PDA Technical Report on Single-use Systems

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Technical Report (TR) on Single Use System (SUS)

• Support implementation of SUS
• A guide, listing the areas to consider
• Easy and fast to read
• Build on the current best practice
• Address regulatory aspects
• Address technical aspects
• Written by suppliers, users and regulatory bodies
PDA Goals for Technical Reports

• PDA TR’s should reflect a global perspective and are educational documents that are based in sound science and discuss meaningful studies and practical applications of the science

• Include not just the “How’s,” but also the “Why’s”

• “Points to Consider” documents;
  – current and applicable references used wherever possible to give further detail and/or support concepts presented

• PDA Technical Reports are not intended to set standards
Approach to the PDA Technical Document

• Who are our Customers?
  – Industry End Users
  – Regulators
  – Suppliers
  – PDA Scientific Approval Board

• What do they want from this report?
  – An understanding of Key Principles and Concepts for selection, use and qualification/validation of Single Use Systems
  – Breath of knowledge to enable people at various levels in an organization to make effective decisions relating to Single Use Systems
PDA Single Use Systems Task Force

Representatives from

- US and Europe
- Regulatory, US and Europe
- Biopharmaceuticals
- Vaccines
- Gene Therapy
- Small Molecules
- Industry Suppliers
- BPSA (Bio-Process Systems Alliance)
# PDA Single Use Systems Task Force

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
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</thead>
<tbody>
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<td>Bill Hartzel</td>
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<tr>
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<tr>
<td>Robin Alonso</td>
<td>Genentech</td>
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<tr>
<td>Russell Wong</td>
<td>Bayer Healthcare</td>
</tr>
<tr>
<td>Stephen Brown</td>
<td>Vivalis</td>
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</table>
A thorough understanding of product and process risks is required in order to have a robust process with demonstrated patient safety, and product availability.

The Pyramid represents the desired state results of any well-executed SUS implementation.
A well designed Manufacturing Strategy including Process Control, and Logistic Controls to support the desired state, patient safety, and product availability.
The outer circle identifies individual strategies required to successfully meet the desired state.
Organization of the Document
Introduction

• Introduce QRM and QbD
  – Philosophical basis of document

• Flexible guidance providing concepts and key considerations so the reader can ask the right questions, and make the best decision for their individual situation

• Present guidance so organizations can make the road map that suits them best.

• Partnership between Supplier and End User
Document Themes

- SUS performance and quality level equivalent or exceeds performance of traditional systems
- Customer Goals
  - Quality
  - Implementation
  - Technologies
  - Business drivers
- Balanced approach 4 key areas to consider,
- Supplier & End User partnership
- Comparative Voice, MUS vs SUS
- Value added outsourcing of activities
- Process and Product understanding
- Qualification
- Logistics Control Strategy
- Manufacturing Strategy
- Business Drivers
- Patient Safety
- US and EU Regulatory considerations
- Risk based approach to decisions
- Flexible approach with points to consider for individual application
- Dialog between SUS Suppliers, and End User Quality systems
Asking the right questions depends on your situation....

- What are your core functions?
- What are your goals?
- What stage is your product?
- What is your core business?
- Will SUS solve a problem you have, or reduce cost?
- Is there a better way?
• Voice of the PDA Community
• 10 topic blocks
  – Quality
  – Regulatory
  – Implementation
  – Business
  – Supplier Relation
  – Risk Assessment
Section 3 – Manufacturing Strategy Decision Process

- Designed to be able to stand alone, if only an overview is required
- Introduction and guide to find more detailed information in the rest of the document
- First section to be drafted and will be the last section to find its final version, to ensure it meets its purpose
SUS Advantages (some)

- Reduced risk for (cross) contamination
- Higher degree of closed operation
- Reduced risk for need for re-scheduling due to equipment operation issues
- Higher flexibility
- Lower capital investment
- Flexibility for changes in market demand
- Less down time (multi use facility)
- Facility set-up time
Asking the right questions depends on your situation

- New facility
- Single product
- Development
- Biological product
- CMO
- Few kg per year

- Established facility
- Multi product
- Commercial production
- Chemical product
- Innovators' Facilities
- Ton of product per year
Guided Decision Process

Is SUS Technically Feasible?

