Keeping up with Single-Use

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07 Oct 15

Outline

• Introduction / Overview
• Technology Survey
• Economics
• Quality
• Single-Use Facilities
• Summary
Introduction

Disclaimer

- Content is the sole responsibility of the presenter
- Products and vendors listed are provided for reference and illustration and are not meant to constitute a complete list or endorsement
Strategic Outlook

Industry Growth
- 15% annual avg.
- ~40 approved mAbs
- >150 mAbs in clinic

New Technology
- Better process yields
- Potent compounds
- Drug delivery

Smaller Markets
- Fewer blockbusters
- Personalized medicine
- Genetic diagnostics

Cost Pressures
- Health care reform
- Biogenerics
- Follow-on drugs

Capacity shortage (captive capacity)
Smaller batch sizes
Smaller R&D budgets

Need for more efficient development & fast, flexible and inexpensive manufacturing capacity

Biopharm Manufacturing Drivers

- Time to market (clinic)
  - Facility start up time
  - Batch cycle time
  - Batch success rate
  - Batch yield
  - Regulatory approval

- Capital investment
  - Facility
  - Process equipment
  - Process utilities
  - Support equipment

- Cost of Goods Sold
Drug Development Uncertainties

**Process development:** Improvements may change process flow or yield dramatically

**Market size & penetration:** Market forecasts imprecise, competition unpredictable

**Technical hurdles:** Process & tech transfer problems can impact need for capacity

**Regulatory delays:** Clinical hold, comparability, non-approvable—all potential setbacks

**Manufacturing flexibility is critical**

Overview of Single-Use
Disposables or Single-Use?

- Marketing (used vs. pre-owned car)
- Application difference
  - Disposables may be re-used (e.g. columns)
  - Single-use is used once and discarded

Industry History

- Single-use components have been around as long as the biopharmaceutical industry:
  - Plastic petri dishes, T-flasks, roller bottles
  - Lab scale filter capsules and TFF devices
  - IV bags & tube welders used in hospitals
- Surge in pilot and commercial use due to:
  - Increase in scale of well-established devices
  - Introduction of new devices
  - Improvements in films and extractables data
  - Economic and operational advantages
Growth of Single-Use

- Started in the lab
  - tissue culture flasks
  - syringe / capsule filters
- Biomanufacturing “staples”
  - capsule filters
  - bioprocess bags
- More functionality being introduced
  - larger scales
  - more types of unit operations
- Increasing industry acceptance & use

Enabling Technology

- Bioprocess bags
- Cell culture systems
- Separations (TFF, filters, centrifuges, rotary drum)
  - Harvest
  - Virus removal / sterilization
  - Concentration / buffer exchange
- Purification (membrane adsorbers, pre-packed columns)
- Tubing welders / connectors / sealers
- Integrating stainless and disposables
BioProcess Bags

**APPLICATIONS:** Delivery of pre-formulated cell culture media and buffers (or concentrates), or collection vessels for product, samples or waste

**CAPACITY:** <10 mL to 1800 L (larger custom)

**VENDORS:** Thermo (HyClone, ASI), Sartorius, GE, Charter

**NOTES:** Typically USP Class VI tested. Can be gamma irradiated. Additional material compatibility info available from most vendors.
Small-Scale Cell Culture

**APPLICATION:** Culture of mammalian, insect or plant cells in suspension

**CAPACITY:** ~10 mL – ~10 L / 25K cm²

**VENDORS:** Corning, Thermo, GE, Sartorius, Millipore

**NOTES:** TC flasks, roller bottles, spinners, shake flasks, hollow fibers, expanded T-flasks, rocking and stirred tank bioreactors

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Mid to Large-Scale Cell Culture

**APPLICATION:** Culture of mammalian, insect or plant cells in suspension (recently microbial fermenters to 500 L)

**CAPACITY:** 50 L – 2000 L

**VENDORS:** GE, Sartorius, Thermo, Millipore, Pall

**NOTES:** Stirred tank design based on bioprocess bag assembly provided as complete, gamma-irradiated, closed system. Differences in drive systems, gas sparging, bag films.
**Cell Harvest**

**APPLICATION:** Separation of cells from growth medium during perfusion or end of batch culture

**CAPACITY:** Up to 120 L/hr

**VENDORS:** Pneumatic Scale/Carr (centrifuge), Spectrum and GE (hollow fiber), Cuno, Pall, Millipore, Sartorius (depth filtration)

