




Applications of Single Use Disposable Technology in Fill Finish Facilities

Connecting a World of Pharmaceutical Knowledge

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Overview

- Technical
 - Technical Suitability
 - System Selection
 - Film Technology
 - Formulation Systems
 - Filtration/Transfer Systems
 - Filling Systems

Getting Started

- Technical Range: Formulation to Filling
 - Initially formulation, then form → filling
- R&D Support (Budget)
- Multiple Vendors
- Wide Range of Capabilities
 - Size Range
 - Formulation Unit Operations
 - Multiple Filling Configurations

Multiple Vendors

- Single Source to Minimize Bag Films
 - Millipore
 - Sartorius Stedim Biotech (SSB)
 - Hynetics
 - Thermo Scientific Hyclone
 - ATMI
 - Xcellerex
 - Meissner

Film Technology

- Proprietary Films
 - Millipore – Sureflex, Pureflex
 - Sartorius Stedim - S71 (2D), S40 (3D)
 - ATMI – TK8
 - Meissner - FluoroFlex®
 - Thermo Scientific HyClone CX5-14 film
- Layers
 - Product Contact
 - Gas Barrier
 - Mechanical/Puncture Resistant Outer Layer
- Tubing
 - High quality, low extractables tubing for pharmaceutical use.

Film Technology

- Testing
 - USP <87>: Biological reactivity tests, in Vitro (Elution Method, Agarose Overlay Method)
 - USP <88>: Biological reactivity tests, in Vivo (Intracutaneous, muscle implantation, systemic studies)
 - USP <85>: Bacterial Endotoxin
 - USP <661>: Tests for plastic
 - USP <788> and EP 2.9.19 : Particulate

Film Technology

- Testing
 - ISO 11737 : Bioburden
 - ISO 11137 : Sterilization of Medical Devices
 - ISO 10993-4: Hemolysis
 - EP 3.2.2.1 – Appearance, Acidity and Alkalinity, Absorbance, Reducing Substances
- Risk Assessment
 - Determines which tests are performed



Vendor Baseline Data Example

- Extractables Tested Using Model Solvents
 - High Purity Water (Milli-Q)
 - 1 N NaOH
 - 1 N HCl
 - 20% Ethanol
 - DMSO

Vendor Baseline Data Example

- Test Methods include:
 - TOC
 - RP-HPLC, IC, ICP-MS, GC-MS
- Testing for Bag Films, Connectors, Tubing, etc.

Customer Testing

- Final Testing with Customer Product
 - Review of Baseline Data
 - Quality Audit of Vendor
 - Risk Based Approach to Identify In-House Testing
 - Stability Indicating Testing on a per Product Basis
- Lab Support Available
 - Vendor Lab Support
 - 3rd Party

Formulation

- Formulation Unit Operations:
 - WFI Charging
 - Agitation
 - Sparging/O₂ measurement
 - pH Adjustment (range: 1N NaOH / 1N HCl)
 - Low O₂ Transmission (EVOH Barrier Layer)
 - Solvent Compatibility (e.g. testing with 20% EtOH, DMSO)
 - Powder Transfer/Addition
 - Liquid Transfer/Addition
 - Temperature Control (range -80° C to +60° C)
 - Sampling

Formulation

- Bag Mixing Systems - Formulation
 - Multiple Vendors –
 - Millipore – Mobius
 - Sartorius Stedim Biotech (SSB) – Flexel Levmix & Magnetic Mix
 - Hynetics Disk-Mixer
 - ATMI – Integrity Mixers
 - Xcellerex – XDM Quad
 - Mixing as low as 10L with bottom mounted mixer (Millipore)
 - Mixing Data Available – contact vendor for your application

Formulation

- Bag Mixing Systems



SSB Flexel for Mag
Mixer



Hynetics
Disposable 750L



Millipore Mobius

Formulation

- Powder Addition (Closed)



HicoFlex



ATMI



Powder Feed Bag

Wash down Line 1/2" Quick Connect Body
(8" Silicone tubing)

Powder Port 3" Tri-Clamp with
integrated seal



Quick Connect
(Q.C.) Body

- Manufactured of Polypropylene (PP) film, a medical grade AD-CT film.
- Individual RBC systems are double polybag.
- Powderfeeder Powder Feed Bags are non-insulated.
- All end fittings are capped or plugged.

