



GOOD PRACTICE GUIDE:

Single-Use Technology

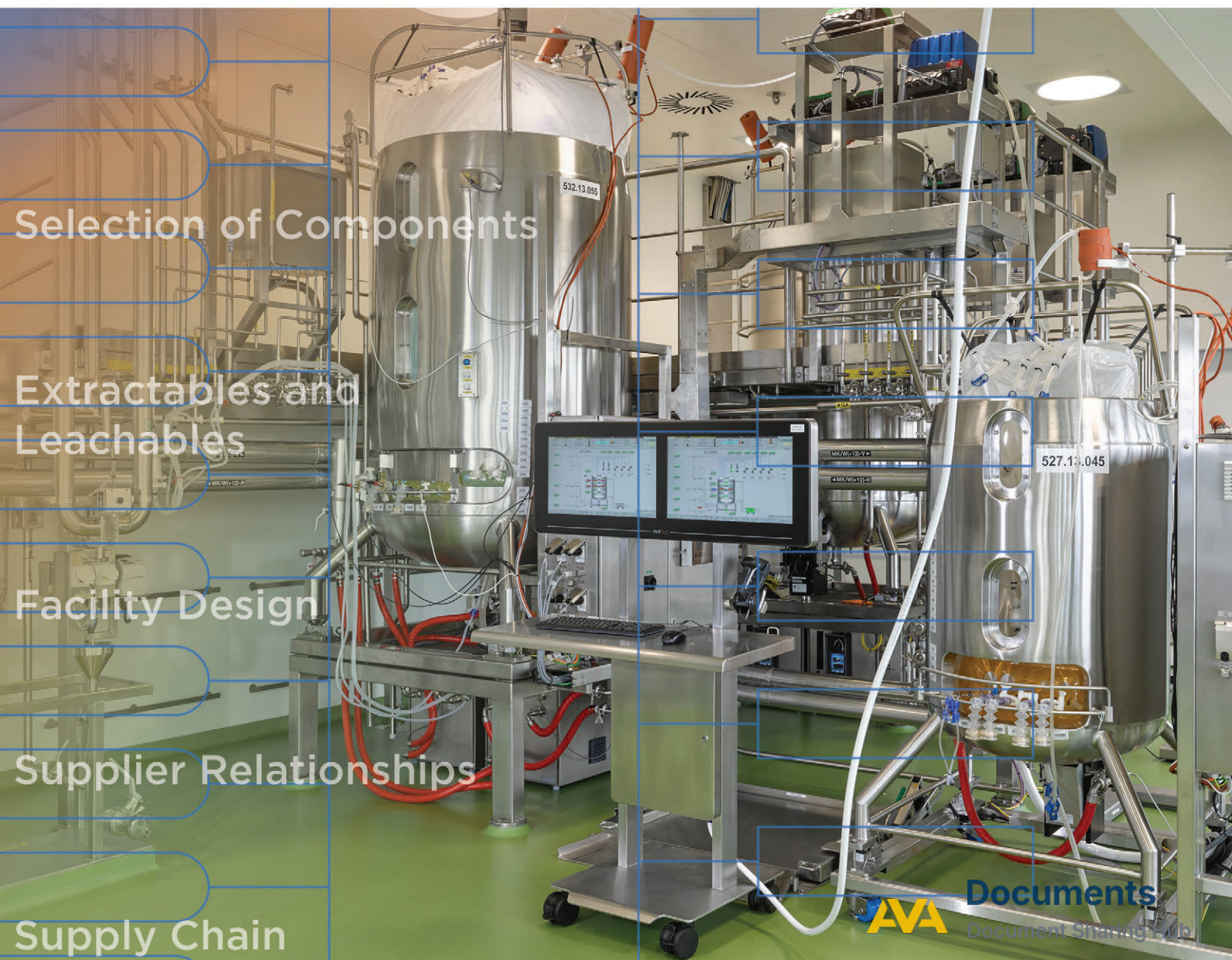
Selection of Components

Extractables and Leachables

Facility Design

Supplier Relationships

Supply Chain





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Preface

The adoption of single-use technology continues to grow in the pharmaceutical industry, particularly in biopharmaceutical processing. Single-use technology offers increased flexibility while significantly reducing the risk of contamination in manufacturing equipment. The risk reduction is especially important in reducing or eliminating cross-contamination for shared production facilities.

The industry evolved from disposable filtration membranes and bags for storage of simple solutions. Current single-use technology includes:

- Systems for mixing solutions such as buffers and media
- Bioreactors and other systems for cell propagation and production of bulk biologics
- Systems for sterilization and storage of culture media and buffers
- Filtration and centrifugation systems for initial bioreactor product clarification
- Filtration systems for cell retention (perfusion) and virus filtration
- Ultrafiltration and diafiltration systems for product purification
- Containers for holding media, buffers, and other fluid/powder
- Transfer systems to move fluid/powder
- Conventional or membrane chromatography systems for product purification
- Storage and transport systems of semisolid pharmaceutical bulk products
- Assemblies for fill/finish operations

Single-use technology addresses the need for equipment that is faster and more flexible to implement while retaining a sterile product flow path. The one-time use of single-use assemblies helps to reduce the risk of contamination and offers shorter turnaround time by eliminating the validation of cleaning and sterilization. As compared to stainless steel equipment, single-use assemblies are lightweight, easy to transport, and flexible to replace in a process train. This leads to saving time in operations that handle single or multiple drug products in common or similar process trains. Improved confidence in process stability, lower capital costs, and shorter turnaround times (i.e., more run time, reduced cleaning, and water usage) are driving the implementation of single-use products in production. This Guide intends to help single-use product end-users and suppliers with the selection, design, and implementation of single-use technology.

Acknowledgements

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Core Team

The following individuals took lead roles in the preparation of this Guide:

Swapnil Ballal	Dr. Reddy's Laboratories	India
Malik Belattar		France
Adam Goldstein, Sr.	Roche/Genentech Inc.	USA
Ekta Mahajan	Genentech Inc.	USA
Katell Mignot-Morau*	Sartorius Stedim FMT SAS	France
Christopher J. Smalley	ValSource (Merck – retired)	USA
David AR Wolton*	PM Group	Ireland

*These individuals went above and beyond expectations to meet deadlines and keep the effort on track.

Other Contributors

The Team wish to thank the following individuals for their significant contribution to the document.

Wayne Flaherty	Compliance Concepts International, Inc.	USA
Niels Guldager	NNE	Denmark
Nick Haycocks	Amgen Inc.	USA
Ryan Hutchinson	GE Healthcare Life Science	USA
Nassrine Lablack	SUTAP	France
Beth McCooey	Genentech	USA
Mark McElligott	Process Design Solutions	USA
Tom J. Piombino, PE	Integrated Project Services, LLC	USA
Kerry Sylvanowicz	MilliporeSigma	USA
Mathieu Tricot	Pharma Biot'Expert	France

Subject Matter Expert Input and Review

Particular thanks go to the following for their review and contributions to this Guide:

Erich H. Bozenhardt	IPS	USA
Sabrina Restrepo, PhD	Merck & Co., Inc.	USA
Marc Vouillamoz	LFB Biomanufacturing	France

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Company affiliations are as of the final draft of the Guide.

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

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Table of Contents

1	Introduction	7
1.1	Background.....	7
1.2	Purpose and Objectives.....	7
1.3	Structure of the Guide.....	8
1.4	Key Concepts/Terms.....	9
1.5	Additional Sources of Information	12
2	Selection and Design.....	13
2.1	Single-Use Components, Assemblies, And Systems.....	13
2.2	Extractables	19
2.3	Process Equipment Design.....	29
2.4	Quality Requirements for Single-Use Products	39
2.5	Supplier Quality and Audits.....	51
2.6	User Requirement Specification Development	60
2.7	Facility Design.....	63
2.8	Waste Management.....	76
3	Implementation and Use	79
3.1	Technology Transfer.....	79
3.2	Regulatory Compliance.....	81
3.3	Leachables.....	87
3.4	Validation	87
3.5	Supply Chain.....	91
3.6	Training	93
4	Program Management	103
4.1	Implementation of Single-Use Technology.....	103
4.2	Risk Management	105
4.3	Change Management	112
4.4	Project Schedules	114
5	Appendix 1 – Additional Information: Regulations and Standards	121
5.1	International Standards.....	121
5.2	United States Regulations and Standards.....	123
5.3	United States Pharmacopeia (USP)	125
5.4	European Standards and Regulations	126
5.5	European Pharmacopoeia (EP).....	127
5.6	Other International Regulatory and Pharmacopeial Organizations.....	127
6	Appendix 2 – Example Training Procedures for Inspections.....	129
7	Appendix 3 – Defective Products and Failure Risks	131

8	Appendix 4 – Additional Information for Risk Management	
	Qualification Attributes.....	133
8.1	Attribute 1: Biocompatibility Testing	133
8.2	Attribute 2: Mechanical Properties	133
8.3	Attribute 3: Gas Transmission Properties	134
8.4	Attribute 4: Compendial Physicochemical Testing	134
8.5	Attribute 5: Animal Origin Control.....	136
8.6	Attribute 6: Total Organic Carbon Analysis	137
8.7	Attribute 7: pH and Conductivity	137
8.8	Attribute 8: Extractables and Leachables	138
8.9	Attribute 9: Chemical Compatibility	141
8.10	Attribute 10: Protein Adsorption Studies	141
8.11	Attribute 11: Endotoxin Testing	142
8.12	Attribute 12: Sterilization (Irradiation).....	142
8.13	Attribute 13: Container Closure Integrity.....	144
8.14	Attribute 14: Particulate Testing	144
8.15	Attribute 15: Calibration of Embedded Instrumentation	145
9	Appendix 5 – Case Study: 2000 L Single-Use Bioreactor – Evaluation and Implementation	147
9.1	Summary.....	147
9.2	SUB Technology Selection.....	147
9.3	Installation of 2000 L SUB in an Existing GMP Facility.....	150
9.4	Project Risks and Mitigation – New Technology	155
9.5	Vendor Supply Chain	156
9.6	Application of Lessons Learned for Future Single-Use Renovations.....	156
10	Appendix 6 – References	159
11	Appendix 7 – Glossary	167
11.1	Acronyms and Abbreviations	167
11.2	Definitions	170

1 Introduction

1.1 Background

The development of drug products from the laboratory to production processes entails risks, investment, and time. Any technology that can impact one or more of these factors is worth an investigation. Conventional stainless steel process equipment has reliably served the industry for many years. With the increasing need to reduce risks and quickly start up processing plants with minimum capital costs, Single-Use Technology (SUT) has been more widely used. This technology has impacted all three factors: risks, investment, and time.

The growth of SUT has been rapid and continues to expand in the industry. The primary components of SUT are polymeric film containers, flexible tubing, and an assortment of connectors and supporting components. The evolution of SUT has prompted the industry to redefine procedures to incorporate SUT into drug manufacturing processes. The application of this Guide starts after a decision to implement SUT is made; that is, all financial assessments have been completed and the results of those assessments support the use of SUT in a process. This Guide is aimed at helping the end-users and suppliers of SUT after this decision has been made.

While SUT provides flexibility, the implementation of SUT into a process requires a well-defined plan that minimizes surprises during the later stages of implementation. This can be a challenge when dealing with a revolutionary technology that is flexible, continues to evolve, and can be customized to the end-user's requirements. To take advantage of the flexibility of SUT, it is important to understand how the single-use products can work together with manufacturing operations. This Guide intends to provide a roadmap for the efficient implementation of SUT with minimum disruption to existing operations.

1.2 Purpose and Objectives

This Guide is centered around getting SUT implementation done right the first time, on schedule, and with minimal costs and few surprises. When surprises arise, this Guide aims to help address them effectively with the least amount of disruption.

This Guide aims to make it easier for single-use product suppliers and drug product manufacturers to select components and suppliers, design, and apply SUT. It intends to achieve this by aligning expectations and capabilities to minimize surprises.

Due to the inherent flexibility of SUT, the process of selecting, designing, and implementing SUT should be performed with sufficient focus while keeping the end state in clear perspective. During the design phase, there are many decisions to be made about the components to use. Focusing too closely on the decision at hand and putting the overall objective in second place can result in a decision that will need to be changed at a later date. The highly flexible nature of SUT allows this to be accomplished. However, it may result in a significant cost later in the project. If too many decisions are made in this way, the flexibility becomes its own hindrance. The objective of this Guide is to provide an efficient roadmap, based on the experience of the authors.

1.2.1 Scope

It is recognized that innovation and the fast evolution of SUT leads to a continuous expansion of available products. This Guide intends to capture the current technology, the components, and how they are designed into processes. The information presented is useful in the following applications:

- Liquid or semisolid storage and transfer
- Cell propagation and production of bulk biologics

- Mixing of powders and liquids
- Filtration and centrifugation
- Heat transfer
- Chromatography
- Fill/finish

1.2.2 **Benefits**

The intended benefits of this Guide include:

- Learning how to select single-use components and design functional systems
- Learning when and how to perform effective extractables and leachables studies
- Learning how to evaluate suppliers of SUT
- Understanding the critical supplier and end-user (customer) interactions
- Learning about the interrelated tasks for implementing SUT

1.3 **Structure of the Guide**

This Guide is intended to be used by those new to SUT while still benefiting those experienced with SUT. While any section of the Guide can be used at any time, those new to the technology would benefit by following a logical progression through the chapters. There are three core chapters. Chapter 2 guides the reader through component selection and equipment design. Chapter 3 takes the equipment into the plant and includes validation and training to yield a successful operation. Chapter 4 deals with program management topics that occur throughout the activities discussed in Chapters 2 and 3.