- Yes → Business Case Acceptable?
  - Yes, Product Risk Acceptable?
    - Yes → Process Risk Acceptable?
      - Yes → Process Control Strategy Acceptable?
        - Yes → Implementation Strategy Acceptable?
          - Yes → Logistic Control Strategy Acceptable?
            - Yes → SUS is feasible
          - No → Process Interaction
        - No → Process validation
      - No → System Integrity Loss
    - No → Operator Safety
  - No → Cross contamination
- No → SUS may not be applicable
Guided Decision Process - 1

- Size, Pressure, Temperature Limitations
- Complexity of the system
- Compatibility

Is SUS Technically Feasible?

→

Business Case Acceptable?

- Flexibility
- Facility utilization
- Balance of capital and operating costs
Guided Decision Process - 2

Product Risk Acceptable? 
- Cross contamination
- Adsorption
- Extractables/Leachables

Process Risk Acceptable?
- System Integrity Loss
- Process adjustments
- Operator Safety
Guided Decision Process - 3

- Process validation
- Measurement quality
- Process interaction

Process Control Strategy Acceptable?

- Regulatory acceptance
- System reliability
- Internal change acceptance

Strategy For Implementation Acceptable?
Guided Decision Process - 4

If the answer is YES to all questions, then implementation of SUS can only be too SLOW.
Is a SUS solution technically feasible? – a moving target

- Structured evaluation of the available technical solutions
- Comparing MUS and SUS solutions
- Moving to more integrated / complex systems
- Technical risk evaluation
- Integration between:
  - MUS and SUS
  - SUS and SUS
  - Different suppliers
Is SUS good business?  
– move from gut feelings to facts

- Balance on fixed and operating costs
- Time to market
- Number of products / batches per year
- “Green” manufacturing - waste handling
- Risk factors – productions failures, contaminations, supplier delivery issues, cleaning validation, etc.
- Facility utilization / flexibility
  - Different products / Different locations
- Time to establish manufacturing facility
Effect of Postponing Decision to Build

Project Survival %

Research | Development | Market

Clinical Trials I,II,III & Registration

40 Month Project: 50% chance of being needed

24 Month Project: 90% chance of being needed

Reducing project duration by 16 months reduces chance of the \textbf{wrong} investment being made by a factor of 5!
Patient safety can never be compromised -

- Extractables and Leachables issues
- Risk evaluation – balancing pro and cons for MUS and SUS systems
- Sanitation and sterilization
- Integrity (leak) testing
- Quality of components / data from SUS sensors
- Supplier Audits / Qualification
- Validation issues
- Acceptance test – installation qualification
A directional risk profile of various SUS applications

<table>
<thead>
<tr>
<th>Complexity of application</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Freeze thaw</td>
<td>Fill and finish</td>
<td>Cell culture Product storage</td>
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<td>Medium</td>
<td>Transport shipping</td>
<td>Mixing</td>
<td>Purification</td>
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<tr>
<td>Low</td>
<td>Buffer storage</td>
<td>Concentration</td>
<td>Clarification Recovery</td>
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</table>

The addition of valves, sensors and manifolds increases complexity and risk.
All the other things that make a project successful or not

- Risk Assessment – logistic issues and combining risk assessments - full picture
- Implementation plan
- Stakeholder management
- Supplier agreements
- Training
- Safety for operators
- Material management – receiving, storage, transport and waste
- Facility layout
SUS Impact on Plant Design
Materials Control
## Components of material risk