HyClone



Filtration/Transfer Systems

- Tubing and Filters
 - Utilizing standard, existing components and filters
 - Low extractables
- Assembled using aseptic connectors
 - Custom assemblies
 - Gamma irradiated
 - Requires the use of disposable filters
 - Flushing of filters
 - Documentation package (QA)

Filtration/Transfer

- Aseptic Connectors



Colder AseptiQuik



Millipore Lynx



Pall Kleenpak



**Sartorius Stedim
Opta**



Filtration/Transfer

- Closed Liquid Connectors



Colder MPX Series



Colder HFC Series



Colder SaniQuik



Colder Sanitary



Colder Steam Thru

Filtration/Transfer/Filling

- Liquid Fluid Path Tubing Connectors
 - Available in Nylon, PP, PVDF



Eldon James Connectors

Fluid Path Configuration

- Isolator Boundary Transfer
- Intermediate Bag Tank
- Automatic Level Control w/Pinch Clamp
- Bag Port Arrangement
 - Filling Accuracy
 - Set-up Ergonomics

Fluid Path Configuration

- Beta Port Bags
- SART

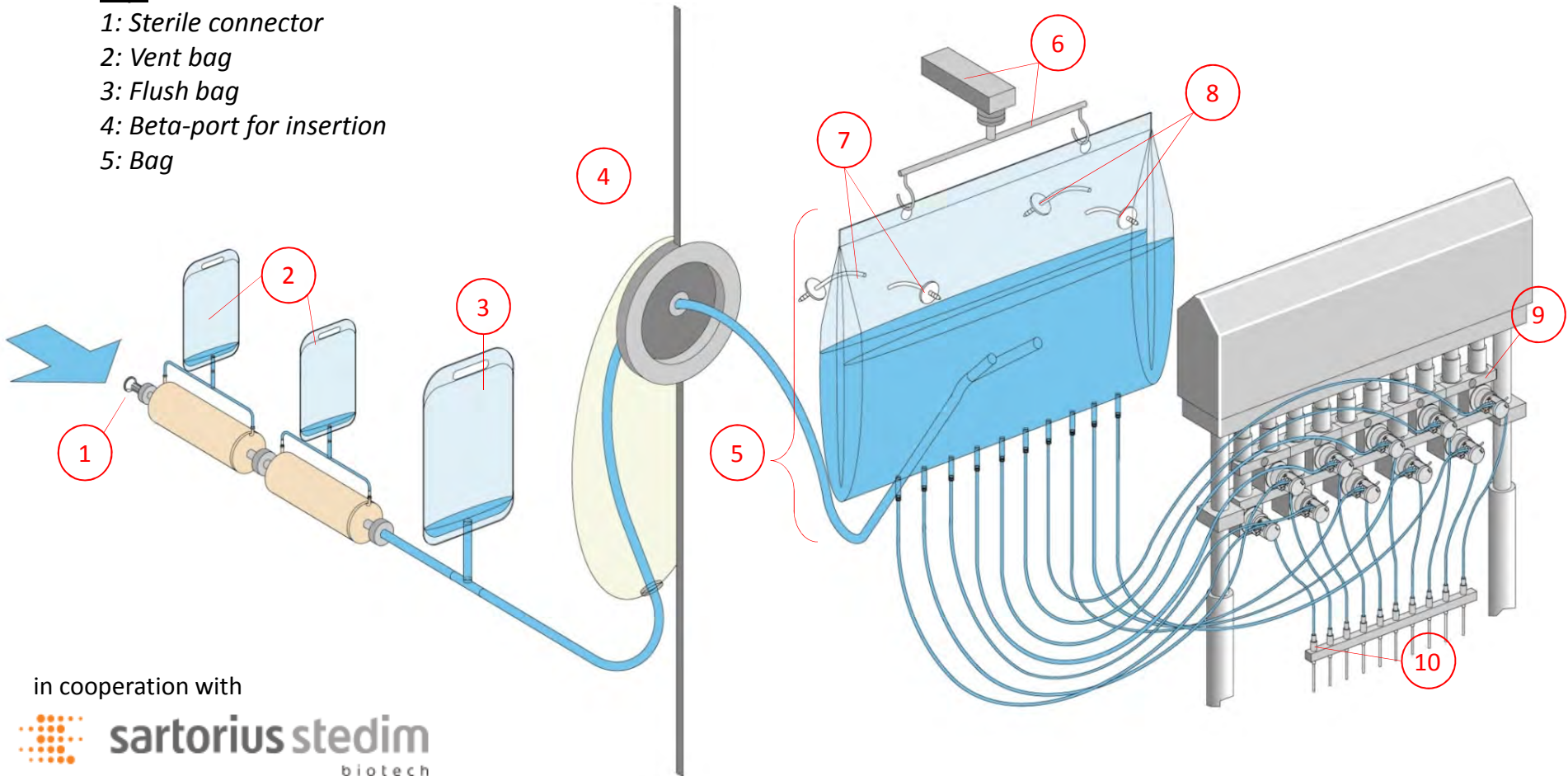


PreVAS Single-Use Dosing System

Application example for system setup in isolator

Key:

- 1: Sterile connector
- 2: Vent bag
- 3: Flush bag
- 4: Beta-port for insertion
- 5: Bag



in cooperation with



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PreVAS Single-Use Dosing System

