Implementation of Single-Use Systems
Benefits and Challenges

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PDA Metro Chapter
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Today's Process Design Challenges

« Better – Faster - Cheaper »

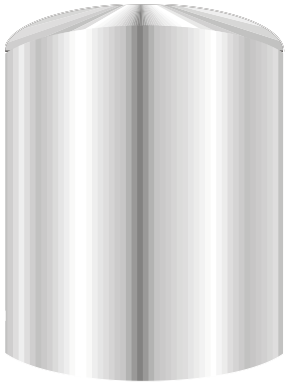
- Quality
- Safety
- Efficiency
  - QbP
  - PAT
  - cGMP

- Reduce time
  - Discovery
  - Development
- Increase speed to market

- Decrease costs:
  - Facility
  - Validation
  - Production
- Increase flexibility

Traditional Manufacturing Processes

- Stainless Steel Equipment
  - Expensive tanks, piping, valves, filter housings, etc.
  - Limited polymers - gaskets, seals, hoses, filters
  - High capital cost with long implementation schedule
  - High risk of cross contamination & bioburden
  - Repeated high cost of cleaning and sterilization
  - Downtime, maintenance

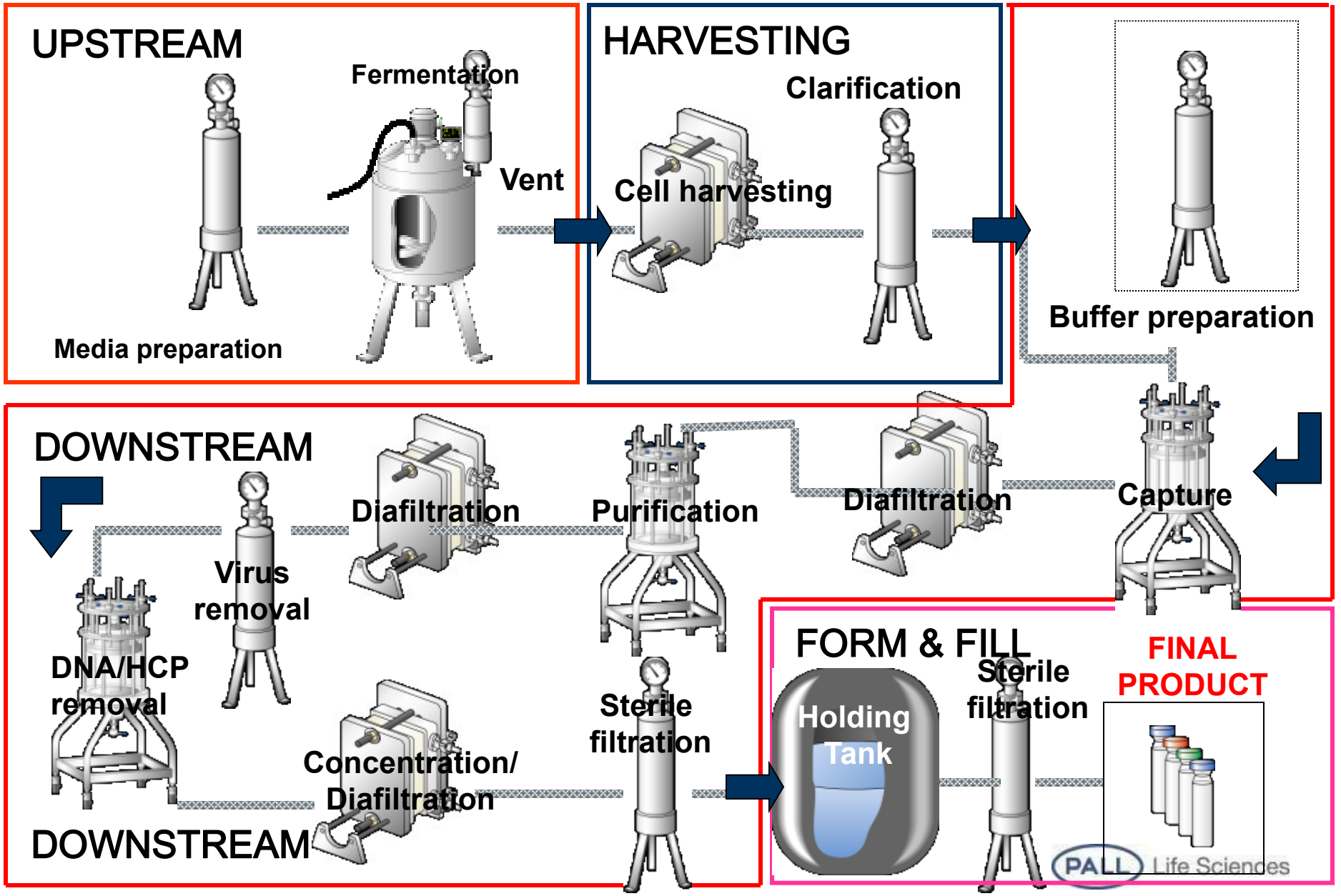




