



GOOD PRACTICE GUIDE:

Single-Use Technology

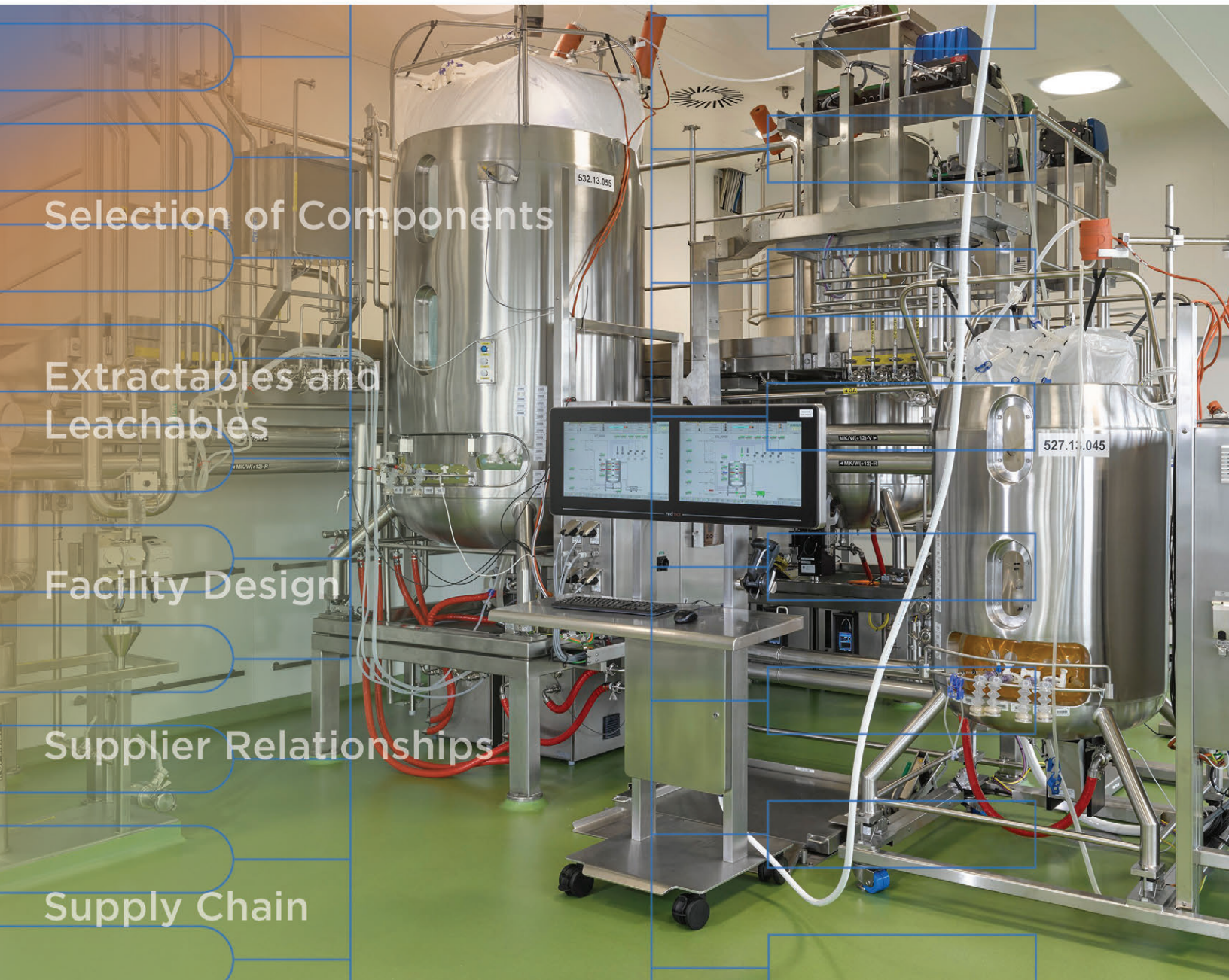
Selection of Components

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.

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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, bag lift, scale, bag carrier, 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.

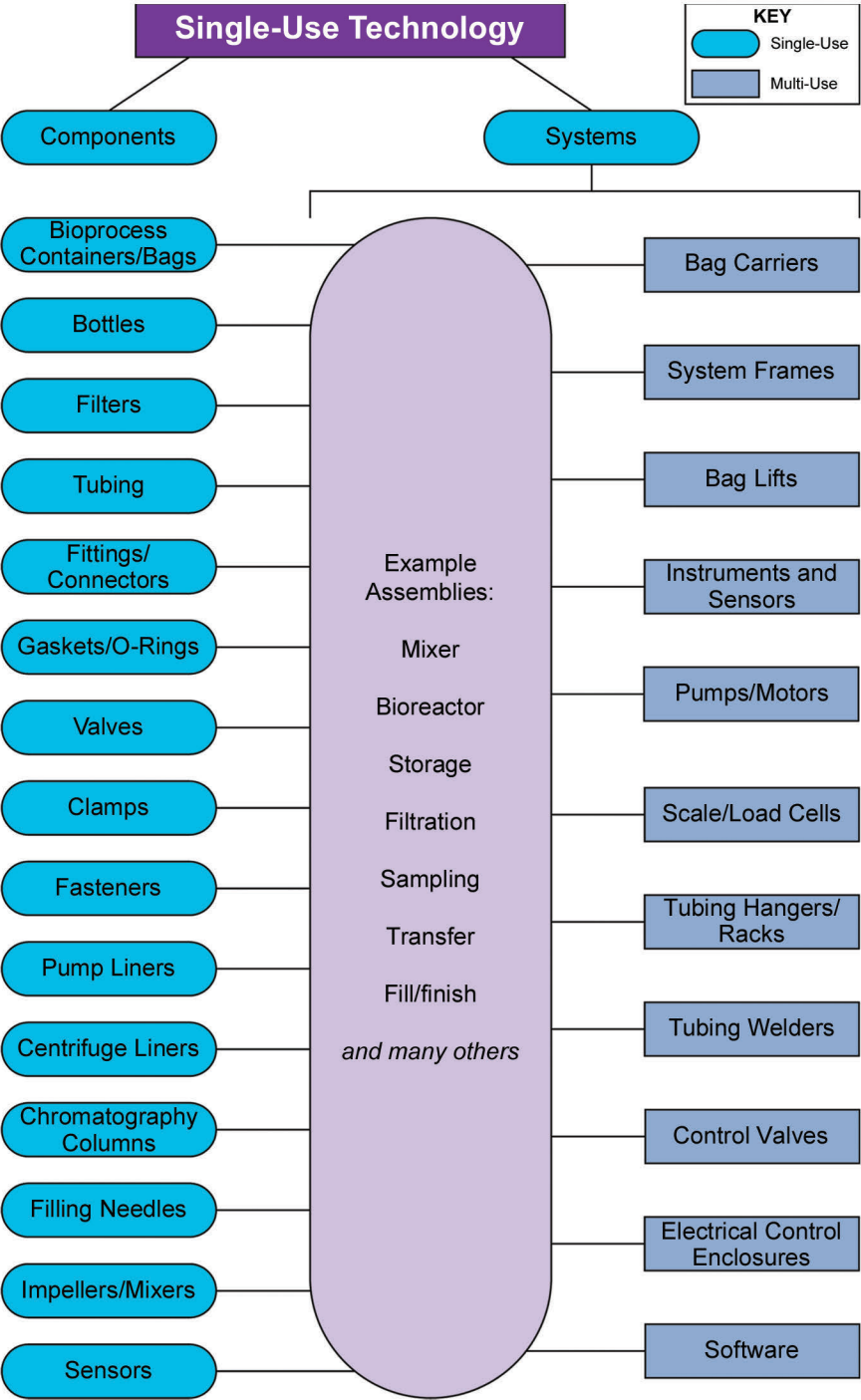
Threshold of Toxicological Concern (TTC): The daily intake of a genotoxic impurity that is considered to be associated with an acceptable risk (excess cancer risk of < 1 in 100,000 over a lifetime) for most pharmaceuticals.

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.

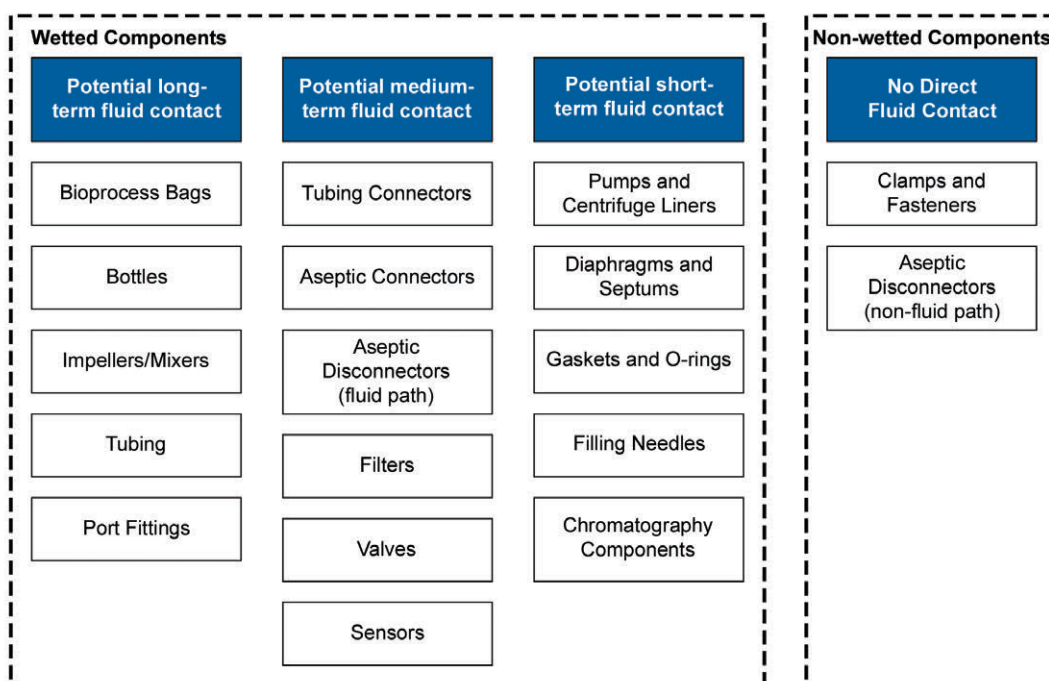
2.1.1 Single-Use Components

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

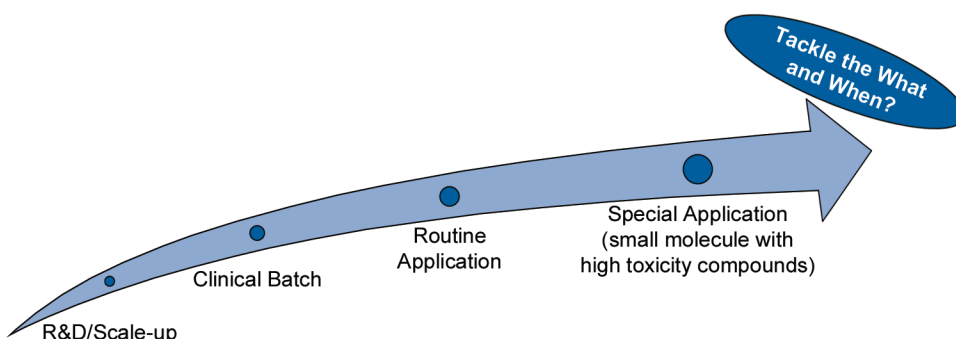
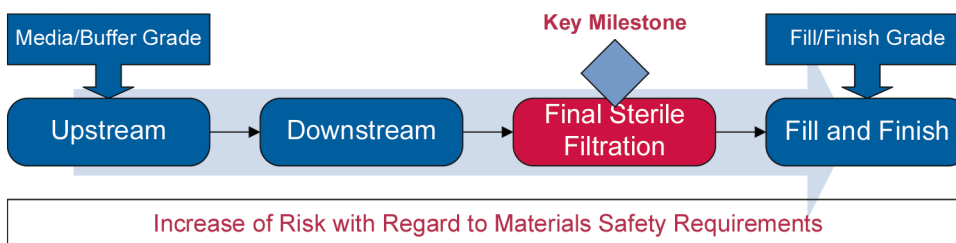


Figure 2.3 provides a high-level overview of the development stages in a typical biological manufacturing process, in relation to increased risk associated with materials safety requirements; that is, the closer the single-use component is to the fill/finish step, the less opportunity that risk mitigation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

Figure 2.3: Process Architecture with Regard to Materials Safety Risks

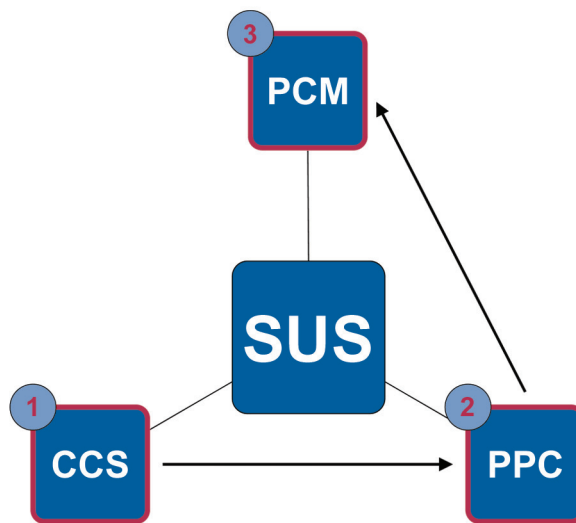


Note for Figure 2.3: For the critical stage, fill/finish application, considerations should include other quality requirements (e.g., particulates burden, integrity failures, and biocompatibility).

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

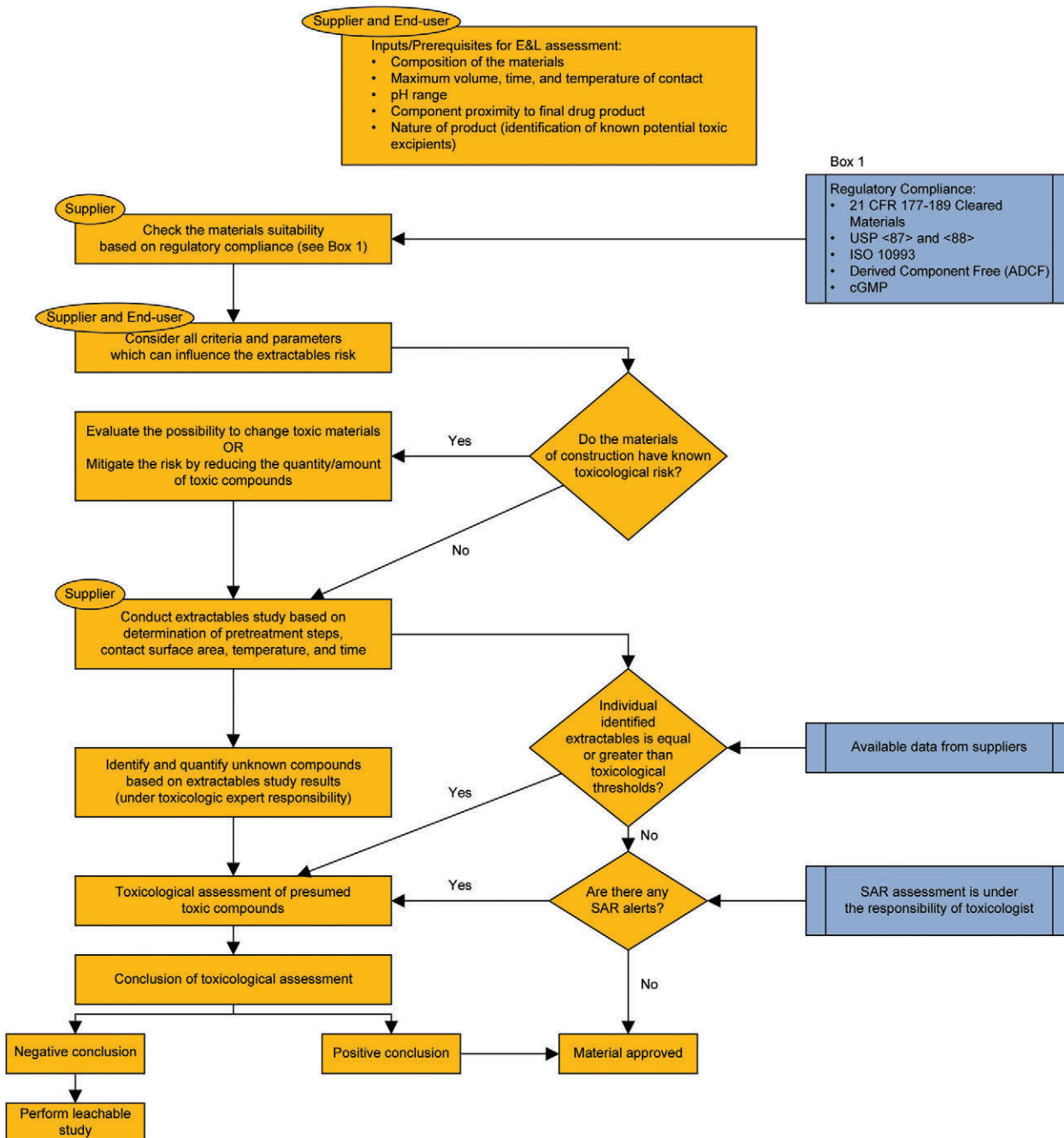


Note for Figure 2.4: Sequential numbering represents a hierarchy started from the CCS, to PPC, and to PCMs.

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

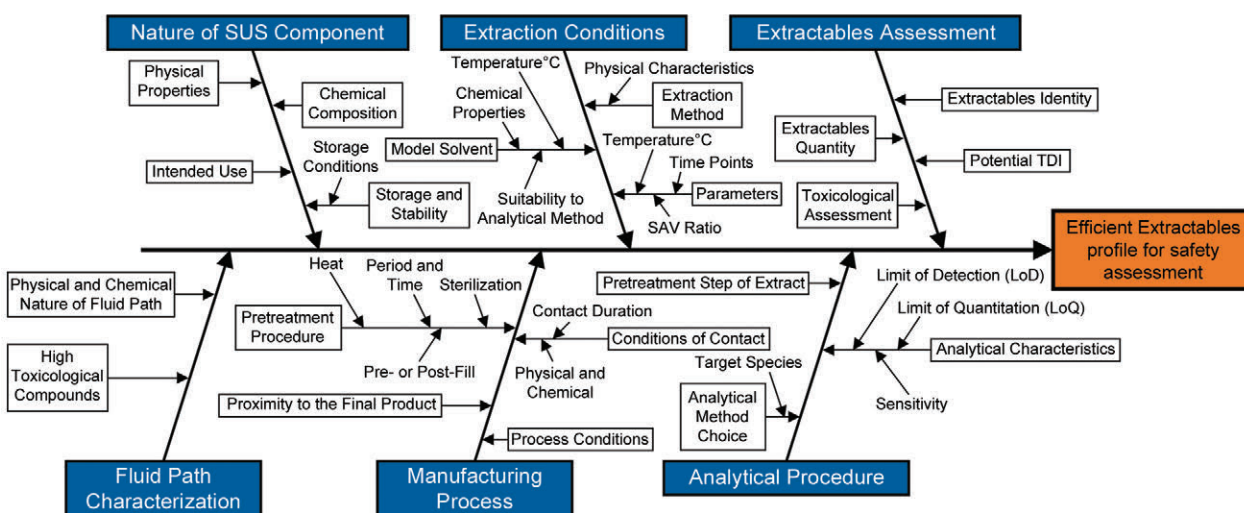
Extraction conditions are critical in determining the chemical profile and levels of individual extractables.

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

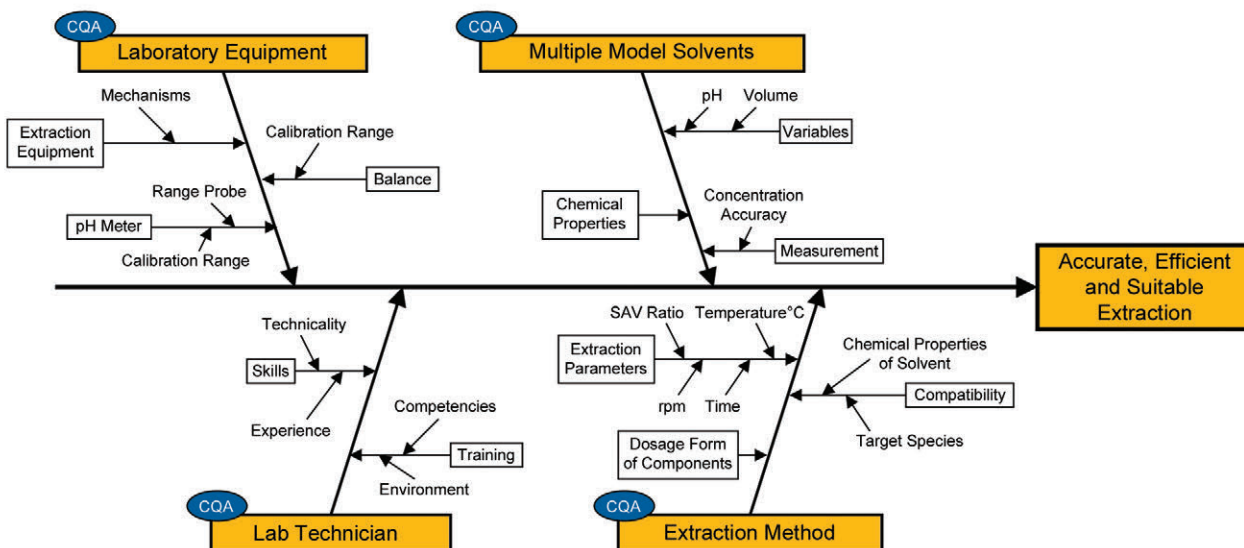
The extraction conditions (including temperature, pH, and time) should be appropriately selected, well described, and justified. Extraction media may include a drug product vehicle and organic solvents of varying polarities, extreme pH, and extreme ionic strength.

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 standardized 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

	<i>Suppliers</i>			
	Component Supplier 1	Component Supplier 2	Assembly Supplier 1	Assembly Supplier 2
<i>Components</i>				
Bags				
Fittings				
Tubing				
Connectors				
Filters				
Valves				
Ports				
Filling needles				
Pump liners				
Centrifuge liners				
Sensors				
Bottles				
Gaskets/O-rings				
Chromatography columns				
Clamps				
<i>Supplier Operations</i>				
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

	<i>Suppliers</i>			
	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).

Biocompatibility of Components

The objective of the biocompatibility study is to detect non-specific, biological reactivity of single-use components. In addition to the E&L studies, stakeholders should assess the compatibility of single-use components with the process or product fluid paths, including with:

- Living systems
- Intermediate products
- Drug substances (chemical entities and biotechnological/biological entities)
- Drug products

At an early stage of the SUS development lifecycle, suppliers should assess the purity and toxicity of the raw materials. Appropriate testing methodology, e.g., based on USP <88> [23], should be executed to characterize the biocompatibility state of both raw materials and the finished SUSs.

While taking into consideration the process flow at the end-user manufacturing facility, a biocompatibility study should also be done to assess the ability of the SUS to be in contact with a process fluid without causing any adverse effects on:

- **Cell culture:** Toxicological and performance assessments
- **Process and product fluids:** Quality and safety assessments
- **Drug substances:** Purity, toxicity, quality, and safety assessments
- **Drug products:** Impact assessment with regard to product quality and long term stability

Documentation that defines the acceptability of single-use components and assemblies include:

- Statement of animal origin
- Compliance with bioburden requirements
- Compliance with bacteriostasis/fungistasis requirements
- Compliance with cytotoxicity (USP <87> [22] or USP Class VI testing per USP <88> [23])
- Compliance with endotoxin test (USP <85> [48])

The specific criteria from the list above should be detailed in the URS.

Compliance with Functional Test Requirements

The single-use component, assembly, or system should meet functional testing requirements defined in the URS. The single-use product should be tested in a scenario with an adequate safety factor to ensure it will operate as desired under normal conditions.

Compliance with Physicochemical Test Requirements

The single-use product should meet applicable physicochemical test requirements, as detailed in USP <661> [20], when used for packaging of drug products.

