Keeping up with Single-Use

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Connecting a World of Pharmaceutical Knowledge

Outline

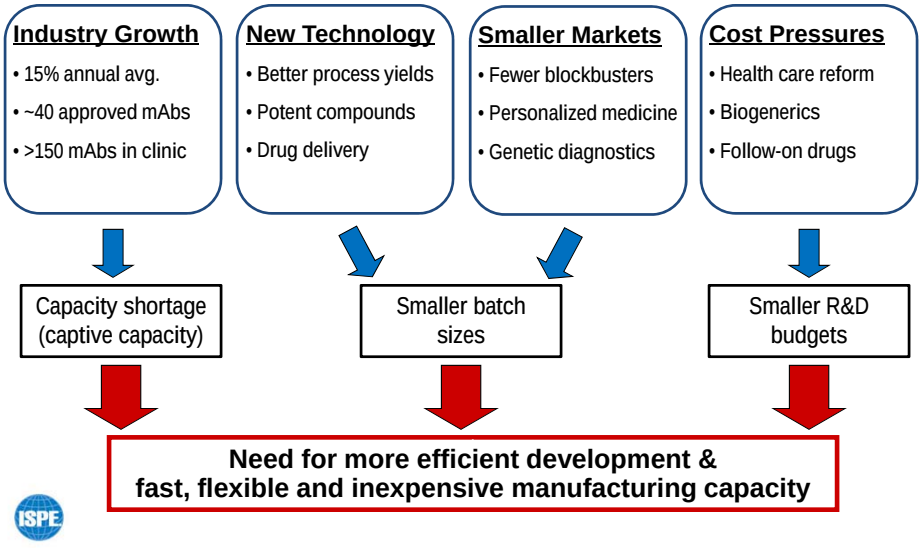
- Introduction / Overview
- Technology Survey
- Economics
- Quality
- Single-Use Facilities
- Summary

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



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

Technology Survey

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 cm^2

VENDORS: Corning, Thermo, GE, Sartorius, Millipore

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

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



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 m^2

VENDORS: Hollow fiber: Spectrum, GE

Flat Sheet: Millipore, Pall, Sartorius, Tangenx

NOTES: Recent introduction of ready-to-use

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.

Connections

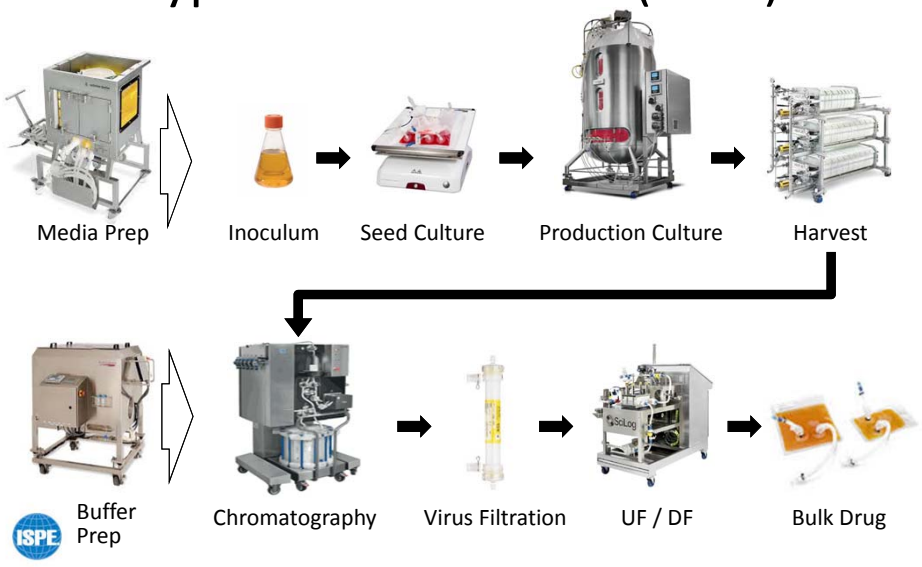
APPLICATION: Connection / disconnection of tubing to bioprocess bags, sample collection or other systems

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)



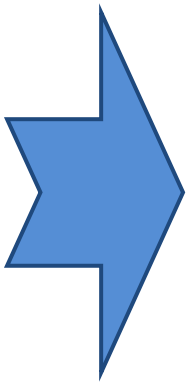
Economics

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)