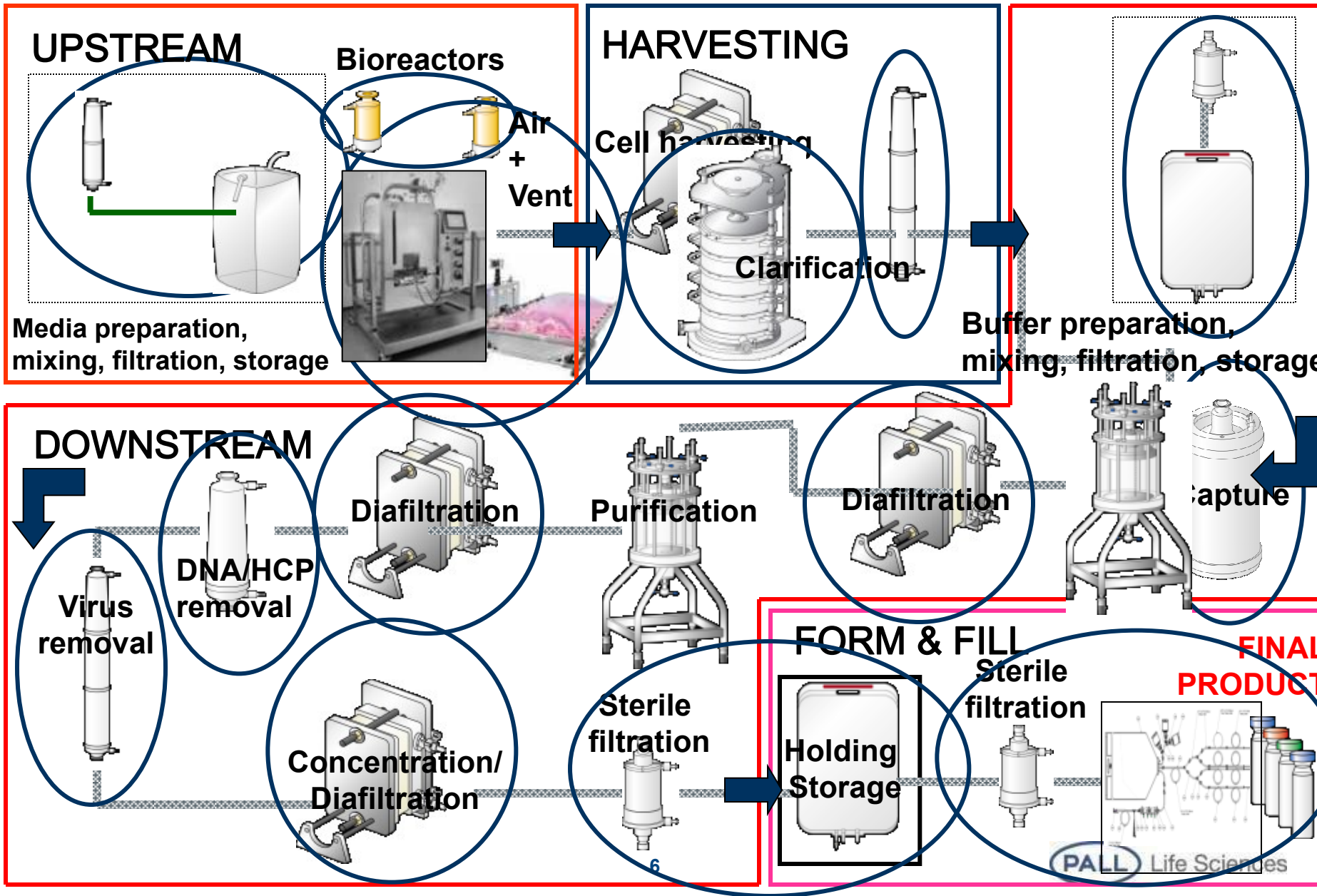
Advantages of Single-Use Systems

- Low installation cost
- Reduced cleaning costs
- Reduced maintenance costs
- Reduced assembly costs
- Reduce/eliminate cleaning validation
- Sterilization and validation by suppler
- Minimizes operator exposure
  - e.g. Cytotoxic drugs
- Free up resources
- Shorten development time for new facilities

Stainless Steel BioPharma Process



Disposable Single-use Process



Regulatory Guidance Specific to Single-use

FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July, 2008)

…technologies … that can facilitate conformance with CGMP and streamline product development include:

- Use of disposable equipment and process aids to reduce cleaning burden and chances of contamination
- To the extent possible, dedicated equipment and or disposable parts (e.g. tubing) is recommended

FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July, 2008)