Compliance with Shelf Life Requirements

Testing should be performed to confirm the stability of single-use products after a specified usage time, as specified in the URS. Stability should be evaluated through functional testing relevant to the component being tested. Shelf life testing may be executed either by accelerated testing or by real time tests; the preference should be defined in the URS. The shelf life requirements should take into consideration the final state of the equipment in use (e.g., if the equipment undergoes gamma irradiation).

Compliance with Particulates Requirements

Specifications for visible particulates should be defined and included in the release criteria for single-use components and assemblies. Testing performed to meet specifications for sub-visible particulates should be based on USP <788> [49]. Since USP <788> [49] targets injections and parenteral infusions, application to single-use components/assemblies may be varied. Therefore, specific expectations on these criteria should be detailed in the URS.

Particulates in the manufacturing environment may also affect the single-use products. The environment is a critical aspect that becomes part of the qualification of the single-use components/assemblies. Refer to Section 2.5 for supplier quality requirements regarding particulates monitoring and control.

For additional information, refer to *BPSA 2014 Particulates Guide: Recommendations for Testing, Evaluation and Control of Particulates from Single-Use Process Equipment* [50].

Integrity Testing Methods

Reviewing of testing methodology is recommended for both the supplier and end-user. Key criteria to consider when assessing integrity include:

- **Structural and mechanical integrity:** Inherent features, characteristics, and ability to maintain integrity when exposed to environmental conditions
- **Sterile and biosafety barrier:** Capacity to prevent biological ingress and egress
- **Leak detection:** Qualitative and quantitative detection per set of test methods (e.g., microbiological ingress, pressure decay)

Suppliers should perform integrity testing of single-use products; this testing should be performed at several levels. For example, structural and mechanical integrity should be tested for films (e.g., puncture, tension, torsion, abrasion) and for welds, individual connectors should be tested for strength and pressure tests, and assemblies should be tested for leaks. Typically, the assembly/system supplier should qualify the materials they have used and provide end-users with justification for their selection.

Integrity testing may be conducted in a variety of ways; it is recommended to define acceptable integrity testing protocols in the URS. While some integrity tests are performed for each single-use product manufactured, some integrity test protocols are based on a subset sample of the quantity manufactured. It is important for the end-user to verify the test protocols for the single-use products to ensure they meet the specified requirements.

Compatibility and Compliance with Sterilization

Single-use components and assemblies may need to be autoclaved or subjected to gamma irradiation for control of bioburden. The gamma irradiation process is normally done by the supplier. If autoclaving is selected as the method of sterilization, this process would be done by the end-user. The single-use components and assemblies should be designed so the components can be exposed to the autoclave conditions while retaining quality attributes needed for the application process. This Guide emphasizes gamma irradiation for sterilization of single-use products.

The single-use product should meet the required irradiation level as defined in the URS. The typical irradiation dose range applied to single-use products is 25–50 kGy (kiloGrays). Doses > 25 kGy should be used to achieve a Sterility Assurance Level (SAL) of 10^{-6} . The qualification of single-use components typically includes the criteria for meeting irradiation level > 40 kGy. Refer to American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI)/ISO 11137 [51] for additional information.

Irradiation of single-use products is commonly performed by a third-party irradiation service provider. The statutory approvals, quality agreement between supplier and irradiation service provide, and sterilization validation packages should be reviewed as part of the compliance check.

2.5 Supplier Quality and Audits

This section addresses supplier quality and audit requirements. This section is intended to be used in conjunction with Section 2.4 for selecting single-use suppliers and to establish consistent quality in SUT implementation.

The roles of the supplier and end-user are strongly linked in the SUT space. While this section is primarily targeted for use by the single-use product end-user, intermediate suppliers may also find parts of this section useful in defining the quality of components and the auditing of their respective suppliers. The process of establishing consistent quality along the entire supply chain allows for more robust final quality to the end-user and, ultimately, to patients.

This section is intended to be compatible with PDA Technical Report 66 [52] and ASTM E3051-16 [41]. These publications emphasize the concept of technical diligence as a way of fostering transparency and open communication within the supplier and end-user relationship.

2.5.1 Establishing Supplier Quality Requirements

A formal quality agreement between the end-user and supplier is an important tool to outline critical roles for each party. End-users should use the quality agreements to define, establish, and document their responsibilities and the responsibilities of the suppliers. The quality agreement should define:

- Scope of agreement and products covered
- Key quality roles and responsibilities
- Change notification and change approval
- Obligations and responsibilities for the quality units of the parties involved
- Communication expectations and points of contact
- Auditing rights (periodic and for cause audits)
- Escalation mechanism and dispute resolution process
- Access to manufacturing, testing, and other data

Ideally, such quality agreements should be independent of supply agreements or technical agreements.

2.5.1.1 Supplier Manufacturing Operations

Manufacturers of single-use products should be aligned with operations that exist at the typical end-user facility. It is advantageous to have all suppliers in the entire supply chain aligned with these operations.

Single-use product suppliers should follow clearly defined methods for controlling and tracking any component, equipment, and procedures used in the manufacturing operations. Equivalent information should be available from all suppliers in the supply chain. Each manufacturer should confirm that this information is available before using a component in the manufacturing operation.

Additional considerations for single-use manufacturing plant operations include:

- Procedures to receive and route products to the inventory location
- Establishing and tracking usability of components once in inventory
- Procedures to approve the components for:
 - Compliance with specifications
 - Certificate of conformity
 - Sterility claim, when applicable (e.g., verify that actual gamma dose matches certificate from supplier)
- Quarantine procedures to handle/discard components with rejected status
- Defining conditions for appropriate storage and handling of components (potential causes of damage should be considered, for instance maximum number of stacked units)
- Identifying components needed for specific single-use assemblies
- Defining controlled environment criteria for:
 - Areas for preparation of components prior to assembly
 - Areas for component assembly
- Establishing conditions and methods for assembly, in-process control, final packaging, and release control
- Tracking all components from their entry (receipt at the manufacturing plant) to their exit (shipment to customer site)
- Establishing periodic inspections to confirm compliance to defined best practices
- Training of qualified operators, including on cleanroom procedures to maintain the cleanliness of the assemblies during storing, unpacking, and installing

Specific procedures, with stronger controls, should be considered for components and/or suppliers for which a long-term record of reliability has not been established.

Quality and supply agreements should be set up with key sub-suppliers to ensure consistent conformity to defined specifications, long term supply, and robust change control.

2.5.1.2 Supplier Quality Assurance

Establishing raw material specifications and process design spaces can significantly reduce raw material variability, strengthen change management, and provide consistent quality attributes. Suppliers should follow a QbD approach to define their design space and manufacturing operations attributes. Proper in-process and release controls should be in place. Quality documentation should be developed, updated, stored, and archived to maintain and ensure quality assurance requirements. A global quality policy should be set up.

Single-Use Product Specification Document

Specifications, developed in collaboration by suppliers and end-users, should be formatted so that the information is presented clearly.

Additional presentation formats can be used to supplement the specification sheet, depending on the nature of the specifications (e.g., intended range of testing results, physical design requirements such as the size), for example:

- Internal drawings
- Spreadsheet of calculations

Periodic review of specifications should be performed to ensure the success of delivery and integration into the end-user facility.

Single-Use Product Codes Management

Suppliers should follow a standardized coding procedure for their components (both catalog and customized). This standardization should be consistent with supplier documentation (e.g., marketing brochure) so end-users can easily identify a component and its associated design.

An incremental system of coding is recommended and could be based on:

- Type of single-use components (e.g., MIX = for mixing system)
- Volume of containers
- Diameter of tubing
- Size of connectors
- Size and nominal pore size of filters
- Type of material of construction (e.g., plastic resin) used to manufacture the single-use component

2.5.1.3 *Supplier Capability Matrix*

The supplier capability matrix, as presented in this section, is useful in identifying supplier candidates with the capabilities to meet specified requirements. The matrix can be used as a tool for the selection of the most appropriate suppliers. Supplier capability assessment templates can be populated with the supplier specific information to compare the respective suppliers' capabilities for each type of single-use product. Two types of templates are presented:

- **Supplier Capability Matrix:** This matrix is based on the identification of the “must have” criteria. Communication with suppliers during this assessment is recommended since suppliers may be able to offer alternatives for the “must have” criteria. An example is provided in Table 2.9.
- **Weighted Supplier Capability Matrix:** This matrix is used to identify the suppliers that meet the most important requirements. It can be used for a foundation for developing the specific criteria and associated importance for the specific process. An example is provided in Table 2.10.

Table 2.9: Supplier Capability Matrix Template

		<i>Suppliers</i>					
Capability	Identify “must have” criteria	Component Supplier 1	Component Supplier 2	Assembly Supplier 1	Assembly Supplier 2	System Supplier 1	System Supplier 2
Control receipt of components							
Inspect components							
Quarantine of received parts							
Inventory control	x						
Storage of components							
Environmental classification	x						
Purchase specifications							
Design of components							
Design of assemblies							
Drawing revision control	x						
Identification of changes							
Notification of changes	x						
Change control procedures	x						
Preparation of components for manufacturing							
Transfer of components to manufacturing							
Monitor cleanroom conditions	x						
Inspection during manufacturing							
Release criteria	x						
Lot control methods	x						
Training of technical and manufacturing staff	x						
Irradiation methods	x						
Packaging methods							
Qualification of suppliers							
Monitor supplier performance							
Audit frequency of suppliers							

Table 2.10: Weighted Supplier Capability Matrix Template

		Supplier Rating			Weighted Rating		
Capability	Importance of Criteria (Low 1 – High 10)	Supplier 1	Supplier 2	Supplier 3	Supplier 1	Supplier 2	Supplier 3
Control receipt of components							
Inspect components							
Quarantine of received parts							
Inventory control	10						
Storage of components							
Environmental classification	10						
Purchase specifications							
Design of components							
Design of assemblies							
Drawing revision control	10						
Identification of changes							
Notification of changes	10						
Change control procedures	10						
Preparation of components to manufacturing							
Transfer of components to manufacturing							
Monitor cleanroom conditions	10						
Inspection during manufacturing							
Release criteria	10						
Lot control methods	10						
Training of technical and manufacturing staff	10						
Irradiation methods	10						
Packaging methods							
Qualification of suppliers							
Monitor supplier performance							
Audit frequency of suppliers							
Overall Rating							

2.5.2 Practices Applied to Meet Supplier Quality Requirements

2.5.2.1 Standard Operating Procedures

Standard Operating Procedures (SOPs) are written procedures which specify how routine activities are to be performed by trained personnel. SOPs provide detailed instruction to facilitate consistent conformance to technical and quality system requirements, and to support data quality. They may describe fundamental programmatic actions, technical actions (such as analytical processes), and processes for maintaining, calibrating, and operating equipment. SOPs should be reviewed and approved by a quality unit.

Single-use supplier manufacturing operations that should have a clearly defined SOP include:

- Manufacturing environment classification and associated cleanroom design
- Gowning and de-gowning in manufacturing areas
- Operation of manufacturing equipment
- Maintenance of manufacturing equipment
- Validation and qualification procedures
- Cleaning procedures and frequency
- Shipping, post-shipping and transportation activities
- Verification of packaging material of construction
- Investigation and sharing of reports related to recalls, non-conforming products, or unexpected conditions

2.5.2.2 *Particulates Monitoring and Control*

Since single-use components and assemblies may come into contact with drug product or process fluids, their environment during manufacture can have direct influence on the quality of the drug products. Control of the manufacturing environment for single-use products is a critical aspect that becomes part of the qualification of the supplier. Aspects that are critical to the handling of parts and the single-use product manufacturing process include:

- Manufacturing environment classification and associated cleanroom design
- Operators gowning and handling
- Closed system for fluid path surfaces
- Process steps that emit particulates (e.g., spallation)
- Process steps that remove particulates (e.g., filtration)
- Frequency and methods for particulates monitoring
- Existence of continuous improvement plan

Environmental classification recommendations for the manufacturing of single-use products are:

- For the manufacture of single-use components and assemblies: ISO 8/Grade C (in operation)
- For final assembly operations: ISO 7/Grade B (in operation)

For additional information, refer to *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities (Third Edition)* [14], which takes the following into account: ISO 14644-1 Classification of Air Cleanliness [15], the 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].

2.5.2.3 Customer Change Notification

Customer change notification procedures should be established to inform customers (end-users or intermediate suppliers) of changes to single-use products. Suppliers should communicate all changes, however small they are deemed, that directly impact the single-use product. For example, changes may be made to the polymer type, additive packaging, film or components manufacturing process, manufacturing location, and sterilization process. A change notification document should be issued to the customer to provide guidance on the changes, including the date the change will occur and opportunities for the end-user to manage the change period.

Change notification is necessary to assess the potential impact of such change on the single-use product, and consequently on process and product quality. The severity of the change should be assessed using a risk-based approach. For example, a change in polymer type would need to be assessed to determine the potential impact on polymer properties and E&L profiles.

For additional information on change management, refer to Section 4.3.

2.5.2.4 Manufacturing Certificates

Manufacturing certificates should be provided by all suppliers along the complete supply chain of single-use components, assemblies, and systems. The complexity of the certificates often depends on the stage of the supply chain prior to manufacturing. An incoming inspection of raw materials is also recommended. Certificate requirements should be included in the URS.

At delivery of single-use products, the supplier should provide all appropriate certificates (including certificates of release) and an irradiation certificate or sterility claim (when applicable). The certificate of release typically includes:

- Product description, reference, batch number, and expiration date
- Related irradiation batch number (if applicable)
- Compliance statements (refer to Section 2.4)
- Batch release testing information (such as product conformity, visual inspection, bioburden, endotoxin, particulates, leak testing, integrity testing, gamma irradiation, etc.)

For additional information regarding the contents of the certificates, refer to ISO 9001 [53] and ISO 13485 [54].

2.5.2.5 Shelf Life

Suppliers should provide expiration dates for single-use products in the post-sterilization stage. The expiration date indicates the validity period during which the supplier guarantees mechanical and functional properties, integrity, and sterility of the single-use product. For a complete single-use assembly, the expiration date should be determined by the worst-case component (the one with the shortest shelf life after sterilization).

To determine the shelf life, suppliers should take into account:

- Sterility testing
- Gas barrier properties
- Structural and mechanical integrity properties (resistance to flexion, puncture, etc.)
- Biocompatibility and physicochemical tests

- Material resistance to gamma irradiation dose
- Packaging integrity

To justify single-use product expiration dates, suppliers should provide aging study data to end-users. ASTM F1980-16 [55] addresses medical devices but may be used as a reference for accelerated aging studies applicable to single-use products.

For end-users, attention should be made to store the single-use products away from light, heat, and moisture for expiration dates to remain valid.

2.5.2.6 Database of Approved Materials

Through a partnership between suppliers and end-users, a database may be generated to list product contact components that have been tested and qualified per the requested technical specifications and quality level. As some materials have the potential to impact product quality, and consequently patient safety, this database should be maintained by the quality department. The approved status should be controlled.

2.5.3 Defining Supplier Audit Requirements

Single-use suppliers, manufacturers, and assemblers should be audited on design, manufacturing process, and supply chain management until delivery to the end-user. The frequency and duration of such audits should be included in the quality agreement.

The supplier audit should cover both manufacturing and technical aspects, with special focus on the following aspects:

- Compliance to ISO 9001 [53] certification (and other applicable standards)
- Management and control of raw materials and components
- Manufacturing process overview
- Sourcing and supply chain strategy
- Manufacturing environment monitoring (microbiological and particulates trending)
- Sterilization process (frequency, procedure, and records of dose audits for irradiation)
- Quality management systems (including quality policy and change management processes)
- SOPs
- Document controls
- Complaint management (with tracking, recording, and corrective and preventative action processes) – see Chapter 7 (Appendix 3) for details on defective products and complaint management methods
- Change management process (with specific focus on major versus minor status)
- Operator training plan and records
- Batch record tracking

The frequency of audits should be established in the quality agreement and determined based on risk of the supplier and type or criticality of the item/service. Important criteria used to define the frequency and depth of audits should include the criticality of the product being supplied and the relationship with the supplier. A frequent audit schedule is warranted for suppliers of products that are key components in the production of therapeutics. Suppliers of SUT products are often classified in this category.

The relationship with the supplier is also important in defining the audit depth and schedule. A less frequent audit schedule could be used for an established supplier that has reliably provided several products over multiple years. Alternatively, a new supplier should be audited frequently until an appropriate level of confidence is established. For example, the frequency may be once a year for new suppliers (where there is a lack of historical performance data) or for highly critical items/service. Meanwhile, the frequency may be less frequent (e.g., every two to three years) for well-known suppliers whose long-term reliability and performance have been documented.

Additional considerations for supplier audits include:

- Obtaining feedback from the end-user's manufacturing staff
- Obtaining feedback from the end-user's purchasing staff
- Environmental monitoring SOPs and reports
- Technical and manufacturing staff training SOPs
- Inventory control SOPs
- Change control SOPs
- Inspection of incoming parts SOPs
- Inspection during manufacturing SOPs
- Packaging SOPs
- Quality control SOPs
- Supplier audit SOPs
- Health and safety SOPs and records
- Job tracking file review
- Quality agreement
- Checklists for audits
- Frequency of audits
- Impact of non-compliance with quality criteria

2.6 User Requirement Specification Development

The URS is used to specify aspects of an equipment (i.e., single-use product) to ensure it is appropriate for the intended application. The URS is a document that the end-user of the product develops and writes; the document is used to convey the requirements to the supplier. It is beneficial to discuss requirements with suppliers during URS generation since ongoing technology advances may open up new options for commercially available systems.

The URS document should define the needs and acceptance criteria based on the intended use. The URS document should contain the specific criteria that need to be met while providing general guidance for non-critical aspects. This will prompt ideas from the suppliers that meet the criteria while allowing the end-user to select innovative concepts for the process.

2.6.1 *Developing the URS Document*

The foundation of the URS is based on knowledge of the drug product and process along with knowledge of the capabilities of the single-use product. Specific requirements should describe:

- Quality requirements for single-use products (as discussed in Section 2.4)
- Supplier quality and audit requirements (as discussed in Section 2.5)
- End-user product and process requirements

Quality Requirements for Single-Use Products

Examples of quality requirements for single-use products to include in the URS are:

- Assembly shall be designed based on the sketch provided with this URS.
- Wetted components in the assembly shall have a complete extractables profile (as detailed in Section 2.2).
- Wetted components in the assembly shall be biocompatible.
- Wetted components in the assembly shall be compatible with exposure to temperature, pH, and pressure conditions during use.
- All components in the assembly shall comply with the particulates requirements.
- Non-wetted components in the assembly shall be compatible with exposure to temperature and pressure conditions during use.
- All components in the assembly shall meet supplier qualification criteria.
- Product certificates shall be provided with the product. These certificates shall confirm that URS requirements are met.

Supplier Audit and Quality Requirements

Examples of supplier quality and audit requirements to include in the URS are:

- Manufacturing area shall be classified and controlled to specified classification area.
- Product inventory shall be tracked by the manufacturer and its suppliers.

- Periodic auditing of suppliers shall be performed, with the frequency based on risk. Audits shall be conducted by the Quality Assurance and Purchasing personnel.
- The process for assembly, packaging, and irradiation (if needed) shall be defined, consistent, and documented.
- Training of personnel shall be documented and include information on training level/method, frequency, and certification (as detailed in Section 3.6).
- A documented change management process shall be followed to handle changes prompted by the end-user or supplier, or changes internal to the supplier.

End-User Product and Process Requirements

Sharing process information and operational constraints are key requirements that should be included in the URS for developing a single-use product that is robust while keeping it focused on the end-user's needs.

Note: Since process specific details may contain sensitive information, the information provided to the supplier can be a partial disclosure, which may suffice in many cases. In other cases, it may be helpful to establish full disclosure (with a signed non-disclosure agreement or other control document) to share additional process details for the design of the single-use assembly.

Tables 2.11, 2.12, and 2.13 provide examples of key criteria in the design of common single-use assemblies. Some assemblies may contain multiple quantities of the components listed; in these situations, multiple tables can be combined and used to define the process/application characteristics of the assembly.

Table 2.11: Example Product/Process Specific Requirements for Bioprocess Container Assembly

Requirements for Bioprocess Container Assembly
Size
Fill rate (with fluid viscosity)
Drain rate (with fluid viscosity)
Vent(s)
Dimensional constraints (if any)
Connection type
Mixing
Sparging
Sensors
Storage time, fluid type and conditions (if used for storage)

Table 2.12: Example Product/Process Specific Requirements for Filter Assembly

Requirements for Filter Assembly
Separation needed or filter pore size
Capacity (volume/time) with fluid characteristics
Pressure profile
Connection type
Frame/support criteria
Pump characteristics (if pump tubing is within assembly)

Table 2.13: Example Product/Process Specific Requirements for Transfer Assembly

Requirements for Transfer Assembly
Flow rate with fluid viscosity
Pressure profile
Connection type
Pump characteristics (if pump tubing is within assembly)

While single-use assemblies can be developed by the supplier from the requirements described above, it is strongly recommended that the end-user includes a sketch of the expected assembly as part of the URS document.

2.6.2 Additional Considerations for Single-Use Components, Assemblies, and Systems

Single-Use Components Versus Single-Use Assemblies

The URS document for single-use components usually contains a subset of the requirements listed for a single-use assembly. The differences are related to the methods of connection of components and for containment of fluids. The same steps would be followed for developing the URS for single-use components as for the single-use assemblies.

Single-Use Assemblies Versus SUSs

Since SUSs integrate single-use assemblies with multiple-use equipment, the URS documents for SUSs are typically more complex than for single-use assemblies. The SUS URS builds on the URS requirements for assemblies and includes additional requirements for mechanical, electrical, and software/controls that add significantly to the complexity of the URS.

For additional information on the development of the URS for the multiple-use portion of SUSs, refer to the following:

- *ISPE Good Practice Guide: Good Engineering Practice* [56]
- *ISPE Baseline® Guide: Commissioning and Qualification* [47]
- *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [36]
- *ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment* [126]

2.7 Facility Design

Single-use products have been incorporated into facility design since the 1980s; however, only recently have companies been altering the adjacency of rooms specifically to adapt to SUSs. This section intends to explain the affected parts of the facility and current trends so that the facility designer can successfully design an efficient and cost-effective next generation facility.

Note: This section is intended to discuss where single-use products can be part of a facility design. Refer to National Institutes of Health (NIH) *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* [57] for biosafety requirements, such as those described for Biosafety Level designated facilities.

2.7.1 Therapeutic Manufacturing Applications

SUT has become more widely used in pharmaceutical and biopharmaceutical applications. The areas where SUT has not been widely adopted are large volume applications or applications where harsh and aggressive chemicals are necessary. Below is a list of key therapeutic applications where single-use products are currently being used:

- Research and development (R&D)
- Cell therapy and gene therapy
- Large-scale protein manufacture (including vaccines and antibody drug conjugates)

Facility designs for the above applications have subtly changed due to the introduction of SUT. Across all of these applications, the following general trends apply:

- Wash/autoclave areas and mechanical space for utilities have been scaled back in size
- Conversely, warehousing space, corridors, lay down areas and waste processing areas have increased in size

Other than the above, the size and adjacency of areas in R&D and fill/finish facilities have not changed greatly from previous designs due to SUT.

For cell therapy and gene therapy, due to the nature of the application, large-scale manufacturing facilities did not exist before the advent of SUT. Currently, these facilities consist of small, flexible, and modular units. However, this application is rapidly developing and due to its current heavy reliance on manual operations, it is likely that automated processing will impact facility designs and the modular facilities may get smaller as a result. In addition, these facilities are being developed specifically with SUT in mind.

Large-scale protein manufacturing facilities have been impacted the most by SUT. Specifically, the adjacency of areas and space available in these facilities are impacted by SUT implementation and the corresponding reduction in traditional stainless steel systems. When SUT is adopted into a facility, there is often a need to make more space available for the movement and storage of bioprocess bag containers (also referred to as totes), both in use and out of use. Adjacency of areas is important if excessive movement and long tubing lengths are to be avoided.