**NOTES:** All product contact surfaces disposable

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**Filtration**

**APPLICATION:** Clarification / sterilization of media, buffers, process intermediates, cell harvest, & particulate removal

**CAPACITY:** Syringe filters to 30” capsules generally available, (larger by custom order)

**VENDORS:** Millipore, Pall, Sartorius, Meissner

**NOTES:** Well established in industry. Trend toward larger capsules (fully disposable). Many available pre-sterilized and integrity tested. Base cost for capsule (most economical for expensive filters).
Tangential Flow Filtration

**APPLICATION:** Perfusion, cell harvest, purification, concentration, and formulation / buffer exchange.

**CAPACITY:** Up to 13 m²

**VENDORS:**
- Hollow fiber: Spectrum, GE
- Flat Sheet: Millipore, Pall, Sartorius, Tangenx

**NOTES:** Recent introduction of ready-to-use

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Virus Removal

**APPLICATION:** Mechanical reduction of viral load by nanofiltration

**CAPACITY:** 15 - 200 L/hr. (depending on pore size, filter medium & process stream)

**VENDORS:** Asahi-Kasei, Millipore, Pall, Sartorius,

**NOTES:** Filter elements expensive vs. larger pore size filters, so incremental cost of capsule less in proportion. Pall and Millipore have dead-end filtration capsules
Chromatography

**APPLICATION:** Flow-through removal of contaminants, bind-and-elute purification of small or dilute process streams

**CAPACITY:** 1 mL to 60 cm columns (85L)

**VENDORS:** Pall, Millipore, Sartorius, Natrix (membrane adsorbers), GE, Repligen (pre-packed columns), GE (skid)

**NOTES:** Membrane adsorbers are functionalized filter membranes. Operated like typical filters but capable of purification similar to ion-exchange chromatography.

Mixing Systems

**APPLICATIONS:** Media and buffer formulation

**CAPACITY:** 10 L to 2500 L

**VENDORS:** GE, Thermo, Sartorius, Millipore, Pall

**COMMENTS:** Based on bioprocess bags. Mixing by piston, recirculation, rocking or impeller. Tank liners are a cheaper, open alternative for less critical applications.
**Tubing Welders**

**APPLICATION:** Aseptic / sterile connection of tubing between bioprocess bags, sample collection or other systems by melting and reannealing tubing  
**CAPACITY:** 1/4” to 3/4” OD tubing  
**VENDORS:** Terumo, GE, Sartorius, Sebra  
**NOTES:** Several devices have been validated by the vendor and/or biopharm manufacturers. Can be used on PVC and EVA (Sebra), or Tygon, C-flex and Pharmed (Terumo, Wave) tubing.

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**Connections**

**APPLICATION:** Connection / disconnection of tubing to bioprocess bags, sample collection or other systems  
**CAPACITY:** <1/8” to 3/4” ID tubing  
**VENDORS:** Colder, Pall, GE, Millipore  
**NOTES:** Wide variety of non-sterile connectors (quick-connects, luer locks, sanitary connections, hose barb). Aseptic connectors (typically permanent) available in several designs. Steamable plastic connectors also available.
Typical Process Flow (mAb)

Media Prep → Inoculum → Seed Culture → Production Culture → Harvest

Buffer Prep → Chromatography → Virus Filtration → UF / DF → Bulk Drug

Economics
Disadvantages of Single-Use

• Cost per batch of single-use components
• Greater dependence on outside vendors
• Increased logistics / material handling
• More material compatibility questions
• Scale limitations (esp. for commercial scale)

Advantages of Single-Use

– Cleaning
– Sterilization
– Engineering
– Equipment lead time
– Utility requirements
– Validation
– Quality / Regulatory
– Space
– Labor

– Time to market
– Capital investment
– COGS
– Shortage of capacity
– Flexibility
Single-Use Interdependencies

- Decrease Mfg. Labor Requirements
- Eliminate Cleaning & Sterilization
- Reduce Utilities (SIP, CIP, USP, WFI)
- Decrease Set-up/Turnaround Times
- Simplify Equipment Engineering
- Decrease Equipment Lead Times
- Increase Plant Flexibility
- Reduce Validation
- Decrease Space Requirements

Eliminating CIP / SIP

**Cleaning & Sterilization:** Single-use operation eliminates need for cleaning and sterilization

- What % of water is used for CIP?
- What % of mfg. labor is used for CIP / SIP?
Engineering & Facilities Advantages

