Single-Use technology
from
Components to Final Filling

MM SU Technology

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Agenda

- Pharm & Biotech industries challenges
- MM quality approach
- Challenges
- Experience
- Future





Pharm & Biotech Industry Challenges

Facilities take between 3-5 years to build, validate and become fully functional

- Capital investment
- Capacity/Productivity
- Product evolution along facility construction
- Validation
- Efficiency and flexibility
- Reduce the possibility of processing errors
- Greater utilisation of production equipment

Pharm & Biotech Industry Challenges

Key Drivers that lead to SU

- **Enhanced Economics**
  - Minimize capital Investment
  - Outsource sterilisation & assembly
  - Reduce labor and on-going validation burden
  - Hour cost of the facility
- **Speed to Market**
  - Fast small scale clinical manufacturing
  - Enables versatile facility design
  - Assists production planning flexibility

Pharm & Biotech Industry Challenges

Single-use or traditional approach

CUSTOMER DATA	CIP/SIP	Single Use System
Investment in equipment	$500,000 (incl. $200,000 ancillary costs)	-- (even less equipment costs)
Setup	2 hours	45 minutes
CIP + SIP-cycle	40 + 75 minutes	-- (arrives ready to use)
Cool down cycle	75 minutes	-- (ready to go)
cleanup	1 hour	15 minutes
Post-Use CIP	40 minutes	-- (throw it away)
Summary	**~ 7 hours and $500k** (qualification and re-validation efforts are not included)	**1 hour and cost of assembly** (easy storage)

Pharm & Biotech Industry Challenges

Single-use - Measurable benefits

(Customer): In fact, we reaped greater benefits than we expected. Initially, the installation of the peristaltic pump and the need for vessel supports (trolleys and totes) added approximately $85,000 to the cost of the facility**. On the other hand, cost savings were achieved because there was no need to purchase** several large vessels and dosing pumps. As a result, the overall savings with respect to the capital investment were approximately $100,000, or about 10% of the total project cost.

… With this single-use filling line, there is no longer any need for pre-use or post-use equipment cleaning, and the time required for equipment preparation, sterilization and set-up is a fraction of that previously required with stainless-steel equipment. As a result, the **total processing time has been reduced** from 19 hours to 1.5 hours, which translates to a more rapid product turnaround time, significantly reduced cleaning-related costs, and a dramatic boost to our competitive position in the marketplace.

…With the single-use system**, we have eliminated the risk** of contamination and **reduced the number** of aseptic connections…

Single-Use technology - What is it ?

- Self contained & pre-assembled (mainly) plastic fluid path
- Usually provided “ready to use” (gamma irradiated)
- Uses a combination of standard and qualified components:
  - Bio-reactors, bags, tubing, connectors, filters, mixers, transfer lines, filling system, sampling solution, etc.