2.7.1.1 Ballroom Versus Dance Floor Concept for Facility Design

The ballroom concept is “a large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems” [58]. These facilities consist of large open spaces where skids could be wheeled in and set up to perform a process. This allowed for the possibility that the process equipment could be changed out, creating a flexible, inexpensive facility consisting of contained systems. However, users of operational facilities have experienced drawbacks with the ballroom design, such as:

- Process equipment is not truly mobile since connections to utilities and drains are often required

- Tubing management is not addressed, causing trip hazards and mix-ups
- Volumes for production continue to increase, creating a need to make systems static in location
- Large lay down spaces are needed for storage
- There is minimal standardization in SUT, leading to minimal opportunities for interchangeability

To address the above concerns, the dance floor concept was created where the equipment is clustered together to create a more compact facility without trip hazards. This approach entails more work to be carried out in concept, basic, and detailed design. Considerations include:

- **Concept Design:** The orientation, clustering, and spacing of the equipment needs to be set in order to provide the compact facility footprint.
- **Basic Design:** The ergonomic aspects need to be considered, such as height of platforms, high level tubing routes, etc. This can be subcontracted to equipment integrators with the added benefit of planning the utilities/electrical/data routing.
- **Detailed Design:** The tubing routing and pipework routing can be 3-D modeled in detail, providing assurance to the end-user that GMP and operational excellence aspects have been considered.

Figure 2.8 shows an example of a dance floor facility.

Figure 2.8: Example of a Dance Floor Facility

Used with permission from Janssen Sciences Ireland UC, <https://www.janssen.com/ireland/>.



For additional information, refer to Wolton and Rayner, 2014 [58].

2.7.1.2 Factory-in-a-Box Concept

Aligned with the flexibility of SUT, newer methods of building facilities and process equipment are available, where a facility is built with standardized modules and then assembled at the end-user site. The development of these facilities is based on a solution where the design starts from the actual production process and then a facility is created around it. This can optimize production and minimize the size of the facility. It is a factory-in-a-box concept with a complete turnkey approach where the manufacturing process is optimized including the validation of the facility and the training of the manufacturing staff. Figure 2.9 shows an artist rendering of a completed factory-in-a-box facility and Figure 2.10 shows an example of modules being transported to a site.

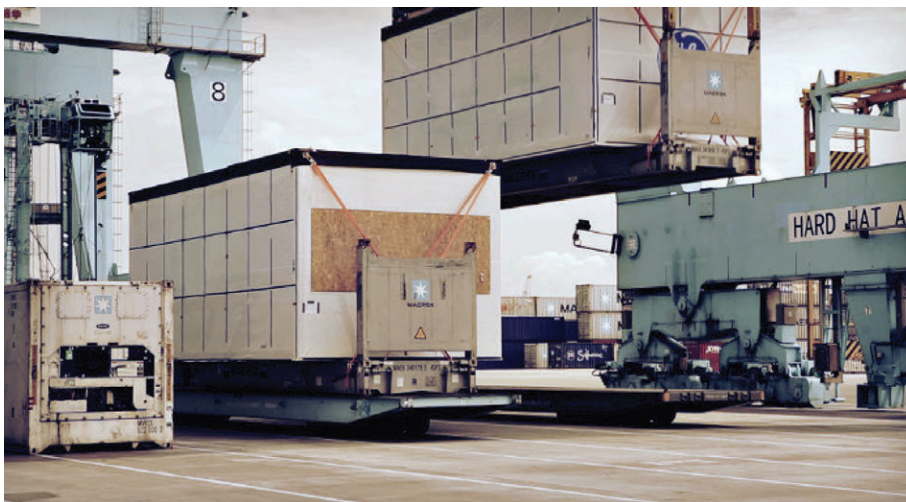
Figure 2.9: Artist Rendering of a Completed Facility

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Figure 2.10: Example of Modules Transported to Site

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The factory-in-a-box option can be considered when planning a new facility or a facility expansion. The modules and the associated processing equipment are built off-site while the foundation of the new facility or the modifications of the existing facility is completed concurrently. Figure 2.11 shows an example of a site with the module installation in progress and Figure 2.12 shows an example after the modules have been installed.

Figure 2.11: Example of Site with Modules Being Installed

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Figure 2.12: Example of Site with Modules Installed

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These parallel activities are to be coordinated so that the once the modules and the processing equipment arrive, they can be installed, validated and be ready for operation. Figure 2.13 shows an example of a facility with the equipment in place.

Figure 2.13: Example of Facility with Equipment in Place

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Figure 2.14 shows an example of a facility with single-use bioreactors and Figure 2.15 shows an example of single-use bioreactors in operation.

Figure 2.14: Example of Facility with Single-Use Bioreactors

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Figure 2.15: Example of Single-Use Bioreactors in Operation

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Complete manufacturing facilities have been placed into operation within eighteen months using this method. This timeline compares favorably when considering the three to five years needed to design and bring a facility to production in the traditional way. The process requires detailed coordination of activities (including on-site preparations) and a disciplined approach to building the modules and associated process units. The process supports placing new production facilities in remote locations with efficiency.

2.7.1.3 Box-Within-a-Box Concept

The box-within-a-box concept is where an empty facility is constructed well in advance of its intended use or where a previously constructed building is used as a starting point. A factory-in-a-box or custom-built facility can then be constructed inside this outer envelope, thus significantly reducing the project timelines.

2.7.2 Bioprocess Area Applications

2.7.2.1 Upstream Operations

The impact of SUT upon facility design for upstream operations depends on the required scale.

Inoculum Preparation

- **Current State**

The inoculum preparation area was an early adopter of SUT. Vials, shake flasks, and roller bottles have been in use for many years. The advent of single-use bioreactors changed the area slightly and introduced more bag handling; however, it did not change the footprint greatly.

- **Future State**

There is a trend to move single-use bioreactor operations from the inoculum preparation area and place them in the main bioreactor area; this has the impact of reducing the footprint of the higher classification area. As single-use products that provide full containment of inoculum operations become available, a separate higher level classification area for inoculum preparation may not be needed; energy consumption is then reduced.

Bioreactors

- **Current State**

Single-use bioreactors up to the 3,000 L scale are currently available. In addition, even in facilities that are categorized as stainless steel, there are a significant number of single-use applications, including feed/media hold, sampling, antifoam addition, transfer lines, etc.

- **Future State**

Processes are being developed using continuous/semi-continuous equipment. This technology results in a reduction in vessel/bag size, enabling a greater use of single-use equipment while significantly increasing the facility throughput. Due to its very nature, connected equipment should be positioned next to each other, meaning that access is likely to be from the front of the skids (similar to the fill/finish area); this results in more compact facilities.

Figure 2.16 shows an example of an upstream facility in which a 2,000 L single-use bioreactor was raised by approximately 30 cm to allow access under the platform and ergonomic access to the air filters on top of the platform. This setup has not affected the ergonomics of installing the bag.

Figure 2.16: Example of an Upstream Facility with Single-Use Bioreactor

Used with permission from Janssen Sciences Ireland UC, <https://www.janssen.com/ireland/>.



2.7.2.2 Downstream Operations

As with upstream operations, the impact of SUT upon facility design for downstream operations depends on the required production capacity and throughput.

Purification

- **Current State**

As with upstream processing, downstream operations tend to be dictated by the amount of product required in any one or more markets. For example, as a rule of thumb if column sizes are above 80 cm in diameter, then it is likely that stainless steel buffer tanks will be required. This is a complex decision that should take into account operational costs, current technology, etc.

- **Future State**

With the advent of continuous chromatography and in-line dilution, the application of SUT in downstream operations is rapidly changing. Buffer volumes may be reduced to a level where SUT becomes more applicable and size requirements for product hold tanks/bags also decrease. Although a reasonable proportion of new equipment remains stainless steel, most facilities will likely be hybrid facilities but with a greater percentage of single-use products; area adjacency discussions become key to the ergonomic success of the designs. Also, as with upstream operations, the downstream operations may begin to resemble the fill/finish area.

Note: The term hybrid used above refers to a facility with both single-use and stainless steel systems that work together. In reality, there are very few truly single-use facilities and those facilities tend to be limited to very small volumes of approximately 10 L.

Bulk Formulation and Filling

- **Current State**

The bulk formulation and fill areas have not changed greatly in room size or classification due to SUT adoption. In the bulk formulation area, the adoption of single-use containers is relatively limited; this may be due to concerns with product adulteration with respect to sterile bulk preparation. The space requirement is primarily dictated by the volume required to process the final formulated bulk; therefore, the space requirements within the room are unlikely to change significantly. However, elimination of CIP and SIP requirements for vessels has a clear benefit in the removal of CIP skids and ancillary equipment, as well as a reduction in pure steam generation capacity requirements. At present, most companies consider bulk fill as high risk, requiring a dedicated room or workspace with higher classifications.

- **Future State**

With the advent of single-use freeze thaw/filling systems, future considerations may be made to fill bulk drug within the purification areas; this is not yet a common practice due to concerns with issues such as viral segregation. In the future, end-users may begin to adopt a less conservative approach as confidence in contained processing grows and lower classifications become more commonplace.

Note: Where facilities have product related requirements (e.g., particulate air) or handle materials hazardous to human health, all applicable standards should be applied.

Final Fill and Finish

- **Current State**

The fill/finish area has utilized single-use components (e.g., needles and associated tubing) in the product pathway on filling equipment for many years.

- **Future State**

- Improvements in the availability and range of single-use components and the increasing use of the new generation peristaltic pump systems have accelerated the adoption of SUT. In newer facilities, it is common practice to interchange stainless steel intermediate tanks with single-use bags on filling machines, through the use of load cell hanger frames.
- The parts preparation area (washing and sterilization) for fill and finish may be impacted by SUT in terms of the scale and requirements. Based on current technologies, certain parts (such as stopper contact parts) still require treatment, but there is an opportunity to look to new and cheaper materials (including single-use) and filling equipment arrangements that could reduce the scale, or even the need, for large washing equipment.

2.7.2.3 Process Support Operations

As described earlier, the size of wash facilities and utilities are impacted in all therapeutic applications. If the facility is likely to operate near or at its operational capacity, special attention is needed; if stainless steel systems are required in the future, the utilities could be significantly undersized. It is important to note that some facilities have been able to remove the wash area and autoclave from their process with the use of CIP and single-use assemblies; this may become a future trend.

2.7.3 Key Considerations, Challenges, and Potential Advantages

Volumetric Process Scale

In bioprocessing areas where the required vessel size is greater than 2,000 L, the following factors should be considered:

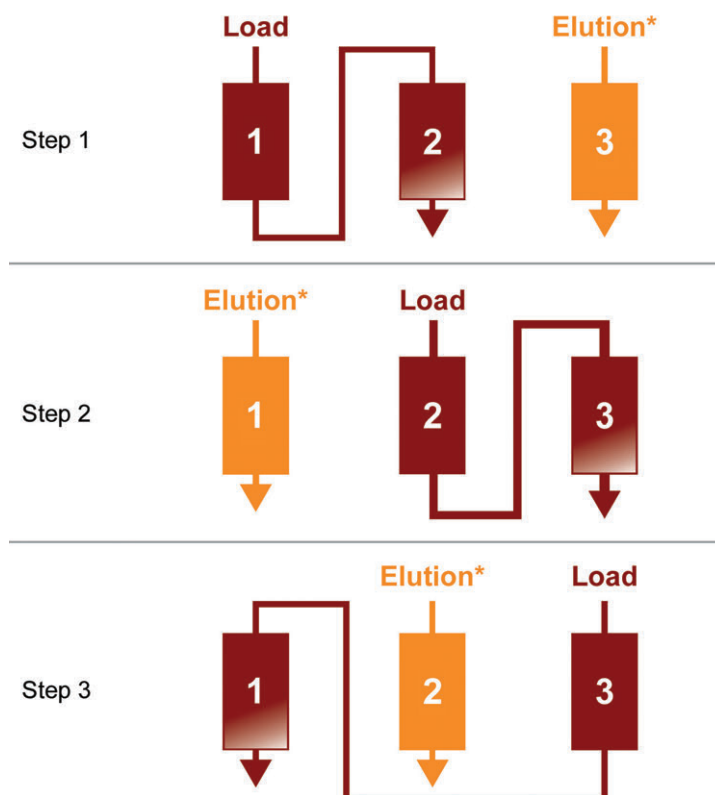
- Physical assembly and handling of the bag
- Tubing size restrictions on fluid flow

There is a threshold where stainless steel systems become more cost-effective than SUSs, in terms of price per gram. This threshold may shift in the future with the advent of continuous chromatography, in-line conditioning, and concentrated buffers.

Continuous chromatography allows for a compact layout of equipment to facilitate liquid transfer between columns. This compact layout minimizes holdup volumes and replaces residence time for the product. Figure 2.17 shows a typical schematic of continuous chromatography.

Figure 2.17: Typical Schematic for Continuous Chromatography

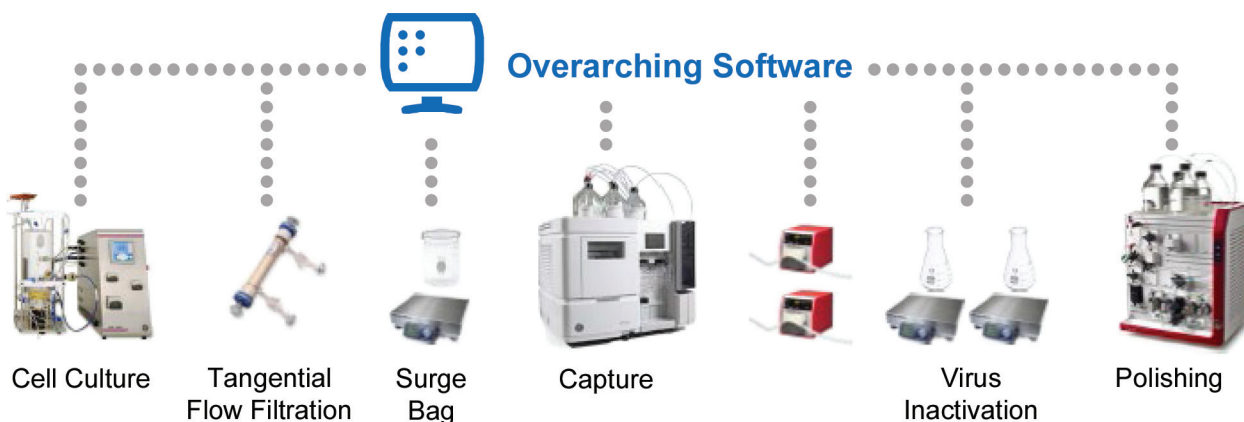
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Continuous processing also impacts the communication between unit operations as interactions between the equipment need to be aligned and coordinated. Unification of the control system and its integration into the facility becomes important. Figure 2.18 outlines an example of this concept where multiple unit operations are linked through a common software/control platform.

Figure 2.18: Example of Multiple Unit Operations Linked through a Common Software/Control Platform

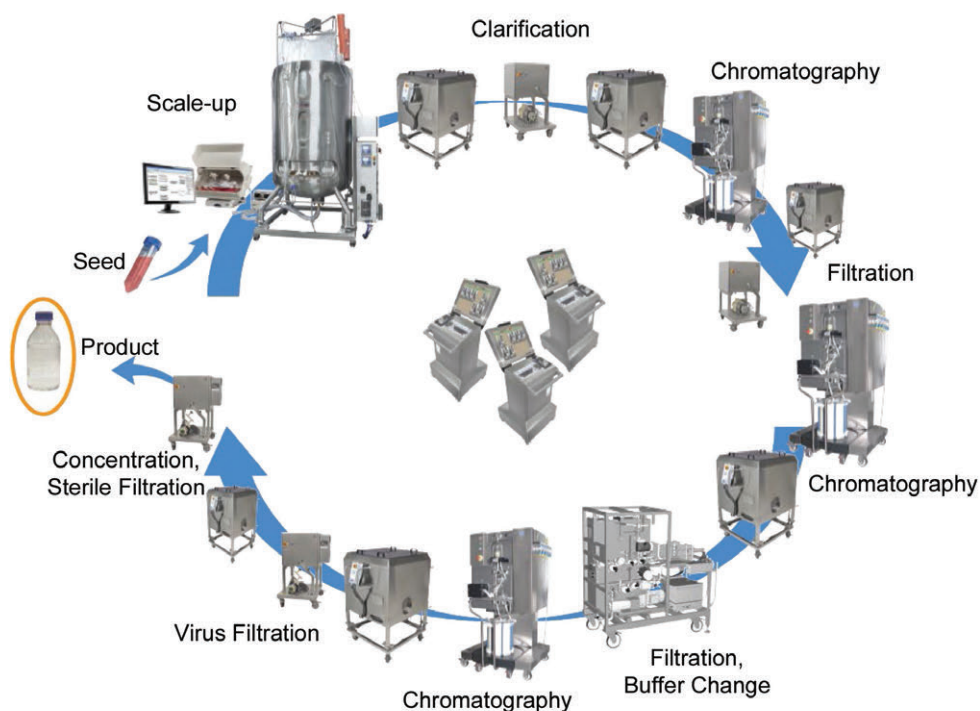
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Continuous processing tends to reduce the need for large pool vessels. Single-use mixers can be used for collecting, combining, and conditioning fluids. Single-use mixers, typically smaller than the pool vessels, provide a similar function with the advantage of smaller space and streamlined operations. Single-use mixers can also be used to prepare media and buffers. A complete biopharmaceutical production process is shown in Figure 2.19. The flexibility of the equipment and integration of the software streamlines operations within a facility, resulting in a compact footprint. Integration of single-use equipment, conventional stainless steel equipment, and a common control/software platform leads to facilities that are more flexible and able to handle multiple products.

Figure 2.19: Example of Integrated Production Process for Biological Derived Therapeutics Applying SUT

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Recent Drivers for Software Integration and Clustering

Continuous processes have the impact of increasing the need for integration/software integrators, as all the equipment needs to work in harmony.

Clustering of equipment into small groups (as shown in the cover photograph) allows for:

- Controlling and monitoring of isolated pressure sensors, pumps, and balances
- Enabling of defined tubing routing between systems
- Reduction of the number of utility drops

Both the clustering and the software integration can be carried out at an off-site integrator. This has the added benefit of a single site for the FAT.

Using Multiple Floors

In a stainless steel based facility, it is common practice to have the media and buffer preparation area on the floor above the processing area. In an SUT-based facility, this practice should be approached with caution. The full liquid height (the length of tubing/pipe and the height of the bioprocess container/preparation vessel) should be taken into account with regard to pressure. For example, a length of 10 m would result in a head pressure of 0.981 bar. If the tubing sets need to be uprated to handle higher pressures, then the cost may increase in addition to introducing an increased risk to the process. Many existing production facilities have high interstitial spaces, and these should also be taken into account.

R&D, Preclinical, Clinical, and Commercial Phases

The phase of a product is important from a facility design perspective. The early product phases tend to require flexible areas that can be readily reconfigured. As the product progresses into clinical and commercial scale, the facilities gradually become more fixed, especially when stainless steel is required. From a facility design perspective, R&D and preclinical activities tend to adopt a lab style environment while clinical facility design adopts more of a ballroom style approach where skids exist as islands either around the outside of the room or in the center. Market supply facilities are commonly a hybrid of stainless steel systems and SUSs or moving towards a dance floor design, where the single-use equipment is static, and the tubing is routed to reduce operator errors and improve aesthetics.

For clinical operations, there is a trend to adopt the strategy of scaling-out processes, instead of scaling-up. This entails keeping the same batch size between clinical and commercial operations which accelerates and simplifies transfers. In this case, clinical operations resemble commercial settings instead of laboratory settings.

GMP Flows

There are two concepts of GMP flow used in hybrid Biosafety Level 1 (BSL-1)² facilities:

- **Two Corridor Concept:** Where there are separate supply and return corridors. Operators enter through one set of doors (via a clean corridor) and leave through another set of doors into a different dirty corridor.
- **One Corridor Concept:** Where operators either:
 - Enter and leave the production area through the same set of doors, or
 - Enter through one airlock and leave through a different airlock, but to the same corridor

² BSL-1 is the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans, but may infect the young, the aged, or immunosuppressed individuals [18, 60].

Selection of the facility GMP flow will depend on performing a thorough risk assessment that takes into consideration the product type (sterile, low bioburden), level of closure, product cross-contamination risks, environmental contamination risks, and other controls. The results of the risk assessment should guide the selection of the appropriate GMP flow concept to be applied for the facility.

Note: It is important to account for the significant amounts of waste that SUT-based facilities create; how this waste is removed from the production floor should be given due consideration.

Ergonomics and Tubing Management

Ergonomics and tubing management are major considerations as more single-use assemblies are being adopted by commercial manufacturing facilities. The dance floor concept for facility design allows for tubing lengths to be minimized. Tubing routing should be factored into facility designs due to its impact on floors/walkways (minimizing trip hazards), ergonomic access, and room aesthetics.

The maximum tube length is another factor to consider since pumping capacity may limit the distance. In addition, some products are light sensitive, and tubing management should include protection of the tubes from light if it is relevant to the process.

Process Connectivity, Closure, and Containment

SUT can strongly influence environmental room classifications and containment design as it relates to open equipment and connection design. General considerations include:

- With the growing understanding and implementation of closed single-use bioprocessing in cell culture, the biopharmaceutical industry continues to challenge some of the historical guidance prescribed for environmental particulate requirements by leveraging single-use containment and aseptic connection advantages to reduce gowning and particulate control.
- SUS applications are growing in the manufacturing of vaccines and in more hazardous combination products (such as antibody drug conjugates that often incorporate cytotoxic agents). The experience gained using SUT in cell culture should be reevaluated to incorporate the biosafety and containment needs associated with personnel and public safety. Overlaying BSL-2³ and BSL-3⁴ on top of GMP guidelines creates complex conflicts in pressurization and airlock sequences, especially when the hazardous materials are stored and processed in single-use tubing and bioprocess container technology. Care should be taken regarding the risks associated with bag and tubing connection breaches; safety is paramount.
- With the above in mind, eliminating the movement of non-hazardous raw materials into the biosafety, contained, or high particulate controlled environment is highly advantageous. In addition to reducing wipe down requirements at classification transition points, the moment that the raw materials enter the contained space, operators are obligated to consider these items as contaminated and/or biohazardous. This then requires decontamination via autoclave and/or chemical or heat inactivation. While a necessity, decontamination of any kind requires energy, time, and money and can often become a facility bottleneck and point of failure and delay. The adjacencies of addition vessels for media and buffer raw materials that serve as inputs to common bioprocess unit operations can be situated above, below, or next to the unit operation outside the containment barrier, given that tubing connections will be passed through transfer ports or valves into the contained environment so that potential exposure at the connections is within an environment appropriate for the hazard.
- Not all SUSs are closed from the start. For example, many single-use harvest filtration technologies for larger scale operations are cartridge based and need to be unwrapped, assembled, and closed in a particulate

³ BSL-2 is appropriate for handling moderate-risk agents that cause human disease of varying severity by ingestion or through percutaneous or mucous membrane exposure [18, 60].

⁴ BSL-3 is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious and potentially lethal infections and that are indigenous or exotic in origin [18, 60].

controlled environment prior to being connected in-line with the process. If the facility design is striving to fully leverage closed system processing in a lower classification environment, the design should accommodate assembly of open equipment in a low bioburden staging area before being moved to the production floor. Hybrid connections between stainless steel systems and SUSs continue to have a similar requirement, requiring some level of low bioburden control at the point of the functionally closed connections.

- Non-aseptic connections and potential for leaks should be considered and preparations made for comprehensive SOPs, personnel safety, secondary liquid containment, and hazardous waste decontamination on-site or off-site.

2.7.4 Storage and Supply

Sufficient storage space should be provided in the warehouse and in the staging areas of the production floor, to account for incoming single-use components, packaging/cardboard waste, and used single-use components. Considerations should be made for a layout that facilitates the flow of waste products. Special entry/exit points may be needed for a smooth transition out of the facility. Pickup frequency by the disposal company is an important factor that defines the storage space and layout. Refer to Section 2.8 for additional information regarding waste management.

Standardization can result in a reduction in the space requirements for the on-site warehouse. Currently, significant contingency stocks are required due to the long lead times of single-use assemblies. If these assemblies are readily available off the shelf, the inventory can be significantly reduced.