**Engineering:** Functionality designed into the single-use component & elimination of CIP / SIP simplifies requirements for re-usable hardware

**Equipment Lead Time:** Simplified engineering typically leads to shorter equipment lead times

**Utility Requirements:** Elimination of CIP / SIP decreases demand for USP / WFI / clean steam generation and CIP skids

Operational Advantages

**Space:** No piping for CIP / SIP, bags collapsible, components removed after use reduces footprint during use & especially after use

**Labor:** Elimination of CIP / SIP effectively out-sources these activities. Decreased engineering complexity may decrease set up time.
Quality Advantages

**Validation**: Single-use eliminates need for cleaning validation, re-use / regeneration studies & bacteriostasis studies for storage solutions. Pre-sterilized components eliminate need for SIP sterilization and/or autoclave loads.

**Quality / Regulatory**: Single-use eliminates chance for cross contamination between batches & products. Eliminates possibility of resistant bioburden (e.g. “objectionable organisms”)

Economic Benefits

**Capital Cost**: ~50% compared to stainless steel facility of same scale.

**Operating Cost**: Break-even to 30% operational savings (not counting depreciation), depending on scale, process and utilization

**Lower Fixed Cost**: Costs are shifted to variable, so plants can tolerate more idle time (ideal for clinical facilities with irregular schedules)
Quality

Regulatory Benefit of Single-Use

Recommendations for complying with CGMP Requirements (cont'd)

- Use available technology and resources to facilitate product development, CGMP compliance, and lessen CGMP burden, i.e.:
  - disposable equipment and process aids
  - prepackaged water for injection (WFI) and sterilized containers
  - contract manufacturing and testing facilities

Joseph C. Famulare, Director Division of Manufacturing & Product Quality, Office of Compliance, CDER, FDA
Presented at: Advisory Committee for Pharmaceutical Science, Manufacturing Subcommittee, 20-21 July 2004
What is Validation?

“Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.”

Guideline on General Principles of Process Validation, FDA, 1987

Validation is a state achieved through qualifications and maintained through on-going quality systems.

Validation Life-Cycle Map
Single-Use Systems

- **TRADITIONAL EQUIPMENT**
  - Permanently installed
  - CIP / SIP (extractables)

- **RAW MATERIALS**
  - Produced in batches by vendor
  - Consumed in mfg. process

- **SINGLE-USE SYSTEMS**
  - Permanently installed hardware
  - Produced in batches by vendor
  - Consumed in mfg. process
  - Extractables

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**Qualifying Single-Use Systems**

- Single-use systems have two components
  - traditional hardware (pumps, sensors, automation)
  - disposable element (consumed/batch ≈ raw material)
- Hardware should be designed and qualified using traditional procedures (ASTM2500)
- Single-use components
  - Perform process functions like equipment
    - “Non-critical” functions (storage, pre-filters, vent filters)
    - Process functions (separations)
  - Have vendor-dependent quality and batch variability like raw materials
Qualifying Single-Use Systems
(vs. traditional equipment)

• Design (DQ)
  – consider scale-up options
  – check temperature & pressure limits
  – determine material compatibility (extractables)

• Installation (IQ)
  – test interface with hardware / permanent equipment

• Operation (OQ) & Performance (PQ)
  – test installation procedures
  – test multiple vendor lots to establish variability
  – develop installation / functionality tests

ASTM2500 alternative—pull work forward & reduce testing

Qualifying Single-Use Systems
(vs. raw materials)

• Include in raw material controls program
  – test multiple lots for performance
  – establish specifications (γ-irr. ≠ sterile)
  – receive, test, release vs. specifications

• Perform vendor qualification
  – ability to supply, control of supply chain
  – manufacturing controls (cleanliness & quality)
  – change control & customer notification
  – testing and release methods
    • sterility • integrity • extractables
Qualifying Single-Use Systems*
(extractables)

• Collect vendor extractables data
• Check material compatibility in design phase
• Perform risk assessment
  – Material compatibility (solvent vs. polymer)
  – Contact time, temperature & surface area
  – Proximity to drug product
    • Upstream vs. downstream
    • Direct vs. indirect product contact
  – Toxicity of extractables (cytotoxicity)
• Perform product-specific testing as required

*Applicable for o-rings, gaskets, diaphragms, flex hoses, UF membranes, chromatography resins, etc. in traditional processes

