Single Use Technologies – Overview and Business Drivers

PDA Single use systems for Pharmaceutical Applications. Melbourne 20th March 2012

Luke Heaven – Director of Marketing (EU/Asia/NEMEA/Cuba)

1. Introduction

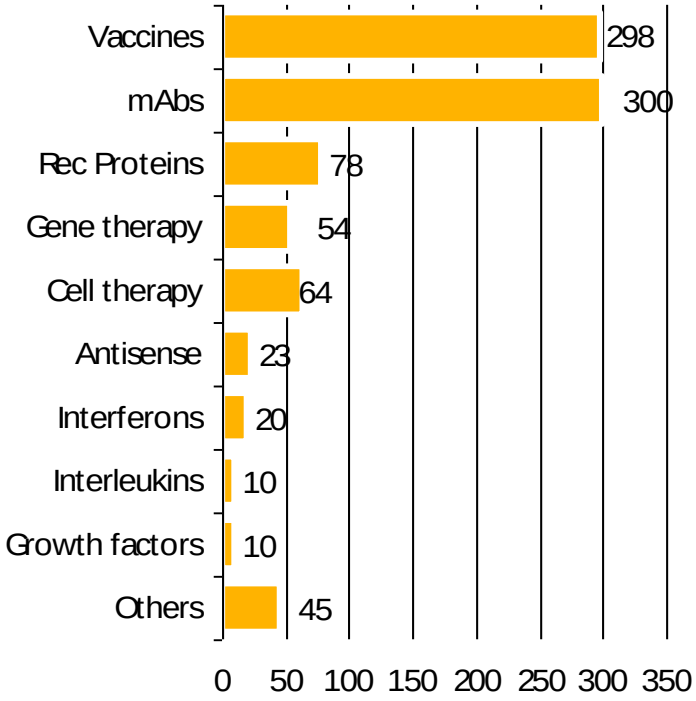
2. Business Drivers for SUS

3. Single-Use Today

4. Summary

Biotech Becomes Predominant Vs Pharma Innovation Drivers mAb's and Vaccines

Biotech Drugs in Development by Product Category*



- >50% of newly approved drugs are biotech drugs
- **mAb's** targets mainly asthma, Crohn's disease, rheumatoid arthritis, or various types of cancer
- Therapeutic **vaccines** development (AIDS, cancer)
- mAb's & vaccines show a strong trend towards SUS

Source: PhRMA 2011 Report Medicines in Development – Biotechnology
* of America's leading pharmaceutical research and biotechnology companies

Future Biopharmaceutical Markets

The most interesting target products for the next future in the biopharmaceutical industries are :

- Monoclonal Antibodies (mAbs)
- Therapeutic Proteins
- Vaccines

The biopharmaceutical market, estimated value and forecast 2009-2015 (Billion $) is shown in the Table below.

Year	2009	2010	2011	2012	2013	2014	2015	Annual Growth %
MAbs	38	41	45	50	55	59	64	6,30
Therapeutic Proteins	61	63	66	69	72	75	78	4,40
Vaccines	18	19	21	23	25	26	28	8,10
Total Market	117	123	132	142	152	160	170	6,70

Source: Business Insights Ltd.

Source: Future Marketing and Sales Opportunities in the Asia Pacific Region, Detlef Lobas – Sartorius Stedim Biotech, 2011

Biotech Processes – Unique Attributes & Needs

- High potency drugs have extraordinary cleaning requirements
- End-user protection has an elevated focus
- Process utilization optimization by multi-purpose use
- Low investment motivation due to high risks of success
- Flexible small scale development process designs
- Fast turn-around and set-up for process capacity increases
- Ease-of-use to assure failure rate reduction

Biotech Industry‘s Challenges
Focus Shift from Kg’s to Cog’s

- Facing the small molecule challenge of the past
  - Price pressure and affordability call for significant reduction of costs
  - Need for process improvement Vs complex regulatory
  - Manufacturing capacity utilization is too low, i.e. ~ 60%
  - Entrance of Biosimilars Vs patent expiration

- Global market shows regional capacity developments
  - Manufacturing capacity increase in Asia with multiple green field projects
  - Mergers, restructuring and capacity adjustments in Europe and NA
  - mAbs and Biosimilars pipeline in LA

- Technology platform approaches for single-use (SUS), hybrid (HS) and multi-use (MUS) systems

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The Drivers in Bio- Pharmaceutical Processes

Safety

No
Cross
contamination

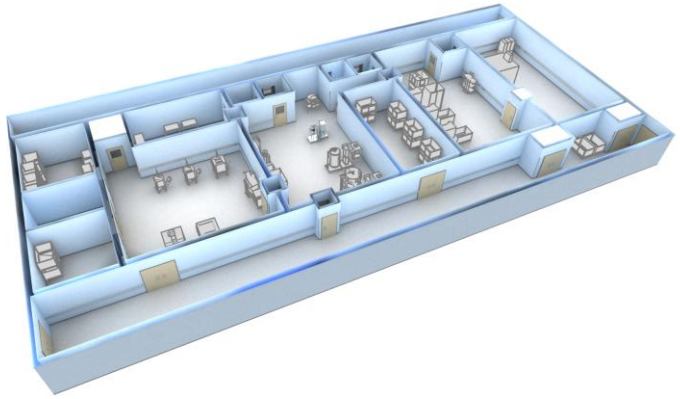
Speed
Value benefit
Process economics (CIP)

Different-
Starting Material
Expression Systems

Efficiency

Quality

The Single Use Market
Benefits of Single Use Technologies are Well Known



Economic Benefits

- Reduce capital investment & commissioning time
- Minimize CIP/SIP validation, utilities & labour
- Reduce foot print & speed up time to market

Improved Safety

- Enhanced user protection via closed systems
- Reduced risk of cross contamination

Flexibility

- Optimize facility layout
- Easy turn around and changeover
- Improved capacity utilization