Single-Use assemblies are often customised to meet defined application

Single-Use Technology
Components and assemblies

Aseptic Connectors and Disconnectors



Mixers, Sampling Solutions and Assemblies

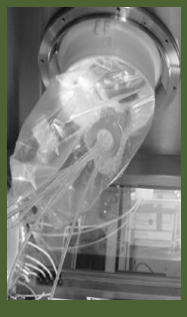


Mobius CellReady & FlexReady Systems





Final Formulation and Filling Solutions

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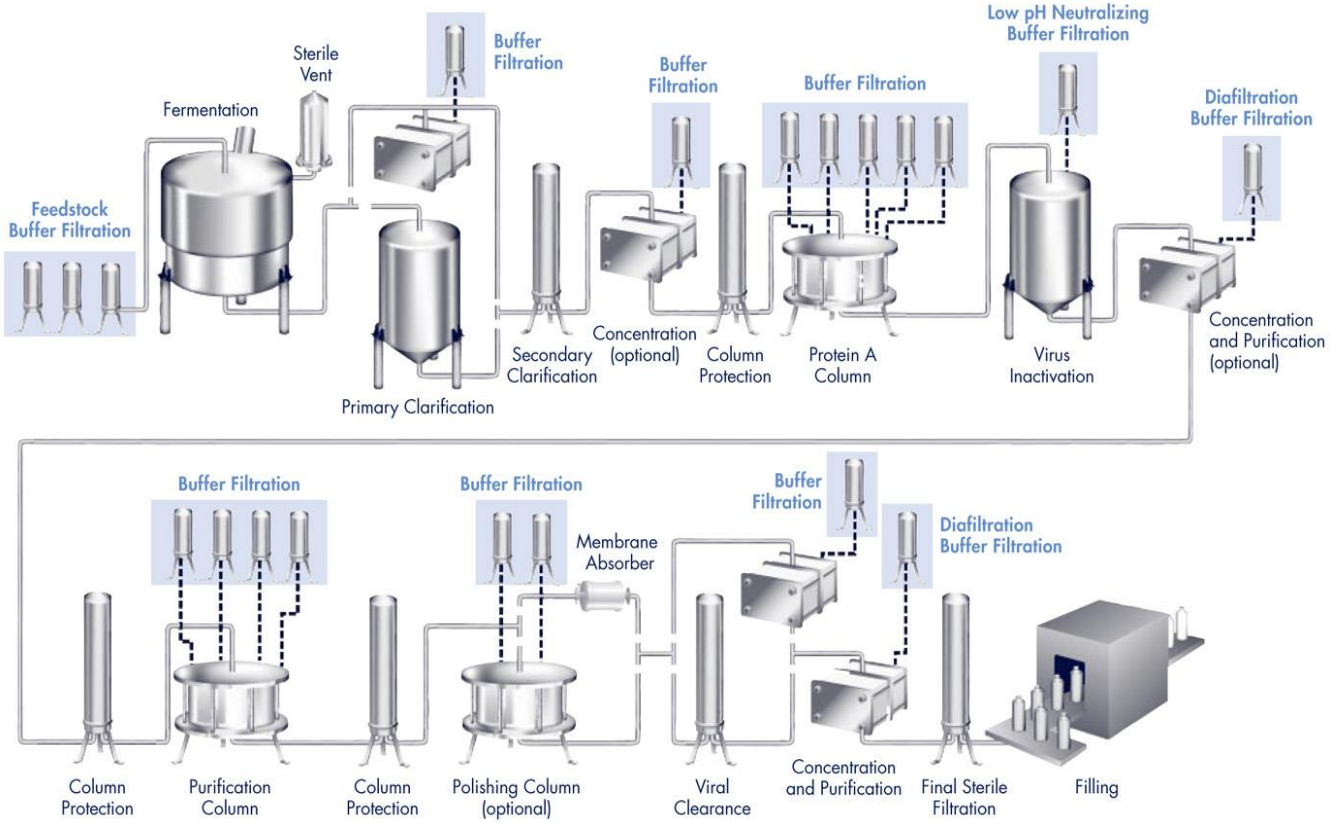
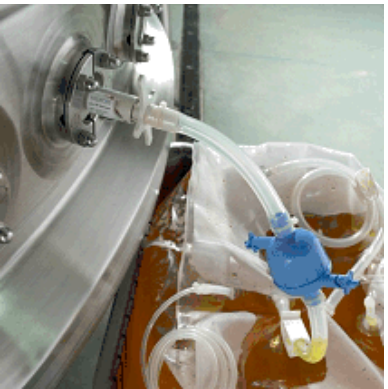
Single-Use Technology