Impact of Single-Use Systems
(eliminating cleaning & sterilization)

• Design (DQ): Decreased engineering
  – no piping
  – less valving, instrumentation & automation (no CIP/SIP)
  – fewer utility tie-ins (CIP skid, steam)
• Installation (IQ): Reduced scope
  – no weld logs / weld inspection, pipe slope inspection
  – less valving, instrumentation & automation to verify
  – fewer utility verifications
Impact of Single-Use Systems
(eliminating cleaning & sterilization)

• Operation (OQ): Reduced testing
  – no spray ball mapping
  – no temp mapping

• Performance (PQ) & Process Validation: Reduced testing
  – no media holds (for sterile equipment)
  – sterile hold time studies eliminated

Impact of Single-Use Systems
(eliminating cleaning & sterilization)

• Cleaning Validation: Eliminated
  – development & qualification of cleaning procedures eliminated
  – qualification of CIP skids & controls eliminated
  – qualification of swabbing, recovery and analytical test methods eliminated

• Cleaning-Related Studies: Eliminated
  – clean equipment hold time studies eliminated
  – resin / membrane reuse studies eliminated
  – storage buffer bacteriostasis studies eliminated
Impact of Single-Use Systems
(on qualification / validation)

STAINLESS STEEL
• Design of CIP/SIP functions
• IQ/OQ of CIP/SIP systems
• Temp maps, media holds
• Cleaning validation
  • swab studies, analytical
  • bacteriostasis studies
  • reuse studies

SINGLE-USE SYSTEMS
• Extractables studies
• Vendor audits

QUALITY / VALIDATION EFFORT

Single-Use Facilities
Biotherapeutic Development Timeline

- **Phase I**: ~1 year
  - 80% Success
  - 76% Risk

- **Phase II**: ~2 years
  - 45% Success
  - 60% Risk

- **Phase III**: ~2 years
  - 75% Success
  - 33% Risk

- NDA Review: ~1.5 years
  - 90% Success
  - 10% Risk

- **Product Approval & Launch**
  - Decision: ~1 year
    - "Buy vs. Make" CMO vs. Build
  - Design: ~1 year
  - Construction: ~2 years
  - Validation: ~1 year

**Manufacturing capacity decisions must be made while risks are high**

Delay or Accelerate Construction?

- **ACCELERATE**
  - Decrease risk of facility delay
  - Mfg phase III product in facility

- **DELAY**
  - Decrease risk of drug failure
  - Improved market forecast
  - Consider PD improvement
## Buy or Build Capacity?

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<th>Pro</th>
<th>Buy</th>
<th>Build</th>
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<tbody>
<tr>
<td></td>
<td>• No capital expense</td>
<td>• Builds capability</td>
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<td></td>
<td>• Fast access to capacity</td>
<td>• Strategic asset</td>
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<td>• No cost between projects</td>
<td>• Control of projects</td>
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<td>• Flexibility</td>
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<td>• Loss of control</td>
<td>• Capital expense</td>
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<td>• Does not build internal capability</td>
<td>• Long lead time</td>
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<td>• Risk</td>
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<td>• Maintenance cost when idle</td>
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## New Possibilities with Single-Use

**Problem:** Buying CMO capacity is a fast, low capital option, but money spent does not build company assets

**Ideal Solution:**
- Buy CMO capacity when risk / uncertainty is high, cash is low
- Quickly establish in-house capacity when risk is low, high product / pipeline demands certain
Considerations for implementation of single-use technology ...

Recent Trends

Continuous Manufacturing: Perfusion cell culture, multi-column chromatography

Closed Processing: Closing process flow path should reduce or remove the requirement for classified manufacturing environment
Summary

- Single-use is well established, increasing trend and increasing scales
- Single-use can save batch labor and decrease scope of qualification / validation
- Single-use systems qualification combines
  - equipment qualification
  - raw material control systems
  - extractables studies (using risk matrix & vendor data)
- Single-use systems may be most beneficial for
  - capacity expansion (decreased space, validation & utilities)
  - multi-product facilities
    - eliminated cleaning validation burden
    - decreased turnaround time between campaigns

Summary

- Single-use enables a manufacturing platform with many benefits compared to standard technology
  - Extremely fast construction / capacity expansion time of 6-12 months
  - Significantly reduced capital cost
  - Decreased cost of operations
  - Easily reconfigured
  - Minimized operating space
Thank You