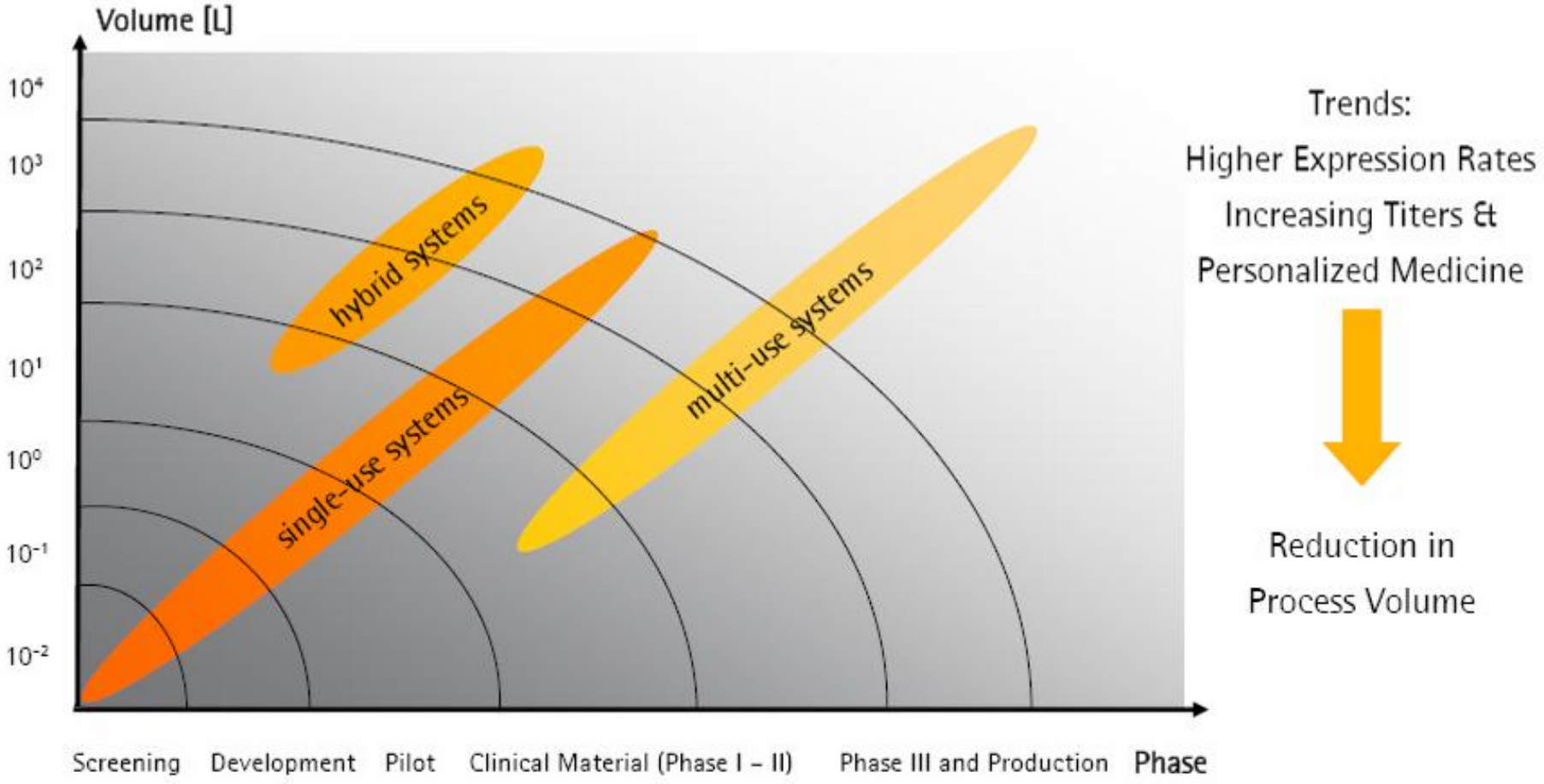
Biotech Industry
Process Improvement Enable Mass Adoption of Single Use

- The Biotech industry has driven the adoption of **Single-Use products,**
- New trend toward single use **unit operations & entire bioprocesses**

- Improvement in **Protein titers** and downstream **purification yields** are the major enabling factors
  - Protein titers growing from < 1g/l to > 5g/l
  - Yield improvement from 30% to >60%
  - 20.000L process scale down to 2.000L

- Single Use BioProcess facility become a reality

When to Apply – Single-use, Hybrid or Multi-use Systems (SUS, HS, MUS)



Hybrid Systems linking Stainless Steel and Disposable Systems

- Product wetted materials stainless steel
- Hard piped
- Transfers by overpressure
- SIP and CIP required

- Product wetted materials from plastics
- Connections by flexible tubing
- Transfers by peristaltic pumps
- SIP and CIP not required

- Starting point for Hybrid Systems are normally Stainless Steel Systems
- Implementation of Disposable (Single Use) sub-systems where feasible
- Implement standardized interfaces between stainless steel and plastics
- SIP and CIP for connecting points only

Drivers for Revamping Projects in Biopharmaceutical Manufacturing

- Life Cycle of installed plants expired
  - Stainless steel 20 to 25 years
  - Instrumentation and automation 10 to 15 years
- Higher automation level for manual operated plants
  - Change manual valve actuators to pneumatic actuators
- Added functionality resulting from process optimization
  - e.g. additional feedings / fed batch for cell culture processes
- Product changes in DSP processes
  - Sizing of process equipment not suitable for changed product titers

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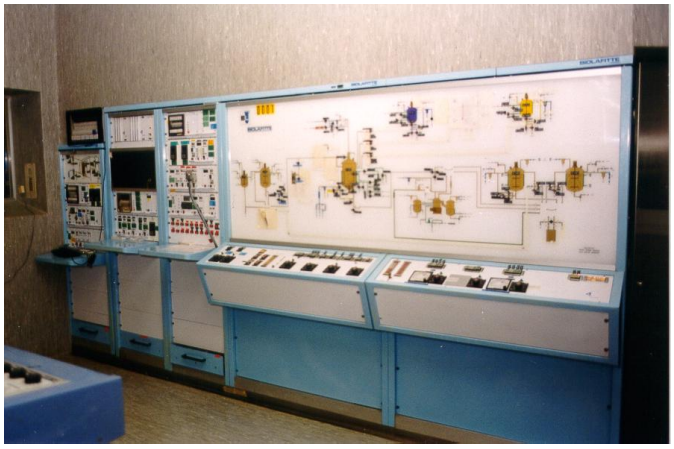
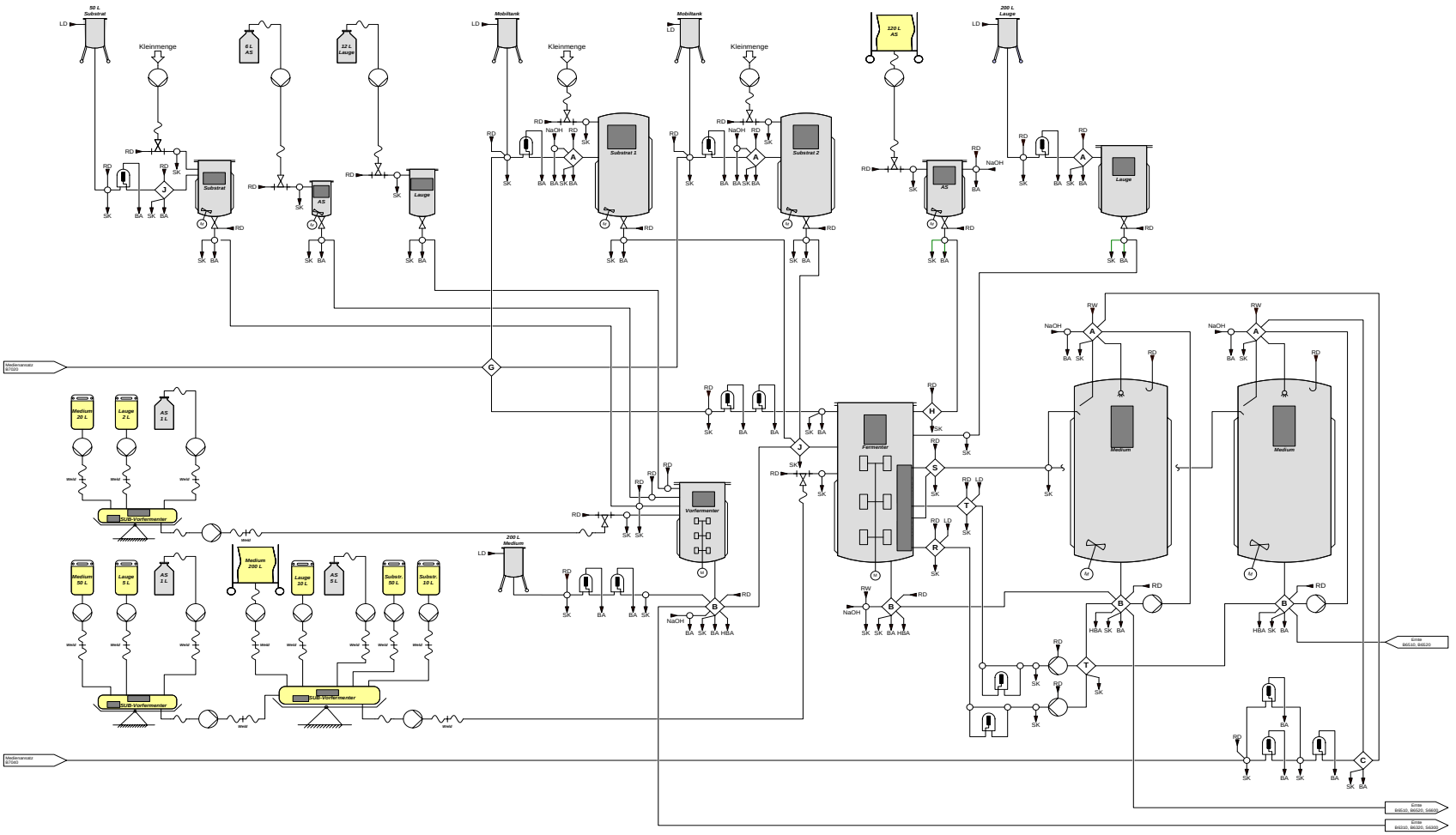