An overview of the Guide is as follows:

- **Introduction:** This chapter provides the overall objectives of the Guide, background information on the technology, and the intended benefits of the Guide.
- **Selection and Design:** Chapter 2 is intended to help the end-user select the components, assemblies, systems, and suppliers. The various sections in the chapter focus on identifying the major criteria for selecting the components for the single-use equipment and the suppliers that can support a successful SUT operation. The chapter details how assemblies are designed and aligned with the multiple-use parts of the system. Chapter 2 deals primarily with the first phase of any SUT implementation process. These activities require strong collaboration between the suppliers and the end-users. An emphasis is placed on how these collaborations are to be maintained and what information is expected to be shared between the two groups.
- **Implementation and Use:** Chapter 3 covers topics which are to follow the completion of the activities of Chapter 2. Once the single-use assemblies, systems, and suppliers have been selected as described in Chapter 2, the focus is on using the single-use products in the end-user operation. Chapter 3 deals with the transfer of the technology into the plant, meeting regulatory requirements, training, validation, and setting up a strong supply chain. The end-users would take leadership in these activities with the supplier providing support.

- **Program Management:** Chapter 4 mostly addresses planning information, including risk management, change management, and project schedules.

1.4 Key Concepts/Terms

This section defines key concepts and terms as they are applied in SUT applications. Refer to Chapter 11 for an expanded listing of definitions.

Analytical Evaluation Threshold (AET): An upper limit, at or above which, identification and quantification of an unknown extractables and leachables should be performed and reported for potential toxicological assessment. This is not applicable to special case compounds such as Polyaromatic Hydrocarbon (PAH, also known as polynuclear aromatic hydrocarbons), Mercaptobenzothiazole (MBT) and N-nitrosamine, which should be evaluated individually.

Compatibility: A measure of the extent to which a Primary Packaging Component (PPC), Process Contact Material (PCM), and/or proximal material will interact with a dosage form. Such interaction should not be sufficient to cause unacceptable changes in the quality of either the dosage form or the packaging component. Such interactions may include (ab)adsorption of the active drug substance, reduction in the concentration of an excipient, leachable-induced degradation, precipitation, changes in drug product pH, discoloration of the dosage form or packaging component, etc.

Container Closure System (CCS): The sum of packaging components that together contain, protect, and deliver the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection relative to product stability to the drug product (e.g., foil pouch).

Extractables: Chemical compounds that are removed from a material by exertion of an artificial, exaggerated force (e.g., solvent, temperature, or time). This is a material specific characteristic and is independent of the drug product with which the material is used.

Leachables: Chemical species that migrate from or through a contact surface into a drug product or process stream during storage or normal use conditions. These are specific to the combination of material and drug product with which the material comes in contact.

Primary Packaging Component (PPC): A component of the container closure system that potentially comes into direct contact with the drug product formulation (e.g., canisters, pumps, actuators, gaskets, syringe plungers, stoppers, etc.).

Process Contact Material (PCM): Component which is in direct contact with the process or product fluid, such as tubing, hose, filter, bag, connector, etc. Also known as process stream contact material.

Proximal Materials: All packaging materials other than the PPC, such as ink, adhesive, label, carton, protective packaging materials, etc.

Qualification Threshold (QT): A level below which a given leachable is not considered for safety qualification (toxicological assessment) unless the leachable presents Structure-Activity Relationship (SAR) concerns.

Safety Concern Threshold (SCT): A level below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects.

Single-Use Assembly: A combination of single-use components/assemblies designed to be in one continuous, and often closed, wetted flow path. The typical assembly is manufactured and sterilized. It primarily contains mechanical components (e.g., bioprocess container, tubing, fittings, etc.) with sensor element(s) or allowance for a sensor element to be mounted by the end-user. The end-user places the assembly on a support structure prior to filling it with fluid. The support structure may also include electromechanical elements (e.g., mixer/motor, balloon, scale, etc.) that interface with the assembly and are integral for its proper use.

Single-Use System (SUS): A combination of single-use components designed to be in one continuous, and often closed, wetted flow path. The typical SUS integrates one or several single-use assemblies with multiple-use electrical/control elements operated by some level of automation. The end-user places the single-use assembly on a support structure prior to filling it with fluid.

Single-Use Technology (SUT): Technology based on applications that utilize single-use components individually or in assemblies and systems that are designed based on these components. Figure 1.1 provides an overall perspective on the relationship between components, assemblies, and systems.

Single-Use versus Disposable: While these terms seem to be used interchangeably, there are significant differences between them. Single-use products are a subset of disposable products. Single-use products are used one time and then discarded. They are typically used for the duration of a process run. At the end of a process run, any drug product is displaced from the single-use product and then the single-use product is discarded. Disposable products are often used only once and discarded. However, disposable products may also be used more than once. If the disposable product is to be used more than once, it is cleaned and sanitized between uses. Performance should be monitored as it normally decreases with each sequential use. Exposure to cleaning chemicals and high temperatures tends to degrade the disposable products resulting in a limited useful life.

Support Equipment/Systems: Support systems that are used in conjunction with single-use equipment. These include temperature control systems for heating/cooling media and restricted access barrier systems.

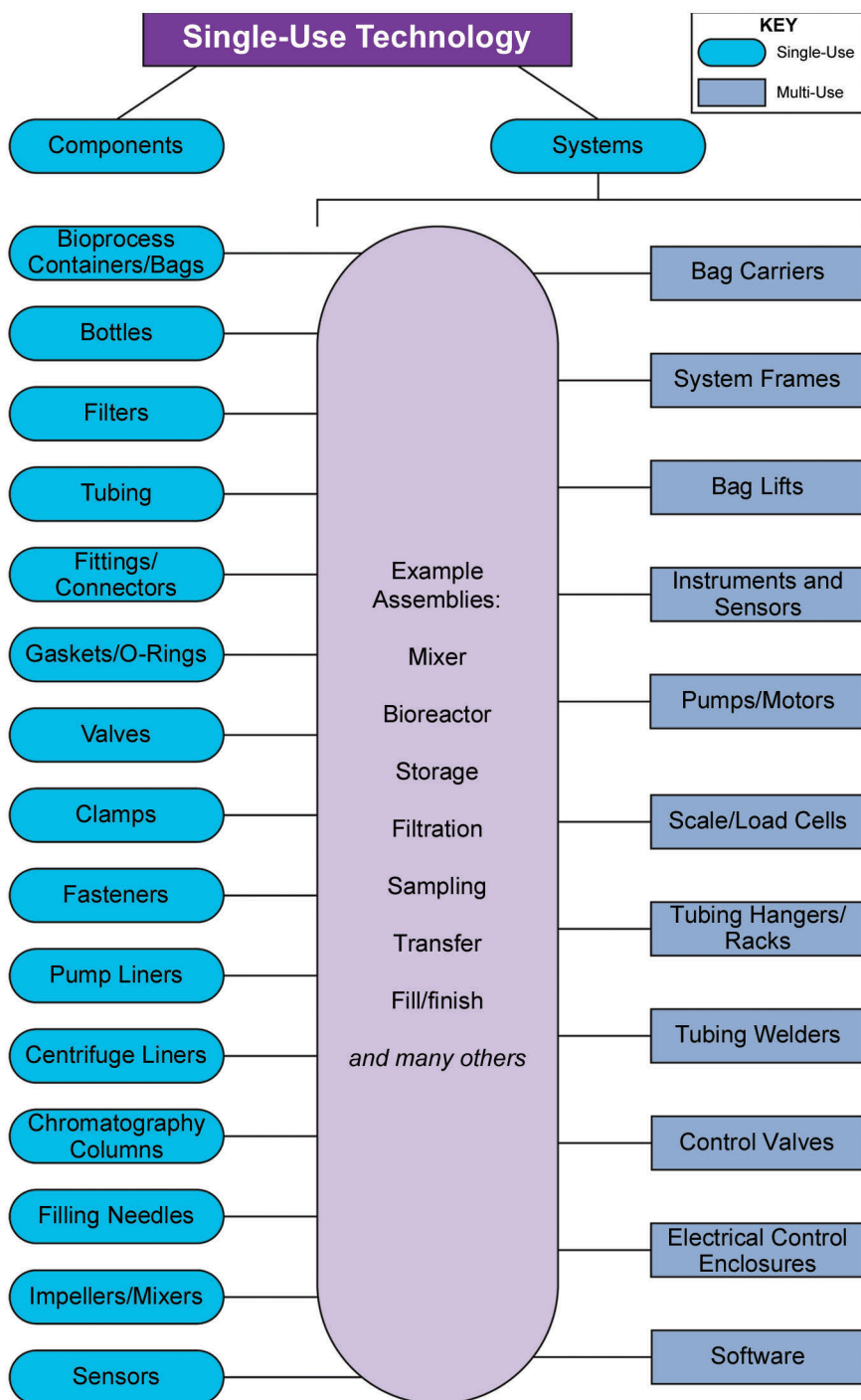
Threshold of Toxicological Concern (TTC): The daily intake of a genotoxic impurity that is considered to be associated with an acceptable risk (excess cancer risk of < 1 in 100,000 over a lifetime) for most pharmaceuticals.

Toxicological Assessment: An evaluation of the estimated Total Daily Intake (TDI), which is considered similar to the Average Daily Intake (ADI) of a chemical species, in order to determine if the level of exposure will present a safety concern to the patient. These evaluations include considerations of available literature data for the specific compound or class of compounds, SAR, and any qualification data (if available).

Tubing Set: An assembly composed of single-use components that is used to connect between unit operations.

Upstream/Downstream Processing: Upstream processing includes the unit operations up to the harvest clarification and recovery from the bioreactor. Downstream processing includes the unit operations that follow such as the filtration and chromatography steps to purify and concentrate the product.

Figure 1.1: Relationship between Single-Use Components, Assemblies, and Systems



1.5 Additional Sources of Information

Other organizations that have formally addressed SUT implementation include:

- A3P [1] – Association for clean and sterile products
- American Society for Testing and Materials (ASTM) [2] – Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products
- American Society of Mechanical Engineers (ASME) [3] – Bioprocessing Equipment (BPE) Standards Committee
- Biomanufacturing Training and Education Center (BTEC) [4]
- BioPhorum Operations Group (BPOG) [5]
- Bio-Process Systems Alliance (BPSA) [6]
- DECHEMA [7] – Gesellschaft für Chemische Technik und Biotechnologie/Society for Chemical Engineering and Biotechnology (Germany)
- Extractables and Leachables Safety Information Exchange (ELSIE) Consortium [8]
- National Institute for Bioprocessing Research and Training (NIBRT) [9]
- Parenteral Drug Association (PDA) [10]
- Pharmaceutical Process Analytics Roundtable (PPAR) [11]
- Product Quality Research Institute (PQRI) [12]
- United States Pharmacopeia (USP) [13]

2 Selection and Design

2.1 Single-Use Components, Assemblies, and Systems

This section lists the single-use products that are commonly used in pharmaceutical manufacturing facilities. Aligned with Figure 1.1, single-use products can be categorized as follows:

- **Single-use components** represent the single-use parts that may be used individually or as a subset of an SUS
- **Single-use assemblies** consist of multiple single-use components connected in various configurations to make a unit operation in the manufacturing process
- **SUSs** integrate single-use components/assemblies with multiple-use parts

Note: This section is intended to cover components, assemblies, and systems most commonly used in SUT and is not intended to be a comprehensive listing.

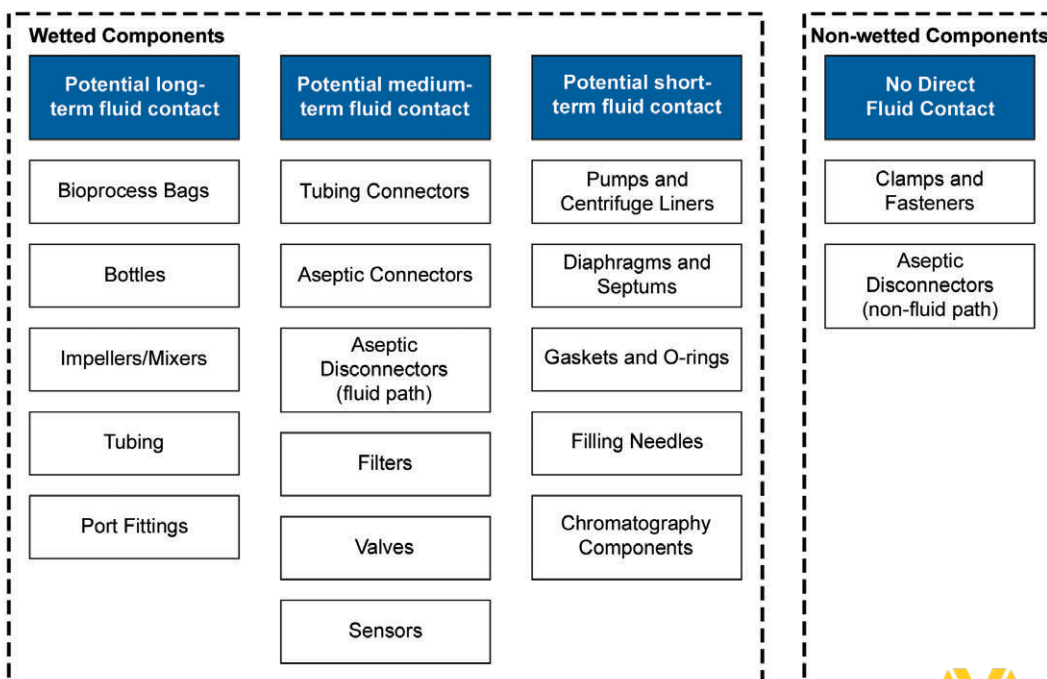
2.1.1 Single-Use Components

Components can be classified into two categories, based on whether the surface(s) will be exposed to a fluid (liquid or gas) when in service:

- **Wetted components** contact the product or process fluid
- **Non-wetted components** do not contact the product or process fluid but may be in contact with wetted components

Wetted components may be further classified based on their potential contact time with product or process fluid, as shown in Figure 2.1.

