

Technical Report No. 66

Application of Single-Use Systems in Pharmaceutical Manufacturing

2014



PDA Application of Single-Use Systems in Pharmaceutical Manufacturing Technical Report Team

Authors

Robert Repetto, MS, MBA, Team Co-Chair, Pfizer

Morten Munk, Team Co-Chair, CMC Biologics

Stephen Brown, Ph.D., BE Vaccines

Jeffrey Carter, Ph.D., GE Healthcare

Niels Guldager, NNE Pharmaplan

Christian Julien, MS, Meissner Filtration Products, Inc.

Duncan Low, Ph.D., Amgen

Ingrid Markovic, Ph.D., Food and Drug Administration

Jerold Martin, MS, Pall Life Sciences

Paul Priebe, Sartorius Stedim Biotech

Christopher J. Smalley, Ph.D., Merck & Co

Russell Wong, Ph.D., Bayer HealthCare

Contributors

Robin Alonso, Genentech

Eberhard Bill, Ph.D., Boehringer Ingelheim

Oki Dzivenu, GE Healthcare

Bill Hartzel, Catalent Pharma Solutions

Eric Isberg, ATMI

Maik Jornitz, G-Con

Michael Kraich, Ph.D., Boehringer Ingelheim

James Robinson, Lachman Consultants

Hillary Russak, Genentech

Robert Shaw, Finvector—FVT Ltd.

Ken Baker, NewAge Industries, Inc.

Sally Kline, Ph.D., Amgen

Mani Krishnan, EMD Serono

Jessica Frantz, Sartorius Stedim Biotech

Disclaimer: The content and views expressed in this technical report are the result of a consensus achieved by the authoring task force and are not necessarily views of the organizations they represent.

Application of Single-Use Systems in Pharmaceutical Manufacturing

Technical Report No. 66

ISPN 1578-0-939459-69-8

© 2011 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

1.0 INTRODUCTION	1	4.8 Materials of Construction	23
2.0 GLOSSARY OF TERMS	2	4.8.1 Fluid Management	28
2.1 Acronyms	3	4.8.1.1 Technological Examples	28
3.0 POINTS TO CONSIDER FOR SINGLE-USE SYSTEM MANUFACTURING STRATEGY	4	4.8.2 Mixing	28
3.1 Single-Use Technologies	7	4.8.2.1 Technological Examples	28
3.2 Business Drivers for the Adoption of Single- Use Systems	7	4.8.3 Fermenters and Bioreactors	29
3.3 Qualification and Verification of Suppliers, Materials, Components, and Completed Assemblies	9	4.8.3.1 Technological Examples	29
3.3.1 Product Risk	10	4.9 Storage	30
3.4 Process Control Strategy Considerations	11	4.9.1 Technological Examples	31
3.5 Implementation of a Single-Use System	11	4.10 Freezing	31
3.5.1 Stakeholder Management	11	4.10.1 Technological Examples	31
3.5.2 Risk Management	11	4.11 Filtration	32
3.5.3 Process Validation and Verification (PVV)	12	4.11.1 Technological Examples	32
3.5.4 Scoping	12	4.12 Centrifugation	33
3.5.5 Project Execution Plan (PEP)	12	4.13 Chromatography	33
3.5.6 End-User Requirements	12	4.13.1 Technological Examples	33
3.5.7 Testing and Documentation	12	4.14 Drug Product Final Filling	34
3.5.8 Supplier Management	12	4.14.1 Technological Examples	34
3.5.9 Logistics Control Requirements	12	4.15 Isotopes	35
3.5.9.1 Inventory and Supply Chain Management	13	4.16 Sampling and Laboratory Analysis	36
3.5.9.2 Waste	13	4.16.1 Technological Examples	36
3.5.9.3 Transportation	13	4.17 Transportation	37
3.5.9.4 Single Suppliers	13	4.17.1 Technological Examples	37
3.5.9.5 Change notifications	13	4.18 Sensors	38
3.5.9.6 Technical Diligence	14	4.18.1 Technological Examples	38
3.6 Implementation Summary	14	4.19 System Integration	39
4.0 SINGLE-USE TECHNOLOGIES AND SYSTEM INTEGRATION	15	4.20 Supply Chain Integration	39
4.1 Introduction	15	4.20.1 Factors Which Affect the Quality of Supply Chain	39
4.2 Comparison of MUS and SUS	15	5.0 QUALIFICATION AND VERIFICATION OF SUPPLIERS, MATERIALS, COMPONENTS, AND COMPLETED ASSEMBLIES	40
4.3 SUI Components and Assembly	16	5.1 Introduction	40
4.4 Technical Feasibility and Risk Assessment Framework	17	5.2 Risks Associated with Using Single-Use Systems	41
4.5 Factors Affecting SUS Design	18	5.3 Single-Use System Assembly	43
4.5.1 Process Compatibility	18	5.4 Supplier Qualification of Single-use Systems	43
4.6 Facility Impact for SUS Setup and Deployment	20	5.4.1 Supplier Audits and Technical Diligence ..	43
4.6.1 Operational Requirements	20	5.4.2 Supplier Quality Agreements and Responsibilities	44
4.7 Applications and Technology	21	5.5 Qualification of Alternative Suppliers	44
4.7.1 Process Connections	21	5.5.1 Qualification of Alternative Sources	44
4.7.1.1 Technological Examples	21	5.5.2 Interchangeability	45
		5.5.3 Using Supplier Quality Documentation	46
		5.6 Extractables and Leachables (E&L)	47
		5.6.1 Material and Supplier Qualification	48
		5.6.2 Toxicity of E&L	52