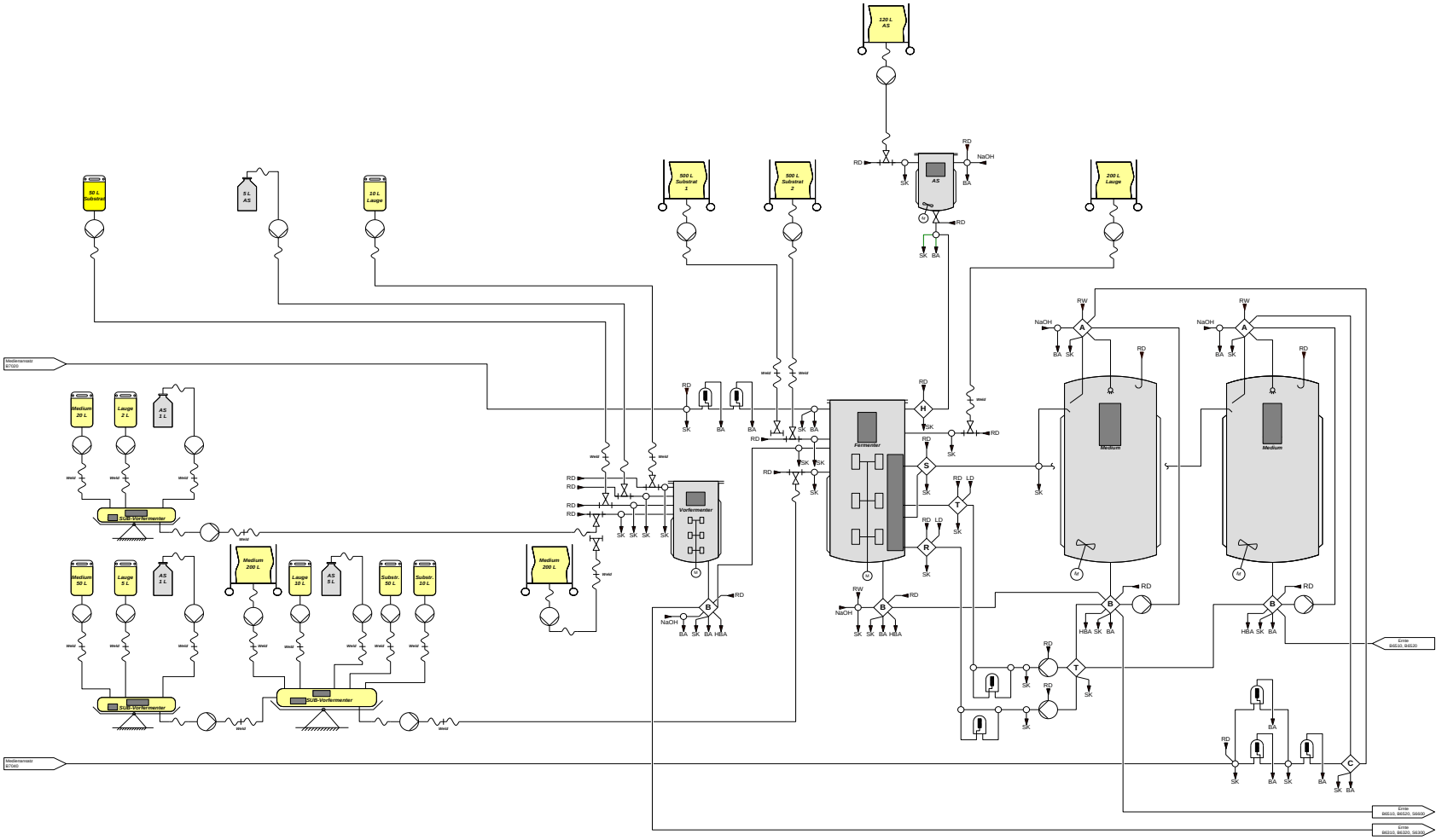
Utilization of Single-Use Systems in Revamping Projects

- Faster realization time by using “of the shelf” pre-engineered equipment
- Less automation, however more manual operations required
- Main applications are addition systems for all kind of media
  - Less complex than fixed piped stainless steel addition vessels
  - Avoid implementation of CIP for old plants
- Replace mobile stainless steel process vessels by mobile bag containers with bags
  - No SIP and CIP required
- Use mobile bags as the transfer system for product
- Allow variability in bag size, especially in DSP processes

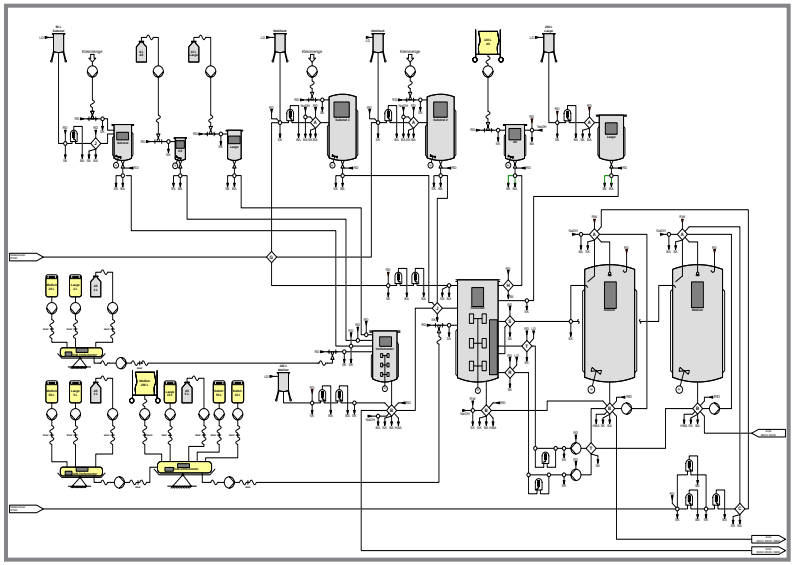

Case Study: Fermentation Expansion Project - Stainless Steel version -

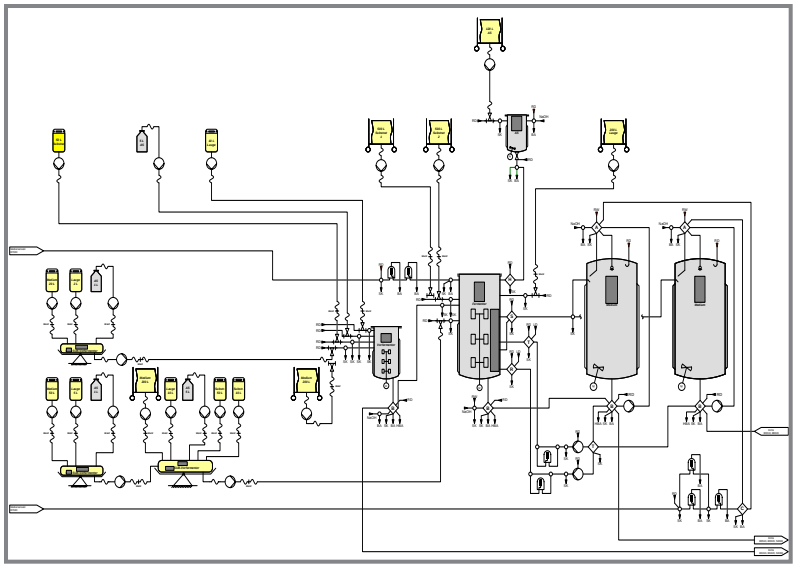


Case Study: Fermentation Expansion Project – Single-Use version.