Biotechnology Manufacturing Process





Single-Use Technology

… and addressing to

We need to prepare

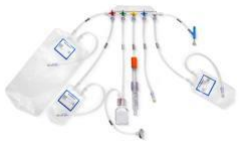
We need to grow

We need to transfer

We need to protect

We need to wait & move

We need to test



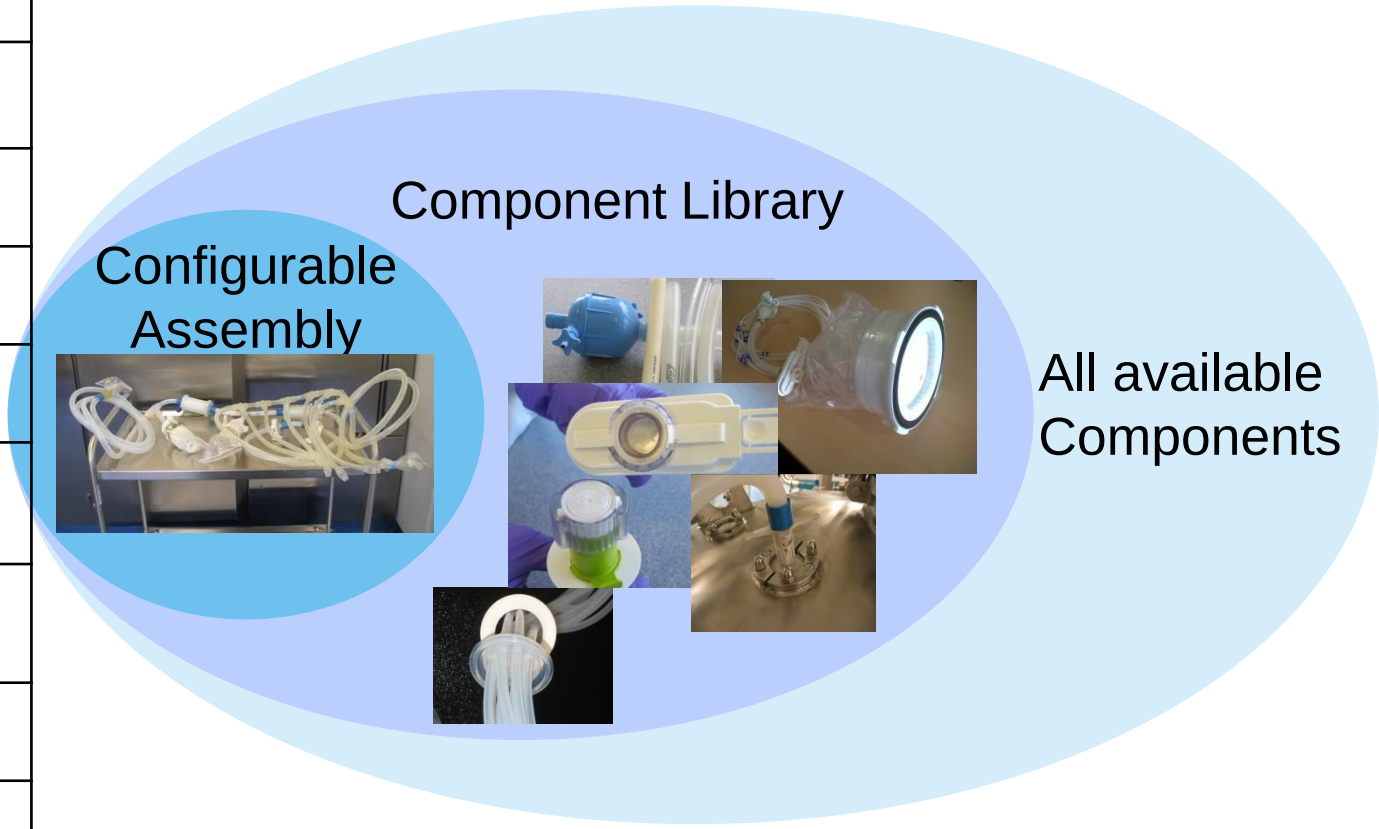
We need to fill

Quality approach

Quality approach

Components choice

Criteria
Gamma compatibility >40kGy
Statement of animal origin
USP<88> Class VI post-gamma >40kGy
USP<85> Endotoxin, post-gamma >40kGy
USP<788> Particulates, post-gamma >40kGy
USP<661> Physicochemical, post-gamma >40kGy
Shelf life >2.5 years, post-gamma>40kGy
Total Bioburden pre gamma
Bacteriastatis/Fungistasis, Post-gamma >40kGy



Quality approach

MM SU Operation

- Close proximity to R&D, Distribution, and Business functions.
- Technology “Center of Excellence”
- Lean six sigma
- Manage network of supply partners manufacturing critical components for MM under exacting quality standards.
- Control of quality systems and QA release criteria

CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

Millipore Corporation
Billerica, Massachusetts, USA

has been approved by Lloyd's Register Quality Assurance to the following Quality Management System Standards:

ISO 9001:2008

The Quality Management System is applicable to:

Design and Manufacture of Membrane, Purification Systems, Filtration Products, Microbiological Media and Services. Management of Subcontract Manufacture of Filtration Products, and Laboratory Test Products. Laboratory Testing Services. Warehousing and Delivery of Finished Goods Received from Millipore Manufacturing Plants and Subcontract Manufacturers. Manufacture of Controlled Pore Glass. Manufacturing of Disposable Bioprocessing Assemblies. Design, Development, Manufacturing, Packaging, and Distribution of Highly Purified Blood Proteins and Biologically Active Factors.