5.6.3	Using Supplier Documentation for Extractables	52
5.6.4	Extractable Testing Standardization	53
5.7	Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathy (TSE) Concerns	53
5.8	The Quality Systems of the End User and Supplier	53
5.9	Quality Management for Single-Use System Implementation	53
5.9.1	Determination of Expiration Date and Shelf Life	53
5.9.2	Dealing with Particulates	54
5.9.3	Sanitation and Sterilization	54
5.9.4	Bioburden Control	54
5.10	Sterilization	55
5.10.1	Irradiation Sterilization	55
5.10.2	Sterilization with Moist Heat	55
5.10.3	Sensor Technology	56
5.10.4	Qualification and Validation	56
5.11	Integrity	57
5.11.1	Testing an SUS for Leaks	57
5.11.2	Leak Prevention in an SUS	58
5.12	Campaigning	60

6.0 BUSINESS DRIVERS FOR THE ADOPTION OF SINGLE-USE SYSTEMS

6.1	Evaluation of Business Drivers	61
6.2	Lifecycle Approach	61
6.3	Opportunity Cost	62
6.4	Cost of Quality	62
6.5	Quantitative Evaluation of Business Drivers	62
6.5.1	Process Assessment	63
6.5.2	Batch Frequency	63
6.6	Operational Model	64
6.6.1	Single- or Multiple-Product Facility	64
6.7	Total Cost Model	64
6.7.1	Shortcut Cost Model Based on Cost of Goods	65
6.7.2	Example of a Shortcut Cost Model	65
6.7.3	Comprehensive Cost-of-Goods Model	66
6.8	Investment Costs	66
6.8.1	Process Equipment	66
6.8.2	Utility Equipment	66
6.8.3	Indirect Equipment Costs	67
6.8.4	Facility	67
6.8.5	Materials	67
6.8.6	Consumables	67
6.8.7	Utilities	68