Figure 2.1: Common Single-Use Components Classified by Potential Fluid Contact Time



Bioprocess bags (also referred to as single-use bioprocess containers) are flexible containers that are made of polymeric material and intended to be used once and discarded. The main applications are storage, sampling, mixing, freezing, and transport of liquids. Other applications include cell culture, fermentation, and powder storage/transfer. These containers have inlet/outlet ports with fittings and associated tubing. Other ports may be available for sampling, sensor placement, and powder entry. The smaller bioprocess bags (typically 30 mL to 50 L) are typically two-dimensional (2-D) and expand like a pillow or sack when filled. As the sizes get larger (typically 100 L to 3,000 L), the bioprocess bags are three-dimensional (3-D) and typically match the shape of the bag container they will be placed into during use (e.g., stainless steel support structures/frames or totes).

Bottles are rigid plastic vessels with volumes that typically range from 1 L to 20 L. Applications for bottles include sampling, storage, and freezing. They may be reusable (multiple-use) for non-critical applications.

Impellers/mixers are used to agitate fluid in a container. Common types include:

- Impeller with magnetic or magnetic-like drive
- Impeller with levitating drive
- Mechanical mixing (e.g., paddle or agitator shaft)

Other mixing options, including rocker units, are also available.

Tubing is manufactured from flexible polymer material and used for fluid transfer with or without pumping. Tubing is available in various diameters, lengths, wall thickness, and shore hardness. Materials of construction vary and include fluoropolymers, thermoplastics, and silicones. Thermoplastic tubing can be heat sealed (for aseptic disconnection) and welded (for tube/tube aseptic connection). Certain types of tubing are specifically designed to be used with peristaltic pumps or to withstand high pressures (e.g., on assemblies designed for filter pre-use integrity testing).

Port fittings are heat sealed to the chamber portion of a bioprocess bag and used to connect tubing, allowing for fluid to enter or exit the bags. Port fittings can also be found on bottles, and these would normally be accompanied by a seal.

Tubing connectors contain hose barb fittings, and may be used to connect tubing of different materials of construction and/or diameter sizes:

- Two pieces of tubing with straight connector
- Three pieces of tubing with T or Y shape connector
- Four pieces of tubing with + shape connector

Connectors are used to make connections between two or more components. Connectors vary, depending on the type of application:

- When ease of use is important but aseptic connections are not required, the following types of connectors may be considered: Luer-Lok® connectors, quick connects (with gendered male/female connectors), and sanitary clamp fittings (commonly referred to as Tri-Clamp®). These connectors may be handled within a laminar flow cabinet (which meets ISO 5/Grade A conditions¹ within) if aseptic connections are required.

¹ For additional information regarding area classifications, refer to *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities* [14], which takes the following into account: ISO 14644-1 Classification of Air Cleanliness [15], the Food and Drug Administration (FDA) September 2004 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [16], and Annex 1 of the European Union GMPs [17].

- When aseptic connections are required, the connectors should prevent any interaction between the fluid and the outside environment. There are two versions of aseptic connectors:
 - Equal complementary elements: This connection consists of two elements that are exactly alike and interchangeable. Tubing fitted with one of these connectors can be joined with any other tubing with the same size connector. These are also referred to as genderless connectors.
 - Matched complementary elements: This connection consists of two elements that are matched and can be connected together. Tubing fitted with one of these connectors can only be joined with a tubing piece that is fitted with a matched complementary element. These are also referred to as gendered connectors.

Steam-in-place connectors may be used between single-use components and stainless steel systems.

Disconnectors are used to make aseptic disconnections. There are two versions of aseptic disconnectors:

- Fluid path aseptic disconnectors need to be pre-assembled on the single-use assembly, usually through hose barb fittings between tubing.
- Non-fluid path disconnectors can be pre-installed or standalone. The concept is based on an external part (plastic piece or stainless steel ring) that is pressed and cut (with multiple-use tool) to allow aseptic disconnection.

Filter capsules (i.e., filter element included in plastic filter housing) of numerous types are used in single-use assemblies. Filters may be classified by several key criteria, such as:

- Filtration mode: dead-end filtration versus tangential flow filtration
- Type of filtration:
 - Sterilizing grade
 - Pre-filtration
 - Depth filtration
- Materials of construction
- Configuration:
 - Parallel plate
 - Pleated membranes
 - Non-woven
 - Hollow fiber
- Filter media features:
 - Polymer type (e.g., cellulose acetate, polyamide polyether sulfone, polyvinylidene fluoride, polytetrafluoroethylene, Polypropylene (PP), Polyethylene (PE), glass fiber)
 - Filter pore size

- Filter surface area
- Hydrophobic/Hydrophilic
- Connection style:
 - Hose barb
 - Sanitary

Valves are used to direct the flow of fluid either as wetted components or as controlled constrictions acting on tubing. The typical valve is composed of several subcomponents that work together to control the flow. There are also simple pinch valves that have a decreasing channel that squeezes the tubing to control the flow.

Sensors of several types have been specifically developed to be single-use and can be integrated into single-use assemblies. As SUT continues to evolve, new types of single-use sensors will be developed and made available. Currently, the available types of single-use sensors include:

- Conductivity
- Dissolved Oxygen (DO)
- Flow
- pH
- Pressure
- Temperature

For applications where single-use sensors are not available or may not be suitable, multiple-use sensors may be used with single-use assemblies. Typically, these sensors are inserted into the single-use assemblies at the point of use via aseptic connections or are attached to the single-use assemblies via a sealed barrier. The types of multiple-use sensors that are most commonly used with single-use applications include:

- Dissolved gases
- Level
- Mixing speed
- Turbidity
- Ultraviolet (UV) absorbance
- Weight (load cells)

Pump liners are components within the pump that make up the fluid path and that create pressure. The pump liners are polymeric components and are replaced after each use. These can be installed as individual components into the pump casings or integrated as part of single-use assemblies.

Centrifuge liners are polymeric liners that are designed to be used in a centrifuge system.

Gaskets and O-rings are used in the connections between two sanitary fittings, within valves, and where two solid (hard) components need to be connected. The materials of construction are numerous and include Ethylene Propylene Diene Monomers (EPDM), PTFE, Viton®, and silicone.

Filling needles are used in final filling operations to transfer liquid product into primary product containers. They are primarily made of stainless steel but some types are made of polymeric material.

Chromatography components: Chromatography columns (pre-packed with resin) are provided as disposable systems but are usually not single-use. Alternatively, membrane chromatography equipment does not need packing and are usually single-use.

Clamps may be used for:

- Connecting two components that have sanitary fitting interfaces
- Compressing or closing the tubing path with:
 - Closure controlled by threaded line with wingnut
 - Closure based on a specific locking position
 - Closure based on ratcheted positions

Fasteners are non-wetted components used to keep the tubing in position on the fitting or port. The main types of fasteners include:

- Plastic zip (or cable) ties with adjustability to variable circumference
- Stainless steel collar sized to fit specific circumferences
- Plastic fastener that extends support over barb edge for select circumferences

2.1.2 Single-Use Assemblies

Single-use assemblies can range from relatively simple units (such as buffer bag assemblies) to complex units (such as bioreactor assemblies). As highlighted in Figure 1.1, many combinations of components can make up single-use assemblies. Examples of single-use assemblies include:

- Buffer storage assemblies
- Mixer assemblies
- Sample manifold assemblies
- Transfer manifold assemblies
- Bioreactor assemblies
- Filtration assemblies
- Chromatography assemblies
- Centrifuge assemblies
- Fill/finish manifold assemblies

Single-use assemblies are available as standardized products or may be customized for specific process needs. Considerations should be made to design single-use assemblies that can be used in multiple steps within a manufacturing facility, benefiting the overall operation in terms of flexibility and minimization of inventory.

2.1.2.1 Bioprocess Bag Assemblies

Bioprocess bags are often bulky and impact space requirements for storage areas. Selecting standardized (versus customized) bags and connections can help to reduce inventory levels, since one assembly design can potentially be used in multiple steps in the process. Considerations for the design and selection of bioprocess bag assemblies include:

- **2-D Bioprocess Bags:** Standard specifications for 2-D bioprocess bags include tubing dimensions for the integral tubing and standardized connectors for sampling. Use of standard designs is recommended to minimize cost and provide flexibility between assemblies.
- **3-D Bioprocess Bags:** Most tubing entry points for the larger 3-D bioprocess bags are from the top. Care should be taken when adding auxiliary components to these entry points as they may require special handling to protect the bag surface.

During selection of the bioprocess container, attention should be taken to ensure that the minimum mixing volume is met and that ample ports are available for additions and sampling. For example, the selection of a standard 1½ inch sanitary fitting on the outlet tube of the mixer bag (for powder mixing) allows for a direct connection to a capsule filter.

2.1.2.2 Manifolds

Manifolds can range from being straightforward to complex in design. They are commonly the second bulkiest portion of the assembly, after the bioprocess bag. Aspects of manifold design and selection include:

- Sizing of tubing diameters and minimizing lengths and bends are important for properly fluid handling.
- The pressure rating of the tubing should be matched for the application, as manifolds are often composed of silicone or thermoplastic tubing. Reinforced tubing is available for applications above the pressure rating of standard tubing.
- Welds and aseptic connections should be used as needed to maintain sterility and flexibility.
- For processes that allow ports to be combined, manifolds can allow the use of standard bioprocess containers without modifications to the number of connections.

2.1.2.3 Filter Assemblies

Typical assemblies consist of normal flow filters, also known as dead-end filters, that are relatively small (less than 10 inch). Depending on whether the application is an open or closed operation, vent filters may be required on bioprocess containers. Disk type filters are typically used on smaller containers or as vents for larger filters. Vent filters on bioreactors are typically full size capsule filters and are provided in a redundant pair with heated jackets. Tangential flow filters are commonly incorporated into pre-designed assemblies to allow for special flow paths required for their operation.

2.1.2.4 Filling Assemblies

Final filling assemblies are specially designed filter assemblies that account for factors such as:

- Venting the filters in a sterile manner
- Filter flush collection

- Low particulate requirements
- Peristaltic pump tubing, if required
- Surge bags, if required
- Single-use needles, if required

2.1.2.5 Mixer Assemblies

Mixer assemblies can also range from simple to complex in design, due to the need for different mixing requirements, probes, avoidance of dead legs, and sampling requirements. Mixer types include bottom mount agitator, top mount agitator, and pump around. There are also different options for how the single-use impeller is coupled to the motor; special attention should be made for high viscosity, high solids, or low particulate applications.

2.1.3 Single-Use Systems

SUSs, as shown in Figure 1.1, are comprehensive units. SUSs are composed of single-use components/assemblies and multiple-use parts. In general, the multiple-use parts are used to:

- Support and provide mobility to the single-use assemblies
- Control the motion of fluids within and between single-use assemblies
- Monitor operating conditions
- Provide process controls for the unit operation or to the entire manufacturing process

The multiple-use parts in an SUS are often complex equipment and considerations should be made to how they interface with single-use components/assemblies. For example, wear or deformation of multiple-use parts can have disastrous impact on the integrity of the single-use components. Multiple-use parts represent conventional equipment, which are not covered in this Guide. For information regarding design and implementation of conventional equipment, refer to *ISPE Baseline® Guide: Sterile Products Manufacturing Facilities (Third Edition)* [14] and *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18] and. To help the end-user select the appropriate equipment for SUSs, this Guide highlights concepts and criteria in Section 2.3 (Process Equipment Design).

2.2 Extractables

Single-use products are made from polymeric materials; one of the key elements to qualifying and implementing such a material is to understand and control the impacts of using it within a defined process. Extractable and leachable (E&L) profiles are a main part of this required impact assessment.

Note: Although “extractables and leachables” is commonly used as one term, these concepts reflect two distinctly different ways of determining the chemical species that may migrate from the component:

- Extractables are removed from the component by exaggerated force, involving high temperatures, high and low pH, and aggressive solvents; this information can be useful for assessing the risk of the component in any application.
- Leachables, on the other hand, are a result of the interaction of the production within the equipment; therefore, related studies use actual product and process conditions to determine which chemical components will migrate from the component. When actual product is not possible for leachables studies (for reasons varying from availability of qualified tests to availability of product), a mimic of the product might be used. The information is specific to the product (or product mimic) and process.