- Use of commercial, prepackaged materials (e.g., Water For Injection (WFI), pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment
- Use of closed process equipment (i.e., the phase 1 investigational drug is not exposed to the environment during processing) to alleviate the need for stricter room classification for air quality

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Qualification of Single-use Equipment

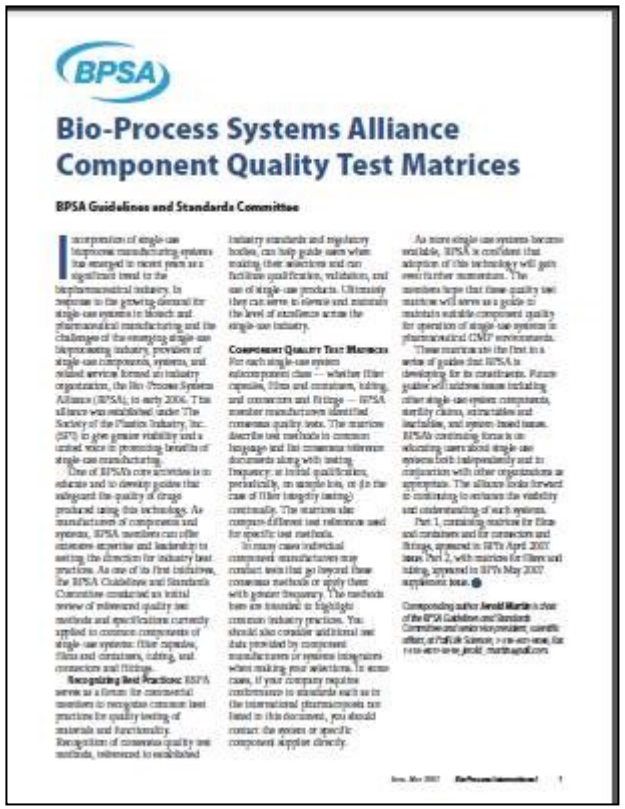
Components

Systems

Processes

Qualification of Single-use Equipment

- BPSA Component Quality Test Matrices
  - Published 2007
  - Available at www.bpsalliance.org
  - Supplier consensus quality tests
    - Biocontainers
    - Filters
    - Tubing
    - Connectors
  - Update 2015 pending
    - Sensors
    - Chromatography



BPSA

Bio-Process Systems Alliance Component Quality Test Matrices

BPSA Guidelines and Standards Committee

Component Quality Tests

Films and Containers

Physical	Chemical/ Biological	Functional
Puncture	Physicochemical	Seal Integrity
Tear	Extractables	
Tensile	Endotoxin	Transport/ Shipping
Permeablity	Biol. Reactivity	Shelf Life

Component Quality Tests

Filter Capsules

Physical	Chemical/ Biological	Functional
Extract NVR	Extractables,	Water Flow/ΔP
Fibers/Particles	Flush TOC, pH, Conductiviy	Bacterial Retention
Pressure/Burst	Endotoxin	Hydraulic/ Thermal Stress
Irradiation	Biol. Reactivity	Shelf Life

Component Quality Tests

Tubing

Physical	Chemical/ Biological	Functional
Tensile, Elongation	Physico/ Chemical	Pressure/Burst
Durometer, Modulus		Kink Resistance
Tear resistance	Endotoxin	Bend Radius
Specific gravity	Biol. reactivity	Shelf Life