6.8.8	Waste	68
6.9	QC/QA and Cost of Quality	68
6.10	Fixed Operating Costs	68
6.10.1	Cost of Capital	69
6.10.2	Depreciation	69
6.10.3	Staff	69
6.11	Project Duration, Time, and Productivity	70
6.11.1	Overall Project Duration	70
6.11.2	Process Operation Time	70
6.11.3	Time Constraints	70
6.11.4	Speed of Process Development	70
6.11.5	Equipment and Process Validation	71
6.11.6	Construction Time	71
6.11.7	Self-Assembly	71
6.12	Logistics	71
6.12.1	Supply	72
6.12.2	Storage	72
6.12.3	Transportation	72
6.12.4	Waste	72
6.13	Disposal of an SUS	73
6.14	Sustainability	74
6.15	The Value Added	74
6.15.1	Value-Added Analysis	75

7.0 IMPLEMENTATION OF A SINGLE-USE SYSTEM 77

7.1	Implementation Road Map	77
7.2	Implementation Themes	80
7.2.1	Stakeholder Management	80
7.2.2	Risk Management	81
7.2.3	Process Validation and Verification (PVV)	84
7.3	Implementation S3: Scoping	85
7.3.1	SUS Strategy	85
7.3.2	Business Drivers	85
7.3.3	Operating Scenarios and Standardization	86
7.3.4	Process Validation Stage	86
7.3.5	Operating Volumes and Storage Requirements	86
7.3.6	Hybrid Systems	86
7.3.7	Connection Principles	86
7.3.8	Campaigning	86
7.3.9	Future Deployment	86
7.3.10	Sourcing	87
7.3.11	Testing Strategy	87
7.3.12	Materials	87
7.3.13	Shelf-Life Policy	87
7.3.14	Procurement	87
7.3.15	Storage	87
7.3.16	Waste Treatment	88
7.3.17	Non-GxP Issues	88

7.3.18 Sustainability.....	88
7.4 Implementation S4: Business Case.....	88
7.4.1 Project Execution Plan	88
7.4.2 Process and Facility Requirements: Basis of Approach	89
7.4.3 Facility-Level Plan	89
7.4.4 Implementation-Level Plan.....	90
7.4.5 Operational-Level Plan	90
7.4.6 Facility-Level Integration Plan	91
7.4.7 Equipment-Level Integration Plan.....	93
7.4.8 Operational-Level Integration Plan	94
7.4.9 Technological Survey	94
7.4.10 Supplier Selection and Supply-Chain Review	95
7.4.11 Extractables and Leachables Database...	96
7.5 Implementation S5: Development	96
7.5.1 User Requirements for Implementation ...	96
7.5.2 Preparing User Requirements	96
7.5.3 Layout and Design	97
7.5.4 Specification	98
7.5.5 Standardization Policy.....	99
7.5.6 Extractables and Leachables	99
7.5.7 Procurement	99
7.6 Implementation S6: Testing and Validation	100
7.6.1 Delivery.....	100
7.6.2 Installation	100
7.6.3 Qualification	100

7.6.4 Training	101
7.6.5 Training Workflow.....	101
7.6.6 An Example of SUS Training	101
7.6.7 Safety	102
7.6.8 Preparation of a Health, Safety, and Environment Plan	102
7.6.9 Health and Safety Issues Related to SUS	102
7.7 Implementation S7: Launch.....	103
7.7.1 Management of Materials.....	103
7.7.2 Routine or Operational Procurement	103
7.7.3 Technical Diligence	104
7.7.4 Quality and Technical Agreements.....	106
7.7.5 Logistics and Storage	106
7.7.6 Waste	107
7.7.7 Post-launch Review	107