A science and risk-based approach to an extractables study, as outlined in this section, is recommended due to its complexity and the need for trace level analysis. Risk factors to be considered during an extractables assessment include, but are not limited to, the surface area to volume ratio, the extracting potential of the process stream or formulation, and the duration of exposure. For example, a storage bag may be static in process contact but long in duration, while a bioreactor bag may be dynamic in process contact but short in the duration of contact.

The topics that are addressed in this section include: roles and responsibilities, regulatory and pharmacopeial expectations, risk assessment, design space, key recommendations for conducting an extractables study, and considerations for extractables testing (selection of lots, extraction conditions and procedures, extraction parameters, testing methodology, and extractables profiles).

Because this Guide deals with SUT applied in the processing of products which are intermediates, the focus of this section is on extractables as it applies to process contact materials, and not to finished dosage forms or containers.

2.2.1 Roles and Responsibilities

Extractables studies represent one of the most challenging aspects of pharmaceutical development. There is a large degree of complexity given by the number of factors that influence an extractables evaluation. The involvement of teams with adequate skills and subject matter expertise from both end-users and suppliers help in tackling each factor efficiently. Table 2.1 provides a template of the typical deliverables responsibilities matrix for an extractables study. Allocation of these responsibilities varies depending on company policy and procedures.

Table 2.1: Example Responsibilities Matrix for Extractables Study

Activity	End-Users					Suppliers				
	Project Manager	Engineering	Subject Matter Expert	Quality/Regulatory Compliance	Process Owner	Project Manager	Subject Matter Expert	Quality Manager	Product Manager	Research and Development
Pre-requirements assessment	C	I	C	A	I	AR	C	A	R	C
Pre-requirements regulatory compliance	C	I	C	A	I	R	C	AR	A	C
Understand product/process/company quality requirements	R	C	C	AR	C	R	C	AR	R	C
Understand quality requirements	AR	C	C	AR	C	C	C	AR	C	C
Definition of User Requirement Specification (URS)	AR	R	C	C	A	I	I	I	I	I
Benchmarking of previous extractables study protocol	I	C	AR	I	C	R	AR	C	C	R
Comparison of results for single-use components	I	C	C	I	I	R	C	C	C	AR
Determination of acceptance criteria based on URS	C	C	AR	I	I	R	AR	C	C	I
Determination of intended single-use components design and use	R	A	R	I	I	R	R	AR	A	I
Gather information from scientific literature	I	A	C	C	I	R	C	C	C	A
Performance of extraction procedure	I	I	I	I	I	R	R	R	R	AR
Comparison of results to acceptance criteria	R	I	C	C	I	R	C	R	C	AR
Toxicological assessment	C	I	A	R	I	R	A	C	C	R
Note: R=Responsible (who does the work to complete an activity or task) A=Accountable (who is ultimately accountable for the correct completion of the activity or task; approval) C=Consulted (whose opinion is sought during the completion of the task; consulted by R) I=Informed (who is kept up to date about the progress of a task and/or its completion; informed by R)										



2.2.2 Pre-requirements

Components which are planned for an extractables study should first meet the following regulatory and pharmacopeial expectations:

- **Requirements for polymeric materials:**
 - Plastic polymers used in manufacturing single-use components should not contain natural rubber, latex, or special case compounds (PAH, N-nitrosamines, and MBT)
 - USP <381> *Elastomeric Closure for Injection* [19]
 - USP <661> *Plastic Packaging Systems and Their Materials of Construction* [20]
 - European Pharmacopoeia (EP) General Chapter 3.1 *Materials Used for the Manufacture of Containers* [21]
- **Requirements for major compendia as appropriate for the intended use of the material:**
 - USP <87> *Biological Reactivity, In Vitro* [22] – in vitro testing is a minimum requirement
 - USP <88> *Biological Reactivity, In Vivo* [23] – in vivo testing is preferred
 - EP 3.2.9 *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders* [24], Japanese Pharmacopoeia (JP) Section 7.03 *Test for Rubber Closure for Aqueous Infusion* [25], and corresponding ISO 10993-1 [26] tests for in vitro and in vivo testing
- **Animal derived Stearates:**
 - EU Commission Decision 97/534/EC [27]

2.2.3 Risk Assessment in Extractables Study

In defining requirements for the design of extractables studies, the risk management tools described in ICH Q9 [28] should be employed. For example, application of quality risk management would consider:

- If an automated component manufacturing process is used
- If the process has been satisfactorily audited
- If a smaller sample may be needed, as opposed to a manually intensive manufacturing and/or inspection process for the component which may dictate a larger sample because of higher probability of variability

SUS extractables testing approach and methodology should be determined based on scientific knowledge and regulatory expectations. Decision trees and other risk assessment tools should be implemented at an early stage of the extractables study definition.

The purpose of these studies, based on testing methodology and toxicological assessment, is to obtain extractables profiles of SUS components considered as PCM in direct contact with the process or product fluid. The risk assessment should consider both patient safety (with regard to the impact of extractables compounds on product quality and safety) and the overall process performance. Extractables studies should integrate regulatory expectations as inputs of the risk assessment. Patient safety should be considered by suppliers in the development of single-use components, and by end-users in the implementation of these components in the drug manufacturing process.

2.2.4 Design Space

2.2.4.1 Basis for Comparative Evaluation

The starting point for an extractables study should be a review of the supplier's data. Ideally, these studies should be performed on materials at the component level, under standardized conditions of temperature, time, surface area, etc. (so the data are comparable) which are representative of the intended use, including steam sterilization or gamma irradiation. Using this data, the end-user can then calculate the maximum amount of extractables based on the surface area and other conditions in the process. The end-user can determine if this poses a risk, taking into consideration the impact of dilution and clearance over the complete process, and if it is necessary, to complement the risk assessment with specific targeted studies.

2.2.4.2 Extractables Study Design Space

The extractables study should be developed based on Quality by Design (QbD) principles described in ICH Q8 [29] to gather all attributes and parameters that enter into the determination of a design space. Scientific variables should be identified to set up Design of Experiment (DOE) for the extraction procedure.

2.2.4.3 Critical Applications

Different requirements of the extractables study could be applied depending on the criticality of application, context, and utilization of SUS components, as illustrated in Figure 2.2.

Figure 2.2: Criticality Scale of Industrial Application

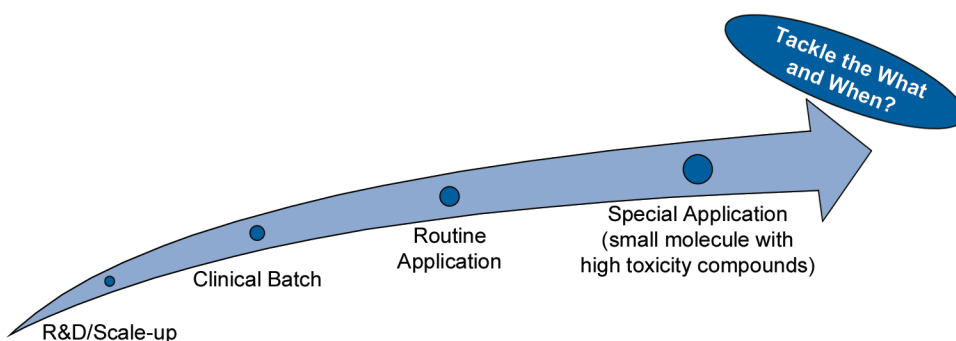
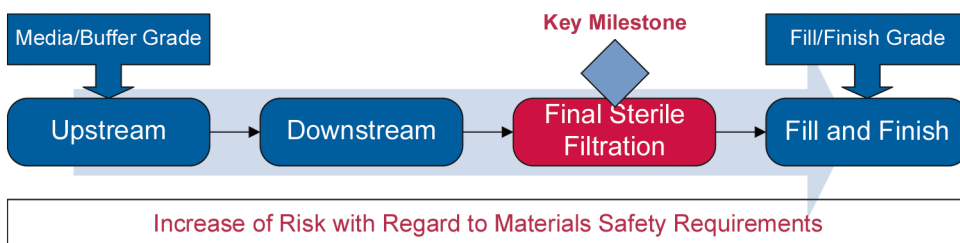


Figure 2.3 provides a high-level overview of the development stages in a typical biological manufacturing process, in relation to increased risk associated with materials safety requirements; that is, the closer the single-use component is to the fill/finish step, the less opportunity that risk mitigation (such as dilution or filtration) can take place.

Figure 2.3: Process Architecture with Regard to Materials Safety Risks

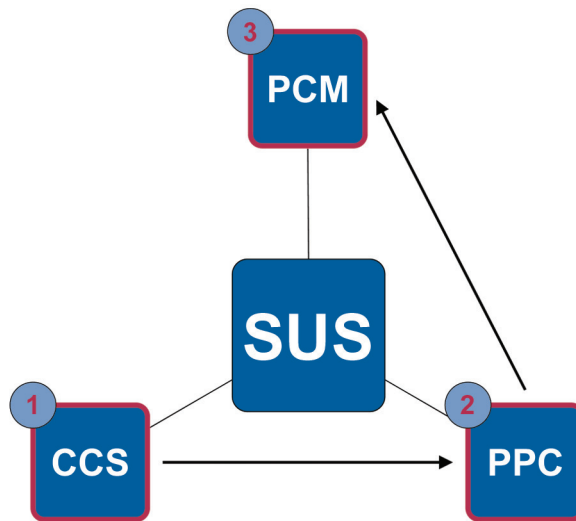


Note for Figure 2.3: For the critical stage, fill/finish application, considerations should include other quality requirements (e.g., particulates burden, integrity failures, and biocompatibility).

2.2.4.4 Consideration of Primary Packaging Component, Process Contact Material, and Container Closure Systems

Extractables studies are usually performed on individual PPCs and PCMs, as a precursor step to leachables studies which are performed on entire systems considered as CCSs. E&L studies should demonstrate the safety and chemical compatibility of the CCS, PCM, and proximal materials used in the processing and intermediate storage of a drug substance. Depending on the final dosage form, the drug product may contact several different packaging materials which can each contribute to the E&L profiles. The duration of exposure to these materials varies greatly depending upon the specific process. Compatible packaging and contact materials should not cause changes to the efficacy, potency, and safety of the drug product. This hierarchy is illustrated in Figure 2.4.

Figure 2.4: SUS Components Considered as CCS/PPC/PCM

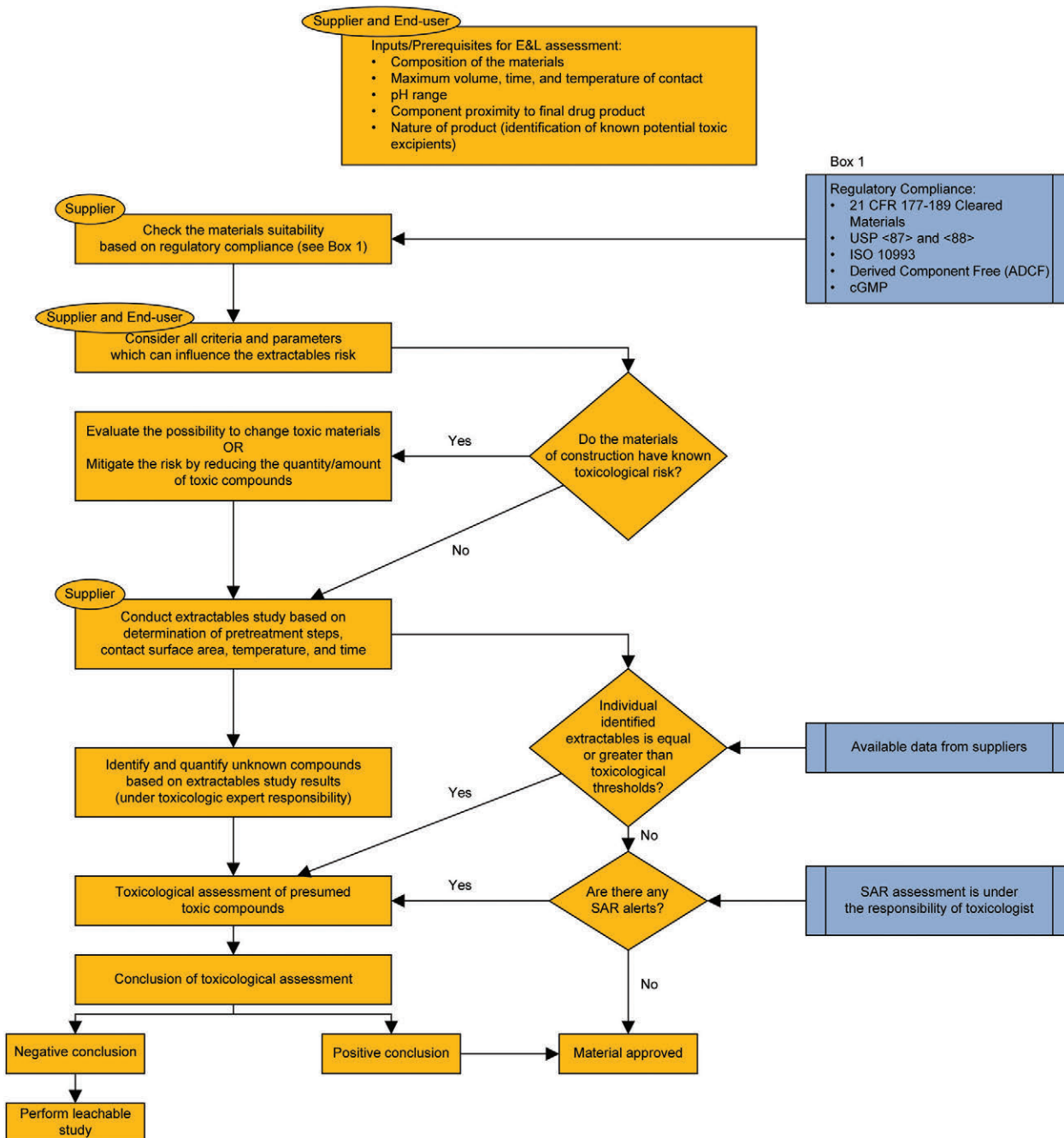


Note for Figure 2.4: Sequential numbering represents a hierarchy started from the CCS, to PPC, and to PCMs.