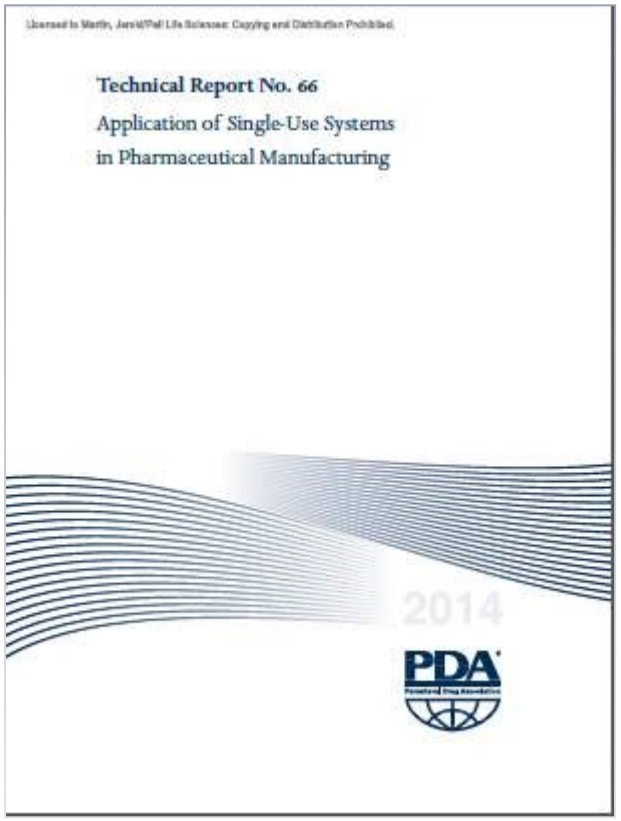
Component Quality Tests

Connectors and Fittings

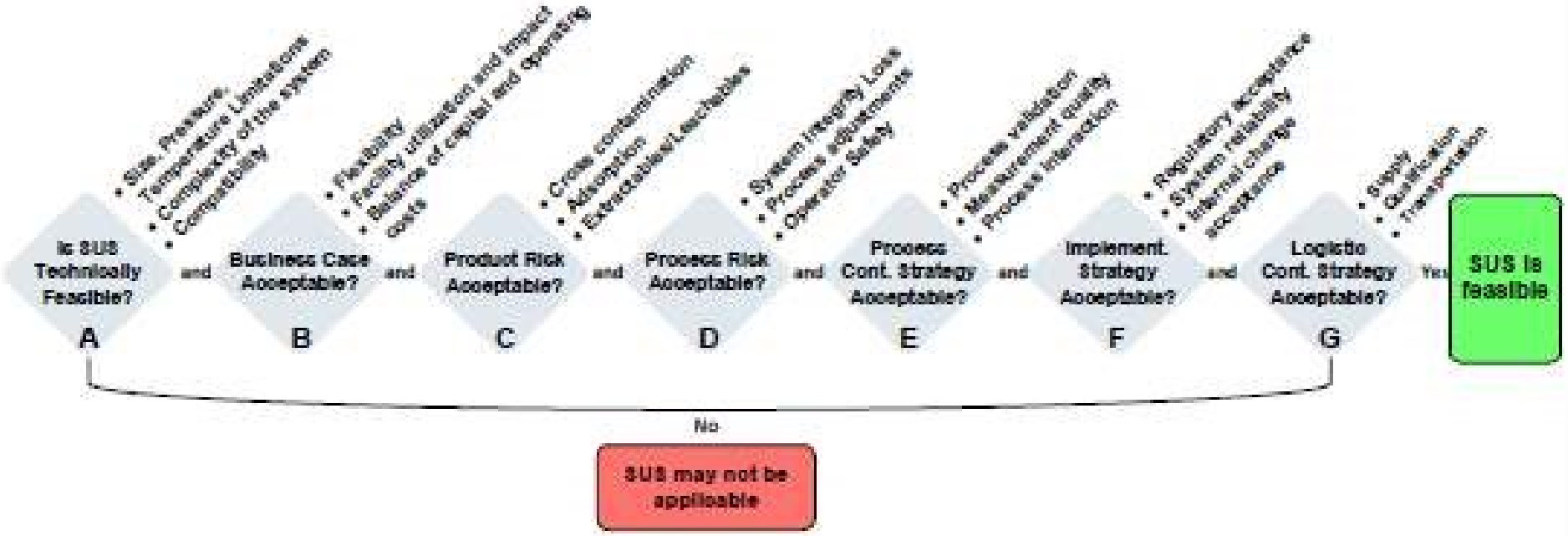
Physical	Chemical/ Biological	Functional
Pressure/Burst	Physico/ chemical	Leak testing
Thermal Resistance		Water Flow/ΔP
Dimensions	Endotoxin	
	Biol. Reactivity	Shelf Life

Qualification of Single-use Systems

- PDA Technical Report 66
  - Application of Single-use Systems in Pharmaceutical Manufacturing
  - User, Supplier and FDA consensus
  - Quality by Design principles
  - Risk-based approach



Manufacturing Strategy : a guided decision process



A structural way to address and evaluate factors for consideration.
Each Step is crucial to successful implementation of new technology.
Negative results at any Step may disqualify SUS from consideration

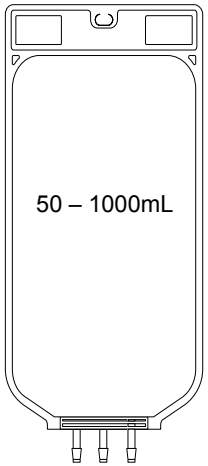
TR66 – SUS Implementation Strategy

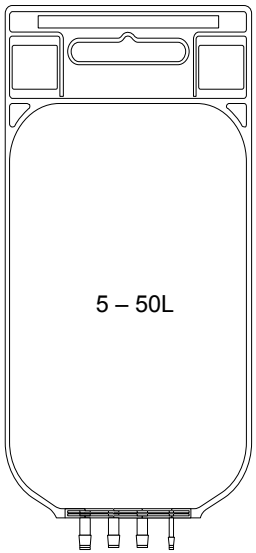
- Technical Feasibility
  - Size, pressure, temperature, chemical compatibility?
- Business Case
  - Capital vs operating costs, facility utilization and flexibility?
- Product Risk
  - Reduced cross-contamination, higher asepsis, leachables?
- Process Risk
  - Leak/integrity loss, operator safety?
- Process Control Strategy
  - Measurements, validation, automation?
- Implementation Strategy
  - Regulatory approval, system reliability, change management?
- Logistic Control Strategy
  - Supply, shipping, inventory?