8.0 APPENDIX I: OVERALL USER REQUIREMENT SPECIFICATION EXAMPLE 108

9.0 APPENDIX II: PROJECT EXECUTION PLAN EXAMPLE 121

10.0 APPENDIX III: TRAINING REQUIREMENTS EXAMPLE..... 135

11.0 REFERENCES..... 136

FIGURES AND TABLES INDEX

Figure 3.0-1	Key Decision Areas for an SUS Manufacturing Strategy.....	4	Table 5.2-1	Risk Complexities of SUS Items and Applications.....	42
Figure 3.0-2	Proposed SUS Decision Pathway	6	Table 5.5.2-1	Component Interchangeability Evaluation	46
Figure 3.0-3	Technical Report Structure Overview....	6	Table 5.5.3-1	Example Supplier Testing and Reference Standards	47
Table 4.2-1	Comparison of MU and SU Systems ..	15	Table 5.6.1-2	Example—Quantitation of Extractables from SU Components after 50 Mrad Gy Irradiation	50
Figure 4.3-1	Anatomy of an SUS	16	Table 5.6.1-3	Identified Extractables from Membrane Filter Cartridges from Several Manufacturers	51
Figure 4.4-1	Implementation of an SUS and the Assessment of Drug Process and Product Risk	17	Table 5.6.1-4	Identification of Extractables from Polyethylene Biocontainers with Ethyl Vinyl Alcohol Interlayer	51
Table 4.5.1-1	Assessment of Process Compatibility	19	Figure 5.11.2-1	Investigation of a Bioprocess Container for Leaks	58
Table 4.6-1	Assessment of SUS Facility Setup and Deployment	20	Figure 5.11.2-2	Identifying the Location of Leaks on a Bioprocessing Container.....	59
Table 4.6.1-1	Assessment of Operational Requirements	21	Figure 6.5-1	Cost Comparison Studies Reference Model.....	63
Table 4.7.1.1-1	Functional Categories of Connectors ..	22	Table 6.5-1	Factors That Affect the Process Model ..	63
Table 4.7.1.1-2	Specific Considerations for Connectors	23	Table 6.6-1	Factors That Affect the Operational Model	64
Table 4.8-1	Plastics Commonly Used in SUS	24	Table 6.7-1	Comparative Evaluation of a New Versus Retrofitted Facility During SUS Implementation.....	64
Table 4.8.1.1-1	Specific Considerations for Fluid Management	28	Table 6.8.1-1	Contributory Factors to Investment Costs	66
Table 4.8.2.1-1	Specific Considerations for Mixing.....	29	Table 6.8.4-1	Main Variable Operating Costs	67
Table 4.8.3.1-1	Specific Considerations for Fermenters or Bioreactors	30	Table 6.10-1	Main Fixed Operating Costs	69
Table 4.9.1-1	Specific Considerations for the Storage of Process Intermediates ..	31	Table 6.13-1	Treating and Discarding Waste from SUSs	74
Table 4.10.1-1	Specific Considerations for Freezing... 32		Table 6.15.1-1	Comparison of Value-Added Activities..	75
Table 4.11.1-1	Specific Considerations for Filtration ..	33	Figure 7.1-1	SUS Implementation Road Map.....	78
Table 4.13.1-1	Specific Considerations for Chromatography.....	34	Table 7.1-1	Focus and Output for Each SUS Implementation Stage.....	79
Table 4.14.1-1	Specific Considerations for Drug Product Final Filling.....	35	Figure 7.2.1-1	An Example of a Stakeholder Power Grid.....	81
Table 4.15-1	Specific Considerations for Isolators ..	36	Table 7.2.3-1	Guidelines for the Application of Risk Management During SUS Implementation.....	82
Table 4.16.1-1	Specific Considerations for Sampling and Laboratory Analysis	37			
Table 4.17.1-1	Specific Considerations for Transportation.....	38			
Table 4.18.1-1	Specific Considerations for Sensors ...	39			
Figure 4.19-1	System Integration	39			
Figure 5.2-1	Example of an Ishikawa Diagram for Determining Risk Sources	41			