2.2.4.5 Decision Tree for Approval of Materials Based on Extractables Study

Figure 2.5 illustrates typical key aspects that should be considered in the approval of materials based on an extractables study.

Figure 2.5: Decision Tree for Approval of Materials Based on Extractables Study



2.2.5 Key Recommendations for Extractables Study

Extractables should be readily identified, quantified, and evaluated for their impact on drug quality (and consequently patient safety) arising from the interaction between process fluids (simulated by model solvents) and polymeric PCM. In the extractables study, the single-use component is considered as PCM. The objective is to obtain a chemical fingerprint of the tested single-use components. The information from the extractables study should be used to support the selection of raw materials in the single-use component manufacturing process.

The overall approach to conducting an extractables study is:

- Benchmarking of previous extractables testing protocols and results for comparable single-use components
- Determination of acceptance criteria based on user requirements, the intended design and use of the single-use component, and scientific literature
- Performing the extraction procedure on the single-use component to be tested
- Comparison of actual results to acceptance criteria and performing toxicological assessment with conclusion

2.2.5.1 Requirements for Processing and Storage of PPC/PCM to be used in Extractables Testing

The PPC and PCM should be processed in the same manner in which they will be processed for use in manufacturing. This includes steps such as washing, lubrication/coating, packaging, and sterilization. They should be held at their specified storage conditions, or as otherwise justified.

2.2.5.2 Requirements for Including Proximal Packaging Components in Extractables Testing

Packaging components and materials which do not directly contact the drug product should be evaluated on a case-by-case basis for their potential to leach chemicals into the dosage form. Polymeric containers with a glass transition temperature below room temperature have a high potential for migration of chemical entities through them. Packaging components (such as label stock, carton, adhesives, inks, varnishes, and lacquers) should be included in the overall extractables evaluation of such containers due to the potential for migration through the polymeric material, especially solvents of adhesives, inks, etc.

2.2.6 Extractables Testing

2.2.6.1 Selection of PPC/PCM Lots

Where practical, extractables studies of PPC, PCM, and proximal materials should be designed to capture lot-to-lot variability (preferably different resin lots, if possible). Multiple lots of PPC/PCM are recommended, when possible, for extractables evaluation. Non-consecutive lots, if available, should be used in the studies. Consideration should be made for the large supplier lots that may be received at the end-user facility on different dates or purchase orders. These may be identified as different lots, but in fact are not reflective of supplier process variability. To determine whether or not multiple lots are needed for an extractables study, an assessment of the point of variability in the supply chain (e.g., manufacturing, batch processing, washing, sterilizing, etc.) should be conducted.

The mass to volume ratio and sample size of the PPC/PCM are important inputs to extractables characterization. Sample preparation should be consistent in geometry for the different PPC/PCM lots. For example, consideration should be made either to use whole components or to cut components into approximately equivalent sizes.

Consideration can also be made to use a small-scale model for execution of the extractables study to support qualification of the large-scale model. This may be more cost effective and allows for easier handling in the extractables study. However, the mass to volume ratio should be maintained as close as possible to the ratio of the original intended size.

2.2.6.2 Extraction Conditions and Procedures

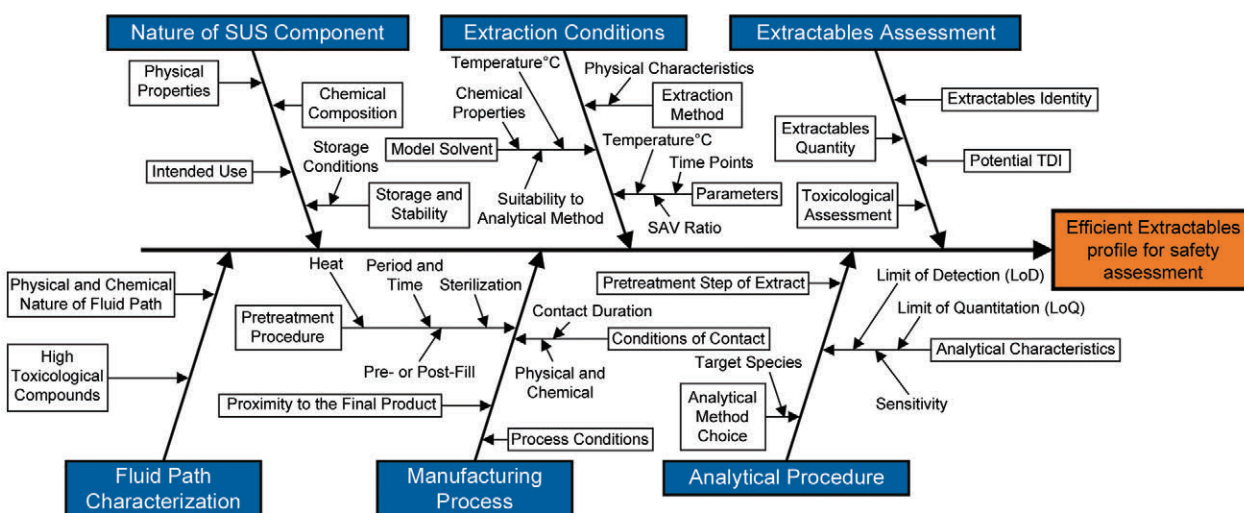
Extraction conditions are critical in determining the chemical profile and levels of individual extractables.

Prior to the execution of the extraction procedure, critical factors should be determined as they could potentially impact the study. An extractables assessment should provide quantitative and qualitative assessment of the safety threshold for individual extractables. The assessment should be based on different key factors, including:

- Fluid path characterization
- Nature of single-use components
- Manufacturing process conditions

These factors are illustrated in Figure 2.6, which is based on the Ishikawa principle, which enables study design and extraction strategies.

Figure 2.6: Diagram of Critical Quality Factors Potentially Impacting Extractables Study



To improve the extraction strategy, fluid path characterization assessment is crucial in determining extractables conditions. The characterization is based on the physical and chemical nature of the fluid path and the presence of high toxicological compounds.

The manufacturing process should be evaluated with regard to process conditions, proximity to the final product, and pretreatment procedures (e.g., autoclaving or gamma irradiation). The conditions of contact between the fluid path and the single-use component support the determination of extraction parameters.

These critical factors help to determine extraction conditions, which are based on parameters including:

- Chemical nature of the extracting media (model solvent)
- Duration of the extraction process and the temperature at which the extraction is performed
- Stoichiometry of the extraction process:
 - Surface area to volume ratio
 - Mass of individual extractable compounds extracted per surface ratio
- Physical characteristics of the extraction method

2.2.6.3 Extraction Parameters

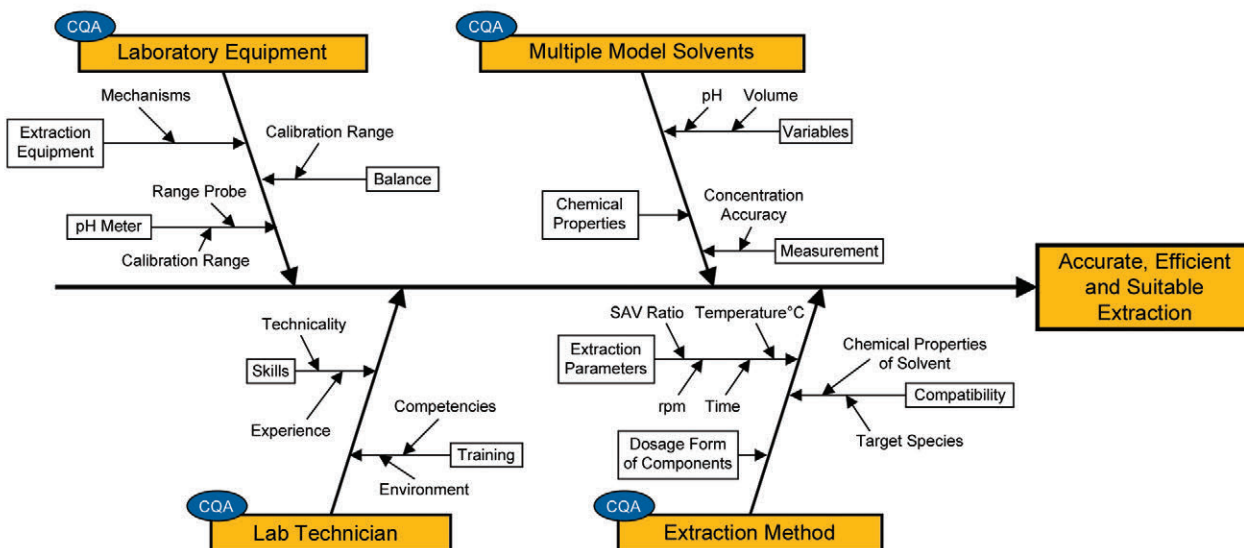
The extraction conditions (including temperature, pH, and time) should be appropriately selected, well described, and justified. Extraction media may include a drug product vehicle and organic solvents of varying polarities, extreme pH, and extreme ionic strength.

Considerations for extraction parameters include:

- Selection of appropriately aggressive solvents, rather than simulating the action of the fluid path
- Performing extractable analysis with multiple substitute solutions
 - Each solution should approximate the effect of one or more of the physical and chemical properties of the fluid path
- Selection of model solvents based on variability of polarities – the power (or capability) of model solvent extraction and their variabilities ensure the largest range of extractable compounds are encompassed
- Volatility of the solvent as a key concern regarding extraction factor and the compatibility of the solvent with the analytical method
- Determining the volume of extraction media using either the surface area of the component being extracted, or the mass of compounds extracted
 - This Guide recommends the use of the surface area of the component in contact with the process fluid path, as it is used in the manufacturing process, to determine the volume of extraction. Thus, only the inner surface area of the component in contact with the extraction media is considered.

Figure 2.7 illustrates the factors for extraction procedures that support accurate, efficient, and suitable extraction.

Figure 2.7: Diagram of Factors for Extraction Procedures



2.2.6.4 Testing Methodology

The levels of the identified extractable compounds should be analyzed and compared to standard guidelines such as the ICH Q3D [30], EP General Chapter 3.1 [21], and USP <661> [20]. In addition, refer to a proposed standard for extractables protocol (Ding et al., 2014 [31]).

Multiple analytical techniques should be performed to cover various types of extractable compounds, based on the volatility of the target species:

- Volatiles
- Semi-volatiles
- Non-volatiles
- Elemental impurities and ions

Analytical methods should be set up for a semi-quantitative assessment of extractable compounds with the following parameters:

- Sensitivity
- Limit of detection
- Limit of quantitation

Multiple analytical methods should be employed to find and identify extractables in the extraction fluid. Refer to Table 2.2 for more information.

Table 2.2: Summary of Analytical Methods for Detecting Extractables

Analytical Method	Target Species
Gas Chromatography–Mass Spectrometry (GC-MS)	Low molecular weight monomers, initiators, antioxidants, UV absorbers, lubricants, process aids, plasticizers, antistatic agents, modifiers, and oligomers
Headspace GS-MS (Dry Powder Inhaler components only)	Monomers, initiators, solvents, and other low molecular weight species
Liquid Chromatography–Mass Spectrometry (LC-MS)	Medium to high molecular weight polar species including antioxidants, plasticizers, lubricants process aids, and heat stabilizers
Liquid Chromatography–Ultraviolet (LC-UV)	Alternative technique to MS detector, UV absorbers and UV domain compounds
Acid Digestion Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)	Metal elements, catalysts, stabilizers, etc.
Ion Chromatography (IC)	Ions, catalysts, and accelerator compounds; only applied to aqueous extraction (Water for Injection, USP)

With the results of the analytical testing, the extractables can then be identified and each evaluated for its potential toxicity, based on toxicological assessments.

2.2.6.5 Extractables Profiles

The PPC/PCM end-user should understand the process for which the single-use component is intended, and the intended use of the drug product being manufactured.