This certificate is valid only in association with the certificate schedule bearing the same number on which the locations applicable to this approval are listed.

Approval Certificate No: UQA 0100466

Original Approval: October 23, 1991
Current Certificate: July 1, 2009
Certificate Expiry: June 30, 2012

Issued by: Lloyd's Register Quality Assurance, Inc.

ANAB ACCREDITED

Quality approach

Business Continuity Plan

Particular focus on Raw Material supply risks

- ❑ Prioritise critical components, materials, and suppliers
- ❑ Define supplier risk assessment process and tools
- ❑ Create mitigation strategies and action plans
- ❑ Review and approve plans
- ❑ Ensure ongoing maintenance of critical suppliers

Business Continuity Plan

Challenges

Connector, disconnection, Valve

Film, Bag, Container, Mixing

Growing

Sampling

Filter, Assembly

Design, Qualification, ...

Challenges

Process constraints

Plastic equipment material have lots of advantages, nevertheless some constraints have to be taken into consideration.

- Chemical
  - Solvent (organic or not)
  - Oily solution
  - Adsorption
  - Irradiation
  - Extractables
  - Product
- Physical
  - Temperature
  - Pressure
  - Duration
  - Gas permeability

Challenge
Safety

Operator

- Adapted equipment
  - Handling
    - Assistance or not
    - Temperature
  - Moving
    - Corridor
    - Door steps
  - Gowning
    - Toxicity (surrounding)
    - Labelling (Tamperproof containers)
- Training

Product

- Premises & controlled area
  - Production
  - Transfer
  - Storage
  - Lockers
    - Gas permeation
- Process
  - Extractables & Leachables
    - Process yield
  - Robustness

Challenge

E&L - Questions to be answered

Efficacy/Strength	Interfere with production process (e.g. Cell growth) ?
Identity & Purity	Interfere with the API and/or excipients of the drug ?
Safety	Is it toxic to the patient and be eliminated ?

Challenge

Safety - Regulatory

FDA

FDA, Code of Federal Regulations, Part 211, “Current Good Manufacturing Practice for Finished Pharmaceuticals”, Part 211.65, “Equipment Construction”, 2005

“Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.”

EU

European Commission, EUDRALEX Volume 4, “Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use”, Chapter 3, “Premise and Equipment”, 2003

“Production equipment shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.”

Experience

Experience
Filtration

Current assembly on the market.

Ready to use filter with its connection lines for sterile or non-sterile applications.

Experience

Vaccine filling

Hybrid approach to reduce process conversion time and cost

- Introduction of a new drug production into an existing manufacturing site cause some challenges
  - How to enable a fast conversion
  - How to ensure sterility of the formulation and filling process

- Estimated time and cost required to integrate aseptic filling process following traditional approach

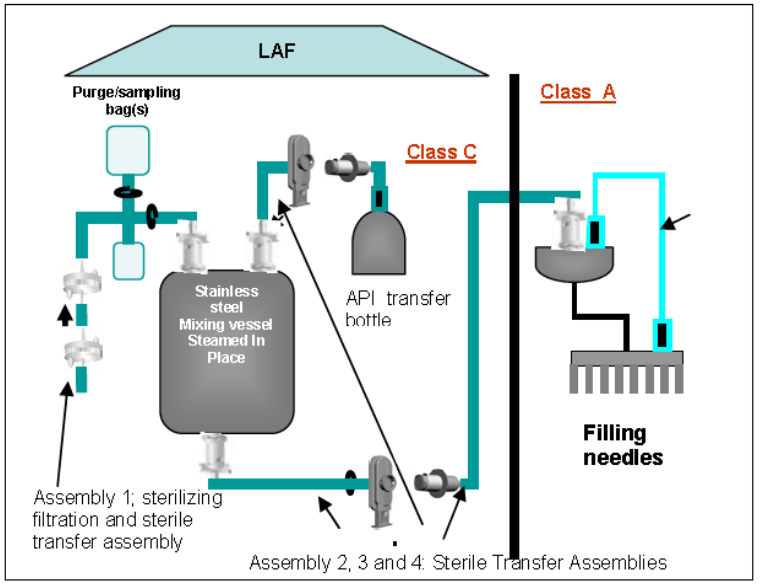
Activities	Time (estimated months)	Costs (estimated costs K€)
Engineering feasibility study	3	100 K
URS for new equipment preparation, construction and purchasing	6	300 K
Revamping works, Installation and start up	4	100 K
Environmental Decontamination and re-classification	1	20 K
SIP and CIP Validation	1	20 K
Total time required	**15 months**	**540 K**