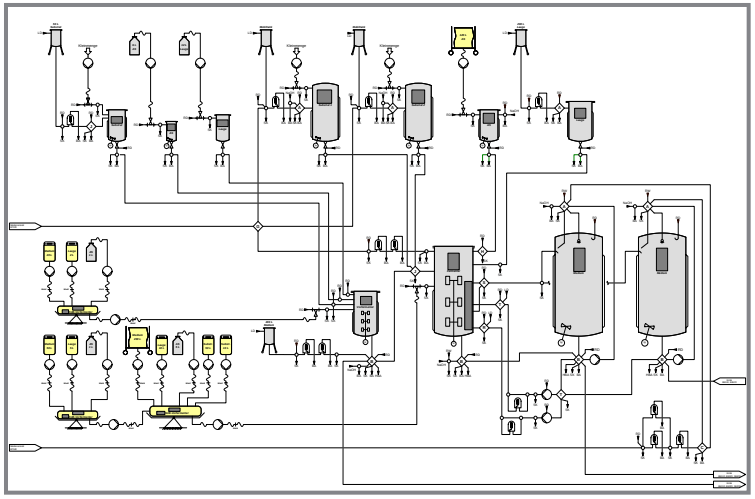
Case Study: Fermentation Expansion Project - Approach -

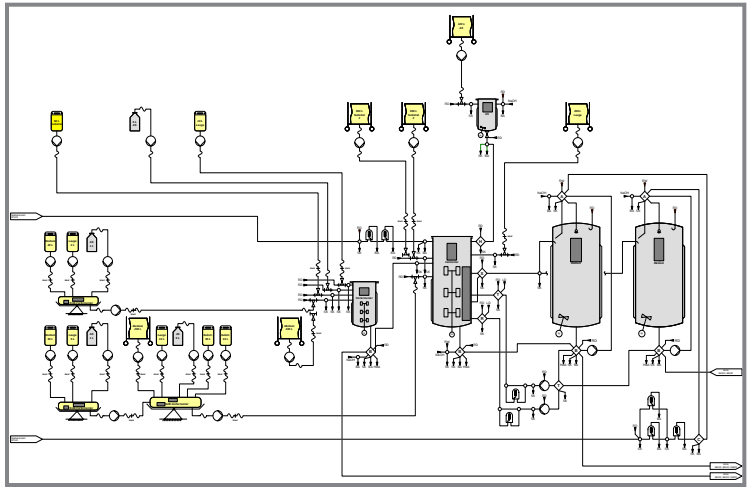




- Seed fermentation train with Disposable Bioreactors (50L, 500L Rocker Systems)
- Keep all addition vessels that need in situ sterilization of media as stainless steel vessels
- Keep all media vessels > 500L as stainless steel vessels
- Replace all addition vessels with sterile filtration of media by moveable bag containers
- Delete all mobile vessels for transportation from media preparation to process area

Case Study: Fermentation Expansion Project - Cost Comparison -





Item	Stainless Steel	Single Use	Savings
Mechanical Equipment	23,4 %	18,1 %	23%
Instrumentation and Control	21,8 %	17,1 %	22%
Manufacturing and Installation	27,9 %	21,9 %	22%
Engineering and Qualification	26,5 %	22,1 %	17%
Transportation	0,4 %	0,3 %	21%
Total	**100,0 %**	**79,4 %**	**21%**

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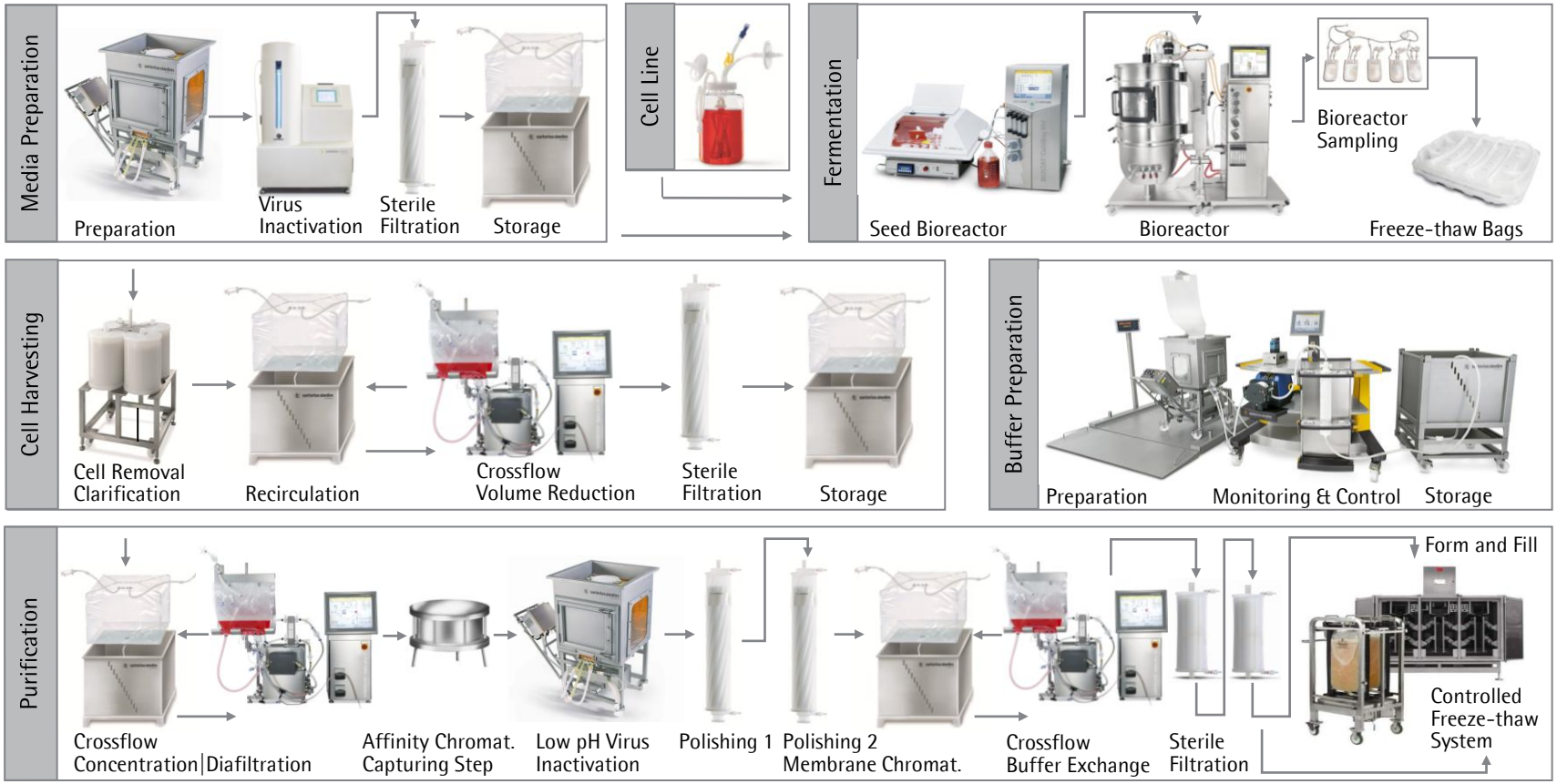
Next Step – is active...