2.7.5 Safety Considerations

SUSs impose a special set of safety concerns due to inherent features of SUT:

- The need to install and dismantle systems brings the operator closer to the system, increasing the need for risk mitigations associated with spills and ruptures
- The possibility to move systems may introduce transportation activity, increasing the need for risk mitigations associated with physical effort and variations in the location of SUSs

Facility design for SUSs should include a health and safety risk assessment as part of the design work. The health and safety plan should consider, and may not be limited to, the following factors:

Safety

- Pressure rating of connectors used between single-use components and stainless steel parts
- Bioprocess bags and single-use tubing at eye level
- Flammables
- Caustic or other hazardous materials, spills
- Potential risk of leakage or rupture
- Tubing on floor, tripping hazards
- Cuts to frozen bioprocess bags, resultant spills
- Equipment malfunctions
- Clamps, fingers

- Stability of mobile stairs
- Loose items in the way, tripping, falling
- Protection rails for glass surfaces (transportation protection)
- Bag container smooth surfaces, rounded corners, no crevices
- Mobile containers over feet, hands squeezed through doorways
- Mobile containers and consumables in designated areas, escape pathways kept free

Health

- Ergonomics for installation, handling and removing containers
- Ergonomics for handling solid waste
- Mobile bag containers at reasonable size and weight
- Room for stacking or maneuvering bag containers in walkways
- Aerosol formation when disconnecting systems
- Odor waste handling
- Provisions for handling spills

For additional information on facility design, refer to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [127].

2.8 Waste Management

This section addresses methods for the handling of single-use products after use. It includes general considerations for waste management methods, which are dependent upon the components used and the nature of the usage.

Generally, biopharmaceutical manufacturing facilities handle soiled components (i.e., contaminated with product solutions) as either biohazardous waste or waste for landfill. In addition, components which contain highly potent compounds require additional control and handling procedures. The handling of this material, which may require special treatment and disposal by authorized waste handlers, may have cost implications.

2.8.1 Decontamination

Decontamination of single-use products refers to the process of rendering it safe for disposal by removing agents that should not be present (e.g., bacterial, virological, chemical).

If required, decontamination can be achieved through high temperature or chemical treatment. These treatments typically include:

- **Autoclave Sterilization:** Moist heat sterilization uses steam heated to 121°C and injected into a chamber.
- **Incineration:** Waste material is burned, and the resultant energy released is typically used to generate usable heat or power. High temperatures during incineration can destroy many pathogens and toxic materials hence incinerators are often used in the disposal of medical waste.

- **Boiling and Maceration:** In relation to the single-use products, maceration means cutting up into small pieces for disposal, reducing the waste volume into the landfill.
- **Chemical Treatment:** Includes washing with sodium hydroxide, bleach, chlorine dioxide, etc.

Combinations of the above treatments may be used. Considerations can be made for whether the decontamination is performed on-site or off-site. Depending on the amount of biohazardous waste generated and the availability of medical waste companies in the region, it may be more cost-effective to utilize off-site decontamination.

Note: Inactivation usually refers to the process of destroying an agent's ability to grow or to be chemically reactive. This term is generally applied to a product or process, rather than to equipment or the environment. For the purposes of this Guide, which relates mainly to equipment, the term decontamination is used.

2.8.2 Disposal

Waste disposal methods include:

- Reduction
- Re-use
- Recycling
- Landfill
- Incineration
- Waste to energy

The primary disposal methods suitable for single-use products are landfill and incineration. Additionally, the packaging within which the single-use products are supplied may be suitable for recycling.

Facilities designed for full utilization of single-use products should consider where their materials go following use and should follow municipal regulations for disposal.

Reduction

To reduce or minimize the amount of waste in the single-use operation, considerations should first be made to minimize the amount used in the process. Review of existing designs may be performed with suppliers to identify reduction and standardization opportunities.

Examples include:

- Minimizing tubing length
- Delivery of multiple units of a single-use product in a combined package
- Increasing the amount of usage within a campaign

Re-Use

While this option can be considered, there are difficulties in implementation (e.g., potential increase in contamination risk) that negate the ease of use benefits of applying SUT. A risk analysis should be performed if this option is considered.

Recycling

The majority of single-use waste is produced from filters and bags. These components are made of several different materials which are difficult to separate and therefore are not easily recycled. Tubing and other assemblies (e.g., systems that have a combination of plastic and metal components) can be separated at the end-user site; these materials could be collected for recycling. While separation for plastic products is not typically a function performed at a pharmaceutical manufacturing facility, the cost of disposal associated with increased volume may make the separation option a cost-effective activity. Third party disposal/recycling companies offer off-site decontamination and recycling programs for select regions.

Landfill

Non-hazardous and decontaminated waste materials may be disposed of in landfills. Landfills are often a cost-effective option for disposal of plastic waste; however, adverse environmental impacts may be observed with landfills (e.g., introduction of contamination risk to ground water sources). It is environmentally beneficial to pursue other methods of waste disposal or to promote reduction of the amount of waste produced.

Note: End-users of single-use products should evaluate the requirements for decontamination of single-use products prior to disposal in landfill.

Incineration

Incineration refers to burning the waste material; the resultant energy released can be used to generate usable heat or power. Incineration may aid in reducing the amount of waste to be disposed of and is commonly used for single-use products. If the biological agent contaminating the material is hazardous and cannot leave the site in its active form, then incineration may be the most cost-effective option.

Waste to Energy Plants

Single-use components have a high calorific value (i.e., energy content) and considerations may be made for disposal in waste to energy plants. This option offers the advantage of a reduced carbon footprint, compared to disposal in the landfills. During site selection, considerations can be made for the distance from the plant to the nearest waste to energy plant in order to reduce the carbon footprint involved with waste transport.

For additional information regarding disposal of single-use products, refer to "Guide to Disposal of Single-Use Bioprocess Systems," *BioProcess International*, November 2007 [59] and ISPE Knowledge Brief: Environmental and Financial Benefits of Single-Use Technology [128].

3 Implementation and Use

3.1 Technology Transfer

Single-use products may be integrated into an existing facility, creating a hybrid system of stainless steel and single-use components, or implemented as an end-to-end solution. While it is possible to create a complete single-use manufacturing train, the majority of SUT implementations are hybrid systems which leverage existing infrastructure. Implementation may be as simple as integrating some fluid processing technology, such as bioprocess bags and encapsulated filters, or may extend to major unit operations including bioreactors and chromatography systems. The availability of single-use solutions, that can address a wide variety of process needs, continues to increase as more suppliers enter the market and technology matures. The technology transfer process for SUSs has commonalities with traditional stainless steel systems as well as unique requirements. Implementation of a bioprocess bag, unit operation, or end-to-end solution requires the same considerations:

- Assessment, selection and design of single-use products
- Supplier risk assessment and sourcing
- Planning and implementation
- Scale-up considerations
- Facility constraints

Assessments should be performed in several areas including organizational drivers and goals, the process, available single-use products, supplier capabilities/availabilities/sourcing, the facility, future scale-up requirements, and regulatory compliance.

Assessment of the process and single-use product should be made with consideration for the overall goal to be achieved by implementation. Goals include, but are not limited to:

- Expanding capacity, scale-out or scale-up strategies
- Eliminating bottlenecks or process fit
- Replacement of a unit operation or obsolete equipment
- Reduction or elimination of cleaning and sterilization
- Reducing unit operation, lot-to-lot, or campaign turnaround time
- Reducing cost
- Improving process assurance, e.g., use of completely closed sampling and fluid handling solutions

Organizational goals and process requirements should be used to develop robust user requirements to evaluate current single-use products to implement in a new or existing facility. Assessment should include consideration of the following factors:

- Material compatibility
- Equipment design and configuration

- Facility configuration and capabilities
- Process requirements (particularly instrumentation and controls)
- Regulatory requirements
- Scale-up
- Risk management
- Supplier capabilities and regional support

For further information, refer to *ISPE Good Practice Guide: Technology Transfer (Second Edition)* [129].

3.1.1 Gap Assessment

When considering technology transfer, a gap assessment should be performed to address inherent changes to match the desired state and to account for potential impacts. Table 3.1 provides an example gap assessment to match process capabilities with available SUT capabilities.

Table 3.1: Example Gap Assessment for Technology Transfer

Items	Process Input/ Actual State	Receiving Unit Desired State	Gap Analysis	Potential Gap Effect	Proposed Mitigation Strategy
Process equipment capabilities against Critical Process Parameters (CPPs)	Instrument precision				
	Instrument capabilities				
	Normal operating range				
	Extractable assessment				
	Bioreactor comparisons				
	Sampling				
Media/buffer manufacturing conditions	Manufacturing recipe precision				
	Manufacturing conditions				
	Adjustments				
Media/buffer storage conditions	Buffer hold conditions				
Bulk drug substance storage conditions	Storage conditions				
	Freezing conditions				
	Container capacities				
	Stability studies				

3.1.2 Planning and Scheduling

Timelines for technology transfer vary depending on the complexity of the process, facility capabilities, staff familiarity with SUT, previous use of SUT, and regulatory compliance requirements. Many technical and quality related activities may be carried out in parallel. As with any new technology, operator training, and generation of SOPs should be incorporated into the transfer schedule.

Once a single-use product has been selected, the lead time for capital equipment is typically less than that of the stainless steel counterpart. If the single-use component is an off the shelf product, it may be readily available at the time of production. Typical delivery time (including plant integration and commissioning and qualification) can be up to six to eight months. However, most single-use components require customization to meet process needs. Sufficient time should be designated to develop user requirements and to generate and approve customized supplier drawings. Typical lead time for customized products is about twelve weeks for already ordered product and up to twenty weeks for a new design. Supplier audits should take place after the selection of a single-use product to support accepting the supplier's manufacturing certificates and to leverage the E&L reports.

Since SUT are intended to be modular and generally do not require utilities for cleaning or sterilization, installation of the equipment can be accomplished quickly. Additional time may be required for very large equipment, such as support structures for vessels that do not fit through doors in the production areas. Walls may need to be removed to place large equipment, adding to the implementation timeline.

Validation packages are typically available from the suppliers for the SUS hardware and software. The duration of the qualification and validation activities is correlated to the complexity of the instrument hardware and software. Installation and qualification should be scheduled well in advance of equipment delivery. With limited single-use units deployed, support services from suppliers may not be as widely available as with stainless steel equipment. As the demand for single-use equipment increases, supplier support will become more readily available.

Sufficient time is required for any technical activities required to take place before engineering runs, such as characterization of bioreactors or testing the chromatography skid gradients. Initial engineering runs should shake out any issues with connections between unit operations.

Scheduling of production batches is process dependent. Considerations for the impact of SUT on scheduling include:

- Single-use products generally do not require cleaning or sterilization; therefore, turnaround time for equipment is reduced significantly.
 - For example, installation and removal of a single-use bioreactor is faster than cleaning and steaming a stainless steel bioreactor of comparable size, even for larger units which may require hoists and more manpower due to the size and weight of the vessel.
- The number of stainless steel tanks is often a limiting factor in media and buffer preparation. With SUT implementation, media and buffer may be prepared and held in totes provided there is sufficient storage space available.

Examples of schedules for technology transfer activities are provided in Section 4.4. These can be used as templates for major tasks or as a foundation to develop more detailed schedules.

3.2 Regulatory Compliance

This section highlights key regulatory aspects for consideration in the implementation of SUT. Currently, there are no specific guidelines available to provide specific direction on the implementation and use of SUT. As such, early adopters of SUT have leveraged related regulations for supporting their product filings and for managing the quality of SUT being used and of the products manufactured using SUT. Such regulations generally define requirements for disposable medical devices, primary packaging of drug substances and drug products, and the control of materials used in drug manufacturing.

SUT can be incorporated in a wide range of applications within a manufacturing process. Due to this diversity of application, the risk to the product and process can range from low (e.g., use of single-use filter for filtration of buffer upstream of the process) to high (e.g., bags used in the filling of a parenteral drug). A large part of the responsibility falls on the drug manufacturer to ensure that single-use materials selected for the manufacturing process do not adversely impact the drug product. Regulators expect adequate data to ensure that the product contacting materials do not introduce contaminants into the product so as to alter the strength, identity, safety, quality, and purity.

3.2.1 Sources of Information

Table 3.2 provides sources of information for regulations, guidances, standards, and industry good practices, which can be used for setting quality expectations of single-use products and to support regulatory filings. Since many regulations and guidelines are designed for finished products and drug substances, and do not necessarily consider unit operations at the early stage of process, end-users should assess their operations and define the extent of adoption on case-by-case basis.

Table 3.2: Sources of Information – Regulations, Guidance, Standards, and Industry Good Practices

Issuing Body	Document Number/Title	Overview
Regulations and Guidance		
European Medicines Agency (EMA)	<i>Guideline on Plastic Immediate Packaging Materials</i> , Reference Numbers CPMP/QWP/4359/03 and EMEA/CVMP/205/04 [60]	Data and information requirements on plastic materials being used as immediate packaging for active substances and medicinal products.
US FDA	Guidance for Industry and Food and Drug Administration Staff: <i>Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process'</i> [61]	Guidance document to assist industry in preparing applications for medical devices that come into direct contact or indirect contact with the human body and use of ISO 10993-1 [26].
World Health Organization (WHO)	WHO Technical Report Series, No. 902: <i>WHO Expert Committee on Specifications for Pharmaceutical Preparations</i> [62]	Guidance on packaging material used for packaging of drug products. Some concepts can be applied to SUSs.
Standards		
ISO	ISO 10993-1 <i>Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process</i> [26]	General principles governing the biological evaluation of medical devices within a risk management process and the assessment of the biological safety of the medical device.
USP	USP <1207> <i>Package Integrity Evaluation – Sterile Products</i> [63]	Guidance on package integrity testing to establish the capability of the container to maintain product quality and microbial integrity.
USP	USP <661> <i>Plastic Packaging Systems and Their Materials of Construction</i> [20]	Standards for plastic materials and components used to package medical articles (pharmaceuticals, biologics, dietary supplements, and devices).
USP	USP <661.1> <i>Plastic Materials of Construction</i> [64]	Test methods, specifications of individual plastics and raw material.

Table 3.2: Sources of Information – Regulations, Guidance, Standards, and Industry Good Practices (continued)

Issuing Body	Document Number/Title	Overview
Standards (continued)		
USP	USP <661.2> <i>Plastic Packaging Systems for Pharmaceutical Use</i> [65]	Guidance on how to establish the suitability of plastic packaging systems used for therapeutic product.
USP	USP <665> <i>Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products</i> [66]	Assessment of polymeric material, component, or system for their intended use and strategy to be adopted for characterization.
USP	USP <788> <i>Particulate Matter in Injections</i> [49]	Procedure and specifications for particulate matter in injections.
USP	USP <790> <i>Visible Particulates in Injections</i> [67]	Procedure and acceptance criteria for inspection of visible particulates in injections.
USP	USP <87> <i>Biological Reactivity, In Vitro</i> [22]	Procedure for assessing biocompatibility of a material/extract using <i>in vitro</i> reaction of mammalian cells. Applicable for plastics or elastomers used as containers to hold drugs or other solutions for parenteral administration (e.g., intravenous bags, intravenous tubes).
USP	USP <88> <i>Biological Reactivity, In Vivo</i> [23]	Procedure for determining the biological response of animals to elastomers, plastic, and other polymers with direct or indirect patient contact.
Industry Good Practices		
ASTM	ASTM E3051-16 <i>Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing</i> [41]	Defines the approach to satisfy international regulatory expectations of SUS use. Also describes the requirements for sourcing, supplying, design, specification, installation, operation, and performance assessment of SUSs.
BPSA	BPSA 2015 Single-Use Manufacturing Component Quality Test Matrices Guide [68]	Harmonized test methods along with testing frequencies and test reference required, etc., focused towards manufacture of single-use components.
PDA	Technical Report 66 <i>Application of Single-Use Systems in Pharmaceutical Manufacturing</i> [52]	Detailed guide on types of SUSs, business case assessment, identification, sourcing and selection of SUSs, application, and regulatory expectation.

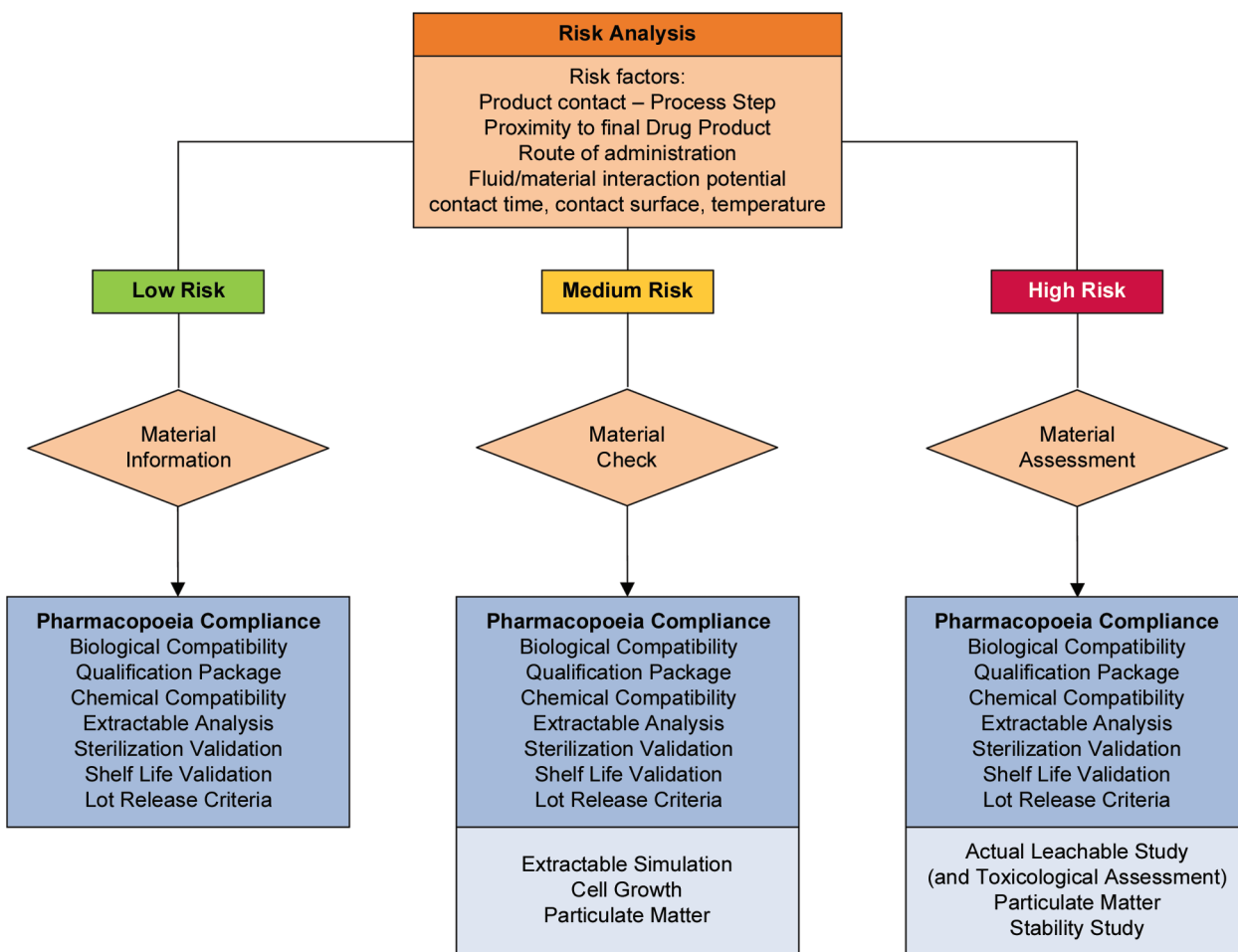
Refer to Chapter 5 (Appendix 1) for detailed listings of international regulations and standards.

Note: It is recognized that there are ongoing developments with industry guidelines and this Guide reflects an understanding of them as of the publication date. It is also recognized that drafts of USP <665> “Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products” and USP <1665> “Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products” were published for public comment in Pharmacopeial Forum 43(4) [69].

3.2.2 Data Requirements

Figure 3.1 provides a simple framework for documentation requirements for plastic packaging material used for drug substance storage; this can be used as a starting point to assess the regulatory documentation required for adopting single-use products elsewhere in the process.

Figure 3.1: Decision Tree for Regulatory Documentation Requirements When Using Plastic Packaging Material for Drug Substance Storage



Note for Figure 3.1: Examples of each risk level are as follows:

- **Low risk:** Buffer preparation upstream of the process
- **Medium risk:** Product transfer at an intermediate step
- **High risk:** Final fill of a parenteral solution

While evaluating various regulatory data requirements, performing a science and risk-based assessment is a key activity; incomplete understanding of the requirements and their applicability may lead to efforts beyond what is needed or may result in insufficient data to support SUT implementation.

Considerations for evaluating the scope and extent of regulatory data needed include:

- Characteristics of the product fluid in contact with the single-use product, such as physical state, organic solvents, surface active compounds, hydrophobic additives, etc.
 - For example, solids in contact with single-use products have a lower risk potential compared to fluids
- Stage where the single-use product is being used
 - For example, the single-use products being used in the early steps of the process, which are followed by purification steps, would have lower risk potential compared to those used in the final stages of purification or drug product manufacturing
- Product contact time and condition
 - For example, tubing and connectors used for transfers have shorter contact time and lower risk potential compared to single-use products used for holding or storing process fluids

Table 3.3 summarizes the common supporting data that drug manufacturers may need for SUT implementation to ensure regulatory expectations for quality and patient safety are addressed; these are based on applicable guidelines, industry practices, and regulatory expectations.

Table 3.3: Common Data Requirements for SUT Implementation

Data Required	Objectives
Extractables Studies (data review and risk assessment)	- Objective of extraction studies is to determine those compounds comprising the material that might be extracted by the process fluid in contact with the material - Considered as necessary requirement if the material used for single-use container is not defined in pharmacopoeias or approved for food packaging - Involves a review of supplier provided extractable data against the intended use of the SUS in the process to determine the need for specific targeted studies
Leachables and Migration Studies	- Required if extractable studies indicate one or more extractables in the appropriate solvent system and the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically unsafe - Migration studies are generally carried out during the development stages. In the absence of developmental migration studies, leachables are expected to be monitored during formal stability studies conducted under normal and accelerated storage conditions
Sorption Studies	Required when changes in the stability of the process fluid are observed during stability studies and hold time studies, due to potential adsorption or absorption of formulation components to the single-use product
Stability Studies	- Stability of drug products, drug substances, intermediates, or hold time studies of media and buffer components upon storage in single-use container - May require accelerated or real time temperature studies

Table 3.3: Common Data Requirements for SUT Implementation (continued)

Data Required	Objectives
Process Comparability	- Required when switching from reusable to single-use to demonstrate the absence of impact on the process - Required for new processes to understand if the materials of construction might create undesirable effects, such as oxidation, precipitation, pH instability over time, etc. - May range from studies limited to a unit operation (e.g., adoption of single-use mixing device) to complex process validation (e.g., when switching from a stainless steel to single-use bioreactor)
Composition and Toxicological Data	If the material of construction for the single-use component is not described in pharmacopoeias, qualitative composition of the plastic material (including additives such as antioxidants, stabilizers, plasticizers, lubricants, solvents, and dyes) and toxicological data are required to assess the use of the SUS in the process

The suppliers of single-use products play a critical role in providing data which is ultimately used for regulatory submissions or for quality impact assessments for single-use products. During the selection of single-use suppliers, considerations should be given to product quality assurance and to supporting various regulatory requirements of the end-user. Refer to Section 2.5 for further information about supplier quality assessments.

A significant number of single-use product suppliers have supporting data compiled in a dossier form which can be shared with the customer as needed. At times, a legal non-disclosure agreement and/or a small access fee is charged by the supplier for sharing such data.

Table 3.4 outlines the common supporting documents provided by single-use product suppliers for regulatory and quality purposes.