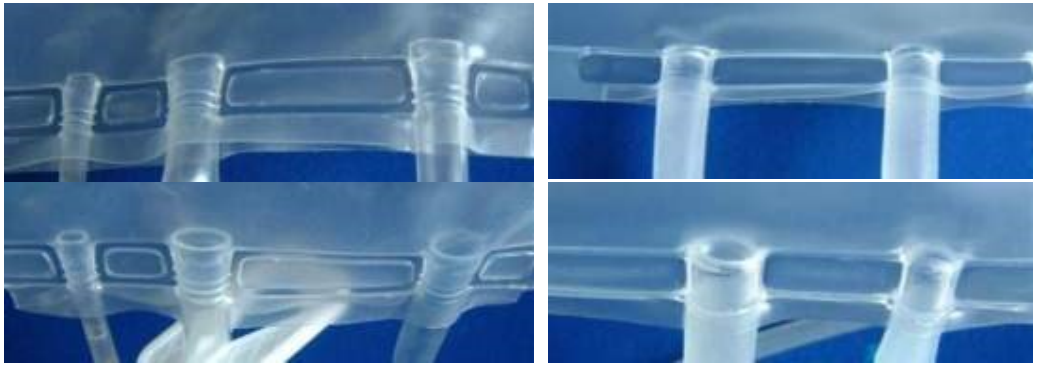
Physical Risk Qualification

Physical Risks – Design Improvements

- Continuous seams
- Molded fitting assemblies (boat design)

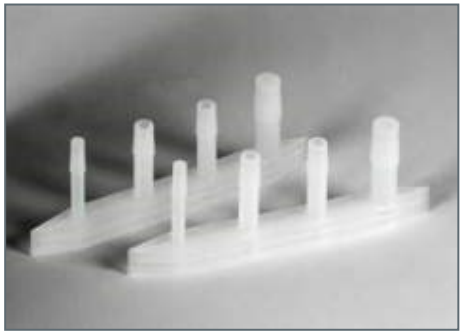


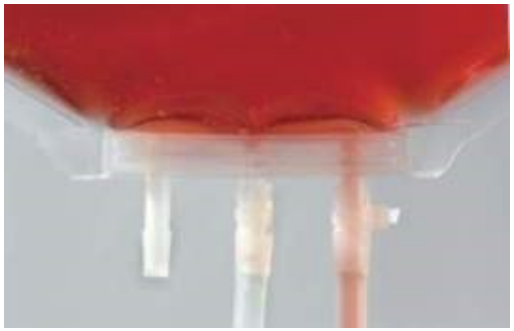




Sealed tube connectors

Molded boat connectors





Physical Risks – Design Improvements

- 2D totes eliminate hanging stresses
- Front-loaded 3D totes + self-filling 3D biocontainers reduce handling, eliminate stress cracking, pulling
- Multi-operation platforms reduce system stresses

Leak / Integrity Testing

- Terminology
  - Leak test – detect gross defects
    - Air pressure hold/decay
    - Tracer Gas (e.g. Helium) leak detection
  - Integrity test – confirm microbial barrier properties
    - No consensus on requirement, test method
- Equipment
  - Biocontainers - Leak test by manufacturer
  - Single-use Systems (bioreactor, tubing manifold)
    - Supplier qualification/tests (pre-release)
    - User qualification/tests (pre- or post-use)

Bioburden Control and Sterilization Qualification

Bioburden Control and Sterlization

- Suppliers
  - Controlled clean manufacturing
  - Bioburden monitoring
  - Gamma irradiation for microbial control
  - Gamma sterilization validation
  - Dose mapping
  - Lot certification
  - Periodic dose audits

Bioburden Control and Sterlization

- Users
  - Reference Documentation
    - Gamma sterilization validation report
    - Dose mapping report
    - Lot certification
    - Periodic dose audit report
  - Audit supplier
    - Ref: Biogen Idec FDA 483 08/02/2013

1) There is no assurance that the firm always challenges the validity of all testing results provided in container-supplier's certificates of analysis as part of supplier qualification procedures. [redacted] (b) (4) bulk bags, used as the container closure system of Tysabri API, are received with certificate of analyses indicating that the bags are sterile and endotoxin free; however, these results have never been challenged and/or verified by the firm.