For parenteral and ophthalmic products, recommendations are provided by the PQRI for Oral Inhalation and Nasal Drug Products (OINDP) [32]:

- Calculate the AET. Identify and quantify any extractables that are greater than the AET. Submit for a toxicological evaluation.
 - If the toxicological evaluation indicates a safety concern with the extractables levels, alternative packaging options should be considered.
 - If the extractables levels do not pose a safety concern, leachables testing should be conducted.
- Develop and validate leachables methods for the identified extractables and also monitor unknown compounds.
 - At each time point, compare unknown leachables levels to the SCT. For any compounds greater than the SCT, identify and update quantification as appropriate.
 - With the resulting leachables data, perform toxicological evaluations and evaluations for interaction (with other compounds that may impact the strength, identity, safety, quality, and purity of the drug product).

Stability issues may arise as a result of the manufacturing process. These include aggregation, changes in protein conformation, and changes in glycosylation on stability. Extractables studies will frequently not be able to detect these effects. Routine release testing is unlikely to detect protein unfolding unless it impacts function. Several analytical challenges may also arise during leachables testing. These include masking effects (interference) and solubilization of leachables by protein due to hydrophilic and hydrophobic sites. As a result, the most effective leachables mitigation strategy includes monitoring leachables over shelf life in the presence of the product and with a placebo alone. Ideally, all PCMs should be qualified and locked in to prevent changes to the chemical stability profile.

In addition to evaluating the individual steps or components for safety and interaction from extractables, the process train should also be evaluated for total contributions, including mitigating factors (such as purification, chromatography, diafiltration, and filtration steps) for reducing extractables.

2.3 Process Equipment Design

This section focuses on the design aspects of process equipment and the operational characteristics of single-use components for implementation of SUT. The topics that are addressed in this section include: sensors, single-use valves, pumps, single-use assemblies, bioreactors, environmental requirements, and considerations for control systems, utility and process support, maintenance and calibration, safety, and cleaning.

Choosing the appropriate components can be one of the most challenging aspects of implementing SUT, especially for transitions from traditional clean-and-reuse systems. Creating detailed user requirements at the beginning of the project is essential in determining which single-use components are suitable for the application. In selecting equipment, primary consideration should be given to suitability with the process. Considerations should also be given to equipment flexibility, customization options, future scale-up requirements, and supplier support.

2.3.1 Sensors

The determination of the level of accuracy needed (as compared to what the traditional system can measure) is important, as sensors may vary in accuracy and cost. For all single-use sensors, it is highly advised to test the accuracy and precision of the device in-house before implementation in the manufacturing facility.

Considerations for the selection of single-use sensors include:

- Fundamental technology behind the sensor (e.g., a rotary flow meter that measures rotations by the reflection of infrared light from the rotor blades will not be reliable when used with colored solutions such as cell culture media).

- Materials of construction (sensors exposed to process solutions and solvents should be assessed for chemical compatibility)
- Compatibility with the desired sterilization method (e.g., chemical, radiation, thermal) to ensure that the calibration of the sensor is not affected
- Calibration strategy (availability of pre-calibrated probes, if required)
- Robustness of the measurement and drift level under actual conditions of use
- Standardized connections (selection of components with specialized connections may result in being locked in with one supplier)
- Allowance for the end-user to perform pre-use steps without breaking sterility

2.3.1.1 Level

Options for level measurements in SUSs include:

- For hanging bags and with an understanding of the density of the process solutions: load cell strain gauge
- For mixers and larger tanks: guided-wave radar [33, 34], floor scale, and load cells
- For bubble traps: gas/liquid detector

2.3.1.2 Flow

Options for flow measurements in SUSs can vary greatly in fixed cost, variable cost, and accuracy:

- Rotary meters are typically less accurate ($\pm 5\%$) and more affordable
- Coriolis meters are more accurate ($\pm 1\%$) and more expensive
- Ultrasonic flow meters can be easily moved but tend to be more expensive
- Magnetic flow meters provide good accuracy for a mid-range expense but are not usable with deionized liquids

2.3.1.3 pH

Options for pH measurements in SUSs include:

- Traditional pH sensors: This is the most straightforward way to bridge pH sensing from stainless steel systems to SUSs. A sensor can be cleaned while connected to an aseptic connector half and then autoclaved. The probe is then attached to the process via the aseptic connector. Advantages of traditional pH sensors include the convenience of using analytical hardware that most end-users are already familiar with and the ability to accurately measure pH across the range used in biological operations.
- Single-use pH sensors: For physiological range readings (pH 5.5 – pH 8.5), single-use instruments can provide similar accuracy to traditional probes. These are essentially a miniaturized version of a standard pH probe with a plastic sheath, which can be inserted into a flow path of the single-use assembly and gamma irradiated. The probe can then be connected to the transmitter before use.

- **Sensor spots:** Another option for physiological range measurements, these solutions are chemical optical sensor spots which are placed on the inside of a clear bioprocess container prior to sterilization. These spots are then read by a fiber optical cable mounted opposite of the bag wall. Based on changes in absorbance and emission of different wavelengths of light, the pH is read. In addition to their limited pH range, certain cell culture media components can affect accuracy. Before implementing a pH patch solution, the end-user should verify its accuracy on their specific media, feeds, and buffers.

Table 2.3 lists the typical accuracy and limits of these pH measurement options:

Table 2.3: Typical Accuracy and Limits for pH Measurement Options

pH Measurement Option	Typical Accuracy and pH Limits
Traditional probe	± 0.01 for pH 2 – pH 12 ± 0.05 for pH 0 – pH 14
Single-use probe	± 0.05 , pH 5.5 – pH 8.5
Sensor spots	± 0.1 , pH 5.5 – pH 8.5

2.3.1.4 Dissolved Oxygen

Similar to pH measurements, the most straightforward way to bridge DO sensing from stainless steel systems to SUSs is to use traditional DO sensors. A sensor can be cleaned while connected to an aseptic connector half and then autoclaved. The probe is then attached to the process via the aseptic connector.

Single-use sensors that use a plastic sheath and similar optical sensing technology as traditional sensors are available. These single-use sensors have a narrower range and higher detectability limit but can provide similar accuracy in typical cell culture ranges.

2.3.1.5 Pressure

Several types of single-use pressure sensors are available. The main differences are accuracy, type of connection (in-line versus T), inner diameter, maximum pressure rating, and cost. It is also common for multiple-use gauges to be added onto single-use instrument Ts in a tubing set; the tubing set and gauge would be autoclaved together. Calibration concerns may drive the need for a pre-use calibration depending on the criticality of the measurement.

2.3.1.6 Temperature/Conductivity

Several options from various suppliers are available for temperature/conductivity meters in a single-use flow cell format. The majority of the available sensors have an accuracy rate of approximately 3%. The major differences between the conductivity sensors offered by different suppliers are the operating conductivity ranges and the available hose barb connection sizes. In deciding between suppliers, the main considerations are the proposed size of the system and the conductivity range of the process.

Another option is a single-use conductivity probe that is pre-connected to a bioprocess bag, pre-calibrated, irradiated, and that provides 2% accuracy (100 mS/cm). Measurement is taken with an integrated four electrode system and temperature sensor.

2.3.2 Single-Use Valves (Flow Path Control)

Opening and closing of flow paths on SUSs is typically performed using manual or automatic pinch valves. The two main types of automated pinch valves are:

- **Pneumatic pinch valves:** Typically used for larger inner diameter (ID) tubing and can hold back greater pressures

- Solenoid valves: Smaller and do not require the system to be supplied with instrument air (usually 90–100 psi)

Pressure control valves are simply pinch valves controlled by a stepper motor, such that they have thousands of positions rather than just open and closed. Due to the stepper motor function, solenoid pinch valves have a greater versatility than pneumatic valves.

Single-use diaphragm-style valves are also available.

2.3.3 Pumps

2.3.3.1 Pump Types

Positive displacement pumps are typically used in situations where accurate flow control is required while handling fluids that are sensitive to shear. This class of pumps is routinely preferred for biotechnology fluids. While there are many types of positive displacement pumps, the main pump types that are commonly used in single-use applications are:

- Peristaltic pumps
- Diaphragm pumps
- Centrifugal pumps

Peristaltic pumps operate with flexible tubing, which is a component used throughout single-use applications. The pump uses a length of tubing that is meant to be easily replaced. Typically, the tubing that goes in the pump should be more robust since it will be pressed within the pump rollers repeatedly. The wear of the tubing will cause a slight drift in accuracy; if there is a need for better flow control over time, a flowmeter can be installed to control the speed of the pump. Overall, the peristaltic pump is more flexible and requires less labor.

In situations where a higher flow rate is required, the diaphragm pump is typically used. The diaphragm pump can provide higher operating pressures and higher flow rates than a typical peristaltic pump. If the process requires a long operating time, a diaphragm pump can operate for longer continuous periods than a peristaltic pump.

In certain perfusion systems, single-use centrifugal pumps may be used. These types of pumps will not build up pressure to the point of a mechanical failure of the SUS, but will vary flow with pressure changes (e.g., filter loading).

2.3.3.2 Typical Materials of Construction

There is a large variety of tubing materials for peristaltic pumps. The selection should be made with the fluid product as a primary consideration. The flexibility, robustness, and other physical characteristics of the tubing are important, and should be tested with the fluid after the chemical characteristics are found to be acceptable.

The selection of material of construction for the diaphragm pumps is similar to the soft goods in traditional stainless steel systems; for example, the housing may be PP, O-rings EPDM, and diaphragms Thermoplastic Elastomer (TPE).

2.3.3.3 Selection of Tubing/Diaphragms

Due to the operating principles and nature of positive displacement pumps, there are resulting pulsations in pressure and flow for the process fluid. It is important to account for this fluctuation in pressure and flow onto the fluid since the pulses can cause stress on shear sensitive fluids.

For diaphragm pumps, the method used to reduce pulsations is to have more and smaller diaphragms (instead of fewer and larger diaphragms) operating in sequence. This is a variable to consider during pump selection, rather than during end-user operation. However, single-use diaphragm pumps typically have a limited selection of diaphragms in their design.

With peristaltic pumps, there is more flexibility when it comes to the end-user's ability to control pulses. Selecting the proper tubing size can reduce the pulsation characteristics of the operation. Selection of the correct tubing is a delicate balance between several factors:

- Given a specific flow rate, tubing with a larger diameter can operate at a lower level of Revolutions Per Minute (RPM) and yield less frequent pulsations. The lower RPM causes less stress on the tubing, which typically can result in a longer operating life.
- The larger diameter tubing also provides for a lower velocity and correspondingly lower shear for the fluid. However, the lower velocity can also cause air to be trapped.

Proper initial pump selection can also mitigate pulsation by selecting pumps with multiple channels.

Additional considerations for the selection of tubing/diaphragms include:

- **Dimensional consistency:** Pump tubing should be flexible and robust. It should be capable of handling the repeated squeezing between the rollers while maintaining its shape, so that a consistent flow rate can be correlated with the RPM of the pump/motor. The change in dimension due to wear during a run needs to be understood and accounted for in the control scheme/feedback if the drift is significant for the application.
- **E&L:** Similar to other components in single-use assemblies, the E&L profiles of the materials should be considered and tested as necessary. Since the tubing is squeezed, stretched, and stressed during its use, it is advisable that leachables testing be done under operating conditions.
- **Spallation of material during operation:** Spallation, which is the fragmentation/breaking of material fragments during use, is another critical parameter that should be confirmed under process conditions (including the specific operating fluid). Conducting an evaluation with the fluid being recycled to the pump will minimize the amount of fluid needed for this evaluation and concentrate any material that may spall off the material, thus make it more detectable in the assessment.
- **Compatibility with sterilization conditions:** The ability of the material to maintain its operational performance after autoclaving or gamma irradiation is also important when it comes to pump tubing and pump diaphragms. The sterilization methods can have a stiffening effect on the material and therefore cause modifications in the correlation of flow rate and pump speed. It would be useful to characterize the tubing performance after sterilization and assess if the change is impactful to the process. Consideration should also be made to the potential reduction of life expectancy of the tubing due to sterilization effects and any impact on tubing welds.

2.3.3.4 Overall Selection Criteria for Pumps

There are numerous factors in the selection of the right pump for the process. These factors are centered on handling the fluid and being able to produce the pressure and flow requirements of the process. The use of SUT adds the additional factor of removing components and minimizing their cost. Recommendations for the methodology in selecting a single-use pump package include:

- **Material compatibility with fluid:** Identify pumps that have single-use materials compatible with the fluid to be handled and that can provide the operating conditions needed for the process.
- **Accuracy of flow rate:** Achieving an accurate flow rate is critical in many processes. The flexibility of single-use components can challenge the stability and accuracy of the pump. There is often a balance that needs to be struck for each process to work optimally with the selected components.
- **Minimum pulsation and stable flow rate:** Pulsations can make it difficult to reach a steady state condition in the process. While it is often most upsetting to the stability of the flow rate, it can also strain components by exposing them to peaks of pressure. Selecting pumps and associated components that minimize pulsations will help to keep the process stable and safe.

- **Ease of replacement of single-use components:** Since single-use components are replaced after every run, ease of replacement is important so that the equipment can be returned to operation quickly and without errors in the reassembly.
- **Synergy in operation with other components in SUS:** For example, applying different size tubing provides more flexibility in the use of pinch valves. Changing the tubing size can allow for similar accuracy from the pinch valve but at a higher flow rate.