Experience

Vaccine filling (Cont'd)

To meet time and requirements

- Use SU technology which fulfil
  - Integrity of components
  - High-Sterility assurance
  - Endotoxin and particles
  - Extractable & leachables levels



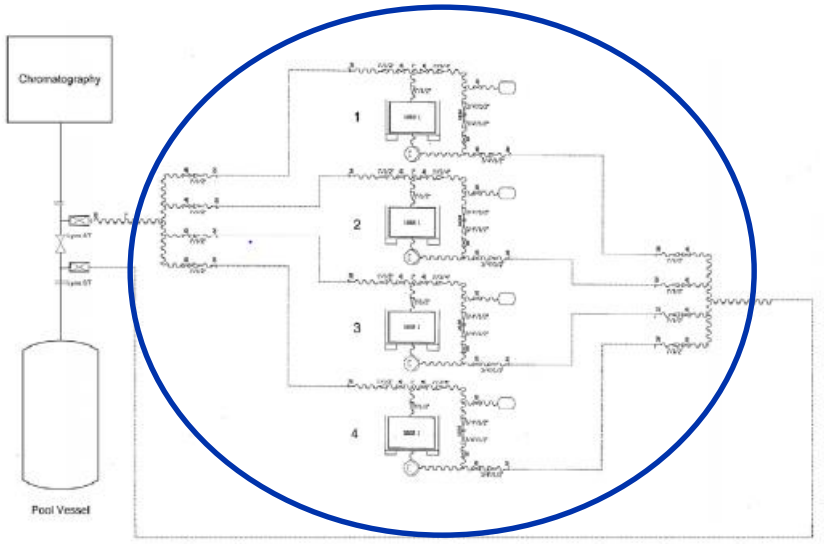
After operators training, Media fills were successfully performed and the first qualification batch was filled **Three months ahead** of the schedule set by the company

Experience

Increase flexibility of downstream process

The project purpose was to implement modification on large chromatography production step adding extra fraction collection possibilities.

- Project challenge
  - **No impact on the original installations qualification**
  - Fast implementation
  - Great flexibility for different process configurations during batches run
  - Fractions should be
    - Homogenised
    - Transferred / Pooled
    - Light protected
    - Weighed
    - Sampled

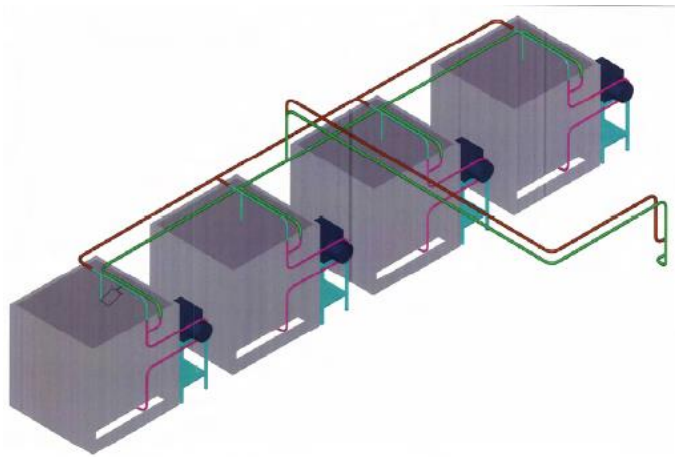


Experience

Increase flexibility of downstream process (cont'd)

Only disposable technology could meet the different criteria, being non invasive for the original production hardware, having fast track building, and process flexibility for the process development, at a fare price

Due to the large equipment volume, components, assembly design (easiness of installation) have to be carefully chosen