Table 7.2.3-2	Directional Risk Profile of SUS Items and Applications.....	83	Table 7.4.6-1	Example of a Regulatory Assessment Table.....	92
Table 7.2.3-3	Risk Management and Mitigation in Current and Future SUS Implementation.....	83	Figure 7.5.3-1	Example of SUS Installation Scope Drawing.....	97
Figure 7.2.3-1	SUS Implementation and the Validation Lifecycle	84	Table 7.7.3-1	Principle Differences Between a Quality Audit and a Technical Diligence Assessment.....	104
Table 7.4.1-1	Typical Contents of the SUS Project Execution Plan	89	Table 7.7.3-2	Some Pertinent Factors for a Technical Diligence Assessment Checklist.....	105
Figure 7.4.5-1	SUS Process and Facility Integration..	90	Table 7.7.3-3	An Interpretation of the SUS Implementation Process	106
Figure 7.4.6-1	Process and Facility Considerations for SUS Implementation.....	91	Table 8.4.3.1-1	Sample Room Classifications	117

Currently in preview, click buy full version

1.0 Introduction

Single-use technology, often described as single-use systems (SUSs) or single-use equipment, has the potential to transform pharmaceutical manufacturing by offering tremendous opportunities to reduce cost, improve flexibility or cycle time, and shorten the time needed to build a manufacturing process for new, lifesaving drugs. This success, however, is very much dependent on how effectively the industry approaches the development and implementation of single-use technology. Ultimately, a new drug can only be successful if it is effective, safe, and available. Traditionally, only a comprehensive understanding of the drug product and manufacturing process can achieve these goals. This remains true as SUS is introduced in place of traditional reusable equipment. Encouraging an open science- and risk-based dialogue during supplier audits and evaluation of SUS supply chains significantly improves an SUS implementation.

This document is intended to provide the reader with critical concepts or points to consider when implementing an SUS strategy in a pharmaceutical manufacturing process. These concepts are intended to be valid both for chemically synthesized small molecules and for bioprocesses that produce large-molecule biopharmaceutical products. However, to be truly effective, many of these critical concepts must start with the design, supply chain, manufacturing, and distribution of SUSs themselves, as many inherent quality attributes can impact either the product molecule or its production process. Pharmaceutical manufacturers and single-use technology suppliers have become partners whose success is dependent on the control strategies implemented.

This document discusses SUSs that are in either direct or indirect contact with the raw materials, intermediates, and pharmaceutical drug substances or drug products. The document does not intend to discuss disposable items related to laboratory activities, final delivery system to the patient, transfusion bags, packaging, or medical devices.

Successful SUS implementation needs a comprehensive approach balancing the product and process goals achieved by using single-use technology. Section 3, Manufacturing Strategy, of this technical report is intended to present an approach that ties together key considerations when evaluating single-use technology. A well-designed manufacturing strategy will address technical, quality, business, and implementation considerations. Each topic has a dedicated section in this technical report, providing a detailed discussion of the associated considerations.

Determining the optimal manufacturing strategy involves concepts from many disciplines. An effective evaluation will have a balanced viewpoint, with input from engineering, regulatory, quality, project management, and accounting. Balancing risks and rewards of an SUS over a multiple-use system (MUS) will help determine the most appropriate manufacturing strategy. Thus, a structured science- and risk-based approach is recommended and should be consistent with principles described in ICH Guidelines Q6, Q7, Q8, Q9, Q10, and Q11. Primary goals, when developing any manufacturing strategy, should focus on controlling impacts to patient safety, product availability, and product and process understanding (1–6).

Only a formal partnership with an SUS supplier can ensure that quality is as good as or better than what is achieved with traditional systems (e.g., a purchase order is not a partnership). SUS suppliers provide equipment that includes the outsourced, value-added activities that the end user no longer performs. These value-added activities are important for the success of both organizations, and a winning control strategy for SUS has elements in both the supplier's and the end user's quality systems.

The concepts and recommendations presented in this technical report were developed over several years of discussion within the task force, at PDA workshops, and at other industry meetings. The authors of this technical report recognize that the conversation regarding how best to implement SUSs is just beginning. Ultimately the success of these systems will be determined by the decisions suppliers and end users make during implementation, and the hope is that this report provides a foundation for the industry to build on.