling line • 1x integrated vial filling line • 2x autoclave • 2x VHP deco • 2x parts washer		Modular isolator (A in C) • RTU components • 3x Standard isolators, • 4x L-flange (tub unpacking, syringe filling, vial filling, vial capping) • Quick VHP airlock • Autoclave ; parts washer	
annual Requalification	+ 2x Washer + 1x Siliconisation + 2x Depyro tunnel		+ VHP Deco Cycle	
Media fills	2 x per line, per year		2 x per dosage form, per year	
Viable/non viable Monitoring	150 samples/batch		30 samples/batch + Physical glove monitoring	Costs for sample processing Potential deviations Potential loss of a batch due to false positive monitoring sample
Gowning	Aseptic gowning (600.- € per siut) Change over time: 1,0 – 1,5 min per FTE/shift		Clean room gowning (200.- € per suit) Change over time: 0,5 min per FTE/shift	~ 26 FTEs for 2 shift operation
Annual Gowning qualification	++++++		n.a.	
Utilities: HVAC, WFI, Clean steam	++++++++		++	Energy costs
Change over	Wipe down + aseptic set up 4 – 6hrs		Wipe down, VHP decontamination + aseptic set up 4 – 6hrs	3.5hrs VHP deco + aeration time
Components	Bulk Vial ~60.-€ per 1000 Bulk PFS ~150.-€ per 1000		RTU Vial ~350.- € per 1000 RTU PFS 500.-€ - 900.-€ per 1000	Less risk for particulate contamination- no glass/glass contact

Summary

Modular Isolator and RTU Components Benefits…

- Options for all relevant dosage forms
- Prepares for high potent drug processing
- Considers a high variability of products with small batch size
- Reduced upfront capital expenditure
- Small cleanroom footprint
- Shortened timelines for project execution
- Shortened timelines for equipment qualification
- L-flange design enables changeover between syringe and vial filler, lyophilizer option
- Relative low running costs
- Increased Sterility Assurance Level (SAL)

Thank you for attention!

Acknowledgements

Brian Greven	BIF-US
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