Experience

multi-product final filling suite with isolator

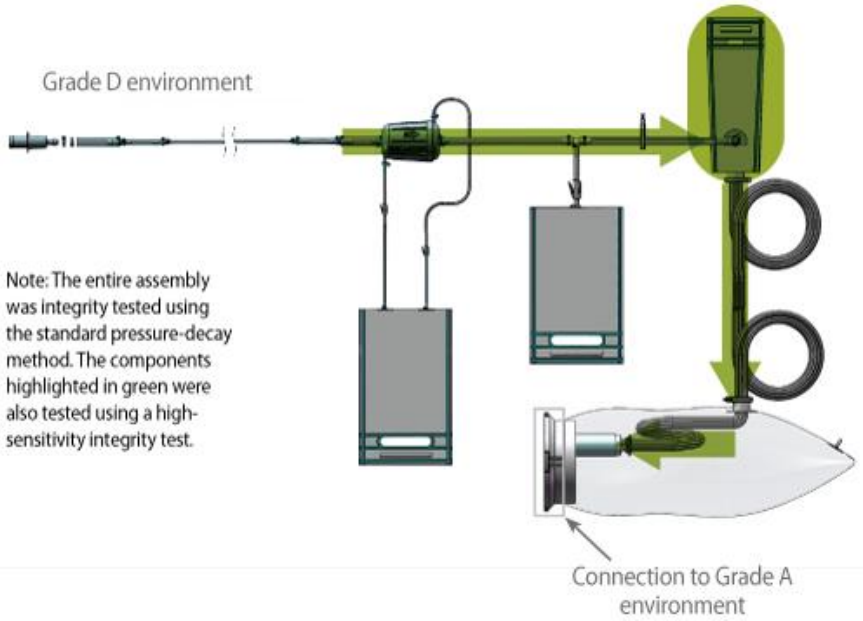
Increase flexibility for multi-product filling by ensuring applicability for high throughput plant (three shifts per day, five days per week) and small-scale products and/or clinical demands

A crucial requirement for commercial implementation was the establishment of a risk-based strategy and a rationale to qualify and validate this application of single-use technology at the Drug manufacturer facility

Experience
multi-product final filling suite with isolator (cont'd)

The risk-based approach identified several key validation activities that were required to reduce the risk of a non-integral single-use assembly having an adverse effect on the drug product including:

- An integrity test that correlated to microbial ingress
- Validation of packaging
- Assemblies shelf-life validation
- Sterilization validation
- Extractable studies
- Product-specific leachable studies
- Dose accuracy



Experience

multi-product final filling suite with isolator (cont'd)

Engagement of regulatory authorities

Drug Manufacturer decided to present their facility design, new technology concepts, control and qualification strategies to local authority bodies as well as to FDA in an early stage of the project.

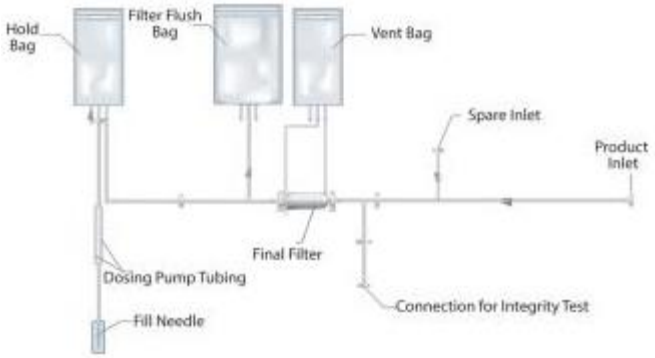
A close, collaborative working relationship between the drug manufacturer and single-use supplier based on openness and transparency was important. Face-to-face meetings were encouraged and were a key element in helping to create a common understanding and set of goals between the two companies. Weekly teleconferences assured continuous alignment and project control.

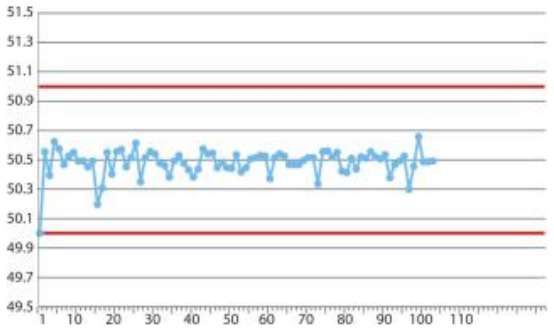
Experience

Life-threatening diseases

From a Dummy model to efficient Filling

- Bacteria retention testing
- Filter Integrity testing
- Chemical Compatibility
- Transfer in production area (VHP)
- Filling accuracy
- Extractables & Leachables
- Integrity of the SU assembly
- Sterility of the SU assembly
- Media fills





Experience

Life-threatening diseases (cont'd)

Just 10 months after the start of the project, the first batch of clinical trial material was manufactured using the single-use equipment. Thus, the task had been successfully implemented by the deadline.