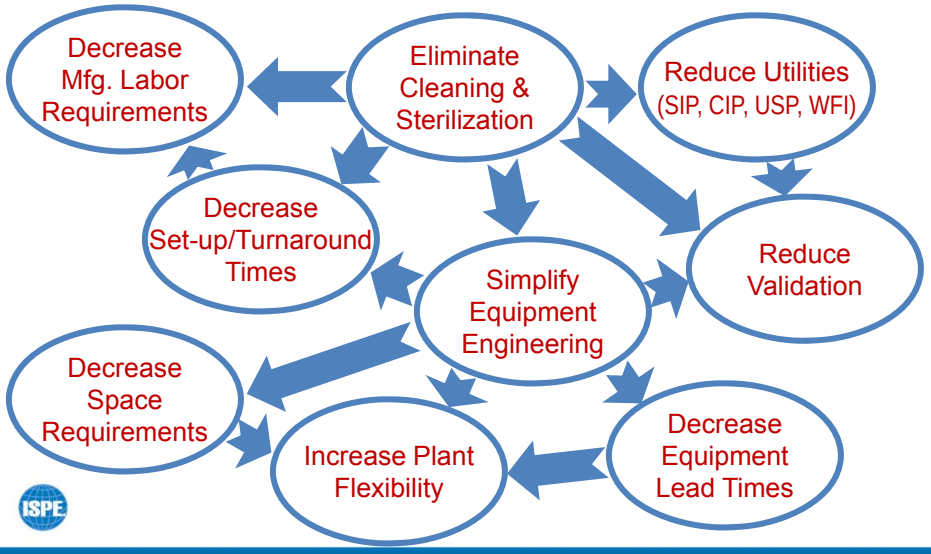
Advantages of Single-Use

- 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



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 & bacteriostatis 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

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

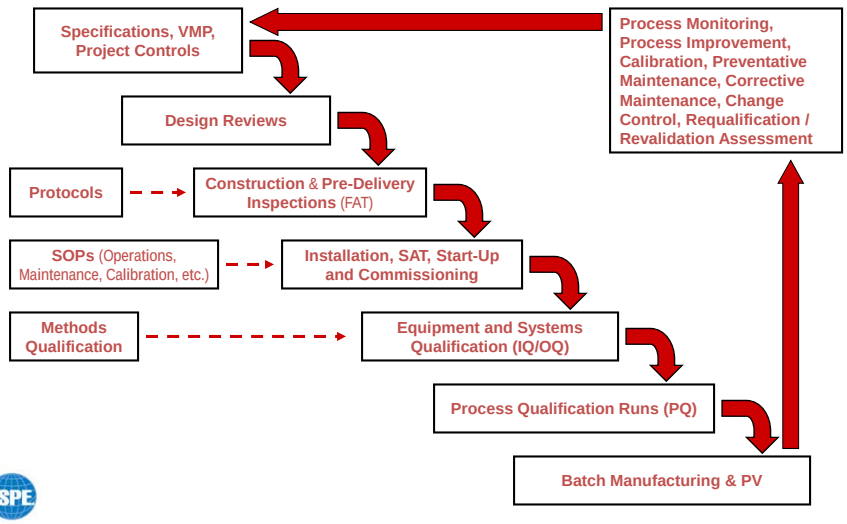
What is Validation?

"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."

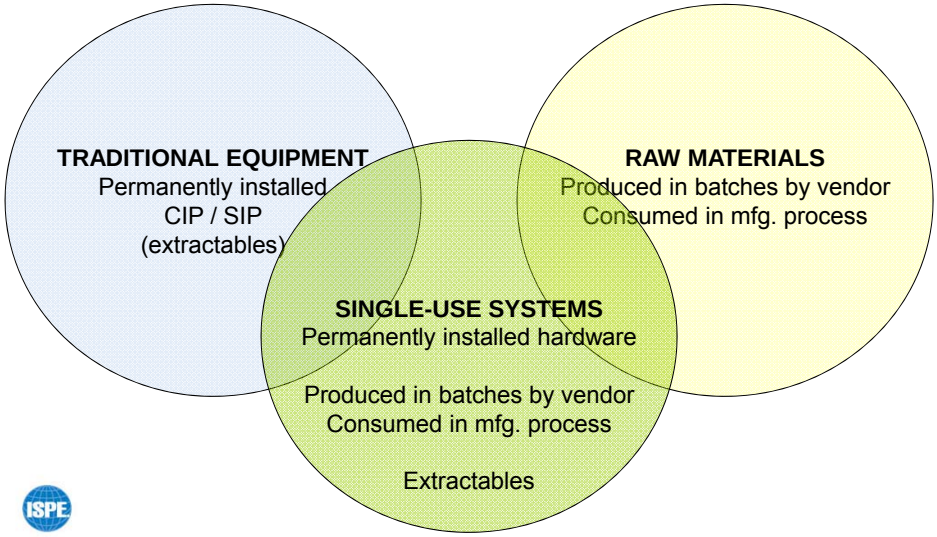
Guideline on General Principles of Process Validation, FDA, 1987

