Single Use technologies in Downstream processing and Fill-Finish

Single use technologies in Biomanufacturing processes
ISPE DACH Conference, Marseille, May 26-26th, 2011

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Presentation outline

*Single Use Technologies in Downstream Processing and Fill-Finish*

- **Purpose:** *Overview* presentation - highlight technical/process/plant floor aspects
- **Background and perspective**
- **SU in Downstream processes**
- **SU in Fill-Finish**
  - **Case:** Compounding

*Disclaimer:*
*Overview* only partial, - not comprehensive
Examples selected for illustrative purpose
360° survey always recommended
Close to 1,700 colleagues at more than 25 locations in 12 countries around the world.
Industry trends

• One example: 900 Medicines and Vaccines against Cancer in testing
• 200+ are Monoclonal Antibody-based (mAb)

• Towards personalized medicine
• More specialized therapies
• More specific (smaller) patient populations
• Orphan drugs
• Biosimilars
• - other factors…

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• Smaller campaigns
• Multiproduct facilities
• More frequent product changeovers

\[\text{MEDICINES IN DEVELOPMENT FOR CANCER*} \]

- PhRMA 2011 Report

*Some medicines are listed in more than one category.
Generalized Biomanufacturing Bulk process flow

• Basis: MAb production process
Centrifugation

- CARR Unifuge
- Disc bowl operation – discharge etc. – integrated with pump/skid
Depth filtration

- Cell removal
- Elimination of cleaning housing, aerosols generation
- Significant solid waste contribution
- Membrane can also have secondary purification effect (HCP, DNA…)

3M Purification  PALL  Sartorius Stedim  Merck Millipore
Column chromatography

- GE Healthcare – also including disposable fluid path
- Prepacked
- Campaign use (not one-time use)
Membrane chromatography

- Flow through polishing (HCP, DNA, Viruses)
- Membrane bound ligands for improved mass transfer area
- No packing, large throughput, buffer and time savings
UF/DF TFF

- Buffer exchange, volume reduction
- Shear
- Pressures
- Flowrates, tube diameters

SciLog

Millipore

JM Separations

Novasep

nne pharmaplan®
Virus reduction filtration

- Timing
- Pressure monitoring
- Flushes
- Integrity testing
Freeze-thaw

- Controlled rate – cryopreservation prevention
- Bag protection
Generalized Biomanufacturing Bulk process flow

- Basis: MAb production process
Generalized Biomanufacturing Fill-finish flow
SU in Fill-Finish: Potentially a good match

- Volumes and flow rates in general relatively low
- Heat and mass transfer demands in general moderate
- Concern more: Repeatability, accuracy, physical stress

- Container/closure, filters already characterized, leachables/extractrables not "new"
- Risk high – everything critical
- Durations relatively short
- Protein concentrations high
Compounding - mixing

- Mixing technology – vibrating, paddle, agitator, levitating impeller
- Circular or rectangular
- Several designs to avoid/reduce particle generation
- Ability to move impeller really slow
Compounding - mixing

- Large range of volumes
- Mobile or stationary
- Visual process

Merck Millipore

Sartorius-Stedim

Hynetics
Powder transfer

- Transfer and rinse from pre-weighed bag
- Very controlled operation
- Very low dust generation to surroundings
Example: Compounding large scale

**CHALLENGE**
- Washing and sterilizing tanks
- Physically moving stainless steel tanks around
- Many tanks in clean, dirty, operation states – housekeeping effort
- Maintenance
Example: Compounding large scale

**SINGLE USE TECHNOLOGY ALTERNATIVE**

- Single use mixing systems – bag plus powder bags
- Floor scale

**POTENTIAL IMPROVEMENTS**

- Fast setup
- Improved ergonomics
- Faster compounding operation

![Sartorius-Stedim](image)
Generalized Biomanufacturing Fill-finish flow
Single use filling

Now available from all well known filling machine suppliers

• Eliminate washing, sterilization
• Fast setup
From Compounding to Filling

- Single use sterile filtration manifold - connect through wall

Recommended reference:

Single use filling flow path

• Enabling formulation-to-filling single use flow path

From Groninger
Filling

- Layout – integration with facility

From Groninger

Flexicon
Generalized Biomanufacturing Fill-finish flow

- Novel pre-washed, pre-sterilized container technologies
- To reduce need for support functions and simplify operations
Reducing support operations

Pre-filled syringes – NEST technology
- Nest arrives with syringes pre-sterilized, gamma-irradiated
- Outside surface sterilized before entry to filling machine (VHP, E-beam…)
- System also potentially useful for introducing assemblies etc.

- Reducing need for wash and sterilization tunnel
Reducing support operations

Pre-sterilized, closed vial system

- Vial and stopper integrated, closed system
- Filling by penetration of seal
- Re-seal by laser beam
- Stopper in place through entire operation

- Eliminating cleaning and sterilization

Aseptic Technologies, Crystal system
Sequence optimization

**Lyophilization cap system**
- Perhaps more optimal sequence – cap in place before lyophilization
- Cap clicks in place by place tray pressure
- Simplifies operations after freeze drying

Lyoseal, Biocorp, biocorp.fr
Presentation message

- Large potential for single use technology
- Industry trends support introduction of single use technology in fill-finish
- Risk management central for successful introduction
Thank you for your attention!

- Now with *single use technology* chapter!!!

**ISPE Biopharm development and manufacturing baseline guide**

- Regulatory
- Qualification
- Process
- Support systems
- Facility
- Scale-up, tech transfer
- Single Use technology

ISPE Baseline Guide Bioprocess...Due 2011