<table>
<thead>
<tr>
<th>Supplier risk</th>
<th>Material risk</th>
<th>Process impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Business continuity</strong></td>
<td><strong>Material safety</strong></td>
<td><strong>Quality</strong></td>
</tr>
<tr>
<td>• Capacity</td>
<td>• Toxicity, carcinogenicity</td>
<td>• Purity</td>
</tr>
<tr>
<td>• Sole sourcing</td>
<td>• Immunogenicity</td>
<td>• Contaminant profile</td>
</tr>
<tr>
<td>• Disaster recovery</td>
<td>• Viral safety</td>
<td>• Product variants</td>
</tr>
<tr>
<td>• Business fit</td>
<td>• Residual solvents, metals</td>
<td>• Point of use</td>
</tr>
<tr>
<td><strong>Supplier Quality</strong></td>
<td><strong>Material complexity</strong></td>
<td><strong>Process performance</strong></td>
</tr>
<tr>
<td>• Audit</td>
<td>• Compendial chemicals</td>
<td>• Titer</td>
</tr>
<tr>
<td>• Change control</td>
<td>• Complex nutrients</td>
<td>• Yield</td>
</tr>
<tr>
<td>• Supply chain transparency</td>
<td>• Integrated systems</td>
<td>• Throughput</td>
</tr>
<tr>
<td><strong>Technical capability</strong></td>
<td><strong>Handling</strong></td>
<td><strong>Facility fit</strong></td>
</tr>
<tr>
<td>• Process/product understanding</td>
<td>• Lot-to-lot consistency</td>
<td>• Available equipment</td>
</tr>
<tr>
<td>• Applications development</td>
<td>• Clumping, particles</td>
<td>• Tankage</td>
</tr>
<tr>
<td>• Service and support</td>
<td>• Cleaning, disposal</td>
<td>• Local regulations</td>
</tr>
</tbody>
</table>
A science- and risk-based approach consistent with ICH Q8

- **Define**
  - Target Product Profile
    - Efficacy
    - Safety
    - Manufacturability

- **Establish**
  - CQA’s
    - Science based, prior experience
    - Linked to TPP
    - Susceptible to variability

- **Conduct**
  - Risk Assessment
    - Link RM attributes and CPP to CQA’s
    - Impact on safety and efficacy
    - Rank order by criticality

- **Verify**
  - Design Space
    - Critical process parameters
    - Process execution requirements
    - Process performance attributes

- **Implement**
  - Control Strategy
    - In-process and end of process controls
    - Use of online and offline controls
    - Real time release

- **Practice**
  - Continuous Improvement
    - Continuous Quality Verification
    - Change within/outside design space
    - Risk-appropriate regulatory approach
Initial assessments prioritize and focus studies. Additional assessments confirm and lead to control and mitigation.

Repeat at multiple points as more information becomes available.

From A-Mab: a Case Study in Bioprocess Development. Available from CASSS and ISPE
Identify the risk associated with SUS

• Product contact vs. non-product contact
• Upstream vs. downstream
• Short term vs. long term
• Leachable components
  – Product and process interactions
• Impact of sterilization
Risk Identification – Organize Information

- Brainstorming, What If?, Mind mapping
- Flowcharting, process mapping, fishbone/Ishikawa
Simple - Risk ranking, pareto, control charts
Complex - Fault tree analysis, PHA, HACCP, FMEA, FMECA

<table>
<thead>
<tr>
<th>Attributes</th>
<th>What If?</th>
<th>PHA</th>
<th>FMEA</th>
<th>HAZOP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Brainstorming technique used to analyze design hazards</td>
<td>Broad qualitative tool used in the early stages of system design</td>
<td>Used to identify system failure points</td>
<td>Systematic technique used to simulate the ways a process can fail</td>
</tr>
<tr>
<td><strong>Complexity</strong></td>
<td>Complex, but easily understood</td>
<td>Simple</td>
<td>More complex to facilitate and understand</td>
<td>Most complex to facilitate and understand</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>Preliminary or detailed design and operations</td>
<td>Early stages of project</td>
<td>Detailed design of process</td>
<td>Detailed design of process and operations</td>
</tr>
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</table>
Limitations of FMEA