Production Sites using single-use & containment technology to produce, for example, a vaccine at the point-of-use



Single-Use Technologies

Bag Technologies

storage

mixing

dosing liquid

powder additions

Purification and Filtration Technologies

depth filtration

cross-flow (UF/DF/MF)

membrane filtration

membrane adsorbers

Connection and Disconnection Possibilities – Full Range of Applications

Connection Technologies

Steam connectors

For Steam to or Steam Through

For Most Tubings

Used in hybrid solutions

Heat Welding

For Thermoplastic Tubings

Aseptic Connectors

For Most Tubings

Dry or wet connection

Membrane or Mecanical Mechanism

Disconnection Technologies

Heat Sealing

For Thermoplastic Tubings

Mechanical

For most tubings

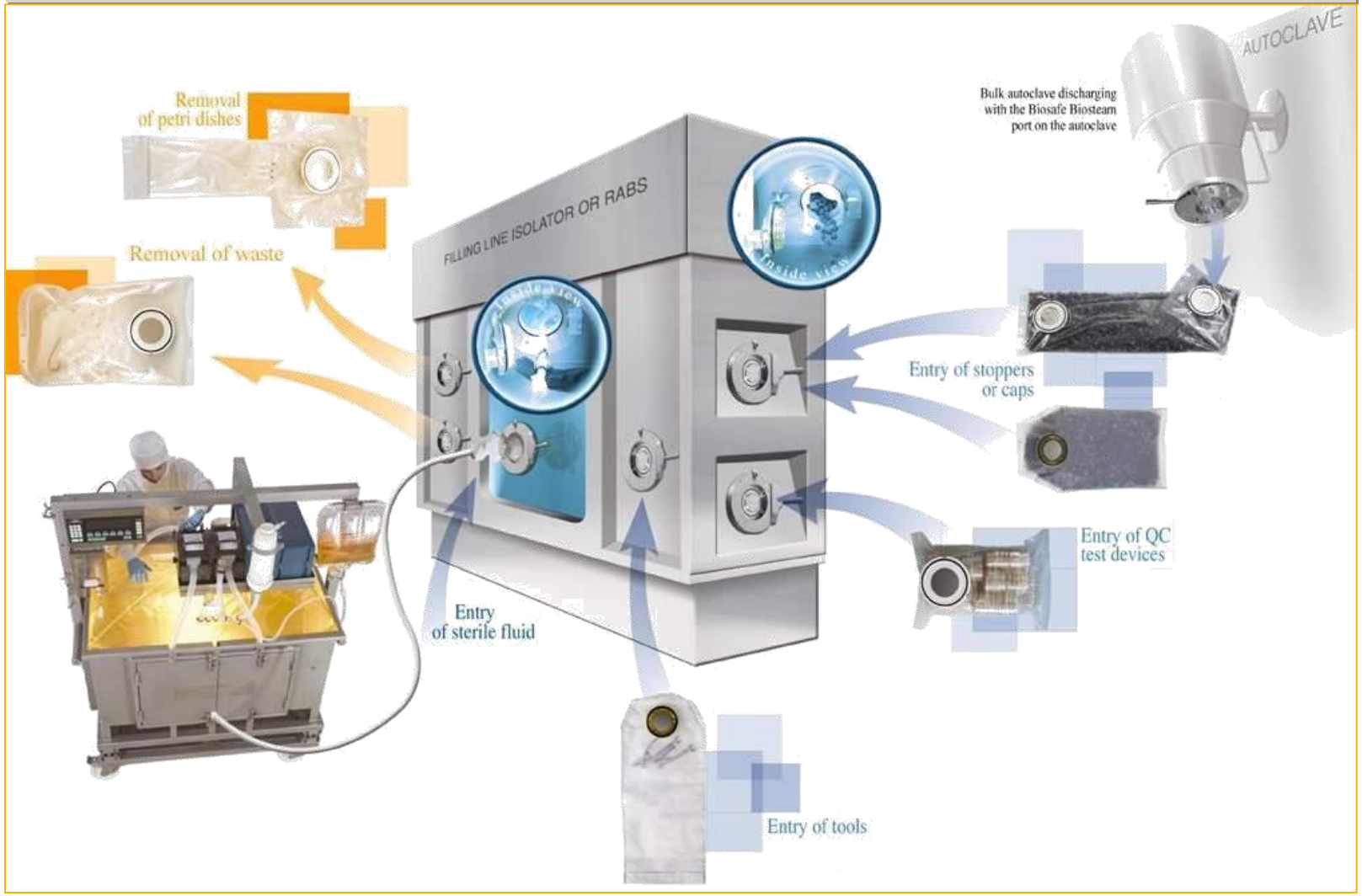
Consists of a disposable element and Tool

Radio Frequency Sealer

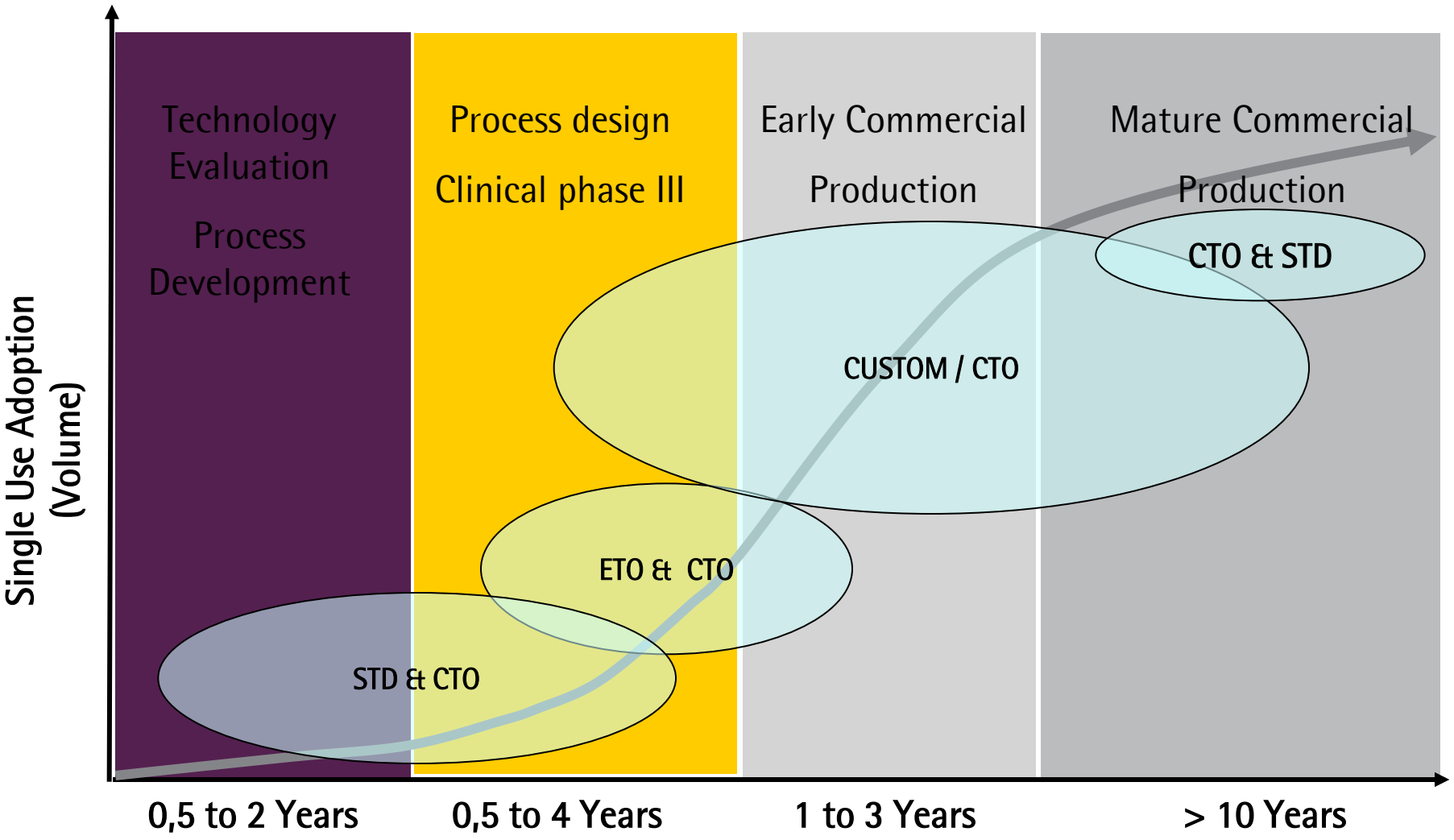
Capable of Disconnecting EVA, PVC Tubing