2.3.4 Bioreactors

2.3.4.1 Design

The primary application of single-use bioreactors is mammalian cell culture. Single-use bioreactors have had limited applicability with microbial cell lines due to limitations in vessel pressure, mass transfer, and venting. Microbial cell lines also present a challenge when the culture becomes heat generating, requiring a jacketed vessel with cooling capabilities, a more expensive option than a thermo-resistive jacket which is suitable for mammalian cultures.

Bioreactors are equipped with vent filters and filter heaters to promote evaporation of condensate. Even with the heaters, filters may be blocked with condensate from the exhaust gases. The bioreactor bag design should be modified to allow for the addition of vent filters, or with a condensate return system/design to help prevent filter blockage. Blocked filters may result in overpressure, process stops, and potential breach of the bioreactor bag.

For inoculation or harvesting of single-use bioreactors, all transfers should be performed by pumping since overpressure is not possible. This is a critical point to consider when dealing with cells sensitive to shear stress, thus transfers should be modeled and assessed. When considering harvesting, tubing size/length can be a limitation compared to the process operating range (time, pressure, and flow rate) applied on the harvest filters.

Ease of use is an important consideration when choosing single-use bioreactors. As the bags are sensitive and complex setup/operations are required for installing and removing bags, end-users should be sufficiently trained. Some types of single-use bioreactors require only a few interventions on the top to install lines and filters without the need for manual lifting. Other designs have specific installation doors, drawers, or lifting devices to aid users during the installation. Other factors to consider include: setup and removal time, number of personnel required to perform operations, and the weight of the new and emptied bag (which may need to be lifted to the top of the machine for installation).

Bioreactor designs range from mirroring traditional stainless steel bioreactors to novel agitation mechanisms. Single-use bioreactors may be customized to the end-user's specification from the options available from the bioreactor supplier. Options are still relatively limited with regard to impeller design, impeller size, and sparger type.

2.3.4.2 Process Transfer/Scale-Up

Single-use bioreactors should be characterized prior to use; a robust scaling factor should be selected for the scale-up strategy. Parameters may need to be adjusted since the single-use bioreactor configuration options are more limited compared to stainless steel bioreactors. The recommended practice is to use an equivalent characterized small-scale model to execute the fitted process to the desired manufacturing mode.

Considerations for applying conventional scale-up approaches in a well-characterized platform include matching the following characteristics:

- Geometric ratio (volume/surface) to retain equivalence between scales
- Oxygen Transfer Rate (OTR) coefficient (kLa) to be kept constant if possible, especially for the same geometric ratio

- Power input per unit of volume (P/V), in kW/m³, to be kept equivalent between scales
- Volumetric gas flow rate per unit volume or gas volume flow per unit of liquid volume per minute (VVM)
- Mixing time which is an important consideration for pH adjustment

Other approaches include:

- Constant volumetric scale-up to maintain shear stress
- Constant tip speed
- Constant VVM correlated to theoretical kLa

2.3.5 Chromatography

The application of chromatography in the biopharmaceutical industry can be categorized into broad categories in relation to SUT, as shown in Table 2.4.

Table 2.4: Chromatography Applications

Type	Skid Flow Path	Column	Complexity
Pass-through	Can be single-use (dependent upon scale and compatibility)	Pre-packed or reusable	Simple
Binding and elution	Mostly stainless steel due to complex flow paths including in-line dilution systems	Pre-packed or reusable	Complex flow path
Large-scale binding and elution column diameter above 80 cm	All stainless steel construction	Reusable	Complex flow path

Chromatography skids with single-use flow paths generally use peristaltic pumps and thus are not suitable for gradient elution, limiting the use of such skids to binding and elution or flow-through chromatography operations.

This area of SUT is rapidly changing with advancements in:

- Continuous processing
- In-line dilution
- In-line conditioning

These technologies impact the flow rates of solutions, often lowering them to be within the limits of SUT. However, single-use components may not be compatible with concentrated solutions. Therefore, it is important that end-users consult with single-use suppliers prior to using single-use assemblies with highly concentrated solutions.

2.3.6 Ultrafiltration

Single-use ultrafiltration membranes/systems are available; however, the vast majority of medium to large scale ultrafiltration systems remain multiple-use. This is mainly due to the cost of the membranes, flow limitations through single-use tubing, and the need to spread this cost over multiple batches. As a result, single-use ultrafiltration tends to be restricted to smaller scale and niche applications.

2.3.7 Environmental Requirements

Environmental requirements are an important consideration for drug manufacturing. The *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18] defines three categories of processing:

- **Open process:** A process that is exposed to the environment and therefore requires environmental conditions to mitigate the risk of contamination from the environment.
- **Closed process:** A process system that is designed and operated such that the product is never exposed to the surrounding environment. Additions to and draws from closed systems need to be performed in a completely closed fashion.
- **Functionally closed process:** Process systems that may be opened but are rendered closed by a cleaning, sanitization, and/or sterilization process that is appropriate or consistent with the process requirements, whether sterile, aseptic or low bioburden. These systems remain closed during production within the system.

For additional information regarding environmental requirements, refer to *ISPE Baseline® Guide: Active Pharmaceutical Ingredients* [35], *ISPE Baseline® Guide: Sterile Products Manufacturing Facilities (Third Edition)* [14], and *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18].

SUSs that use ready-to-use flow paths with aseptic connections are compatible with the reduced environmental requirements of closed or functionally closed operations. A process closure risk assessment should be performed to identify the required classification and segregation needed for different process steps.

Hybrid systems, such as a stainless steel vessel connected to a single-use flow path, are a typical application. A system that has any clean-and-reuse portion should be cleaned, closed, and returned to its sterile state. The multiple-use portion should then be treated like any other multiple-use equipment. If this system can be returned to its closed sterile state, then it could also be reconnected to single-use components and operated in an area with lower area classification as a functionally closed system. The stainless steel vessel could be opened if needed, connected to a single-use flow path via a steam through connector, cleaned, and then steamed in place. Once the vessel has been through a steam-in-place (SIP) cycle, the connection is engaged and the hybrid system is both sterile (or bioburden controlled) and closed.

2.3.8 Control Systems

The control systems used for SUT are currently unique to the SUT manufacturer. Skid manufacturers should:

- Follow Good Automated Manufacturing Practice (GAMP®) for selection, design, and qualification of the control system
- Use modern Open Platform Communications (OPC) communication and the most current hardware
- Allow open standards to end-users since closed systems prohibit the inclusion of these systems into a Good Manufacturing Practice (GMP) area

Additional recommendations for control systems in single-use operations include:

- The skid automation should be designed to enable end-users to handle multiple scales.
- The automation system should be designed to display process and system relevant operational parameters. There should be a feedback loop for every control parameter; for example, agitation should have a feedback loop to check the motor speed to set point.
- The control system should include a network interface card (i.e., Ethernet adapter card) or some form of data collection point. The control system should also have a batch manager.
- Connectivity to the network should be considered since the lighter weight of SUSs allows for more mobility. For example, a single-use mixer with load cells could be used for formulation in one location and then wheeled to a different location for dispensing. There would need to be data ports at both locations, or the system would need to be designed with a wireless radio. To maintain the formulated weight, the system would need to be configured to retain the last value on power loss or be fitted with a battery power supply.

For additional information, refer to *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [36].

2.3.9 Utility and Process Support

2.3.9.1 Electrical

Considerations for electrical systems in single-use operations include:

- The main contribution to the electrical load in a single-use operation is primarily due to motors and temperature control. The motors can be those applied to pumps, centrifuges, blowers, and mixers. Temperature control units can be present in a variety of locations including mixer containers and bioreactors.
- An inventory of motors and temperature control units is the first step in assessing facility fit for electrical requirements. While the bulk of the electrical loads are attributed to the above components, smaller loads like lighting and control system operation also need to be accounted for when defining electrical utility requirements.
- Unlike stainless steel skidded systems, electrical connections on SUSs are typically cord and plug. The lighter weight of SUSs makes reconfiguration of the equipment within the suite (e.g., due to process changes or to improve ergonomics) possible as long as potential utility needs, like power, are strategically placed in the suite.

2.3.9.2 Process Gases

The facility should have lines for the process required gases, with drops located at the specific unit operations that require the gases. The equipment should be designed for the typical needs of that unit operation. The lack of a true pressure rating on SUSs, bioprocess bags in particular, may require different gassing/venting control schemes from equivalent stainless steel systems.

2.3.9.3 Water

Water is a key component in most processes, including those utilizing SUSs. For smaller scale single-use operations, water can be provided by using bagged water or bagged solutions prepared off-site. Since bagged water can address the bulk of water needed in smaller scale processes, purified water lines may be eliminated from operations. For larger scale (or higher volume) single-use operations or hybrid facilities, water systems typically have a lower number of use points than an equivalent stainless steel facility. Due to temperature sensitivity of SUSs, ambient versus hot distribution loops with multiple point of use coolers should be evaluated for these facilities. Refer to the *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [37] for additional information.

2.3.9.4 Drains

Considerations for drains in single-use operations include:

- Leveraging the closed system abilities of SUSs, which could allow for the systems to be located in a classification that allows an open drain
- Collection of process waste in single-use bags and moving it out of the process area for manual neutralization

The decrease in, or elimination of, Clean-In-Place (CIP) activities may reduce pH neutralization demands for drains.

2.3.10 Maintenance and Calibration

Maintenance requirements are generally reduced for SUSs. Skid manufacturers should consider the following design aspects related to end-user maintenance requirements:

- Including the number of pinches for automated pinch valves as part of the automation, which would enable maintenance of pinch valves and help to prevent process failures
- Allowing easy access to single-use components (pumps, valves, etc.) for regular maintenance
- Arranging the tubing, connectors, and filters for accessibility and with sufficient support (e.g., to maintain open flow paths without putting strain on any connections)

Supplier calibration can be used for single-use components and may need to be coupled with on-site post-use calibration. Suppliers should be compliant with ISO/IEC 17025 [38] or equivalent. Suppliers should follow proper quality procedures and provide supply chain visibility to end-users. The suppliers of single-use components should provide transmitter calibration procedures as part of the turnover package.

2.3.10.1 Safety

Basic safety considerations are similar for SUSs and stainless steel systems. For example, all systems should have emergency stops (E-Stops) local to the system to stop operations in accordance with governing safety regulations.

Additional safety aspects that factor into the design of SUSs include:

- Even though single-use manifolds are designed for aseptic connection and disconnection, the system should have secondary containment to capture any leaks during system disassembly.
- Biosafety aspects of the process should be considered, and any additional containment or inactivation procedures should be in place.
- Pressure sensors should provide feedback to the pump motors to prevent leakage due to bag/plastic rupture.
- For processes with toxic buffers/drugs, the system should contain guards surrounding the tubing to capture any fluid if tubing bursts during operation. In all cases, spill control/clean up procedures should be in place.
- The hardware mounted on the frame (e.g., pumps with exposed drive shafts) should have locally compliant guards or shields around the shaft to prevent personnel contact with them.
- The electrical power and instrumentation wiring, as well as control panels, should be designed, fabricated, and erected in accordance with current governing codes and be appropriately listed (e.g., Underwriters Laboratories (UL) [39]) to minimize the exposure of technicians and other personnel to electrical shock hazards.

2.3.10.2 Cleaning

Single-use operations minimize cleaning activities in the end-user facility. While process line cleaning is eliminated for fully SUSs, non-product surfaces should still be wiped or washed to keep the non-product contact surfaces clean. This cleaning should be in accordance with a facility's procedures on room cleaning and improvement steps into the processing suites for the designated area classification. For additional information regarding end-user facility and equipment cleaning, refer to *ISPE Baseline® Guide: Active Pharmaceutical Ingredients* [35], *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities (Third Edition)* [14], and *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18].

Single-use components are typically packaged in sealed containers that protect them from contamination from the environment until the components are put into use. Some single-use assemblies are packaged in multiple containers (usually bags) that should be cleaned or wiped and removed as the assemblies move into stricter area classifications. Care should be taken in choosing sanitization methods since certain solvents may be absorbed into or otherwise adversely impact certain plastics. The intended use of sanitizing agents (including chlorine dioxide and vaporized hydrogen peroxide) should be communicated between the end-user and single-use suppliers to assess the impact on hardware and selection of plastics.

2.4 Quality Requirements for Single-Use Products

This section addresses fundamental criteria for quality requirements associated with SUT implementation. This section should be read in conjunction with Section 2.6 (User Requirement Specification Development) and Section 3.2 (Regulatory Compliance).

In addition to the information provided in this section, the science and risk-based approach described in ASTM E2500 [40], ASTM E3051-16 [41], and ICH Q8, Q9, and Q10 [29, 28, 42] should also be followed. A risk assessment should be completed at each key decision point.

2.4.1 Defining Quality Requirements

As identified in Section 1.4, SUT incorporates single-use components, assemblies, and systems. The requirements for each category are addressed in the following sections.