Application example for system setup in isolator

Key:

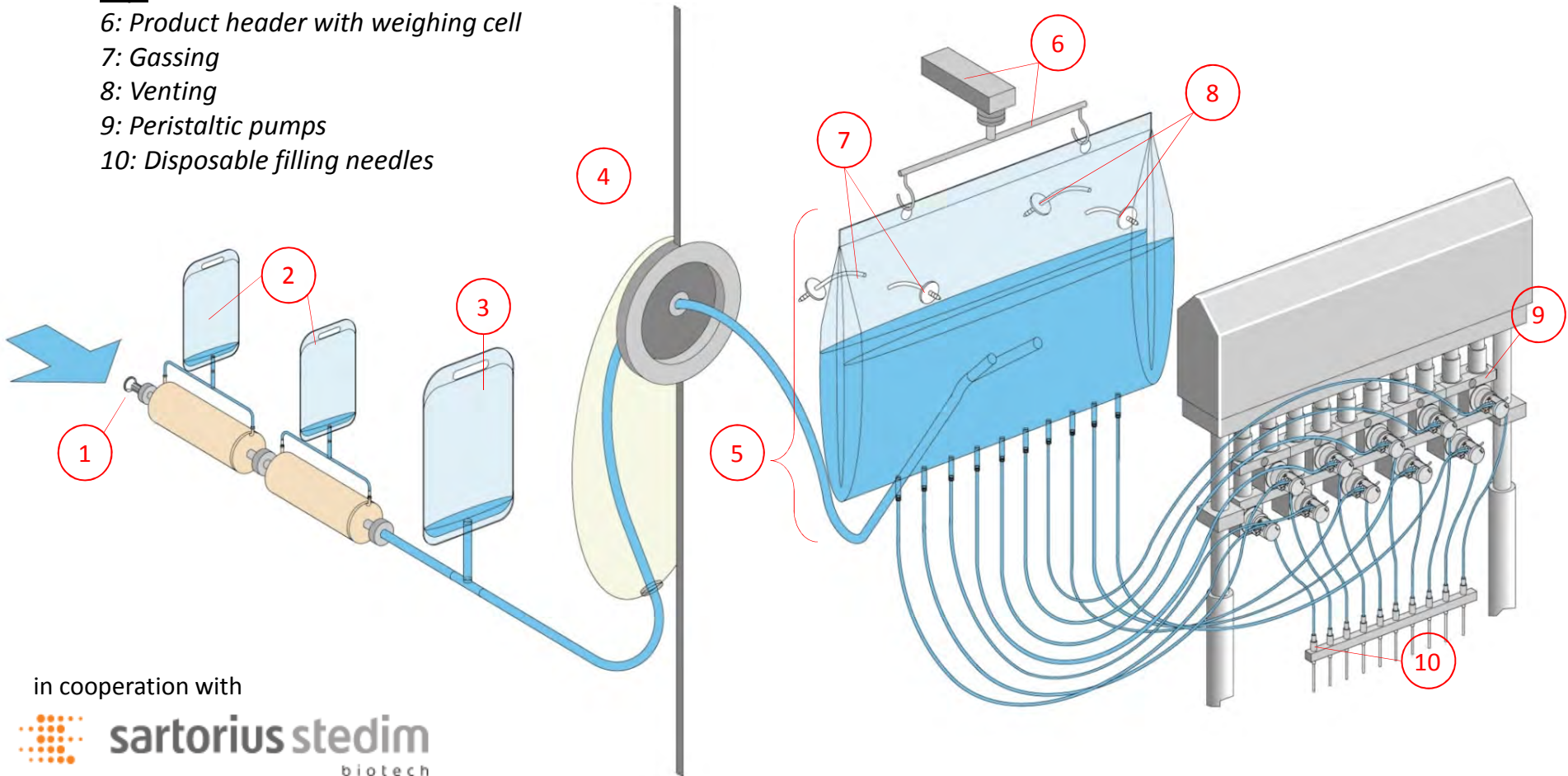
6: Product header with weighing cell

7: Gassing

8: Venting

9: Peristaltic pumps

10: Disposable filling needles



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Filling Systems

- Peristaltic Filling
 - Proven Technology
 - Low Shear
 - Simple, Inexpensive Fluid Path
 - Improved Fill Accuracy and Speed
 - Servo Drive Pumps
 - Pump Head Geometry
 - Accuracy Comparable to PD Systems
 - Improved Ergonomics
 - Multiple Vendors – Bosch, Groninger, Inova, IMA, B&S