Single-Use Technologies

Aseptic Transfer Systems



Single Use Technology Adoption Model



Newest Requirements in the Single Use Market
Summary From most recent Industry Surveys

1. Product **quality**, **robustness** and **integrity**
2. Product delivery reliability & long term **assurance of supply**
3. **Change control** with timely notifications & comparability protocols
4. **Product & technology** portfolio with superior performance
5. **Standardization & Technology Integration** with improvement on scalability & ease of use
6. **Documentation & technical support**: Qualification test, QC test, validation & training support

Quality, assurance of supply & change control

Technology development & Integration

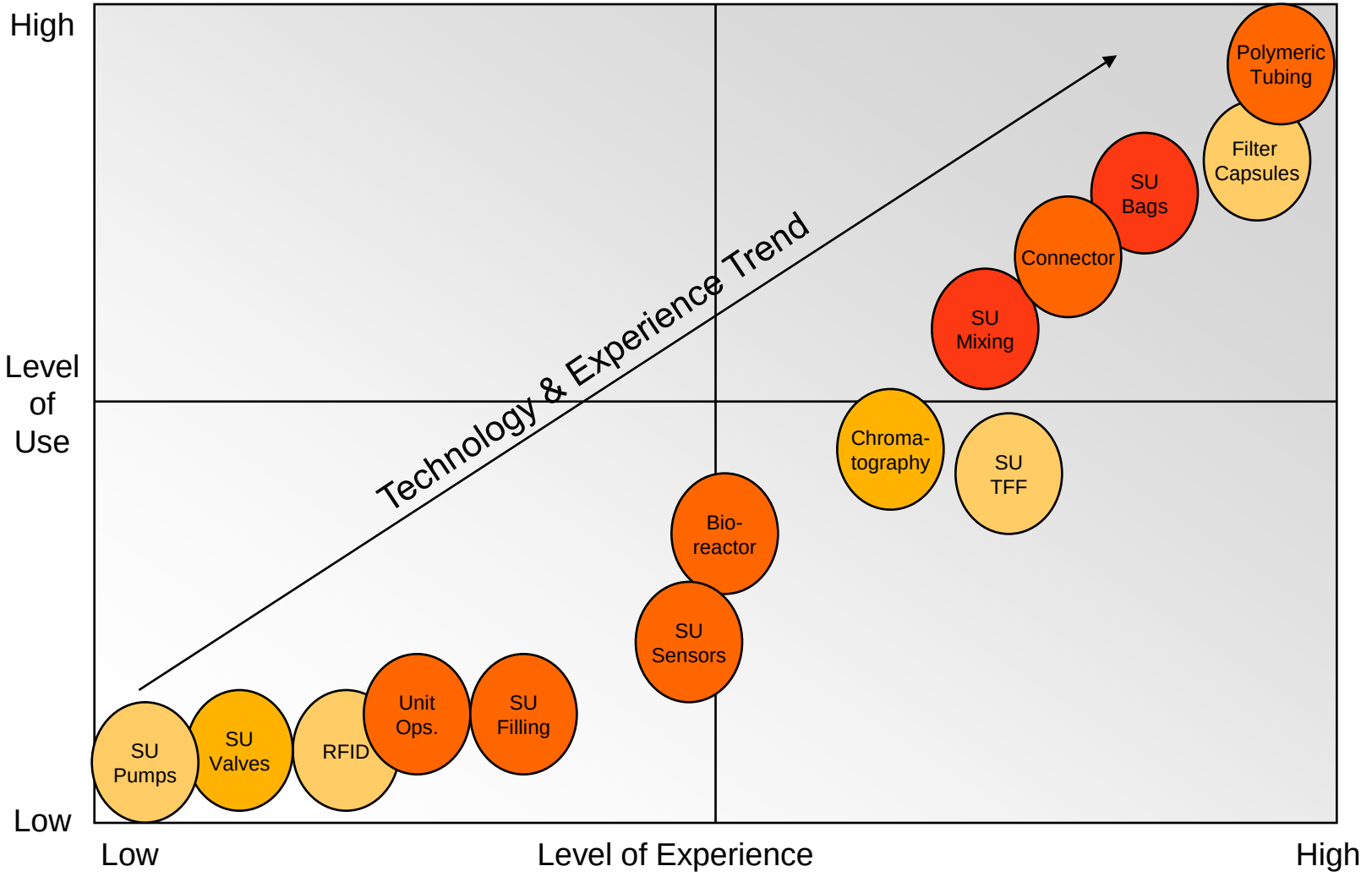
Technical Documentation & Support

BioProcess INTERNATIONAL

Aspen Brook consulting, inc.

BIOPLAN ASSOCIATES, INC.

Single-use Technology Next Moves

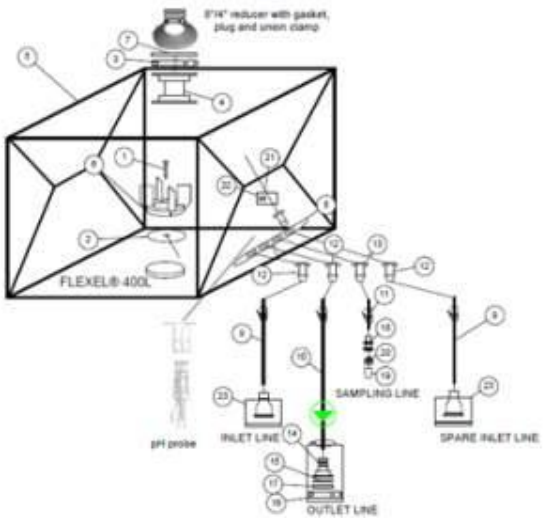


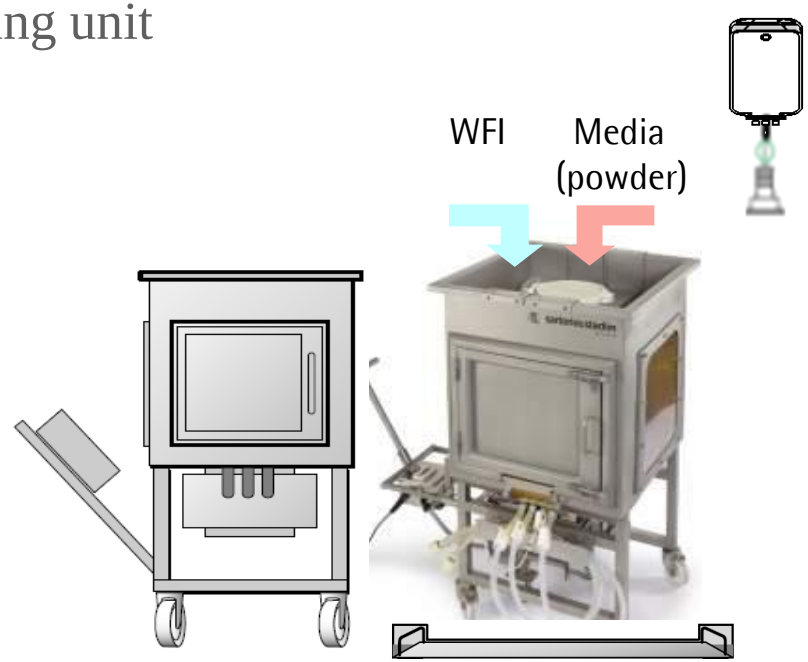
End-user requirements create innovative opportunities