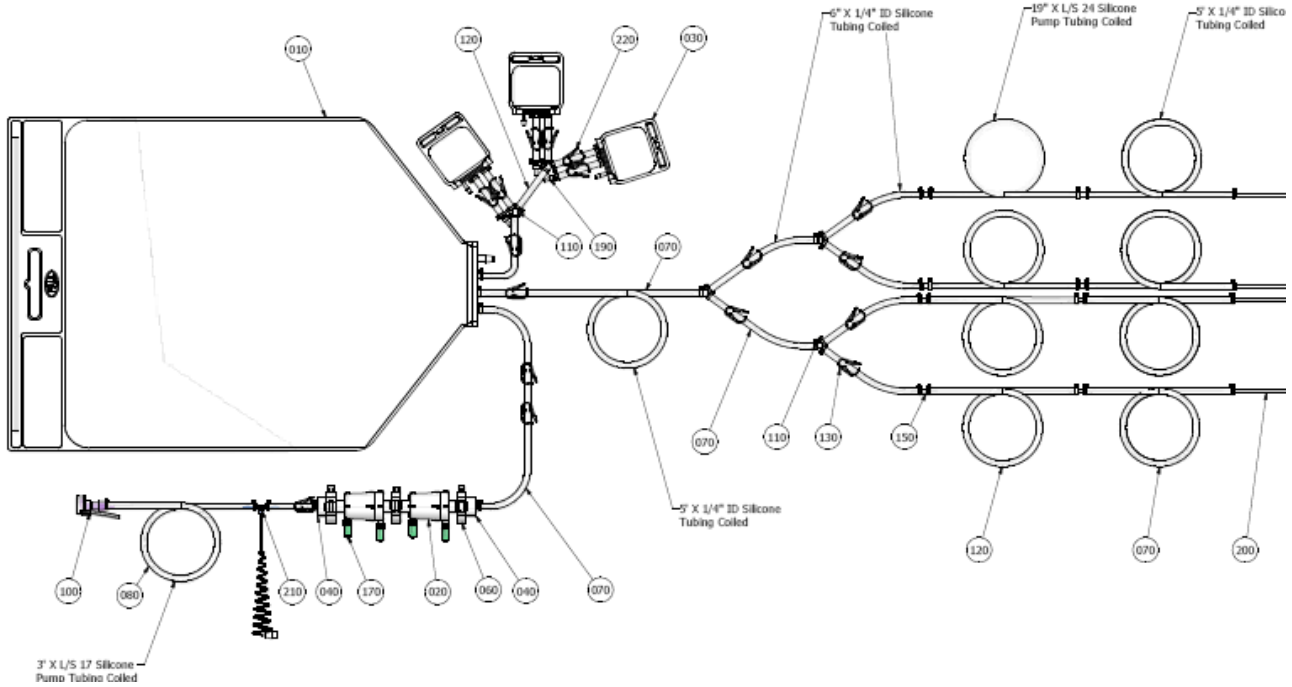
Sterilization Standards

- ANSI/AAMI/ISO 11137:2006
  - Sterilization of health care products - Radiation
  - (Parts 1 – 3)
- AAMI TIR33:2005 (supplement)
  - Sterilization of health care products - Radiation
  - Substantiation of a selected sterilization dose - Method VDmax
- Single-use Industry Collaboration
  - BPSA Guide published 2008
  - Application of standards to single-use systems
  - Available at www.bpsalliance.org

Particulates Risk Qualification

Particle Risks in Single-use Systems

- Potential to contaminate final dosage and cause harm to patients
- Post-filtration filling systems
- Aseptic processes without inline filtration



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Potential Sources of Particles in SUS

- Resin hoppers / bins must clean
- Components
  - Filters, biocontainers, connectors, tubing
- Biocontainer and system assembly
  - 2D and 3D biocontainer manufacturing
  - Tube cutting
  - Hosebarb fitting
- Environment
  - Operator gowning and training
  - Mfrg & assembly air quality

Particle Limits - Compendial Tests

- Visible Particles in Drug/Vaccine Products
  - USP <1>: Injectables
  - “essentially free of visible particles”
- Subvisible (microscopic) Particles
  - USP <788> Particulate Matter in Injections
  - Methods, limits for >10-25 µm and >25 µm particles
- SUS Particle Testing
  - Apply USP limits (to rinse effluents)
  - No industry guides, standards or regulatory guidance

Visible Particle Qualification

- "Essentially free" is undefined
- SUS cannot be "inspected" when empty
  - QbD engineering of component mfr and assembly
  - Supplier operator "surveillance" as final check
  - Supplier test "worst case" surrogate system for periodic monitoring
- User "surveillance pre/post filling
  - Significance of single visible particle in bulk?
  - Risk of being missed during bulk or final inspection?