- Not good at prioritizing very low frequency catastrophic events (shutdown, recall)
- Doesn’t differentiate between products, processes and sites
- Differentiation between random negative events and deliberately targeted criminal activity
- There are simple precautions we should take even if the risks are very low
## Analyse risk in terms of point of use and potential consequence

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<tr>
<th>Category</th>
<th>Material risk</th>
<th>Consequence</th>
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<tr>
<td>DP Components</td>
<td>Adulteration</td>
<td>Product recall</td>
</tr>
<tr>
<td>Product containers</td>
<td>Viral contamination</td>
<td>Manufacturing shutdown</td>
</tr>
<tr>
<td>Terminal filters</td>
<td>Discontinuation/shortage</td>
<td></td>
</tr>
<tr>
<td>Viral filters</td>
<td>Material quality failure</td>
<td>Release test failure</td>
</tr>
<tr>
<td>Bioreactor bags</td>
<td>Material process modification</td>
<td>In process failure</td>
</tr>
<tr>
<td>Resins</td>
<td>Material variability</td>
<td>Process performance</td>
</tr>
<tr>
<td>In-process filters</td>
<td>Extraneous matter</td>
<td>Nuisance</td>
</tr>
<tr>
<td>Media bags</td>
<td>Price increase</td>
<td></td>
</tr>
<tr>
<td>Generic filters</td>
<td></td>
<td></td>
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The addition of valves, sensors and manifolds increases complexity and risk.
Comprehensive characterization is a pre-requisite to understanding variability

• **Surface Morphology**
  – Optical microscopy (polarized and stereo-microscope)
  – Scanning Electron Microscopy (SEM)

• **Surface Chemistry**
  – X-Ray Photoelectron Spectroscopy (XPS)
  – FTIR-microscope and Raman-microscope
  – Energy-dispersive X-ray spectroscopy (EDS)

• **Surface Hydrophobicity**
  – Tensiometry (contact angle)

• **Leachable/Extractable**
  • NMR, FTIR, HPLC/MS, GC/MS, ICP-MS.
Impact goes beyond physicochemical testing

• USP <88> for Class VI Plastics is NOT representative of cell culture requirements
  – See USP <87> “Cytotoxicity”

• Consider impact of E/L on media and SUB performance as well as buffer and drug product
  – Impact on cholesterol dependent cells
  – Impact of multiple passages

• Impact on other process steps
  – Residual silicone from tubing can significantly depress bubble points of filters
Follow a defined path to qualification and control
Use of supplier documentation

- Definitive for film design/manufacturing
- Starting point for extractables and leachables
  - Assess for relevance
- Sufficient for low risk/impact applications
  - Short term exposure
  - No drug product contact
  - Upstream step
- Critical review is required when comparing suppliers
User Quality Systems

• Receive, quarantine, inspect and release
• Testing will depend on the application
  – Mostly confirmation to drawings, supplier data
• Off the shelf vs. custom
• Acceptable particulates
  – On bag
  – In film (cosmetic vs. compromises integrity)
  – In bag (where’s the filter?)
Validating an SUS

• Process validation remains the responsibility of the pharmaceutical manufacturer
• Leveraging supplier data requires an understanding of how it was developed
  – Materials of construction
  – Testing procedures (e.g. pyrogens, heavy metals, solvents, E/L)
• System design may require features to facilitate validation
  – Alternate receiving vessels to accommodate testing
• Integrity testing
  – Desirable, but not necessarily realistic or achievable
• Campaigning
  – Surge vessels, columns
SUS in the real world

• What if there’s a leak?
  – Before or after use?
  – Buffers and media filtered prior to use
  – SUB’s – positive pressure prevents ingress? – maybe
  – Product container integrity is compromised