Application Driven Unit Operations

- The Market Development as brought about new innovations in Application Driven Unit Operations to assure highest flexibility
- These innovations increase the standardization level and allow Qbd in a ‘plug and play‘ package
- Introduction of single-use probes to allow Process Analytical Technology (PAT) approaches in single-use arena
- Realization of automation concepts to achieve operational excellence
- Assurance of process performance, safety, quality & security of supply is maintained though strategic co-operation intitiatives between technology owners

Example - Set-Up of the mixing unit



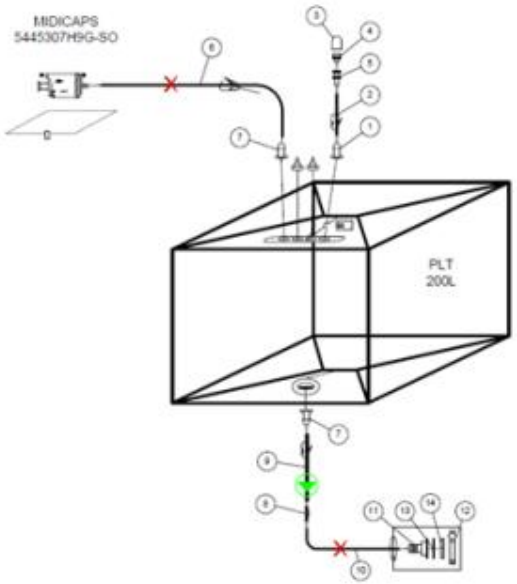


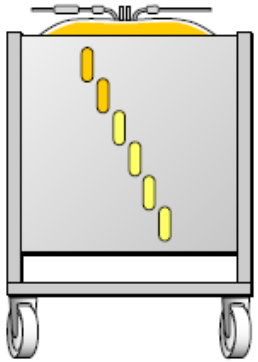
1. Insert mixing bag assembly into bag holder

2. Move mixing system on floor scale

⇨ The mixing unit is ready for buffer preparation

Example - Set-Up of the storage unit(s)

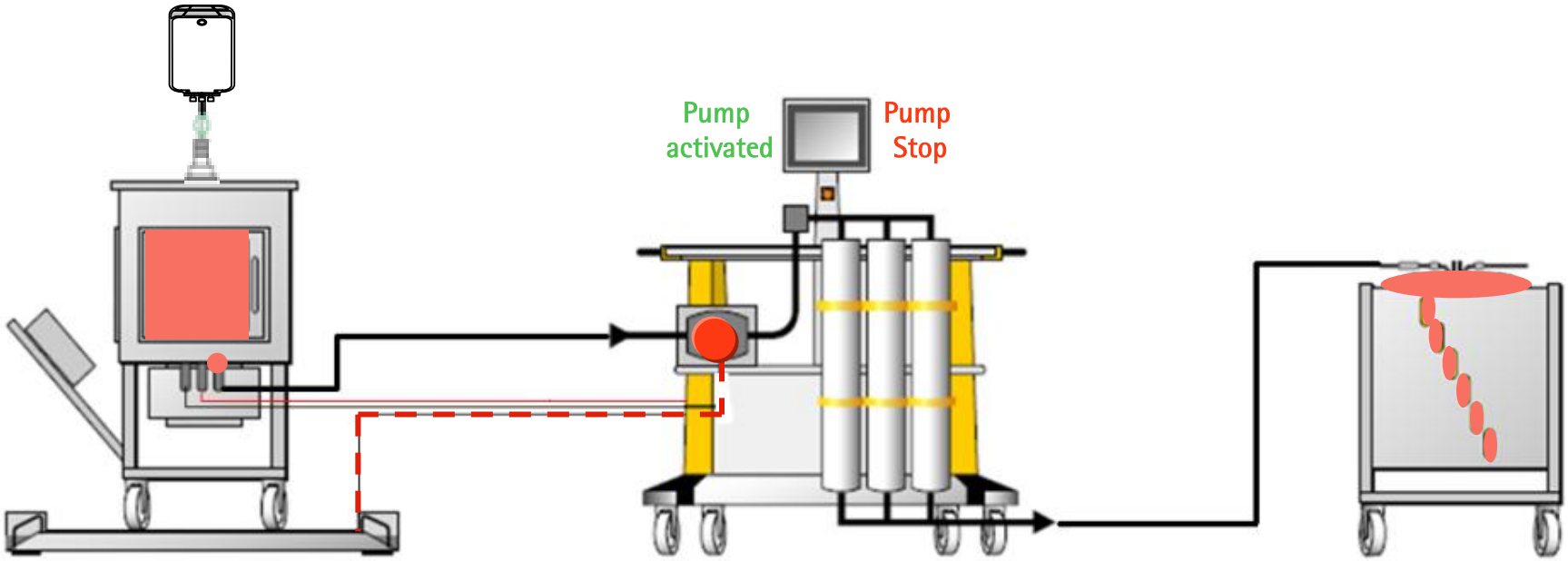




1. Insert storage bags into bag holder

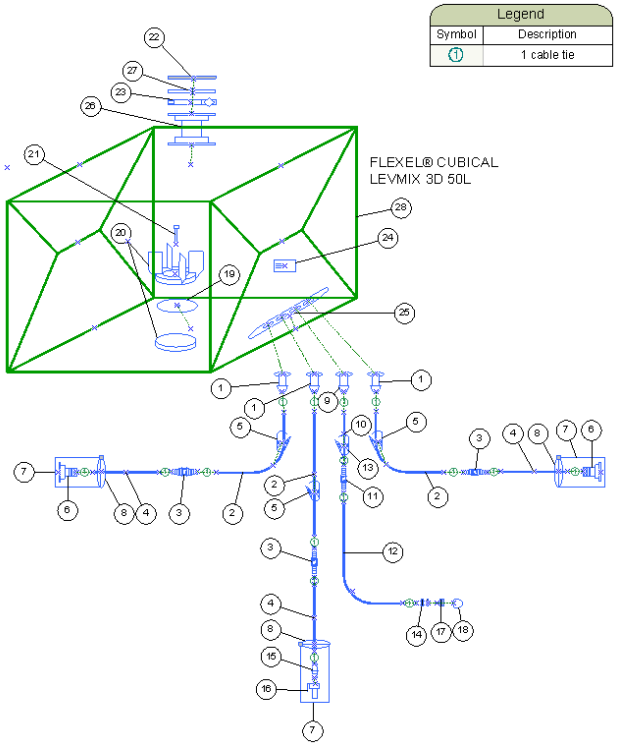
⇨ The storage unit(s) are ready to be connected with the mixing bag assembly

Example Operation: Automated pump stop after fluid transfer by weight control



⇨ Automated pump stop after filling the particular storage bag !