Table 3.4: Common Data Provided by Single-Use Product Suppliers

Data Supplied	Contents/Expectations
Product Composition	Qualitative composition of the plastic material (including additives such as antioxidants, stabilizers, plasticizers, lubricants, solvents, and dyes)
Pharmacopoeia Compliance	Certificate of compliance for pharmacopoeia requirements (such as monographs on packaging materials)
Extractables Study Data	Extractables data against diverse set of solvents and the toxicological profile of extracted compounds
Statement of Animal Origin	Certification indicating absence of animal derived components in manufacturing of SUSs or compliance to the applicable requirements of Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) regulations
Sterilization Validation	Validation data and assurance level of sterilization methods employed, including validation of specific minimum gamma irradiation dosage for products sterilized using irradiation
Endotoxin Test Results	Evaluation and quantification of bacterial endotoxins using pharmacopeial test methods
Biological Reactivity – <i>in vivo/in vitro</i>	Evaluation of the response of mammalian cell cultures/animals to extracts of polymeric materials and exposure to polymeric material
Particulate Matter	Presence and quantification of particulate matter using pharmacopeial test methods

3.3 Leachables

As discussed in Section 2.2, extractables and leachables (E&L) profiles are integral to qualifying and implementing single-use products. Leachables are the chemical species that migrate from or through a contact surface into a drug product or process stream during storage or normal use conditions. The supplier-provided extractables information can give preliminary indication of the potential chemical species that may impact the single-use product. The leachables evaluation should be done by the end-user, with a strong focus on the conditions of the therapeutic product or its precursor that is processed in the single-use product. While the two terms E&L are often discussed together, they are executed at different times and by different entities. Therefore, this Guide correspondingly separates the two topics to represent the actual activities.

Some interactions between the dosage form and packaging/polymeric contact materials may give rise to E&L that can be readily identified, quantified, and evaluated for their impact on patient safety. However, leachables are often present at extremely low levels and the analytical methods should be capable of detecting and quantifying trace levels of these compounds. Other leachables may show up in stability studies, and may pose a risk to safety and efficacy via interactions with the formulation.

For example, a well-known industry case study [70] is the issue arising from the common use of Irgafos 168® compounds (antioxidant additive) in the composition of single-use bioreactor films. Originally Irgafos 168® compounds have shown no cytotoxic effects in numerous studies. However, an oxidative-derivate from this compound, Bis(2,3-di-ter-butylphenyl)phosphate (bDtBPP) was shown to have a cytotoxic effect once the bioprocess container was gamma irradiated and used on a selected cell line, Chinese Hamster Ovary cells. This case study shows the importance of risk analysis. The existing film formulation had been used, and continued to be used, satisfactorily with cell lines that are less sensitive to bDtBPP. A new film composition was introduced, with reduced concentration of Irgafos® 168 in the polymer formulation, without adversely affecting polymer properties.

As an additional example, low levels of leachable iron may catalyze oxidation of a preservative and other excipients, leading to formation of protein-preservative adducts. Therefore, even if extractables by themselves do not pose a safety risk, safety and product quality should be assessed with appropriate risk assessment and risk mitigation strategies for leachables.

For a detailed approach to assessing leachables risk, refer to the *BioPhorum Operations Group (BPOG) Best Practices Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems used in Biopharmaceutical Manufacturing* [71].

3.4 Validation

Once the design phase is complete, validation of the single-use products can begin. An assessment should be performed to evaluate and quantify all potential risks associated with the single-use products and their introduction to the manufacturing process. A cross-functional team is recommended to conduct a thorough and robust assessment; the team members would be critical contributors to the Failure Mode and Effect Analysis (FMEA) protocols for evaluating the impact on the manufacturing process. For more information on specific criteria to consider, refer to Process Validation in Manufacturing of Biopharmaceuticals [72].

Knowledge of the process, single-use products, and contact solutions are essential for a thorough assessment. The intended use or application of single-use products influence the extent of the testing and evaluation required for its safe introduction. It is helpful to understand the single-use materials use, contact time, and proximity to the final drug product. The following information should be gathered:

- Product application
- URS

- Supplier product documentation of the single-use product, including specifications and drawings
- Contact solutions
- Proximity of the single-use product to the final process step
- How the single-use product will be used
- Ancillary equipment impact, such as tubing welders, pumps, etc.
- Sanitization/sterilization requirements

Supplier qualification, as well as analysis of leachables, would be nearly complete at this point in the SUT implementation project lifecycle. Although not part of validation, the team doing the validation should be closely involved and aware of the results of the supplier qualification and single-use product leachable analysis prior to the start of validation activities.

A review of supplier data should be performed prior to performing in-house testing (i.e., end-user on-site testing). For high risk applications (such as injectables, ophthalmic, and inhalation), the single-use product should be tested with applicable solutions and in the same state as it is intended to be used by the end-user (e.g., gamma irradiated). For low risk items, a thorough assessment should be performed to determine necessary testing.

3.4.1 Supplier Data Review

Suppliers typically provide a set of information which includes manufacturing, compendial, and additional data. End-users should evaluate the supplier provided information to ensure the data supports the intended use of the single-use product; data accuracy should also be confirmed to verify that it is suitable for verification. The data review should be performed as a prescreening, prior to performing any in-house testing.

Note: The manufacturer/supplier name and part number should be assigned; this ensures that the design is locked.

An outline of supplier provided data is as follows:

- Materials of construction, shelf life, and sterilization validation statement
 - A worst case assembly, which includes every component used in any assembly, is typically utilized to test and monitor shelf life and sterilization. The supplier should provide a statement indicating that the worst-case assembly is representative of the specific single-use product.
 - Sterilization validation should be based on ANSI/AAMI/ISO 11137 [51].
- Biocompatibility test results (core requirement for polymeric materials having product contact) per USP <87> [22] and USP <88> [23] methods
- Mechanical properties test results for the applicable properties of each SUS
 - Refer to ASTM F2097-16 [84] and BPSA 2015 Single-Use Manufacturing Component Quality Test Matrices Guide [68]
- Gas transmission properties of containers constructed of plastics, as tested per appropriate ASTM [2] methods
- Physicochemical test results for components constructed of plastics, such as high-density PE, low-density PE, PP, Polyethylene Terephthalate (PET), Polyethylene Terephthalate G (PETG), and poly(ethylene-co-vinyl acetate) per USP <661> [20] or EP 3.1.3 [73] requirements set forth for these plastics

- Statement of animal origin
- Chemical compatibility charts
- Endotoxin test results per USP <85> [48] and EP 2.6.14 [74], which is a requirement for single-use products with product contact and which need to be sterile and pyrogen free, per the intended application
- Particulate test results per USP <788> [49], EP 2.9.19 [75] and EP 2.9.20 [76] for product contact single-use products and supplier statement indicating the systems and processes in place to reduce or control particulates
- Documentation for single-use products that have embedded instrumentation providing data utilized for controlling and monitoring processes

For the details of the testing requirements, refer to Chapter 8 (Appendix 4).

3.4.2 In-House Testing

The extent of in-house testing for single-use products required depends on the application in the process and availability of supplier and in-house data. It is acceptable to use the supplier provided data and limit in-house testing based on assessment of risk and suitability of available use.

Refer to Section 4.2 for a risk assessment model which can be used to determine the extent of in-house qualification required according to a calculated risk score.

If multiple assemblies are to be qualified at the same time, then testing can be limited to representative bag sizes and configuration. The assembly design and use should be fully understood. Single-use products to be tested should be in the same state as intended use by the end-user (e.g., gamma irradiated). Protocols and test plans with predetermined acceptance criteria should be used in the validation. Reports should be created summarizing the outcome. Validation documents are reviewed and approved by the appropriate quality unit.

For single-use products that are utilized in high risk applications (e.g., products administered by injection, ophthalmic, and inhalation), in-house testing should be performed to mitigate the risk that the single-use product and the contained solution are not compatible.

Solution Stability Testing

A solution stability study should be performed to ensure the quality and safety of a solution in a single-use container. Solution stability in bags may be compromised by several factors. High concentration or high pH solutions may be compromised by extractables from, or by reaction with, the bag film itself. Solutions depleted of ions may be compromised by leachables from the bag film. Representative solutions should be selected for testing with these factors in mind. Considerations should be made for solutions that present unique challenges. Testing should be set up to ensure that the representative solutions, along with Water for Injection (WFI), are evaluated using their formulation criteria, storage conditions, and expiry period.

Recommendations for solution stability testing are as follows:

- Gather all solutions that will be held by the single-use container. Compare the solutions to each other, looking at their constituents, pH, temperature, etc. If possible, representative solutions should be identified for further testing using the comparison criteria. Any criteria solution, such as a final formulation, should be tested on its own. WFI should also be tested since it lacks any other constituents and can pull chemicals out of polymers.
- The ratio of surface area to volume is considered critical for solution stability, whereas the bag size itself is not considered to be critical. Testing should be done with smaller sized bags while still adequately sized to allow for adequate sample volumes. Each bag should be filled to only half of its full capacity.

Note: During production, bags should not be used at less than half of its full capacity since stability and E&L studies are typically carried out at 50% fill volume as the worst case. Using lower volumes may result in challenging the suitability of the bag for its purpose. Therefore, a risk assessment should be done when the production volumes are less than the volumes used for the stability and E&L studies.

- Take samples at identified time periods, typically time zero and 25%, 50%, 75%, 100%, and 100% of expiry period. Prior to sampling, perform a visual inspection. Formulation criteria (typically pH, conductivity, and microbial limits for those solutions promoting growth) and any specific chemical analysis should be identified for each solution. Multiple single-use products are often used to test one solution so multiple sampling is not required. Evaluation of stability should be based on consistent test results at various time points. Consider using conductivity readings. Each test sample should be free of visible particulates and signs of precipitation or crystallization. The sample should not change color. The bags should not show any signs of physical deterioration.
- For cell culture media, the solution should be tested as indicated above. Additionally, small-scale cellular growth studies should be performed to ensure that there is no impact to cells with the use of the single-use product.
- If material is to be mixed within a single-use product, representative solutions should be identified within the solution stability study. Solution criteria along with processing time should be evaluated in the study.

Container Integrity Testing

To check the integrity of sterile single-use containers, media fill studies may be carried out. Recommendations for media fill studies include:

- Fill the single-use container with a medium, such as Tryptic Soy Broth (TSB). The medium is a challenge solution that promotes more growth than other solutions.
- Pay special attention to the external surface area, which is the critical factor. A larger surface area presents greater exposure to possible microbial contamination. Therefore, if multiple sized bags are being qualified, testing of the largest sized bag of each style should be used with the bag filled to capacity.
- Visually inspect the bags prior to any sampling. Sampling should be completed in an aseptic manner. Bioburden should be tested. Growth promotion should be evaluated at day zero and at the end of the study to ensure that the medium supports growth.

If the single-use product is used as the primary container for a drug product, simulation studies should be performed per applicable pharmacopoeia and regulations for aseptic drug product manufacturing.

Filter Validation

If a filter is a part of the single-use product, filter validation should be considered. Typically, all information for a normal flow filter can be gathered by the supplier. Considerations should be made for the following elements: hydrophilic, effective filtration area, maximum pressure, maximum flow rate, temperature range, recommended flush agent with time and volume, materials of construction, biological reactivity, temperature and radiation stability, endotoxin testing, non-fiber releasing, product chemical compatibility, extractables, and water permeability testing. Where the filter is being used for sterilization (i.e., sterilizing grade filter), several of these tests should be conducted by the end-user, including retention studies, integrity test determination, and compatibility studies.

Shipping Validation

For single-use products that are shipped, further validation should be performed to ensure integrity is maintained throughout the shipment. Key recommendations for shipping validation include:

- Identifying a shipping container that can hold the required packing material at the specified storage conditions for the duration of shipping
- Securing a carrier for consistency of pickup and delivery
- Evaluating the solution at the start and end of shipment, considering the testing described above

3.5 Supply Chain

A robust supply chain is composed of many aspects in the process of establishing a strong relationship with suppliers and sub-suppliers. This section aims to highlight recommendations for developing this relationship. Reviewing this section early in the relationship with suppliers can help to establish a predictable supply based on shared commitments.

3.5.1 Quality Requirements

Confirm or Finalize Quality Agreement with Suppliers

The quality agreement is a key document to maintaining a robust supply chain for a process using SUT. This document should be drafted once a supplier is selected and the order for prototypes is being placed. As discussed in Section 2.5, the quality agreement is a comprehensive document that often needs to go through multiple review cycles within each organization involved in the agreement. The agreement typically covers quality, service, and financial topics, necessitating agreement from several departments within each organization. Negotiation of this agreement should start during the prototype evaluation stage, allowing for time to resolve any issues and to have the agreement ready for approval by the start of production.

Confirm Audit Schedule

Auditing of suppliers is an important aspect for any organization dealing with SUT. End-users, as well as intermediate suppliers, should discuss audit plans during supplier selection. See Section 2.5 for details regarding supplier audits. Once the supplier is selected, a preliminary audit schedule should be defined. The first audit may occur at supplier selection or prior to the first order. The confidence in the supplier typically dictates how early the auditing process starts. Periodic audits are recommended, with the schedules being defined as soon as practical with all suppliers of single-use products.

3.5.2 Lead Times and Order Processing

Confirm or Agree Upon Lead Times for Individual Assemblies

During the design and selection of single-use assemblies, considerations should be made for using one design of the assembly in multiple locations in the operation. This can provide advantages in lead times and inventory levels. Lead time becomes an important factor when balancing the use rate and inventory level. It is important to get firm commitments from the supplier on the lead time. Shorter lead times often result if an established order schedule is worked out.

Confirm or Negotiate Pricing for Recurring Orders

At this point in SUT implementation, there should be defined prices for each assembly or sets of similar assemblies. The quantities needed are now established and recurring order schedules can be defined along with the associated pricing. This can provide financial benefits to the buyer and ability to plan for the supplier.

Develop and Agree on a Predefined Order Schedule

Once the production process is in operation, it is helpful to develop a long term (months or years) order schedule. Similar to recurring orders, this schedule benefits the buyer and supplier.

3.5.3 Complaint Management**Confirm Process for Handling Complaints and Investigations**

This topic is often overlooked until issues arise with the product received; at that time, it is usually an urgent matter. Best practice is to define the process and expectations prior to a complaint occurrence. This includes confirming with the supplier the specific process to be used and whom to contact for any complaint to be entered into the supplier's system.

Confirm Return and Crediting Process for Defective Products

Complaints often activate investigations, which usually require a return of the defective product for evaluation. Smooth return of the product is a key factor in timely investigations. Therefore, it is important to understand aspects such as:

- How to initiate the return process
- Decontamination activities required prior to returning the product
- When to expect credit for the returned product, if warranted

Establish Expectations and Response Time for Complaints and Investigations

Investigations can take weeks or months. Understanding the communication expected during the investigation process keeps relevant parties up to date. This is another aspect that should be understood as early as possible in the relationship between suppliers and end-users.

Corrective Action Preventative Action (CAPA) Plan

It is helpful to clarify the typical implementation plans for CAPAs, including the timeline, in the case that the investigation results in a CAPA.

3.5.4 Security of Supply**Establish Inventory Requirements at End-User and at Supplier**

The use rate and lead time of specific assemblies combine to define the foundation for inventory levels. This topic often arises when working out long term or blanket contracts with the supplier. Having an inventory at the supplier warehouse as well as at the end-user warehouse helps to retain commitment from both parties in maintaining a strong security of supply. During contract negotiations, the levels of inventory at the supplier should be clarified.

Agree on Change Notification Timelines

Change notifications throughout the supply chain impact the end-user. Understanding the change notification process of the supplier and any sub-suppliers can reduce surprises in availability of products. Critical factors to convey to the supplier include:

- What is considered a notifiable change

- Whom to contact to provide a change notification
- The time needed by the end-user to assess and approve a change
- The time needed by the end-user to implement a change

Confirm Business Continuity Plans for Suppliers of Critical Single-Use Assemblies

In addition to following the activities suggested in this section of the Guide to ensure a robust and secure supply, a supplier business continuity plan should also be reviewed. Business continuity plans clarify the commitment of the supplier to keep the product available under unforeseen circumstances and to provide defined alternatives. A review of the business continuity plans relative to the single-use products that are unique (particularly assemblies) and have long lead components should be conducted to ensure the assemblies are available under any conditions of supply chain disruptions.

3.5.5 Service, Maintenance, and Ongoing Training

Preventative Maintenance

A preventative maintenance service agreement for the mechanical and electrical components (pumps, controls, etc.) of the SUSs should be established.

Training

Consider establishing periodic training programs for new staff or refreshers for existing staff. Suppliers can be an excellent resource to provide this training.

3.6 Training

SUT has grown in both complexity of design and criticality of application in the past twenty years. Initial implementation focused on media and buffer storage applications; since then, supplier innovations and industry awareness of SUT advantages have broadened acceptance to critical process steps. The main advantages of SUT include improved flexibility and manufacturing throughput as well as reduced labor and risk for cross-contamination; these benefits can only be expressed if the end-users are properly trained. Therefore, operator training is a key factor for successful implementation of SUT.

This section focuses on the impact of SUT on procedures in terms of handling and failure risk, training considerations for SUT implementation, and recommendations for building an effective training program for SUT.

3.6.1 Impact of Single-Use Technology on Procedures

3.6.1.1 Comparison of Operations for Stainless Steel Systems and SUSs

For decades, operations have primarily been based on stainless steel equipment and piping. Facilities have been designed for stainless steel systems and the associated SOPs are well defined. In general, the operators are well trained, with years of experience based on full integration of the equipment in the training programs. Even with the increasing level of automation available for SUT, stainless steel systems still allow for a higher degree of process automation and process control; these factors generally reduce the risk of human error.

While most stainless steel based facilities operate using process automation, SUSs involve many operations that are carried out manually by operators. However, there are some equivalencies in the activities that occur with traditional stainless steel systems versus SUSs. For example, installation of proper hardware (spools, steam traps, etc.) is replaced by installation of the appropriate assembly and verification of proper connections. Table 3.5 provides a comparison of typical operations for stainless steel systems versus SUSs.

Table 3.5: Comparison of Typical Operations for Stainless Steel Systems versus SUSs

Stainless Steel Systems	SUSs
Cleaning, sterilization	• Check material and sterilization certificates • Check packaging integrity • Visual inspection • Check for container cleanliness
Calibration of probes (DO, pH, temperature, conductivity, etc.) in defined intervals or prior to use	• Check calibration certificates (for single-use probes that are supplied pre-calibrated) or calibration prior to use
Installation of filters or other consumables	• Check for correct assembly of the SUS (or assemble single-use components, as applicable) • Check for correct fitting of single-use components and of proper connectivity between different SUSs
Installation qualification and reevaluation of fixed pipes and valves	• Connection of tubing lines • Check correct assembly before each use • Check connections against specifications before use • Check clamps
Filter integrity testing	• Also needed for SUT along with additional check for connection integrity

3.6.1.2 Increase in Manually Performed Steps

With SUT implementation, there may be changes associated with the facility and personnel and material flows, for example:

- Equipment is often mobile and may be placed closer together
- Production room sizes can become smaller
- Room classifications can change since SUSs may be considered as closed systems
- Additional raw materials (such as single-use components) are transferred from storage to production areas
- SUSs are transferred post-use for decontamination and/or disposal
- Fluid transfer from zone to zone can change since SUT allows for optimizing the process flow by using aseptic transfer systems

In general, there is an increase in manually performed steps by the operators. Considerations for increased or different steps include:

- Receipt, inspection, storage, and transfer of SUSs to production areas
- Inspection before use to eliminate potential risk (e.g., checking the irradiation label and checking for damage during shipping or storage, missing components, and incorrect tubing engagement)
- Connection and disconnection of single-use assemblies and, in certain cases, assembly of standalone components
- Installation of single-use components in the proper holders, with associated accessories

- Management of proper connectivity between SUSs
- Handling of flexible tubing and associated clamps/valves which replace rigid piping and stainless steel valves for transfer of fluids
- Manual steps which replace CIP/SIP operations
- Handling of different kinds of connectors, disconnectors, welders, and sealing operations
- Control of pumping and filling operations
- Filling and draining of peristaltic pumps, as required for operating certain SUSs
- Point of use leak testing
- Handling of single-use sensors, including calibration, for process monitoring
- Sampling steps from a variety of SUSs (with different types of bags, tube welders, connectors, sampling devices, etc.)
- Manipulation of aseptic transfer doors (e.g., for zone to zone fluid transfer or for transfer of stoppers to the filling line)
- Manual control of working pressure (such as for bioprocess containers which cannot withstand overpressure)
- Handling of bioprocess bags, for which the procedures may differ based on the application (cell propagation, storage, mixing, freezing, etc.), type of bag container (tank, drum, etc.), volume (e.g., settling a bag in a container is different for 100 L versus 3,000 L), and supplier
- Labeling of bioprocess bags after filling (label location should ensure proper identification while avoiding any risk for glue or ink migration)
- Operating different types of hardware (such as motors, welders, sealers, automated systems, freeze and thaw stations, etc.), accessories (jacket, load cells, powder holder), and automation systems, particularly for complex SUSs
- Transfer of SUSs post-use to additional steps (such as storage or shipping) or to be rinsed/decontaminated before disposal

Health and safety aspects of the increase in manual operations should be considered, especially with respect to ergonomics and safety hazards due to tubing on or near the floor.

Certain critical operations, such as preparation for shipping, freezing/thawing, or final filling, require additional skillsets and competencies and specific handling procedures.

SUT implementation risks should be minimized through appropriate procedures and controls along the different steps of operation. The increase in manual steps (compared to automated stainless steel systems) directly impacts operator tasks as well as the planning of work. A time and motion study may be useful in determining the time necessary for an operator to carry out specific process steps using SUT (particularly those where multiple SUSs are connected and disconnected) at a defined rate of performance; appropriate planning can then be performed.

3.6.1.3 Failure Risk Related to SUT

Based on an industry survey [77] and the experience of the authors of this Guide, a primary risk related to SUT is breakage/leakage of the SUS leading to loss of production material and potential contamination and safety issues. Due to the polymeric nature of single-use bioprocess bags (i.e., plastic films that can be sensitive to tears and punctures), there is an increased risk of failure during handling.

While improvements have been made by suppliers to the overall quality of SUSs (such as robust plastic films, extensive assembly qualification, strong process control, and release testing), damage to SUSs can often be traced to handling issues during receipt, transfer, storage, or use.

Furthermore, investigations for leaks associated with bioprocess containers (see study cited in PDA Technical Report 66 [52], Reference 57: Beh et al., 2005 [78]) concluded that leaks primarily occur in areas where the bag chamber is handled by operators, at the top and the bottom. From the study, the distribution of leak locations is as follows:

- 61% bag chamber
- 18% sampling manifold
- 12% connector
- 9% tubing

Leakages can be related to improper operations and handling, such as:

- Use of improper tools to open cardboard box
- Use of improper cart or techniques to transfer the SUS into the production area
- Use of sharp objects in close proximity to the SUS
- Use of improper containers
- Rough handling during setting or filling

Therefore, in addition to equipment and design optimization, the leakage risk can be significantly reduced by ensuring proper usage through end-user awareness of main root causes for leaks and operational training.

3.6.2 Training Considerations for Single-Use Technology Implementation

A rigorous training program should be established to mitigate the risk of deviations through harmonization of good handling practices and efficient knowledge transfer. The better the training is, the lower the risk of failure will be.

In general, training is needed in the three following situations:

- Initial training for new implementation of SUT
- Recurring training refreshers all along the process lifecycle
- Corrective action in case of malfunction or failure (complaint occurrence)

SUT suppliers can provide specialized support and expertise to end-users with regard to training. Suppliers can provide guidance and recommendations on how to properly store, inspect, handle, and discard the SUSs; this information can be used to support the creation of end-user internal SOPs. However, the main focus should be on hands-on sessions to allow for the end-users to practice with conditions as close as possible to the actual process.

Once a core team has been fully trained, considerations can be made to establish a mentorship program; those operators who have demonstrated good practice and proper handling techniques may be nominated as mentors to provide training for new staff. These mentors would also act as the main representatives for:

- Performing regular training refreshers
- Requesting design improvements or harmonization (such as to improve ergonomics or upgrade the design to align with new needs/features)
- Proposing process optimization (such as improving interconnectivity between SUSs and/or for transfer flows)

Retraining should be planned when major changes occur in the SUS design.

Periodic on-the-job retraining helps to ensure transmission of process knowledge and contributes to continuous improvement. Periodic retraining is also an opportunity to identify possible design changes or process optimizations to enable improved reliability.