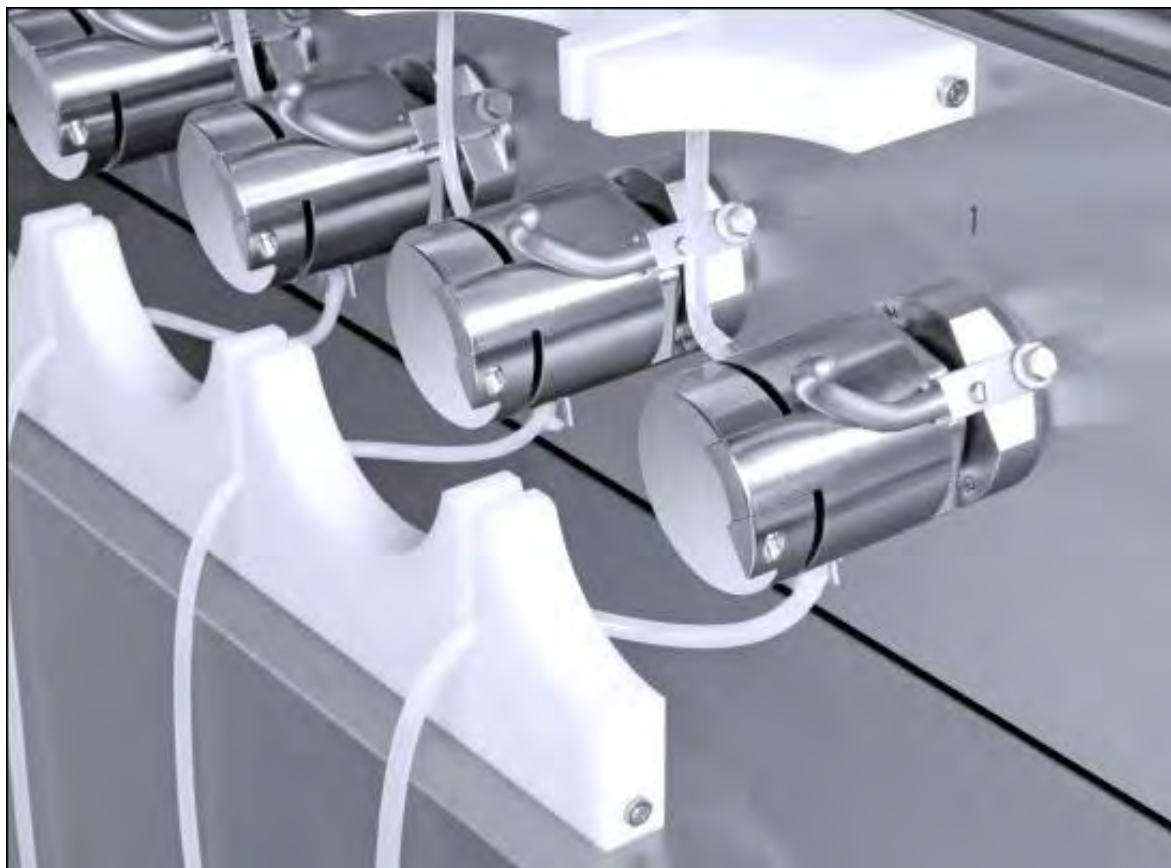
Filling Systems

- Level Control
 - Pinch valve
 - Automatic by filler
 - Weight or non-contact
- Intermediate Tank
 - Bag or re-usable vessel
 - Venting / Inert gassing
 - Pressurization (non-disposable)
- Recirculation
 - Bag configuration

Filling Systems

- Filling Combi-systems
 - SS Rotary Piston
 - Peristaltic
 - PreVAS (Bosch only)
- Peristaltic Pump Trolley
 - Integrate with current filler
- Ergonomics
 - Pumps in isolator, post-VHP assembly

Peristaltic Filling



PreVAS Single-Use Dosing System

Operator Installing PreVAS



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Peristaltic Pump Cart



Advantages

- Reduced risk of cross contamination
- Improved product segregation
- Improved operator safety (elimination of exposure during cleaning operations)
- Reduced capital equipment costs (→ operating costs)
- Improved manufacturing flexibility

Advantages

- Elimination/reduction of cleaning validation
- Ease of new product introduction into facility
- Faster path to media fills
- Reduced documentation costs
- Reduced equipment storage footprint

Disadvantages

- Increased operating expenses for disposables
- Increased R&D costs to establish test methods/protocols for single use – 1 time expense
- Organization Change Required

Costs

- Capital vs. Operating Costs
 - Flexibility
- Cost Analysis – Modeling
- Cost Examples:
 - 100L mixing bag: \$550
 - SU Fill Path, beta bag, 10L intermediate bag, 4x peristaltic pumps, w/disposable needles, pre-sterilized: \$4,000 – 5,000k
 - High Volume Costs?
 - Bag mixing station – plastic \$30,000



Special Thanks To:
Millipore
Bosch
Sartorius Stedim

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