• Training, inspection and handling procedures

• Failure rates of 1 in 500 or better
  – 1 failed run in 4 years for 3 bags in a seed train and 40 batches
  – Compare to probability of failing a questionable integrity test

Share information on process capability to be able to provide regulators with data on the level of risk
Materials management - no pain, limited gain

• Low impact mtlms are relatively easy to alternate source
  – Decreases exposure at a single supplier
  – Gain experience of alternative suppliers’ quality system
  – Financial benefits a consideration

• High impact materials require more work to qualify
  – Addresses higher risks (supply interruptions, recalls)
  – Lower frequency of use
  – The back-up may fail before the primary

• Maintain high levels of support and service from suppliers
Conclusions

• Suppliers are an integral part of the quality system

• Unprecedented levels of transparency and data sharing and management are required

• Those who fully embrace true partnerships will be the most successful
Quality Attributes – Sterilization and Particulates
Quality Attributes that need to be qualified

- Extractables and Leachables (E&L)
  - Primary difference between qualification requirements of SUS and classic Multiple-use Systems

- Sterilization and Particulates
  - Need a full understanding of supplier data and recommendations that support the validation effort
  - Determination of sterilization methods
  - Assembly environment impacts bioburden and particulate levels
  - Any process steps such as rinsing
Sterilization

- Irradiation is the leading means of providing a sterilized SUS by a supplier
- Ionizing radiation readily penetrates plastics
- Dosing is well characterized
- Representative Master Product SUS for
  - Bioburden
  - Low ‘Verification’ Dose (VDmax) sterility
  - Calculation of a suitable dose for 10p6 SAL (per ISO 11137)
- Typical dose is ≥25 kGy
- Irradiation needs to be performed **prior** to almost all other qualification tests on irradiated components
  - Will affect E&L and physicochemical tests, among others
- Caution - double dose sterilization prior to qualification tests may not be appropriate
Sterilization may not be necessary

- Intrinsic bioburden is Low
- Applications similar to plastic bottles for oral products

Bioburden reduction may be sufficient

- 25 kGy or lower dose exposure (8 – 10 kGy)
Sterilization: (cont’d)

- Irradiation causes formation of free radicals
  - Increases E&L
  - Can degrade some polymers
- Re-sterilization should not be done
Sterilization: (cont’d)

- Moist Heat (Steam) - alternate means of providing a sterilized SUS

- Difficulty in assuring steam penetration & equilibration to all fluid contact surfaces
  - Vent filters may need to be added
  - Positioning to prevent condensate build-up
  - Systems may not be able to be sterilized fully assembled
    - Subsequent aseptic/sterile connections
Sterilization: (cont’d)

• Moist Heat (Steam)
  – Can Increase E&L
  – Can degrade some polymers

• If qualification is performed on 2x sterilized SUS units, re-sterilization on package failure or other issues could be possible(?)
  – Otherwise, re-sterilization should not be done
Sterilization: (cont’d)

• Except for Interfaces, SIP is not commonly used
  • Most SUS cannot withstand pressure in situ

• Gas Sterilization (EtO) is not commonly used, nor is VHP
  – Gas and reaction products may remain within the plastic material and become leachables
Particulates:

- Limits for particulates should be based on applic’n
- Particles embedded in the plastic film or molded part do not need to be addressed
- Methodology should follow USP <788> “Particulate Matter in Injections”
  - Acceptance criteria are not applicable to upstream processes
  - Particulate specification for upstream process components/SUS can be based on process requirements
Particulates: (cont’d)

- Some SUS suppliers can perform particulate shedding/release testing to investigate the robustness of their manufacturing process
  - Typically Class 100,000/Grade C Clean Rooms
- Users can qualify SUS by testing fluid path rinses
  - Initially lot samples, then periodic audits
  - Consider peristaltic pump effects on tubing
Acknowledgments

- Bob Repetto, Pfizer
- Morton Monk, CMC Bio
- Duncan Low, Amgen
Questions