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

Validation Life-Cycle Map



Single-Use Systems



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

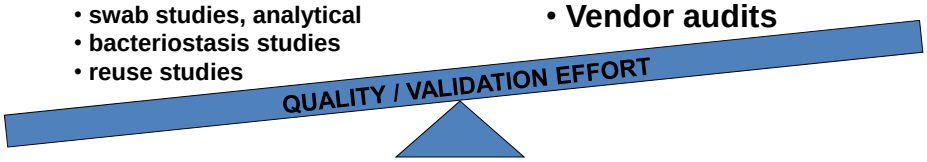
(on qualification / validation)

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

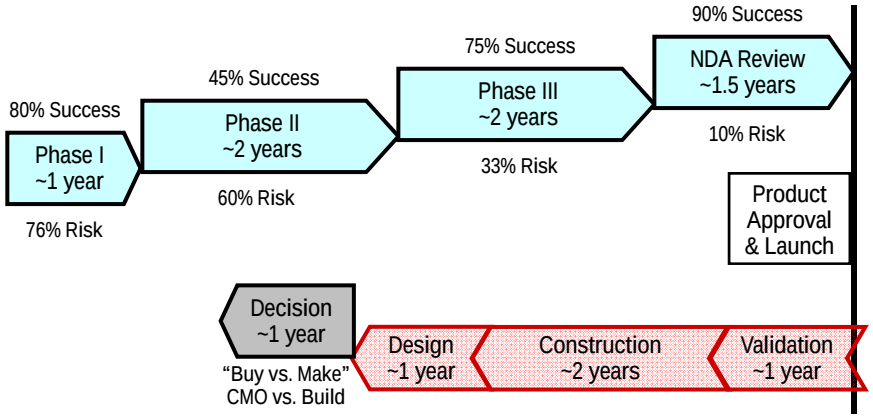
SINGLE-USE SYSTEMS

- Extractables studies
- Vendor audits



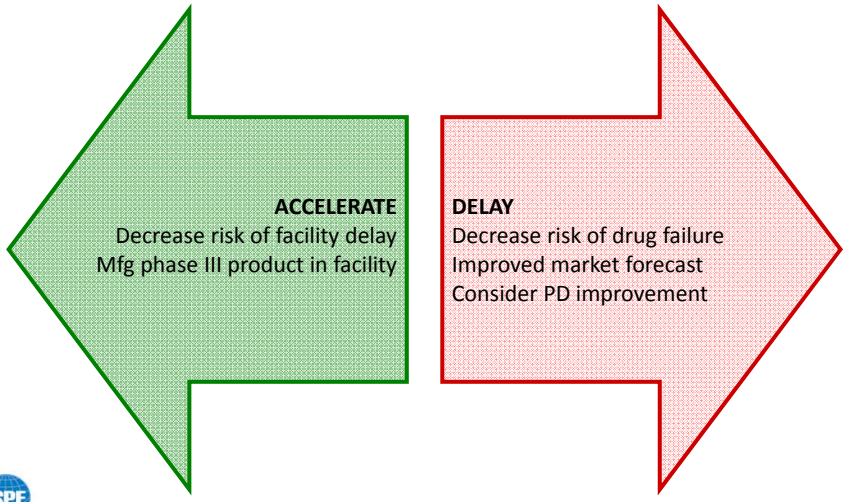
Single-Use Facilities

Biotherapeutic Development Timeline



Manufacturing capacity decisions must be made while risks are high

Delay or Accelerate Construction?



Buy or Build Capacity?

	Buy	Build
Pro	• No capital expense • Fast access to capacity • No cost between projects	• Builds capability • Strategic asset • Control of projects • Flexibility
Con	• Loss of control • Does not build internal capability	• Capital expense • Long lead time • Risk • Maintenance cost when idle

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 …

Connectivity

?

Automation & Control

?

Facility Layout

?

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