Project Milestones	Activity
March 2012	Creation of the dummy model
March 2012	Supplier selection interviews
April 2012	First drawing
May 2012	First test run
June 2012	Final drawing
July 2012	Completion of the filter validation
September 2012	Completion of additional extractables
October 2012	Validation of the filling equipment with three media fill runs
November 2012	Filling of the first batch of clinical test material

Experience

Formulation to Final Fill example

Experience

Articles and few EU SU users

Recent articles

- **Single-Use Technology for Syringe Filling**

BioPharm international, March 2014

http://www.biopharminternational.com/biopharm/issue/issueDetail.jsp?id=23609

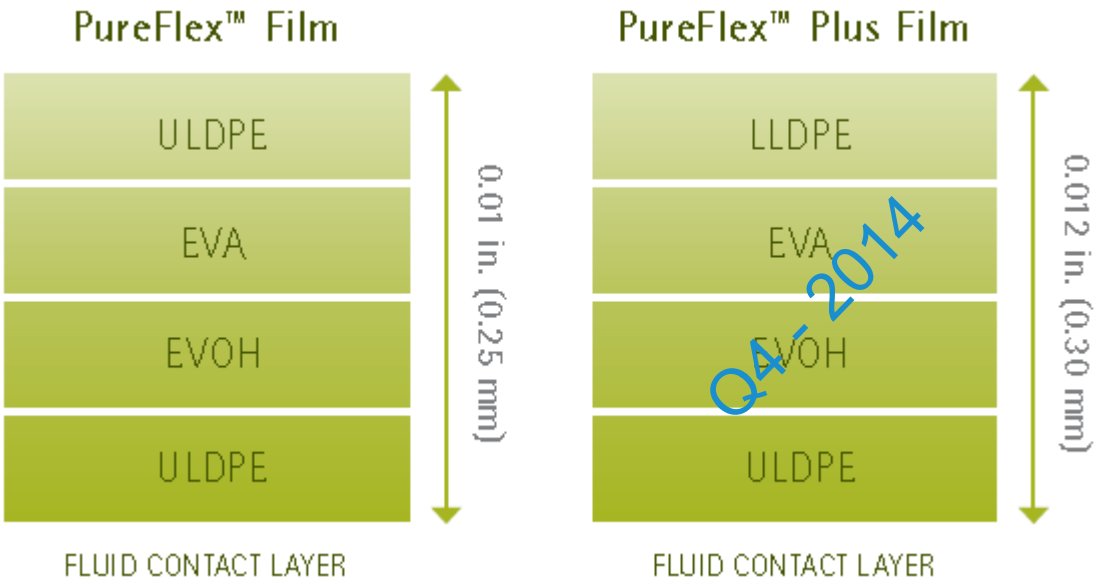
- **Establishing Single-Use Assemblies on Filling Equipment**

Bioprocess International, April 2014

http://www.bioprocessintl.com/journal/supplements/2014/April/Establishing-Single-Use-Assemblies-on-Filling-Equipment-351081

Future

Future
Film



"Plus" version is designed to meet demanding applications

- Maximize process robustness and resistance to leak formation
- Minimal changes to PureFlex™ film structure

Future
Film (cont'd)

Protocol Variable	Range
Film	PureFlex™ and PureFlex™ Plus
Extraction solution	Milli-Q® water, 1N NaOH, 1N HCl, 50% Ethanol, 10% DMSO, pH 10 WFI, pH 3 WFI, 1% Tween 80, 5M NaCl
Temperature	RT, 45˚C
Sterilization	> 45 kGy gamma irradiation and non-gamma'd
Duration	120 days
Analytical methods*	TOC, HPLC, IC, GC-PT, GC-HS, GC-DI, ICP

- Demonstrates equivalence of PureFlex™ to PureFlex™ Plus
- Full extractables study in line with industry draft recommendations (BPSA, BPOG)

Future
and what else ?