Robustness of Single Use Assemblies



Single Use Systems are built from multiple components assembled together to provide the expected design & functional requirements

- **Product robustness** relies on
  - The Quality and Robustness of the Film Material
  - The quality of each component & raw material
  - The validation of each assembly

- **Security of supply** relies on
  - The supply chain,
  - The material specification
  - The change control policy

Documentation
Validation & Extractable data

Mechanical properties

Barrier properties (ASTM)

Integrity

Biocompatibility (USP, EP)

Physico-chemical test

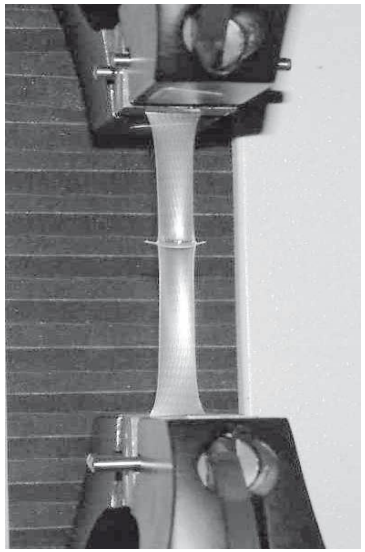
Stability test in WFI

Chemical resitance (ASTM)

Gammasterilisation (ISO111137)

Extractable

Bacterial ingress testing



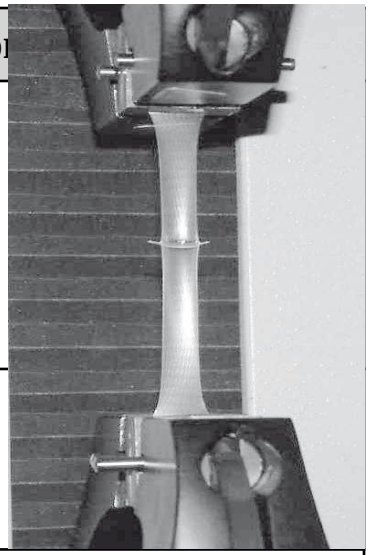
Documentation
Product Certificates of Release

Monitoring tests
Bacterial Endotoxins test USP<85> and E.P. 2.6.14
USP<788> and E.P. 2.9.19 : Particulate
ISO 11737: Bioburden
ISO 11137: Sterilization of Medical Devices
ISO 14644: Cleanrooms environmental controls

Lot release tests
100% visual testing of bag and seal
100% air pressure leak test (where possible)
Technical drawing compliance
Dimensional check
Packaging and labelling inpection
Gamma sterilization

Documentation
Mechanical & Physico-Chemical Validation data

Qualification Tests	Tests usually performed after gamma irradiatio
Mechanical Properties	Ultimate Tensile Strength (UTS) Elongation at break Secant Modulus at 2% Toughness, Resistance to tearing Flex Durability, Impact resistance
Barrier Properties	Barrier to Water Vapour (ASTM F1249) Barrier to Oxygen (ASTM D3985) Barrier to Carbon Dioxide (ASTM F2476)
Integrity	Seal Strength Integrity, **100% bag integrity testing**
Biocompatibility	USP < 87> Biological reactivity tests, In Vitro USP < 88> Biological reactivity tests, In Vivo
Physico-Chemical Tests	European Pharmacopéia (E.P.3.1.5 PE with additives for Containers) BSE/TSE Status (E.P.5.2.8) USP < 661 >
Stability of WFI	USP and EP
Chemical Resistance	ASTM D543-06 "Method for resistance of Plastic to chemical reagents"



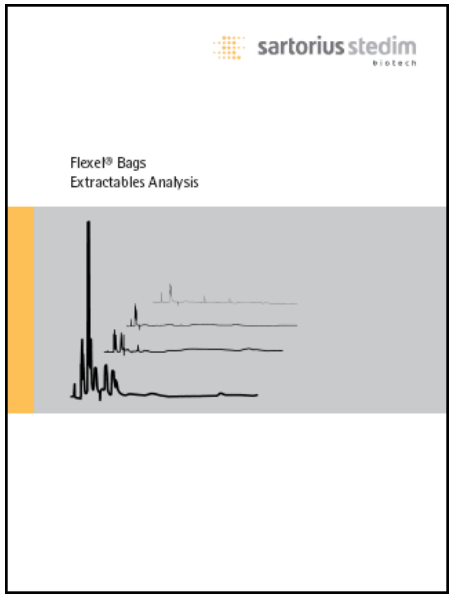
Documentation
Gamma Sterilization Validation Data

ISO 11137

	PROCESS VALIDATION	PROCESS CONTROLS
Establishment of minimum Sterilization dose	STERILIZATION CYCLE DEVELOPMENT 1. Bioburden Quantification 2. Bioburden Identification 3. Bioburden Resistance Assessment	MAINTENANCE OF STERILITY 1. Bioburden quantification 2. Identification & resistance 3. Environmental monitoring 4. Dose audit
Establishment of maximum material compatibility dose	SHELF LIFE 1. Functional performances 2. Package integrity 3. Biocompatibility 4. Sterility	PRODUCT PERFORMANCES 1. 100% Visual inspection of bags 2. 100% Package inspection 3. Endotoxins, particles
Reproducibility of dose Magnitude & distribution	IRRADIATION PERFORMANCE QUALIFICATION 1. Dose mapping and limit setting 2. Density range and limit setting	GAMMA IRRADIATION PROCESS CONSISTENCY 1. Product density 2. Min and max irradiation dose monitoring

Documentation
Extractable Validation Data

Extraction model	Time
HCl (pH < 2.5)	4m
WFI	4m
NaOH (pH > 11)	4m
100% ethanol	4m



TOC quantification

METAL analysis 20 – 500 ppb

VOLATILE leachables or compound (VOC)

- GC/MS: Identification and ½ quantification, 5 – 50 ppb

½ VOLATILE leachables (SVOC)

- GC/MS Identification and ½ quantification, 50 ppb

NON VOLATILE leachables (NVOC)

- LC/MS. Identification and full quantification, 1-5 ppb

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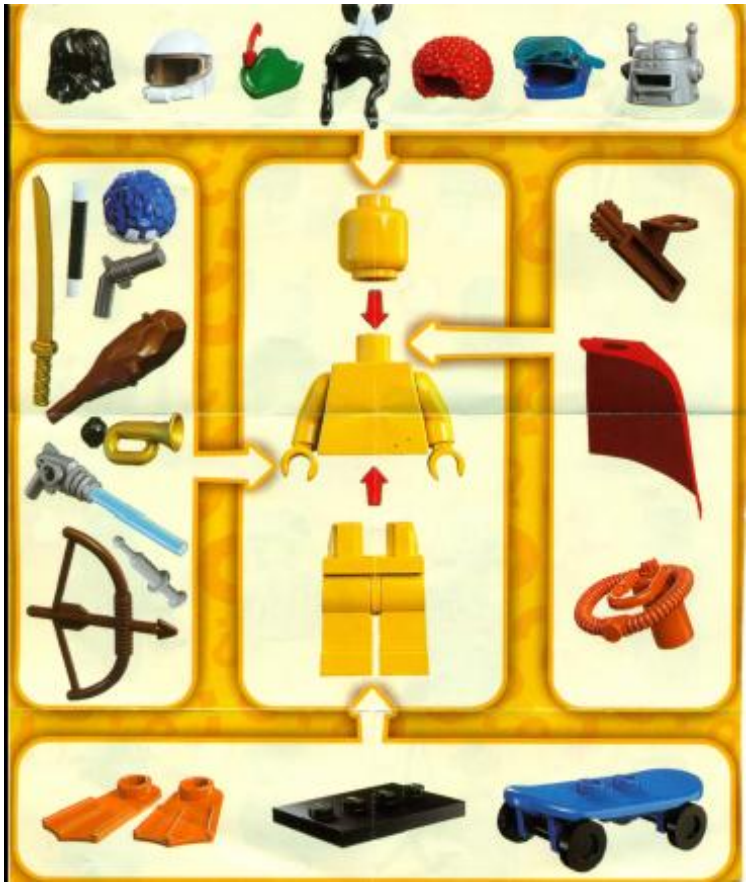
How Do Configurable Single-Use Systems Support The Customer Needs ?

1. Reduction in cleaning and sterilization operations
2. Minimization of validation efforts for cleaning validation
3. Reduced risk of cross contaminations
4. Enhanced flexibility through better adoption to multi product scenarios and product demands
5. Reduced facility construction time
6. Reduced time to market

The “Plug & Play” Concept is Here to Change Biomanufacturing



- Single use systems can be easily configured using existing SU platform technologies
- They are standardized, easy to validate & ready to use for each process step in Up- and Downstream Processing
- Single use systems consist of standardized, movable hardware equipped with flexible, pre-sterilized Single-Use process equipment

Thank You For Your Attention !