As with any equipment, insufficient operator training may result in:

- Damage to SUSs during use, which could lead to loss of product (and time)
- Increased quality complaints and decreased confidence in SUT
- Increased production costs due to higher consumption of SUSs
- Slowdown of production, underutilization
- Increased demands on supervisor time
- Dissatisfaction due to operators being inadequately prepared to perform the tasks
- Decreased performance of the SUSs

3.6.3 Building an Effective Training Program for Single-Use Technology Implementation

3.6.3.1 General Considerations

A generic training model can be applied to SUT implementation with a clear focus on explaining the failure risks related to improper use and providing opportunities for operators to practice all manually performed steps. Training should be supported by supplier documentation (operating manual, maintenance recommendation, and spare part lists) and compliance with GMP requirements. Good Documentation Practices should be applied to the SOPs, work instructions, and training assessments.

The trainer should consider the following points:

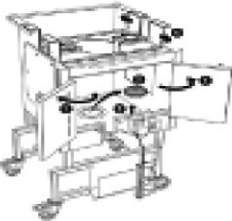
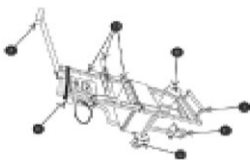
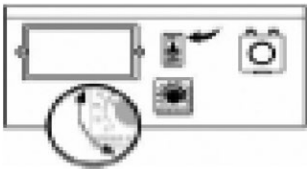
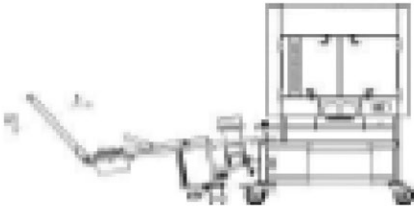
- Adapting the training session to the specific skill set of the staff in attendance
- Understanding and accounting for the process flow and working environment in which the SUT is used
- Adapting the handling procedures, as needed and as much as feasible, to any constraints in the working environment

The supplier should provide recommendations for inspection and troubleshooting, instruction for use (maximum operational pressure, maximum flow rate, minimum/maximum working volumes, etc.), and clear guidance concerning techniques for avoiding bag stress during storage, setup and deployment.

A useful tool for transferring and maintaining knowledge is to record the training video and create visual aids such as pictures of correct versus incorrect examples. The training videos are useful for supporting the training of new staff.

Working instructions can be useful as a supplement to SOPs. These contain clear instructions with pictures of the equipment, step by step procedures, and warnings on points for special attention) and should be easily accessible or placed directly at the point of use; the purpose is to increase operator awareness and efficiency. Refer to Figure 3.2 for an example of a working instruction.

Figure 3.2: Example of Working Instruction for a Single-Use Mixing System

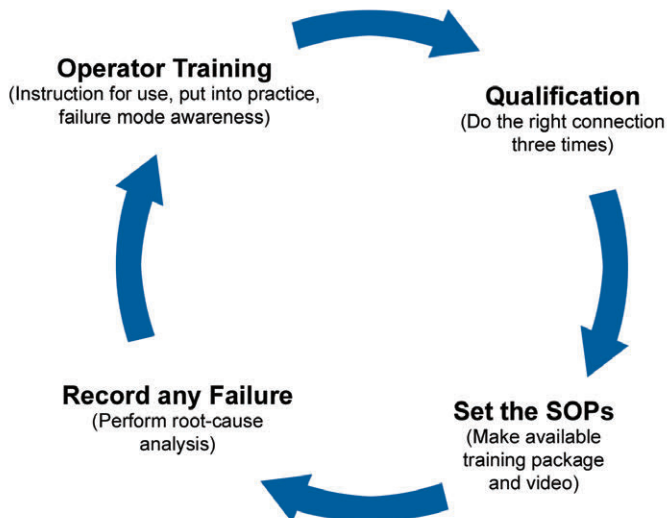
Working Instruction		Company Name	
Use of Mixing System			
Document Reference: xxxxx	Revision: xxxxx		
Effective: xxxxx			
Concerned working area: xxxxx			
Name	Position	Creation Date	Signature
Container	Motor	Consumable	
Identification Number	Identification Number	Reference(s)	
		Picture(s) of label(s)	
Procedure			
• Illustrations of each equipment and parts • Illustration of each using steps (eventually right/wrong pictures for specific point of awareness)  		List all requested checks before start: • Check SUS label(s) and irradiation tag • Check over pouches integrity • Check cleanliness of container • Check that SUS fits the container List all steps to get the equipment started, run and stopped: • Carefully unpack the mixing bag • Open the container door • Install the mixing bag in the container • Close the container door • Closed all clamps • Connect the motor to power supply • Connect the motor to the container • Connect bag filling line to liquid supply • Open clamp from bag filling line • Push start button (light will switch on) • Turn on the speed button to xxx RPM •  Points to consider  Risks awareness	
Safety (pictograms showing any specific care to prevent operator safety)			

The following concepts are applicable to training for SUSs, ranging from simple transfer sets to bioreactors and mixing systems:

- Provide hands-on training to the operators and ensure sufficient skills and comfort level to work with the SUS
- Inform operators of possible things that could go wrong with the systems
- Forecast regular training refreshers and process review for potential optimization
- Apply root cause analysis in case of failure
- Monitor impact of corrective actions

A training program should start with a “watch it” step followed by a “do it” step, supported by an evaluation of training performance. Refer to Figure 3.3 for an example training plan overview.

Figure 3.3: Example of Training Plan Overview for an Aseptic Connector



3.6.3.2 Timing for Training

Training should be introduced as early as possible (during the earlier testing and validation phases) and be intended as an integral part of the SUT implementation project. Involving the operators from the beginning of the implementation process (during initial technical evaluation and prototype testing) helps to enhance interest levels and to reinforce confidence in the technology. Choosing SUT based on factual analysis (design, technical specification, quality, cost, and assurance of supply) may not be sufficient to prepare an optimal implementation. Involving operators early in the process helps to prevent complications or delays in the adaptation period.

Especially when implementing changes in a facility from traditional stainless steel systems to SUSs, it may be valuable to consider hands-on sessions (through demonstration or evaluation of single-use products) in the early project phase. Feedback from the operators can be used to support the engineering work and help to create SUS designs that are fit for purpose. Early involvement of operators provides opportunities to:

- Start passing on good practices regarding proper handling of SUSs
- Adapt the SUT design to real process conditions and constraints (operator interviews can provide practical insight into the daily usage of the SUSs)

- Optimize the process flow to enhance efficiency and flexibility

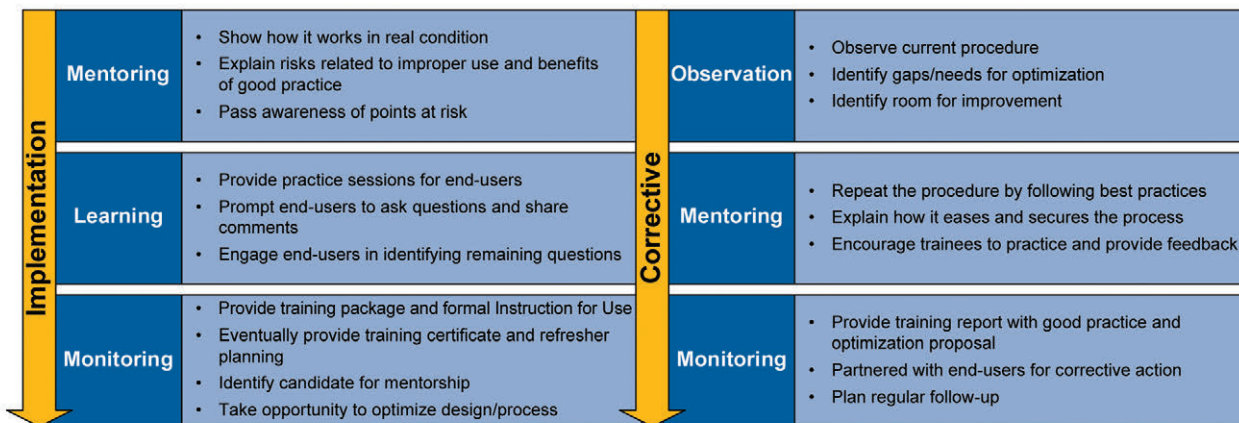
Table 3.6 provides examples of specific training topics to cover depending on the project stage.

Table 3.6: Example Training Topics by SUT Implementation Project Stage

Before Technology Transfer	During Technology Transfer or Validation	After Validation
• Familiarization with SUT • Awareness of sensitive nature of bags • Storage and handling of bags and assemblies • Managing and layout of tubing • Awareness of why kinking, pulling, and twisting of tubing are unacceptable in SUT • What and how to inspect	• Installation of specific bags and assemblies • Consistent handling of tubing • Connections to auxiliary equipment • Installation and calibration of sensors	• Troubleshooting • Complaint management • Changes implementation • Topics that need periodic updates

Figure 3.4 summarizes a three-step sequence that could be applied to the training program, depending on the purpose (implementation or corrective). When training for new implementation, educating is performed first; when retraining or performing corrective training, an initial observation step is crucial for the further steps.

Figure 3.4: Proposed Sequence for Training Depending on Purpose



3.6.3.3 Specify Content According to Complexity and Audience

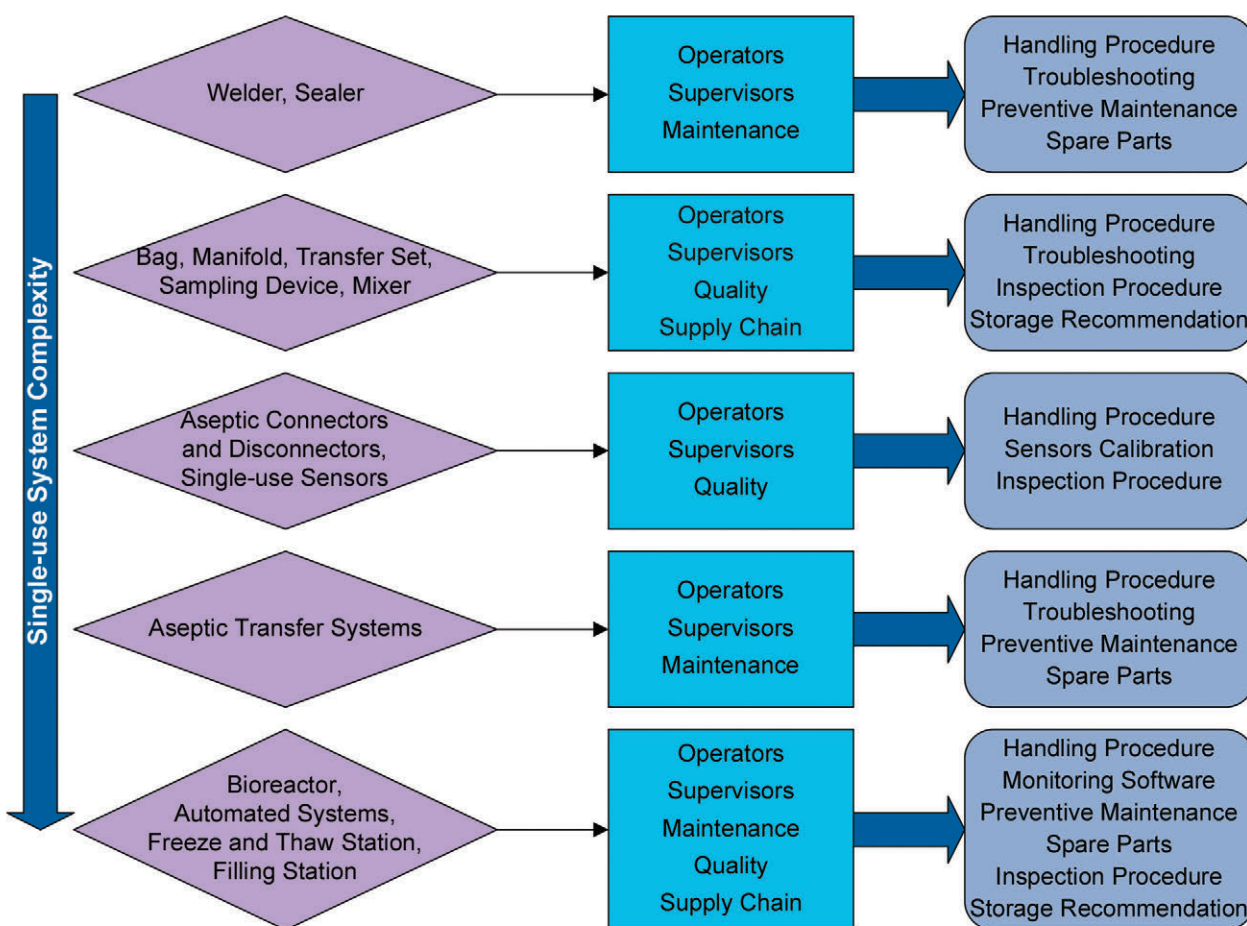
The specific content and time required for training depends on factors such as:

- Process scale and working environment (e.g., handling a 3,000 L storage bag is more complicated than handling a 50 L bag, and working in a higher classification area requires additional time and precautions for the training)
- Complexity of the SUSs (bioreactors and automated systems for unit operations require more in-depth training)
- Focusing on different aspects related to SUT, depending on the tasks of the various stakeholders including:
 - Supervisors and operators (performing daily work with the systems)
 - Supply chain personnel (performing procurement, warehouse, and disposal functions)

- Quality control personnel (performing inspections)
- Maintenance personnel
- Purpose of the training:
 - Refresher or corrective training (after failure occurrence) should focus on specific key points related to proper handling
 - Training on new SUT should focus on how to handle the systems and the purpose of the procedures, with detailed presentation of the system features and formal instructions for use

The training requirements should be based on the classification of SUSs according to complexity and the applicable stakeholders. This concept is depicted in Figure 3.5.

Figure 3.5: Defining Training Requirements Based on Complexity and Audience



As highlighted earlier in this section, it is beneficial to implement hands-on training for the operators in the early phase before final implementation, in order to ease SUT adoption. However, formal training, in compliance with GMP requirements, should be implemented once the SUSs are delivered, installed, and qualified.

Suggested timing for formal training on specific systems includes:

- For hardware such as sealers, welders, or aseptic transfer doors, training can be planned just after the SAT. The maintenance personnel should be included in the training sessions.

- For mixers, bioreactors, and automated systems, training is often scheduled at the same time as qualification. Supply chain, quality, and maintenance personnel should be included in the training for awareness.
- Training for inspection of single-use components and assemblies should be conducted prior to routine receipt of these products as described in Chapter 6 (Appendix 2).
- A planned program for training based on the recommended example schedule shown in Section 4.4.6.

4 Program Management

This chapter is aimed at providing guidance on the implementation of SUT in a manufacturing operation. The topics highlighted cover the project phases from when a decision is made to implement SUT to when the SUT is operational in a manufacturing process.

While implementation methods applied to SUT are similar to those of stainless steel systems, there are characteristics of SUT that require emphasis on certain aspects of the implementation process. These include:

- Strong collaboration with suppliers
- Risk management and change management throughout the process
- Flexible schedules to handle the development of single-use assemblies
- Interface/connection of SUT with stainless steel technology

This chapter is primarily focused on the risk management, change management, and the implementation schedules. As SUT is a relatively new technology, there is a fair amount of development that often arises during SUT projects. This development can result in changes, and attention to risk management and schedules are important to a smooth implementation. Section 4.2 guides the end-user on the criteria for a comprehensive risk assessment specific for SUT implementations. Section 4.3 provides an overview of typical changes associated with SUT operations. Section 4.4 presents templates for timelines and dependencies of tasks that are expected. These templates can be used as a first draft for planning the implementation.

4.1 Implementation of Single-Use Technology

4.1.1 *Assessing Supplier Capabilities*

End-users should assess suppliers for their capability to supply the required single-use products. The dependence on suppliers, particularly with regard to sourcing, should be properly handled and managed. Primary SUT suppliers should define a sourcing strategy to ensure business continuity, e.g., from film suppliers or other unique components, to ensure the needs of their end-users can be fulfilled.

The general checklist below represents a subset of topics critical when assessing supplier capabilities:

- Complete evaluation of SUT suppliers by the end-user (purchasing) – the choice of a supplier may be defined by criteria such as:
 - Financial aspects
 - Technical knowledge and support
 - Flexibility/adaptability
 - Quality
 - End-user's process criticality
 - Qualification and validation of their own supply chain (i.e., raw materials suppliers)
- Assessment of the risks to supply delays

- Implementation of quality audit plans for all suppliers, including auditing of their change management system
- Evaluation of automation integration (automation portion of the SUS into the end-user automation system)
- Evaluation of flexibility of the supplier to work with the end-user to make their SUS easy to maintain/calibrate

Refer to Section 2.5 for more detailed information along with methodology and matrices for assessing suppliers.

End-users should source at least two suppliers that meet the implementation team's needs. Having dual-sourced single-use products in the process can provide buffer against vendor supply issues that may impact the manufacturing process.

4.1.2 Confirming Supply Security

Supply security is another key factor during implementation of SUT. End-users should request details from single-use product suppliers about their supply security process. Suppliers should confirm the strength of such systems by demonstrating it is reliable, robust and secured.

The supply security process should be managed by all stakeholders. Responsibilities are shared during the supply process, which should be a collaborative effort. All stakeholders should determine and reach agreement with each other's requests and operational expectations.

During the implementation and management of supply security, key factors include:

- For SUT suppliers:
 - Anticipation of sales and the management of storage area to be compliant with requirements from the end-user
 - Providing warranty on delivery times by targeting an elimination or reduction of delay
 - > Anticipation of procurement and raw material (especially resin) supplying
 - > Planning sufficient reserve manufacturing capacity
 - Implementing quality procedures to improve single-use components and equipment quality, supply chain flexibility, and manufacturing productivity (both at single-use products manufacturers plants and raw materials supplier plants)
- For SUT end-users:
 - Implementing quality procedures for supplier facility audits
 - Reducing the risk of failure in the supply security chain by using a dual sourcing strategy
 - Managing sourcing, sales orders, and stakeholders commissioning plans

4.2 Risk Management

New technology can carry risks that arise from many sources. While SUT is becoming established in the pharmaceutical manufacturing environment, it is still evolving with improvements routinely incorporated into the equipment and operations. These improvements often trigger changes and associated risks that need to be minimized. The types of risk that can arise during the implementation of SUT include:

- Material compatibility
- Availability of products
- Changes in source materials
- Leaks or performance issues
- Inventory fluctuations

Risk management should be applied throughout the implementation of SUT. Risk assessments should be conducted at the beginning and at multiple points of the implementation program. At a minimum, an FMEA should be done at the beginning of the implementation that addresses at least the potential risks listed above. Refer to the *ISPE Baseline® Guide: Commissioning and Qualification* [47] and ASTM E2500-13 [40].

One of the more important risk categories for SUT deals with materials since the single-use components and assemblies are often customized and implemented in new applications. Therefore, the rest of this section is intended to provide a consistent compliance approach to demonstrating suitability of a given SUS for its intended use in manufacturing. Different applications of SUT are guided by user requirements which guide the total requirements for design, selection, qualification, procurement, and implementation considerations.

4.2.1 Risk Assessment Approach

The risk assessment model presented in this Guide involves the calculation of a risk score representing the potential risk of the Process Contact Material (PCM) that the SUS consists of. For a given risk category, additional required in-house qualification should be performed, or leveraged from existing data, and documented. Both supplier and in-house (if necessary) qualification data packages are required to demonstrate suitability of the PCM for its intended use.

The steps for the risk assessment model are:

- Step 1: Identify user requirements for the PCM
- Step 2: Obtain PCM validation data package from the supplier
- Step 3: Perform risk assessment
- Step 4: Execute in-house qualification studies required based on the risk score
- Step 5: Perform risk mitigation

The steps to qualifying PCMs for manufacturing applications include identifying specific supplier qualification requirements, which are drawn from the qualification attributes listed below. Other qualification attributes which are specific to an application may be added.

There are fifteen critical qualification attributes to consider. A full description of each attribute is provided in Chapter 8 (Appendix 4).

- Attribute 1: Biocompatibility Testing
- Attribute 2: Mechanical Properties
- Attribute 3: Gas Transmission Properties
- Attribute 4: Compendial Physicochemical Testing
- Attribute 5: Animal Origin Control
- Attribute 6: Total Organic Carbon (TOC) Analysis
- Attribute 7: pH and Conductivity
- Attribute 8: Extractables and Leachables (E&L)
- Attribute 9: Chemical Compatibility
- Attribute 10: Protein Adsorption Studies
- Attribute 11: Endotoxin Testing
- Attribute 12: Sterilization (Irradiation)
- Attribute 13: Container Closure Integrity
- Attribute 14: Particulate Testing
- Attribute 15: Calibration of Embedded Instrumentation

In advance of conducting qualification activities, it is recommended that an audit of the supplier be completed. This audit can determine in advance how well the PCM might perform against applicable elements for qualification.

With the results of the risk assessment and the elements required to be taken into consideration for qualification, PCMs from appropriate suppliers are chosen for qualification activities.

If qualification results are inconclusive or variable between PCM batches, additional controls may need to be placed on the PCM as part of the supplier manufacturing process or when PCMs are received by the end-user for manufacturing. The qualification results ultimately lead to the incoming requirements as part of the normal quality acceptance of PCM batches.

Additionally, other requirements should be taken into consideration. These include:

- Establishing the expiration dates for the PCM, with sufficient justification and supporting documentation
- Determination of any pre-use testing
 - In addition to any incoming PCM testing, there may be a need to confirm the quality of the PCM installed or just prior to use
 - In the absence of specific guidelines, an evaluation and justification should be made to establish any requirements

- Determination of any post-use testing
 - There may be instances where there is a regulatory requirement to confirm integrity post-use (e.g., vent filters)
 - In the absence of specific guidelines, an evaluation and justification should be made to establish any requirements

4.2.2 Risk Assessment – Calculation of Risk Score

The purpose of the risk assessment is to determine the extent of in-house qualification required according to a calculated risk score for each PCM. The risk assessment model presented in this section takes into account the potential risk to product quality and patient safety. Certain risks should be mitigated by supplier quality systems and upfront evaluation such as chemical compatibility and Class VI certification [23]. Supplier audits should be performed to ensure full traceability of the PCM to its raw materials.

As an example, a risk assessment model may be formulated to calculate the risk score as follows:

$$\text{Risk Score} = A \times B \times C \times D$$

Where: A = Route of administration

 B = Proximity to final product

 C = Contact time

 D = Surface area to volume ratio

This risk assessment model can be applied to assess the relative risk of an individual PCM and to determine the amount of in-house qualification data required. For each risk factor, the score can be classified as high (risk score = 10), medium (risk score = 5), or low (risk score = 1).

Risk Factor A: Route of Administration

For the risk assessment, the following information should be recorded:

- Product name that the material will be used with
- Statement of the dosage form

Table 4.1 lists example assignments of risk factors for routes of administration along with non-exhaustive examples of drug formulation. The risk classification for the route of administration is based on the FDA Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Documentation* [79].

Table 4.1: Risk Classification Based on Route of Administration

Risk Classification for Risk Factor A	Route of Administration	Examples of Drug Formulation
High (Risk Score = 10)	Inhalation/Nasal	Inhalation aerosols and solutions Nasal spray Nasal aerosols Inhalation powders
	Injection (> 10 exposures per life)	Injectable suspension and solutions Sterile powders and powder for injection
	Ophthalmic (> 10 exposures per life)	Ophthalmic solutions and suspensions
Medium (Risk Score = 5)	Injection ($\leq$ 10 exposures per life)	Injectable suspension and solutions (e.g., vaccine) Sterile powders and powder for injection
	Ophthalmic ($\leq$ 10 exposures per life)	Ophthalmic solutions and suspensions
	Internal application	Implants Rectal/vaginal creams and solutions
Low (Risk Score = 1)	Transdermal	Transdermal ointments, creams, lotions, and patches
	Internal irrigation	Nasal rinse solutions
	Topical	Topical lotion, cream, solutions and suspensions Topical powders Topical aerosols
	Oral	Lingual aerosols Oral solutions and suspensions Oral powders Oral tablets Oral capsules (hard and soft gelatin)

Risk Factor B: Proximity to Final Product

The likelihood of an impact on the quality of the product is generally greater as the process moves downstream, i.e., towards the manufacture of final drug product. In certain cases, such as biologics, the risk may also be high at vulnerable upstream points. Knowledge of the process, the contact materials, and the product should be applied to assign an appropriate risk level. It is therefore important for the validation team to collaborate with the formulation team to understand these sensitivities and requirements.