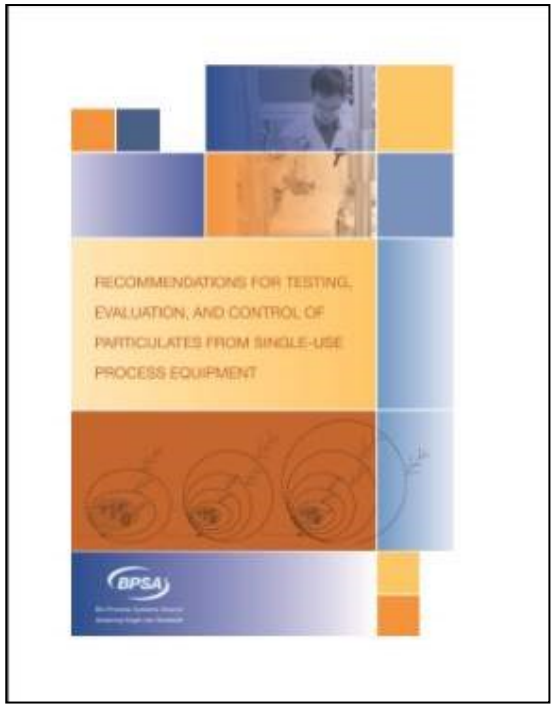
Reduction of Particulate Risks

- "Non-particle-releasing" filters
  - Flushed in manufacturing
- Optically clear biocontainer films
- Multilayer film extrusion
- Cleanroom assembly
  - ISO 7 (Class 10,000 / Grade C)
- Operator gowning and training

BPSA SUS Particulates Guide

- Recommendations for Testing, Evaluation and Control of Particulates in Single-use Process Equipment

Part I:	Introduction
Part II:	Particle Risk
Part III:	Particle Characteristics & Quantification
Part IV:	Particle Measurement Methods
Part V:	Single-Use Technology Lifecycle
Part VI:	Methods of Control for Suppliers
Part VII:	Particulate Evaluation as Part of End User Manufacturing
Part VIII:	Deviation Response/Mitigation Plans
Part IX:	Summary and Conclusion
Part X:	BPSA-recommended Next Steps
Part XI:	Terms and Definitions
Part XII:	References



- Available at www.bpsalliance.org

Chemical and Biological Risk Qualification

Regulations and Guidance – Chemical Risk

- Drugs: US FDA 21 CFR § 211.65(a) Equipment

  "*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.*"

- Biologicals: 21 CFR § 600.11 (b) Equipment
  - *"All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use...."*

Regulations and Guidance – Chemical Risk

- Similar Statements in GMP Regs and Guidelines
  - Equipment for API manufacturing
  - Containers for bulk drug substances
  - Containers for drugs
  - Containers for biologics
  - Final dosage containers
- These are user responsibilities
- Equipment suppliers can add value by providing extractables data
  - Help users to assess risks of potential leachables

Chemicals in Polymer Formulations

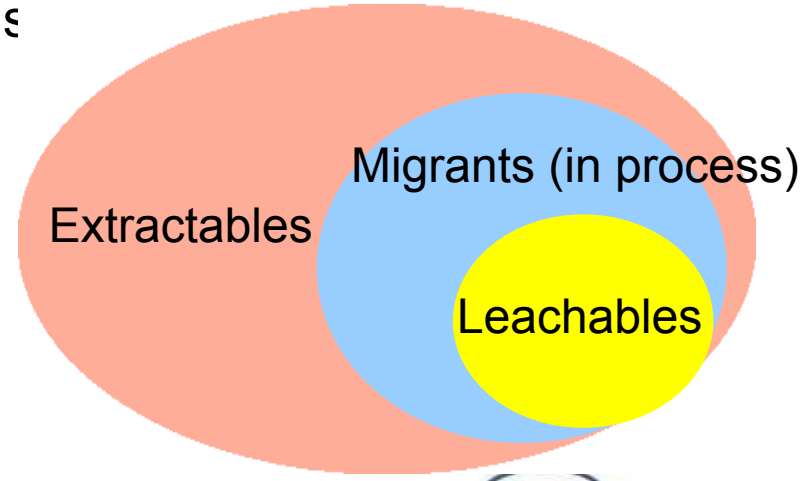
- Polymers
  - Oligomers
  - Unreacted monomers
- Additives
  - Polymerization agents, pore formers
  - Stabilizers, antioxidants,
  - Anti-static agents
  - Processing / extrusion / mold release agents
  - Colorants

Materials/Component Biological Safety

- Quality by Design – Material Prequalification
  - USP <88> Biological Reactivity Tests, *in vivo*, for Class VI plastics
    - Extractions in saline, ethanol, polyethylene glycol, vegetable oil
    - Systemic toxicity evaluations
  - USP <87> Biological Reactivity, *in vitro*
    - MEM cytotoxicity
- Post-sterilization Component Qualification
  - Autoclave at >121-135 ºC or Gamma to 50 kGy
  - Repeat compendial tests on mfr'd/treated materials

Leachables, Migrants, Extractables

- Chemicals that can migrate into (dissolve in) process fluids or product
  - Leachables – in final product dosage
  - Migrants ("in-process leachables") – in process fluids
  - Migrants (per FDA) – leachables from external sources
  - Extractables – potential leachables
    - Exaggerated dissolution conditions
      - Stronger solvents,
      - Higher temperatures
    - Aid in predicting in "in-process" and final dosage leachables