2.4.1.1 Quality Requirements for Single-Use Components

The following requirements for components are primarily used by the manufacturers of single-use assemblies and systems. End-users of single-use products may also use these requirements for purchasing individual components and as prerequisites to overall requirements for single-use assemblies. Considerations for single-use component quality requirements include:

- Extractables profile of wetted components (refer to Section 2.2)
- Biological and chemical compatibility of wetted components with the product or process fluid
- Integrity (structural and mechanical integrity, closure integrity for containers/bags and bottles)
- Resistance and compatibility to temperature, pH, and pressure conditions during use and treatment (e.g., gamma irradiation or other sterilization techniques applied)
- Qualification of components (including critical requirements for use of components in assemblies)
- Limits for bioburden and endotoxin
- Limits for particulate matter

- Manufacturing environment for components
- Inspection of components on receipt
- Inventory control of components

Since there are commonalities with the product quality requirements for different single-use components, the assessment process may consist of grouping components with common requirements. A primary approach to the component assessment is based on two categories: wetted components and non-wetted components.

As discussed in Section 2.1, single-use components may be classified as wetted or non-wetted, based on whether it contacts the product or process fluid. The more extensive requirements apply to wetted components. Examples of the wetted component groupings include:

- **Film, tubing, and connectors:** These are basic to any assembly
- **Bottles, filters, instruments/sensors, mixers:** These are common components
- **Liners for valves, pumps and centrifuges:** These are more specialized

While the non-wetted components typically require a less extensive list of requirements, considerations should be made for any contact between the wetted and non-wetted components and for the potential impact of non-wetted components on the environment of the wetted components. Both types of components are exposed to treatment conditions (e.g., gamma irradiation, autoclaving, and shipping) and how one type responds to these conditions can impact the other type. Examples of these non-wetted component groupings include:

- **Clamps, fasteners, and affixed labels:** These have contact with the wetted components
- **Bubble wrap, protective foam, pack-out bags, boxes, packaging tape, and labels:** These can impact the environment of the assembly

Table 2.5 summarizes the suggested quality requirements for components based on each classification (wetted and non-wetted).

Table 2.5: Suggested Quality Requirements Based on Classification of Components

Quality Requirements	Wetted	Non-wetted
Extractables profile	A	
Biological and chemical compatibility	A	B
Integrity	A	B
Compatibility with temperature, pH, and pressure	A	A
Compliance with qualification criteria	A	A
Limits for bioburden and endotoxin	A	
Limits for particulate matter	A	B
Manufacturing environment	A	A
Inspection	A	B
Inventory control	A	A
Note: A indicates required. B indicates useful. No letter indicates not needed.		



2.4.1.2 Quality Requirements for Single-Use Assemblies

Quality requirements for single-use components also apply to single-use assemblies. Additional requirements for single-use assemblies are related to manufacturing of the assembly and delivery to the end-user. These suppliers are sometimes referred to as system integrators.

In addition to the above requirements for single-use components, considerations for single-use assembly quality requirements include:

- Qualification and control of clean room environment (particle control)
- Handling of components from inventory storage to clean room environment
- Inspection (in-process and post-manufacturing)
- Manufacturing methods and controls
- Integrity testing of manufactured assembly (structural and mechanical integrity)
- Training of assemblers and other manufacturing personnel
- Sterile barrier bagging and packaging
- Sterilization
- Manufacturing certificates
- Compliance with shipping requirements (such as per ASTM D4169-16 [43] or International Safe Transit Association (ISTA) [44] standards)

2.4.1.3 Quality Requirements for Single-Use Systems

SUSs consist of two groups: single-use components/assemblies and multiple-use parts. The requirements for single-use components/assemblies are addressed in the earlier sections. This section focuses on multiple-use parts. Examples of multiple-use parts include:

- Bag carriers, system frames, tubing racks, and bag lifts
- Pumps, motors, load cells, instruments, and control valves
- Electrical, wiring, and control enclosures
- Software

The multiple-use parts can be further classified into two categories based on common quality requirements: mechanical and electrical/controls.

For the mechanical parts of the system, considerations for quality requirements include:

- Material of construction and compatibility with the operating environment (e.g., corrosion resistance)
- Surface finish
- Compliance with mechanical strength (stiffness, bending, pressure), including after sterilization

- Particulate presence and generation potential

For the electrical/controls parts of the system, considerations for quality requirements include:

- Compliance of electrical system design with National Electrical Code® (NEC®) [45] or local electrical codes
- Ergonomics of control Human Machine Interface (HMI)
- Compliance with area classification (class, division, and zone)
- Software compliance with 21 CFR Part 11 [46]
- Particulate generation potential of moving parts (motors, fans, pumps)

2.4.1.4 Supplier Assessment Matrix

Component Supplier Matrix

The component supplier matrix is useful in identifying supplier candidates that can provide components meeting specified requirements. The matrix can be used as a tool to:

- Assess the availability of components. With the rapid development of SUT and introduction of new components, it is important to account for the availability of any state-of-the-art components. Components that are available from multiple sources are often more established in their use and have reduced supply risks.
- Identify specific component quality requirements that are readily available from suppliers. The matrix can help to identify specific suppliers which can meet the quality requirements. In case of requirements that cannot be met by suppliers, the results of this matrix can be used to identify and plan the work needed to meet the established quality requirements.

Table 2.6 provides an example template for the component supplier matrix.

Table 2.6: Component Supplier Assessment Matrix Template

	Suppliers			
	Component Supplier 1	Component Supplier 2	Assembly Supplier 1	Assembly Supplier 2
Components				
Bags				
Fittings				
Tubing				
Connectors				
Filters				
Valves				
Ports				
Filling needles				
Pump liners				
Centrifuge liners				
Sensors				
Bottles				
Gaskets/O-rings				
Chromatography columns				
Clamps				
Supplier Operations				
Manufacturing and quality certificates				
Qualification of manufacturing environment				
Control of manufacturing environment				
Handling of component (manufacturing to inventory storage)				
Inspection (in-process and post-manufacturing)				
Training of manufacturing personnel				
Past experience and organization history				
Local office and technical support availability				

Assembly Supplier Matrix

Table 2.7 provides an example template for the assembly supplier matrix, which may be used in the same manner as the component supplier matrix.

Table 2.7: Assembly Supplier Assessment Matrix Template

	Suppliers			
	Assembly Supplier 1	Assembly Supplier 2	System Supplier 1	System Supplier 2
Components				
Bags				
Fittings				
Tubing				
Connectors				
Filters				
Valves				
Ports				
Filling needles				
Pump liners				
Centrifuge liners				
Sensors				
Bottles				
Gaskets/O-rings				
Chromatography columns				
Clamps				
Assemblies				
Bags or bottles with tubing assemblies				
Mixer assemblies				
Bioreactor assemblies				
Sampling assemblies				
Supplier Operations				
Manufacturing and quality certificates				
Qualification of manufacturing environment				
Control of manufacturing environment				
Handling of component/assembly (inventory storage to clean room)				
Inspection (in-process and post-manufacturing)				
Manufacturing methods and controls				
Integrity testing of manufactured assembly				
Training of assemblers and other manufacturing personnel				
Sterile barrier bagging and packaging				
Sterilization				
Compliance with shipping requirements				
Past experience and organization history				
Local office and technical support availability				

System Supplier Matrix

Table 2.8 provides an example template for the system supplier matrix, which may be used in the same manner as the component supplier matrix and the assembly supplier matrix.

Table 2.8: System Supplier Assessment Matrix Template

	Suppliers			
	Assembly Supplier 1	Assembly Supplier 2	System Supplier 1	System Supplier 2
Assemblies				
Bags or bottles with tubing assemblies				
Mixer assemblies				
Bioreactor assemblies				
Sampling assemblies				
Systems				
Equipment frame				
Bag carrier				
Instruments				
Pump				
Centrifuge				
Bag lifts				
Tubing hangers/racks				
Electrical/control enclosure				
Scale/load cells				
Software				
Supplier Operations				
Manufacturing and quality certificates				
Qualification of manufacturing environment				
Control of clean room environment (particulate control)				
Inspection (in-process and post-manufacturing)				
Manufacturing methods and controls				
Integrity testing of manufactured assembly				
Training of assemblers and other manufacturing personnel				
Sterile barrier bagging and packaging				
Sterilization				
Compliance with shipping requirements				
Conduct Factory Acceptance Test				
Start-up support				
Support with Site Acceptance Test				
Past experience and organization history				
Local office and technical support availability				

Once the supplier candidates are identified, the supplier capability matrix can be used to further the move towards selection of the most appropriate suppliers. Refer to Section 2.5 for further information about the supplier capability matrix.

2.4.2 Checking Single-Use Product Quality

The performance of a single-use product is often dependent on many factors during the manufacturing process and subsequent handling throughout the product's life. It is important that the complete histories of single-use components and assemblies are tracked and documented. All involved parties along the supply chain should be fully engaged in this activity. Regulatory requirements for the end-user may involve the auditing of this information; availability of the information will streamline audits for all participants in the supply chain.

This section outlines who should be collecting and accumulating relevant information on single-use components and assemblies.

Note: The multiple-use components or parts that make up the SUSs are handled during the Factory Acceptance Test (FAT) or Site Acceptance Test (SAT). For further information regarding FATs and SATs, refer to the *ISPE Baseline® Guide: Commissioning and Qualification* [47].

Quality Aspects to be Checked by Suppliers – typically apply to single-use components at receipt through single-use assemblies at release to ship:

- At receipt (of components)
 - Package conditions
 - Visual check of components (performed by trained inspectors)
 - Compliance with specifications
 - Presence of certificates
 - Inspection of components (such as quantity and labeling)
- During manufacture of assembly
 - Structural and mechanical integrity of components
 - Compliance with manufacturing drawings
 - Integrity of assembly
 - Visual inspection for proper assembly of components
- At release to ship
 - Compliance with manufacturing requirements
 - Clearance with endotoxin/particulates criteria
 - Compliance with packaging requirements
 - Confirmed irradiation level

It is important that the inspection of components is performed by trained personnel who are familiar with the specific component criteria that need to be met for acceptance. Training for the inspection of single-use components and assemblies should be conducted as described in Chapter 6 (Appendix 2). During handling, care should be taken to ensure the components retain critical characteristics during transfer in/out of the inventory and in the assembly operation. Records for inspections should include acceptance/rejection criteria as well as references such as the item number, part number, revision letter, lot size, and inspector's name.

Quality Aspects to be Checked by End-Users – typically apply to single-use assemblies:

- At receipt (of assembly)
 - Package conditions
 - Outer package and inner package label inspection
 - Visual check for the integrity of the sterile barrier (presence of vacuum)
 - Assembly layout within package
 - Presence of certificates
 - Visual check of assembly
 - Sterility/irradiation marker check
- At use
 - Compliance with assembly specifications
 - Compliance with assembly drawings (key aspects such as end connection types, filter size, etc.)
 - Confirming the inlet/outlet connection points

It is important that the handling of assemblies is performed by trained personnel. The personnel should be familiar with the specific assembly and the critical steps to follow for moving it from the package to use in manufacturing operations.

2.4.3 Methods Applied to Meet Single-Use Product Quality Requirements

The methods described below are intended to provide a strong foundation for single-use product quality requirements. Suggested work flows and content for specific documents are provided in this section to support the development of quality requirements.

2.4.3.1 Quality Management System

Quality by Design

A QbD approach, as described in ICH Q8 [29], should be applied as part of SUT implementation.

Communication Flow

Successful SUT implementation depends on streamlined communication flow between the supplier and end-user. The communication flow should be established to ensure the supplier follows the User Requirement Specification (URS) written by the end-user. Assigning a key project contact from the supplier and from the end-user is recommended.

Typical activities between the suppliers and end-users consist of these interactive steps:

- The end-user:
 - Writes the URS
 - Reviews and approves drawings
- The supplier:
 - Confirms understanding of the URS
 - Provides material data, advice on applying typical designs, component lists, and operation manuals
 - Submits drawings
 - Meets agreed upon manufacturing/delivery schedules for production of single-use products

Refer to Section 2.5 for additional information regarding supplier quality and audits.

Quality Risk Management

Quality Risk Management (QRM) methods, as described in ICH Q9 [28], should be applied for defining the quality requirements for single-use products. Understanding and assessing the product and process risks, with communication to upstream suppliers and downstream end-users, are key factors in defining acceptable quality requirements.

Acceptance/Rejection Inspections

Documented methods for the acceptance/rejection of materials should be used throughout the supply chain. These methods should be aligned with the release to ship criteria defined by suppliers for products manufactured and shipped to their customers. The receiver should inspect all materials received, according to established criteria for purchasing the material. Any non-conforming material should be identified and placed in quarantine or returned to the supplier. The quality unit should ensure control of acceptance inspections.

2.4.3.2 Development of Design Specifications

Functional and technical design specifications should be defined by the end-users, with support from the suppliers. These specifications are used by suppliers (in collaboration with the end-users) in the development of single-use assemblies/systems.

The input for determining these specifications should include the user requirements and overall quality requirements. Critical aspects (in terms of ensuring product quality and patient safety, as described in ASTM E2500-13 [40]) should also be considered when developing the functional and technical design specifications.

2.4.3.3 Qualification of Single-Use Components and Assemblies

Qualification practices should include defined and acceptable methods to qualify single-use components for their use in the manufacture of single-use assemblies and systems. Qualification criteria are often geared towards producing material for specific application requirements. Considerations for the main criteria to be included in the qualification process are listed below. For the details of the testing performed to meet these criteria, refer to Chapter 8 (Appendix 4).