Table 4.2 lists example assignments of risk scores based on proximity to final product.

Table 4.2: Risk Classification Based on Proximity to Final Product

Risk Classification for Risk Factor B	Proximity to Final Product	Comment/Justification
High (Risk Score = 10)	Manufacture of dosage form without dilution or purification step and filling into the final container closure system.	Any contaminants will be filled in the container and consumed by patients.
Medium (Risk Score = 5)	Compounding of drug product involving dilution or purification step before filling. Production of active substances which will be > 50% concentration in the final drug product.	All steps including diafiltration, purification, filtration and/or dilution > 50% will provide synergistic effect in reducing contaminants in the final product.
Low (Risk Score = 1)	Production of active substances including all media and buffer preparation.	All steps before compounding will inherently have lower risk due to the fact that all the downstream process steps will reduce/dilute contaminants as the process progress.
Note: Not all of the above categories for proximity to final product risk factor will be used at every site (e.g., if a site only performs filling of final product, then all contact materials will be high risk for that area of production).		

Risk Factor C: Contact Time

Contact time is the total exposure time that the material is in contact with the product. If the solution just flows through, then the contact time is short and it can be rated as low risk. Long contact times would likely be the down/dwell time when the solution is in static contact with the PCM or during the entire mixing period where solutions are agitated in the mixing tank/bag. If the contact fluid is flushed after the stoppage, the allowable downtime without flushing should be used to determine the risk score for contact time.

If the material is in solid phase, it should be rated as low risk regardless of the contact time.

Table 4.3 lists example assignments of risk scores based on contact time.

Table 4.3: Risk Classification Based on Contact Time

Risk Classification for Risk Factor C	Contact Time	Comment/Justification
High (Risk Score = 10)	> 7 days of exposure time	SUSs will be treated as an intermediate/shipping storage vehicle if materials will be stored beyond 7 days.
Medium (Risk Score = 5)	between 48 hours and 7 days of exposure time	Intermediate or bulk may be stored in bags up to 7 days for further processing.
Low (Risk Score = 1)	< 48 hours of exposure time	Production campaigns can be filled within 36 to 48 hours.

Risk Factor D: Surface Area to Volume Ratio

The greater the ratio of the contact material surface area to the product volume (such as batch size), the greater the potential risk for leachables, adsorption/absorption of active ingredients/excipients, and chemical reactions with the contact material.

The worst-case surface area to volume ratio is a single-use product with a smaller process volume since it usually has higher surface area/volume ratio. The smallest batch size usually represents the worst-case scenario. The lower the volume, the more concentrated any potential leachables would be.

Surface area can be calculated based on the dimension of the contact materials. For items such as gaskets and O-rings, the surface area in contact with a solution can be estimated. Overestimating the area covers worst case scenario.

For gases (e.g., nitrogen), the risk should be classified as low since the risk of a gas removing substances/leachables from the contact material is very low.

Table 4.4 lists example assignments of risk scores based on the surface area to volume ratio.

Table 4.4: Risk Classification Based on Surface Area to Volume Ratio

Risk Classification for Risk Factor D	Surface Area to Volume Ratio	Comment/Justification
High (Risk Score = 10)	Surface area to volume ratio > 0.01 cm ² /ml	A safety factor of > 15-fold relative to extraction condition per USP Class VI testing [23]
Medium (Risk Score = 5)	Surface area to volume ratio in the range 0.01 – 0.001 cm ² /ml	A safety factor of between 15 to 150-fold relative to extraction condition per USP Class VI testing [23]
Low (Risk Score = 1)	Surface area to volume ratio < 0.001 cm ² /ml	A safety factor of > 150-fold relative to extraction condition per USP Class VI testing [23]

Determination of Final Risk Level

After the calculation of the final risk score using the risk score equation above, the final risk level is assigned as follows:

- **Low:** calculated risk score ≤ 1,000
- **Medium:** calculated risk score between 1,001 and 4,999
- **High:** calculated risk score ≥ 5,000

Documentation of the risk score calculation for each PCM should be included in the PCM qualification report. The final risk level can be used to determine the additional in-house qualification studies required.

4.2.3 Execute In-House Qualification

Based on the final risk level of the PCM, the required in-house qualification activities can be determined. Considerations can be made for using subcontractor services for testing.

Regardless of final risk level, in-house qualification requirements should always include:

- Leak/pressure/crack verification
- Tear evaluation (for bags)
- Sterility evaluation (for sterile-supplied PCM)
- Endotoxin evaluation (for sterile-supplied PCM)
- Integrity testing (for 0.2 µm filters, whether sterilizing or for bioburden reduction)

Where the final risk level is medium (calculated risk score between 1,001 through 4,999), additional in-house qualification requirements should include:

- Sorption testing
- Spallation testing (for peristaltic pump tubing)

Where the final risk level is high (calculated risk score $\geq 5,000$), additional in-house qualification requirements should include:

- pH change evaluation
- Leachables testing
- Particulate evaluation

Once the required in-house qualification requirements are identified, there are several approaches to reducing the amount of testing. These approaches include:

- Utilizing existing data from suppliers and in-house data
 - In most cases, existing data from the supplier and in-house data can be utilized without the need to perform additional work. Careful evaluation is necessary to ensure the existing data supports the intended use of the PCM. Risk is also a consideration in evaluating supplier documentation. Only formal and official documents issued by the supplier should be admissible. Supporting data needs to be provided using an appropriate format (e.g., official statement or executive summary) and registered in an adequate tracking system. A traceable formal document from the supplier should be used in place of information from a web site.
- QbD approach
 - The QbD approach involves using data for a higher risk PCM to qualify the same PCM in the same or lower risk categories. The PCM categorized as high risk can be qualified to bracket lower risk category PCMs if all of the following criteria are met:
 - > Same grade of resin and material of construction
 - > Same supplier/manufacturer
 - > Used for the same/similar drug substance, drug product, or excipient
 - All samples can be prepared in accordance with QbD principles to represent worse case and bracket uses in less severe conditions.

- Paper exercise
 - For certain low risk applications, in-house qualification studies can potentially be satisfied with a paper exercise to meet qualification requirements without the need to perform testing.

A combination of these approaches in one PCM qualification can be considered. If in-house qualification testing is required, the testing can be designed for individual PCMs or for a group of PCMs. It is important to first understand the advantages and disadvantages of each approach and the future implication with regard to data leveraging, material changes, and alternate supplier qualification.

4.2.4 Risk Mitigation

Following qualification activities, the report conclusion should highlight any of the tests in which additional controls may need to be placed on incoming materials. Routinely, if the qualification package is complete and compliant with all acceptance criteria met and without inconclusive test results, the PCM is accepted with minimal incoming test requirements. These incoming requirements should minimally include:

- Confirmation of materials (correct PCM and site of manufacture)
- Confirmation of sterility status, if applicable
- Review of Certificate of Analysis (COA) for any prescribed supplier testing and certification
- Confirmation of packaging integrity or packaging configuration

If any qualification studies are inconclusive, incoming controls should be placed on the PCM. Likewise, deviations encountered during the use or processing of the PCM may also be an indicator for placing controls on the incoming PCM.

If the material does not meet the minimum requirements, there are remediation options such as:

- Selecting another supplier
- Requesting the supplier to generate the test data
- Performing in-house qualification
- Implementing a risk mitigation step in the process, if possible

4.3 Change Management

Change management is an important element of a pharmaceutical manufacturing quality system. Change management processes should be applied to ensure control of the system and the process it belongs to. With the rapid development of SUT, implementation of a structured change control process within a change management system allows for smooth operations and predictable compliance with regulatory requirements. Whether introducing SUT into an operation or maintaining an existing operation, changes will routinely arise. Changes may come from product improvements, availability of new types of products, or phasing out of products as they become obsolete due to improved products.

This section covers typical changes associated with SUT operations, and typical methods/activities that are applied in change management.

For detailed information on the steps of effective change management, refer to *ISPE Product Quality Lifecycle Implementation (PQLI®) Good Practice Guide: Part 3 – Change Management System* [80]. In addition, refer to the BPOG paper “An Industry Proposal for Change Notification Practices for Single-Use Biomanufacturing Systems” [81].

4.3.1 Typical Changes Associated with Single-Use Technology Operations

Typical changes associated with SUT operations can be categorized as maintenance/improvement changes and major disruptive changes. Examples of these changes include:

- Maintenance/improvement changes
 - Operational improvements
 - Change in drawing format or documentation
 - Storage location
 - Transit route
- Major disruptive changes
 - Material of construction or formulation
 - Obsolete component
 - Manufacturing methods (process parameter or equipment)
 - Manufacturing location
 - Dimensions of component
 - Supplier of single-use product
 - Sterilization supplier/location

Change management with SUT operations can be a complex process due to the number of stakeholders (e.g., compounders, manufacturers, assemblers) and raw materials involved in the supply chain. Primary suppliers (who may use secondary suppliers to source components) should ensure total ownership of delivered single-use assemblies and provide full transparency. The following aspects should be addressed:

- Supplier's definition of change
- Supplier's qualification process for alternative raw materials sources (e.g., resins, additives, films)
- Supplier's change management process, including:
 - Customer notification and agreement on lead times for such change notifications
 - Mitigation activities, such as inventory of raw materials

A robust supply chain communications process is a major requirement for effective change management. The supply chain communication can be enhanced by implementation of the following:

- Quality agreement

- Periodic audits
- Predefined and direct communication channels

Changes can also be managed by securing the supply, more specifically, qualifying alternative sourcing for single-use products. To address this topic, the PDA Technical Report 66 [52] presents the concept of single-use component interchangeability. This interchangeability can be considered when there is no impact on process performance and product quality. It is dependent on intended function, processing conditions, and fit for purpose evaluation. Further evaluations (such as compatibility and leachables testing) may need to be conducted for most cases other than like-for-like.

4.3.2 *Typical Methods/Activities Applied in Change Management*

The level of evaluation depends on change criticality and is related to the intended use and processing conditions (risk-based approach) of the SUS. In some cases, the comparability data provided by the supplier may be sufficient to support the assessment.

The following methods/activities are typically performed to support the change evaluation step of the change management process:

- E&L tests
- Functional tests
- Robustness tests
- Mechanical strength evaluation
- Interaction with other components
- Shelf life

4.4 Project Schedules

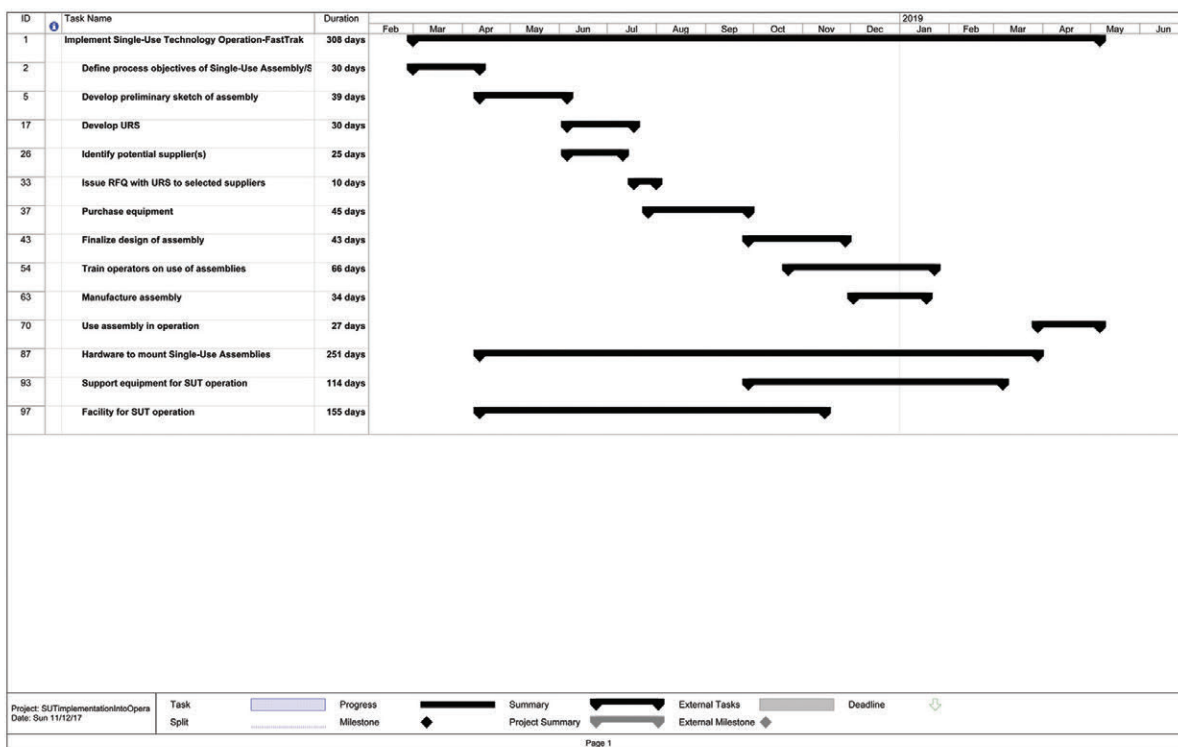
This section provides example schedules that capture important tasks in the various phases of SUT implementation. The schedules are structured to allow for selected tasks to be accomplished in parallel while optimizing the use of time and resources. Running activities in parallel reduces the overall project time; however, this may cause spikes in the resources required and usually decreases the efficiency in the use of resources. The schedules are intended to help the reader identify the time commitments for the tasks and prepare or adjust accordingly. The reader should use these example schedules to develop customized schedules to fit the specific project requirements.

4.4.1 *Single-Use Technology Implementation into Operations with Qualified Components*

The example schedule provided in Figure 4.1 targets the overall implementation tasks. It is based on the following conditions which allow for fast SUT implementation:

- All components used in the assemblies are qualified to be used in the process
- E&L information has been developed and is available for the specific process fluid

This example schedule helps identify tasks that require more time to complete. The time-consuming tasks are arranged in parallel with other tasks to expedite the implementation process while retaining an efficient use of resources.

Figure 4.1: Example Schedule (Top Level Tasks) – Operations with Qualified Components

Note: Even if all components are qualified, the complete assembly may be new in terms of component engagement or dimensions (e.g., tubing length or diameter). It should be tested to check if it fits into the process (e.g., tubing length, connections, etc.) through technical checks with samples and prototype testing.

4.4.2 Single-Use Technology Implementation into Operations with One or More Components that Need Qualification

Similar to the example in Section 4.4.1, these schedules target the overall implementation tasks. However, these schedules are based on the condition that one or more of the components used in the assemblies need to be qualified to be used in the process. These schedules also incorporate time for conducting extractables tests. These time-consuming tasks are arranged early in the process and in parallel with other tasks to expedite the implementation process. Two example schedules are provided: Figure 4.2a shows the top level task groups and Figure 4.2b shows the details of key tasks.

Figure 4.2a: Example Schedule (Top Level Tasks) – Operations with One or More Qualified Components that Need Qualification

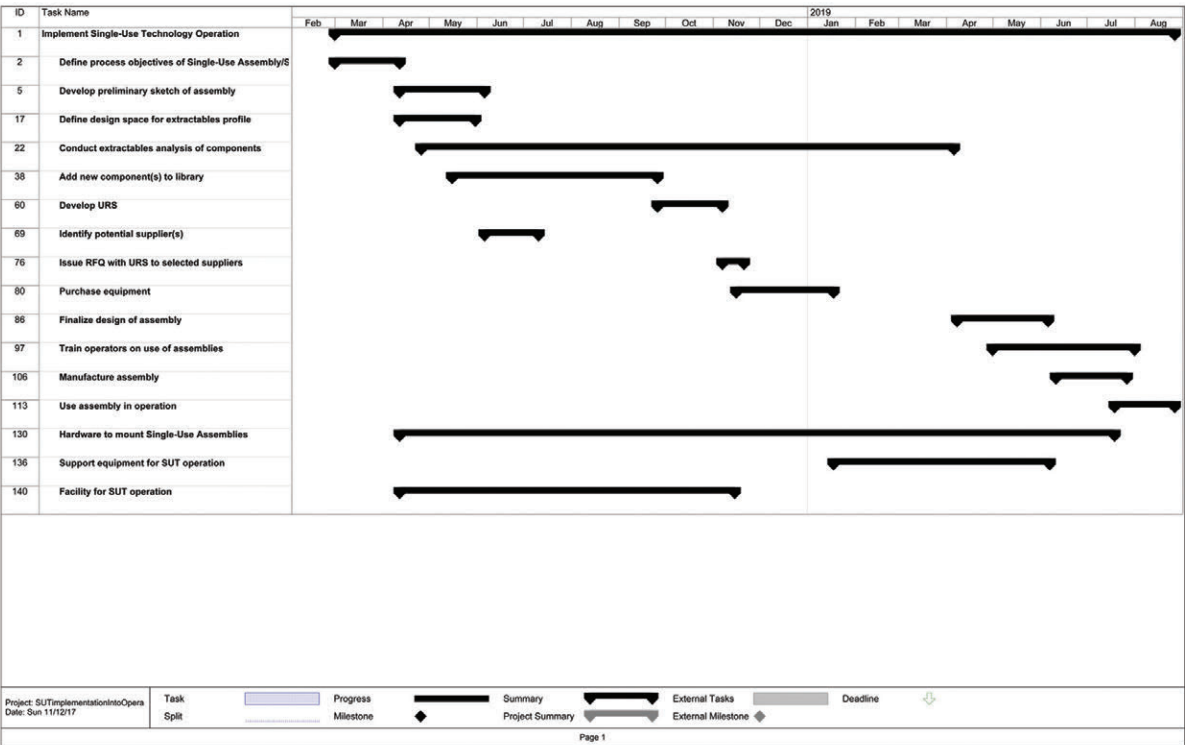
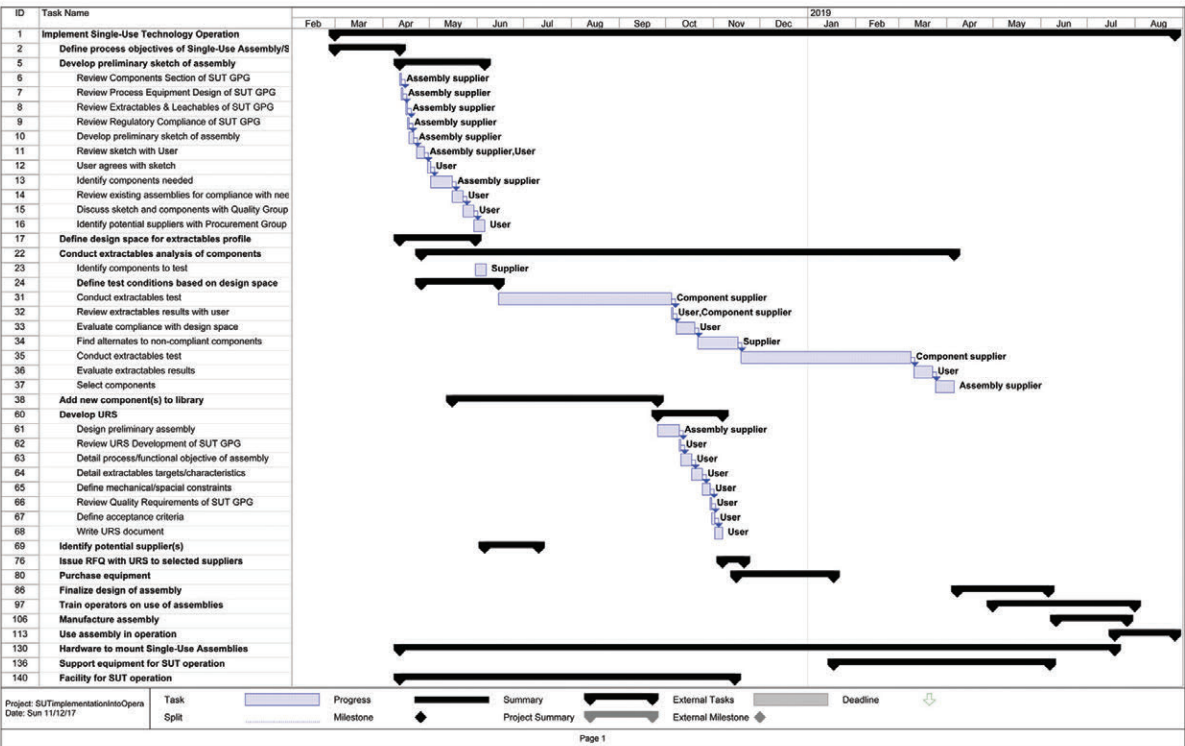


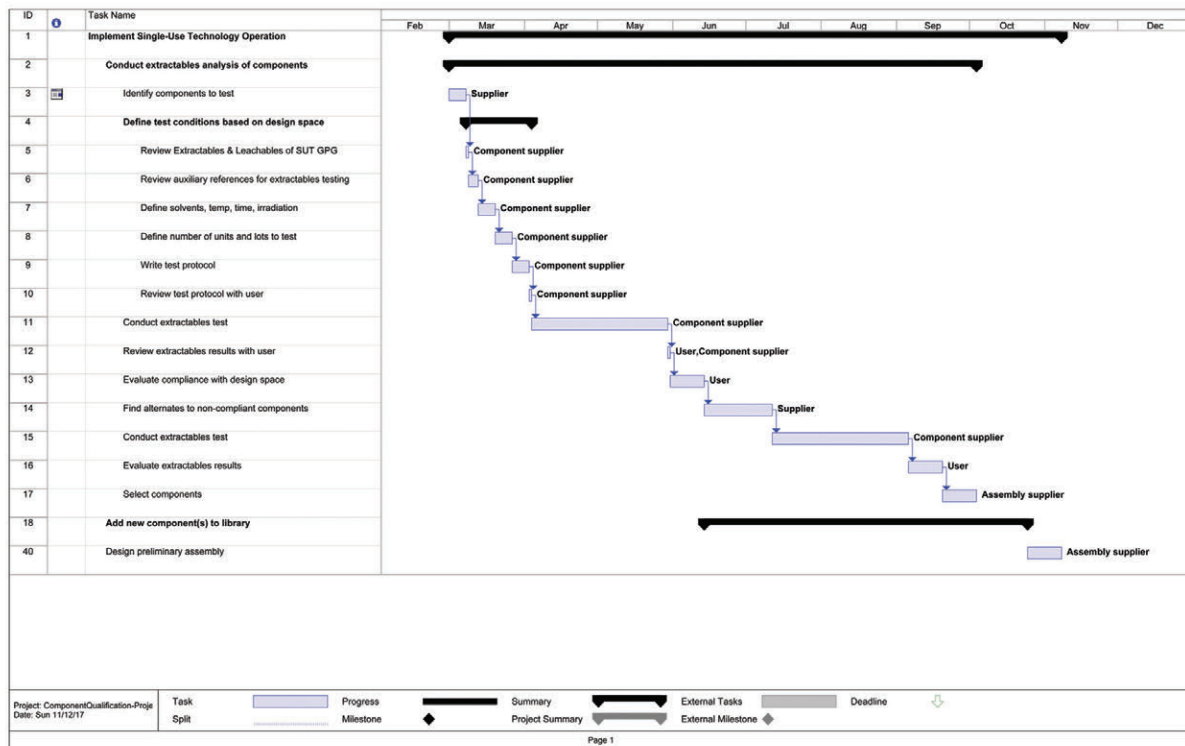
Figure 4.2b: Example Schedule (Detailed Key Tasks) – Operations with One or More Qualified Components that Need Qualification



4.4.3 Qualification of Single-Use Technology Components

The example schedule in Figure 4.3 shows the tasks to conduct a qualification of components. It primarily focuses on extractables testing. The schedule is based on the condition that fundamental information on gamma irradiation compatibility, functional compliance, and shelf life information is available from the component supplier. Review and confirmation of compliance is performed as the component is added to the component library.

Figure 4.3: Example Schedule: Qualification of SUT Components



4.4.4 Introduction of Single-Use Technology into Operations

These schedules are based on a broad scope to introduce SUT in bioprocessing. It expands on the schedule presented in an ISPE Knowledge Brief [82]. It includes tasks on container/component qualification within a fast implementation schedule. Two example schedules are provided: Figure 4.4a shows the top level task groups and Figure 4.4b shows the details of key tasks.