Industry Recommendations

- BPSA Extractables Guides (2008, 2010)
  - Consensus of suppliers and independent labs
  - Reviewed with FDA and users
  - Many successful approved applications
  - Risk-based approach
    - Water and ethanol extractions
    - Other solvents as applicable (e.g. high/low pH)
    - Broad analyses (e.g. FTIR, LC-MS, GC-MS, ICP-MS)
  - Available at www.bpsalliance.org

Standardization of Extractables Testing

- BPOG user group proposal to suppliers
  - Multiple extraction solvents
  - Sample size/area, extraction volume
  - Extraction conditions (temperature, times, dynamics)
  - Multiple time points
  - Specified analytical methods
- BPSA Counter-proposal from suppliers, users
  - Agreement in principle
  - Technical justifications, exceptions, cost concerns
  - How will results be used?

Standardization of Extractables Testing

- USP Standards and Regulators
  - Revision of USP <661> Containers – Plastic
  - Proposed Inclusions:
    - 661.1 Plastic Materials of Construction
    - 661.2 Plastic Packaging Systems for Pharmaceutical Use
    - 661.3 Manufacturing Systems
  - New General Chapters
    - 1663 Extractables Testing
    - 1664 Leachables Testing
    - 1665 Toxicity Assessment of Leachables

Standardization of Extractables Testing

- BPOG
  - Mahajan, E. et al., Pharma Eng. May/Jun 2012
  - Dong, W. et al., Pharma Eng, Nov/Dec 2014
- ASTM
  - E2097 - Std Gde for Determining the Impact of Extractables from Non-Metallic Materials …
  - Revised standard in development
- ASME-BPE - standard in development
- PQRI / FDA – Thresholds and Characterization If Leachables and Extractables in Parenterals and Ophthalmic Drug Products (PODP)USP
- USP – Revisions of USP 661, SU standard in development

Cytotoxicity in Single-use Bioreactors

- Identification of a Leachable Compound Detrimental to Cell Growth in Single-Use Bioprocess Containers
  - Hammond, M. et al. (Amgen), PDA Journal of Parenteral Science and Technology, Vol. 67, No. 2, March–April 2013
- Poor cell growth attributed to trace leachable from one PE film
  - bis(2,4-di-tert-butylphenyl) phosphate (bDtBPP)
- Irradiation degradant of Irgafos 168
  - Antioxidant added to scavenge hydroperoxides

Cytotoxicity in Single-use Bioreactors

- Widely publicized but rare event (few)
- Effects observed at initial screening or later
  - Irradiation dose or ageing effects
    - Potentially but unconfirmed
  - Shipping effects
    - One case attributed to overheating on dock (volatiles)
  - Formulation changes
    - Change management and notification

- Review: Martin, J - Cytotoxicity Risks in Single-use Media and Bioreactor Containers, Biopharm Intl, Feb 2004

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Quality by Design in Materials for Single-use Systems

Supplier Materials Selection

- Quality by Design
  - Reduce risk of undesirable migrants and leachables
- Avoid unsafe Extractables / Leachables
  - No rubbers (only Pt-cured silicone gaskets and o-rings used)
  - No latex, no polyvinyl chloride (no phthalates), BPA
  - No known genotoxicants, no Class 1 solvents
  - Animal-free or BSE/TSE statements
  - pH resistant polymers for pH adjusters, buffer prep,' e.g. polypropylene and polyethersulfone (PES)
- Supplier Disallowed and Controlled Substances
  - e.g., www.pall.com/pdfs/About-Pall/E962.pdf

Quality and Supply Chain Security

Consistency Risk - Change Control

- Supplier Audits
  - Raw materials and components
  - Manufacturing controls
  - Quality system
- Quality Agreements
  - Raw materials and component suppliers
  - Supplier Change Notifications
- Industry Collaboration
  - BPSA Quality Agreement Template
  - Available at www.bpsalliance.org

BPSA Quality Agreement Template for SUS Contents:

- Introduction
- Effective Date
- Scope
- Other Agreements
- Amendments to Quality Agreement
- Term of Quality Agreement
- Use of Third Parties
- Product Specifications
- Resolution of Quality Issues
- Choice of Law: Jurisdiction, Compliance Requirements
- Right to Audit
- Product Quality Notification
- Complaints
- Animal--Derived Materials
- Validation/Qualification
- Documentation and Records
- Change Control
- Deviations
- Reprocess/Rework
- Production and In Process Controls, Packaging and Labeling
- Storage and Distribution
- Inspection and Test Equipment
- Control Recalls, Corrections, Field Actions
- AX 1: Definition of Product
- AX 2: Roles and Responsibilities
- AX 3: Key Contacts
- AX 4: Product Specifications

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