Figure 4.4a: Example Schedule (Top Level Tasks) – Introduction of SUT into Operations

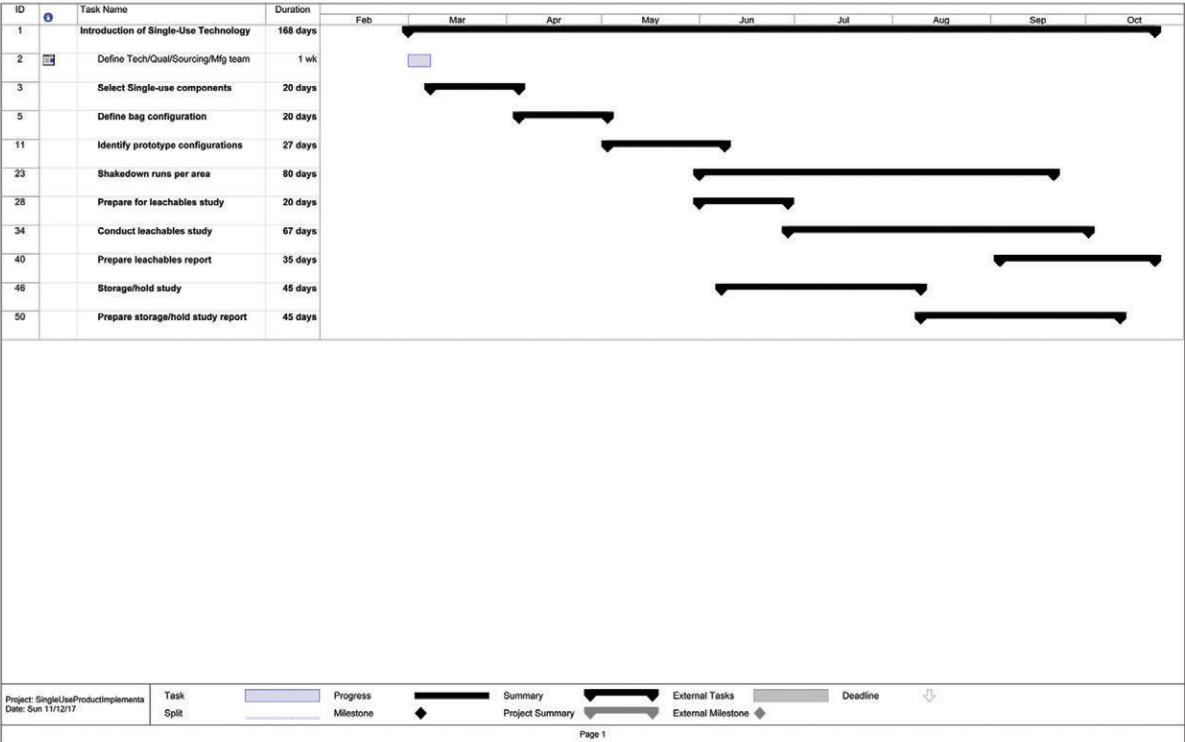
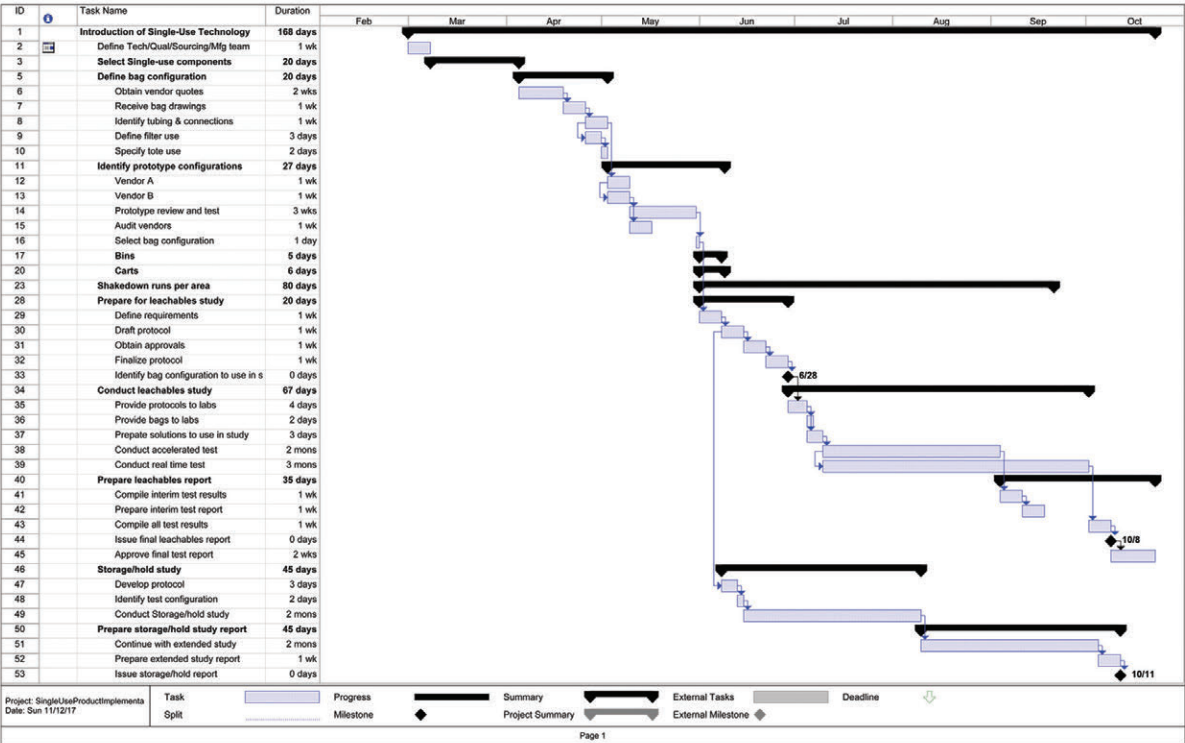


Figure 4.4b: Example Schedule (Detailed Key Tasks) – Introduction of SUT into Operations



4.4.5 Technology Transfer

These schedules are intended for technology transfer of SUT via scale-up into another bioprocess operation. Two example schedules are provided: Figure 4.5a shows the top level task groups and Figure 4.5b shows the details of key tasks.

Figure 4.5a: Example Schedule (Top Level Tasks) – Technology Transfer

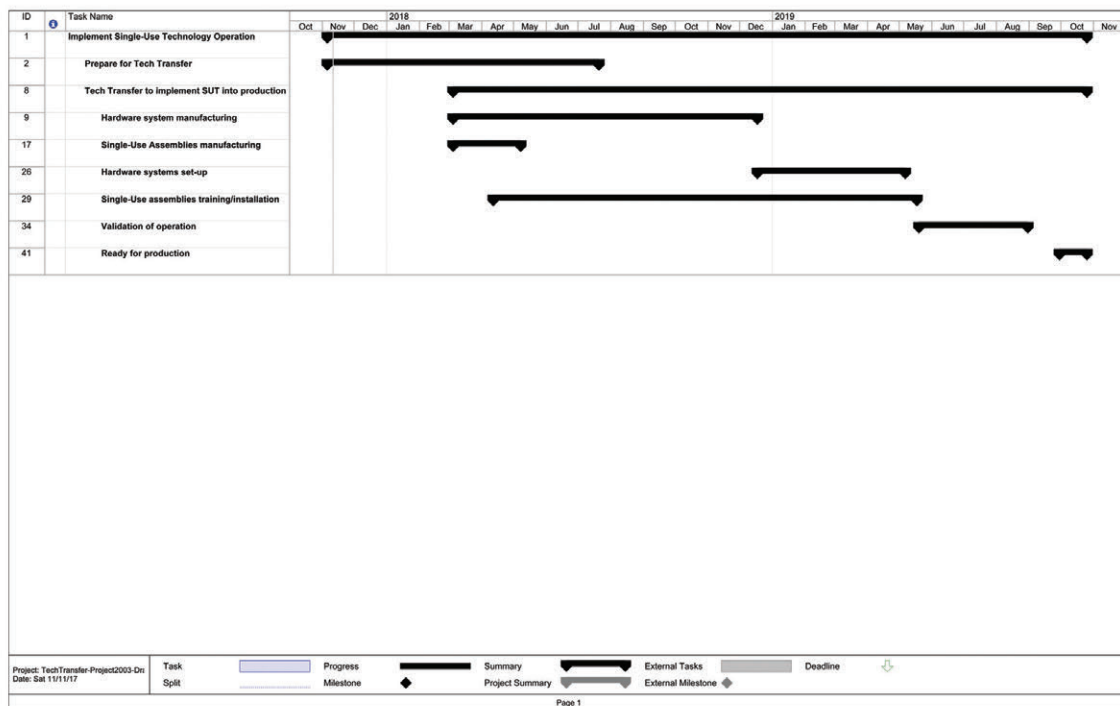
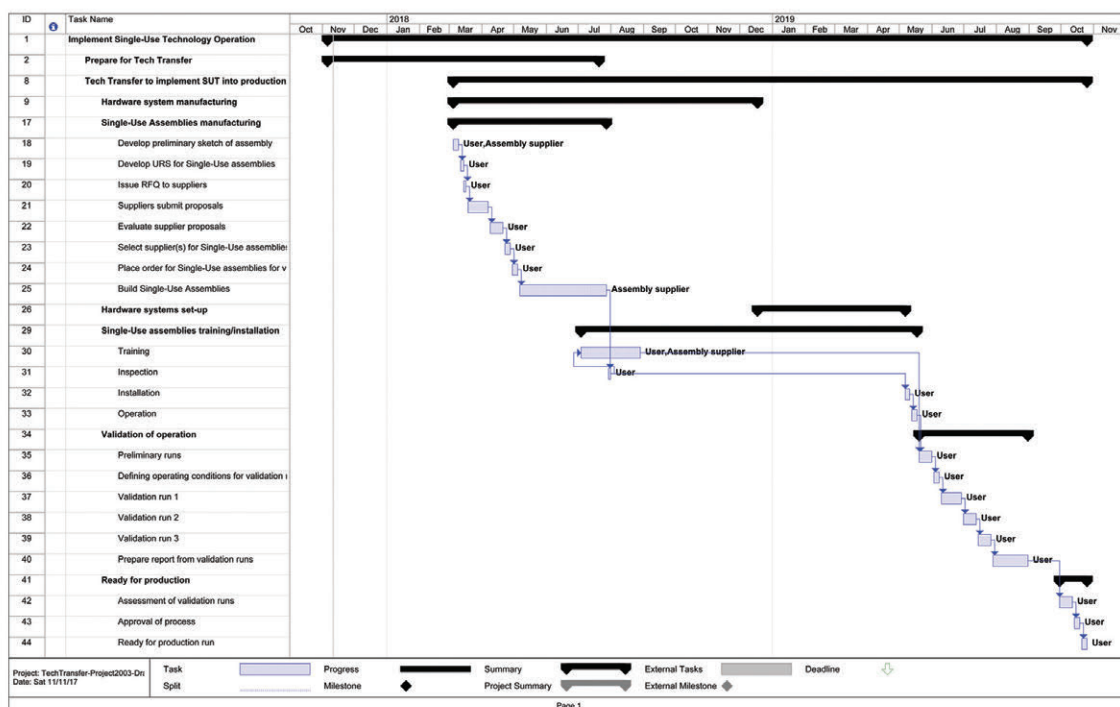


Figure 4.5b: Example Schedule (Detailed Key Tasks) – Technology Transfer



4.4.6 Training

These schedules identify tasks related to an example training program for SUT implementation. Two example schedules are provided: Figure 4.6a shows the top level task groups and Figure 4.6b shows the details of key tasks.

Figure 4.6a: Example Schedule (Top Level Tasks) – Training

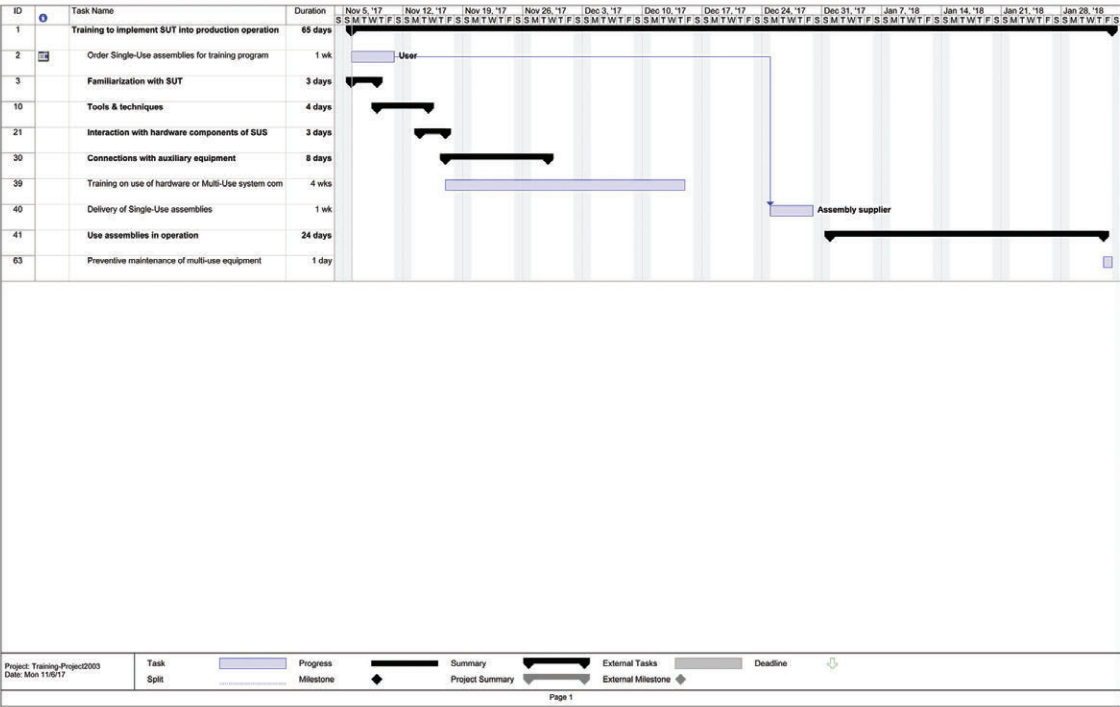
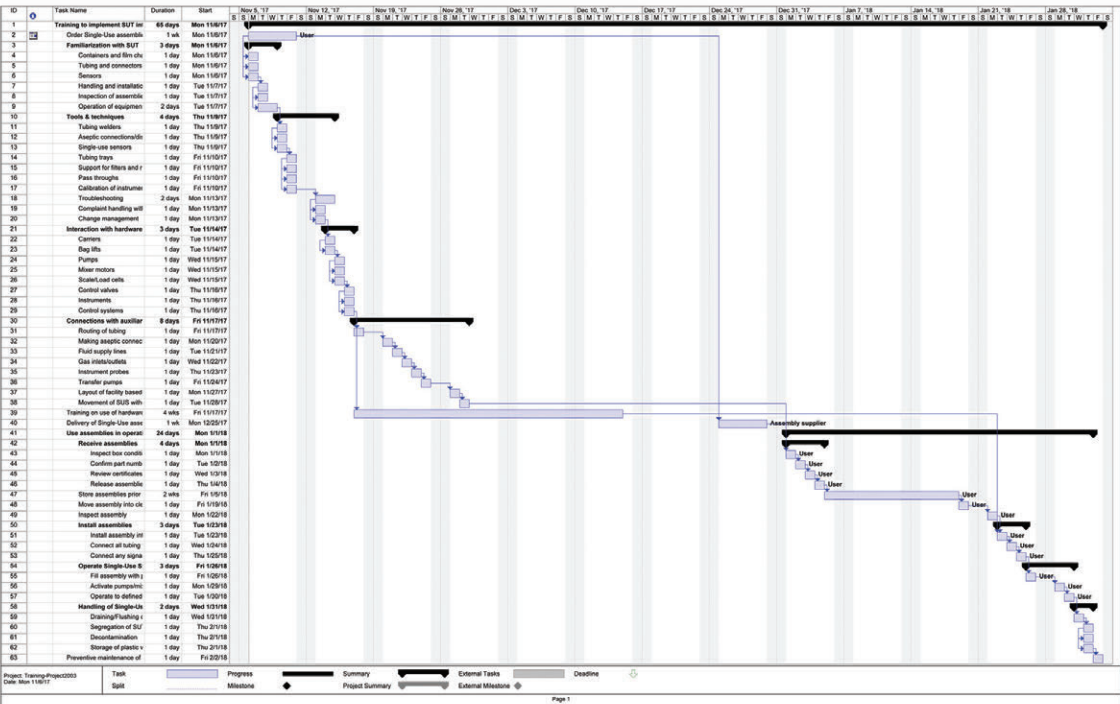


Figure 4.6b: Example Schedule (Detailed Key Tasks) – Training



5 Appendix 1 – Additional Information: Regulations and Standards

Note: The tables in this appendix are not intended to be all inclusive.

5.1 International Standards

International Council for Harmonisation (ICH)

Standard/Document	Title/Description
ICH Q1A-Q1F	Stability
ICH Q3A-Q3D	Impurities
ICH Q7	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
ICH Q8	Pharmaceutical Development
ICH Q9	Quality Risk Management
ICH Q10	Pharmaceutical Quality System

International Organization for Standardization (ISO)

Standard/Document	Title/Description
ISO 9000:2015	Quality management systems – Fundamentals and vocabulary
ISO 9001:2015	Quality management systems – Requirements
ISO 9004:2018	Quality management – Quality of an organization – Guidance to achieve sustained success
ISO 10001:2018	Quality management – Customer satisfaction – Guidelines for codes of conduct for organizations
ISO 10002:2018	Quality management – Customer satisfaction – Guidelines for complaints handling in organizations
ISO 10003:2018	Quality management – Customer satisfaction – Guidelines for dispute resolution external to organizations
ISO 10005:2018	Quality management – Guidelines for quality plans
ISO 10006:2017	Quality management – Guidelines for quality management in projects
ISO 10007:2017	Quality management – Guidelines for configuration management
ISO 10012:2003	Measurement management systems – Requirements for measurement processes and measuring equipment
ISO/TR 10013:2001	Guidelines for quality management system documentation
ISO 10014:2006	Quality management – Guidelines for realizing financial and economic benefits
ISO 10015:1999	Quality management – Guidelines for training
ISO/TR 10017:2003	Guidelines on statistical techniques for ISO 9001:2000

International Organization for Standardization (ISO) (continued)

Standard/Document	Title/Description
ISO 10019:2005	Guidelines for the selection of quality management system consultants and use of their services
ISO 10993-1:2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
ISO 10993-3:2014	Biological evaluation of medical devices – Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
ISO 10993-4:2017	Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
ISO 10993-5:2009	Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity
ISO 10993-6:2016	Biological evaluation of medical devices – Part 6: Tests for local effects after implantation
ISO 10993-10:2010	Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization
ISO 10993-11:2017	Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
ISO 11135:2014	Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices
ISO 11137-1:2006	Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
ISO 11137-2:2013	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose
ISO 11137-3:2017	Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects of development, validation and routine control
ISO 11138-1:2017	Sterilization of health care products – Biological indicators – Part 1: General requirements
ISO 11138-2:2017	Sterilization of health care products – Biological indicators – Part 2: Biological indicators for ethylene oxide sterilization processes
ISO 11607-1:2006	Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems
ISO 11737-1:2018	Sterilization of Medical Devices – Microbiological Methods – Part 1: Determination of a population of microorganisms on products
ISO 11737-2:2009	Sterilization of Medical Devices – Microbiological Methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
ISO 14161:2009	Sterilization of health care products – Biological indicators – Guidance for the selection, use and interpretation of results
ISO 14644-1:2015	Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration
ISO 14644-8:2013	Cleanrooms and associated controlled environments – Part 8: Classification of air cleanliness by chemical concentration (ACC)
ISO 14644-9:2012	Cleanrooms and associated controlled environments – Part 9: Classification of surface cleanliness by particle concentration
ISO 15747:2018	Plastic containers for intravenous injections
ISO 19011:2018	Guidelines for auditing management systems

5.2 United States Regulations and Standards

US Food and Drug Administration (FDA)

Standard/Document	Title/Description
FDA Guidance for Industry (February 2008)	Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
FDA Guidance for Industry and Food and Drug Administration Staff (June 2016)	Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process”
United States Code, Title 21	Federal Food, Drug, and Cosmetic Act (FD&C Act)
21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 211	Current Good Manufacturing Practice for Finished Pharmaceuticals
21 CFR Part 211.65	Equipment construction
21 CFR Part 211.94	Drug product containers and closures
21 CFR Part 600.11(b)	Physical establishment, equipment, animals, and care – Equipment
21 CFR Part 600.11 (h)	Physical establishment, equipment, animals, and care – Containers and closures
21 CFR Part 801	Labeling
21 CFR Part 820	Quality System Regulation

Association for the Advancement of Medical Instrumentation (AAMI)

Standard/Document	Title/Description
AAMI TIR17:2017	Compatibility of materials subject to sterilization
AAMI/ISO TIR16775:2014	Packaging for terminally sterilized medical devices – Guidance on the application of ISO 11607-1 and ISO 11607-2
ANSI/AAMI ST79:2017	Comprehensive guide to steam sterilization and sterility assurance in health care facilities
ANSI/AAMI ST67:2011/(R)2017	Sterilization of health care products—Requirements and guidance for selecting a sterility assurance level (SAL) for products labeled ‘sterile’
ANSI/AAMI/ISO 10993-7:2008/(R)2012	Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals

American Society for Testing and Materials (ASTM)

Standard/Document	Title/Description
ASTM D1709-16ae1	Standard Test Methods for Impact Resistance of Plastic Film by the Free-Falling Dart Method
ASTM D3985-17	Standard Test Method for Oxygen Gas Transmission Rate Through Plastic Film and Sheeting Using a Coulometric Sensor
ASTM D4169-16	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM D543-14	Standard Practices for Evaluating the Resistance of Plastics to Chemical Reagents
ASTM D7386-16	Standard Practice for Performance Testing of Packages for Single Parcel Delivery Systems
ASTM D882-18	Standard Test Method for Tensile Properties of Thin Plastic Sheeting
ASTM E1640-13(2018)	Standard Test Method for Assignment of the Glass Transition Temperature by Dynamic Mechanical Analysis
ASTM E165/ E165M-12	Standard Practice for Liquid Penetrant Examination for General Industry
ASTM E2500-13	Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
ASTM E3051-16	Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing
ASTM E432-91(2017) e1	Standard Guide for Selection of a Leak Testing Method
ASTM E498/ E498M-11(2017)	Standard Practice for Leaks Using the Mass Spectrometer Leak Detector or Residual Gas Analyzer in the Tracer Probe Mode
ASTM E499/ E499M-11(2017)	Standard Practice for Leaks Using the Mass Spectrometer Leak Detector in the Detector Probe Mode
ASTM E515-11(2018)	Standard Practice for Leaks Using Bubble Emission Techniques
ASTM F1249-13	Standard Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor
ASTM F1608-16	Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)
ASTM F1886/ F1886M-16	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
ASTM F1927-14	Standard Test Method for Determination of Oxygen Gas Transmission Rate, Permeability and Permeance at Controlled Relative Humidity Through Barrier Materials Using a Coulometric Detector
ASTM F1929-15	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration
ASTM F1980-16	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ASTM F2095-7(2013)	Standard Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates
ASTM F2097-16	Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products

American Society for Testing and Materials (ASTM) (continued)

Standard/Document	Title/Description
ASTM F2338-09(2013)	Standard Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method
ASTM F2391-05(2016)	Standard Test Method for Measuring Package and Seal Integrity Using Helium as the Tracer Gas
ASTM F392/F392M-11(2015)	Standard Practice for Conditioning Flexible Barrier Materials for Flex Durability
ASTM F88/F88-M-15	Standard Test Method for Seal Strength of Flexible Barrier Materials

5.3 United States Pharmacopeia (USP)

Standard/Document	Title/Description
USP <85>	Bacterial Endotoxins Test
USP <87>	Biological Reactivity, In Vitro
USP <88>	Biological Reactivity, In Vivo
USP <381>	Elastomeric Closure for Injection
USP <661>	Plastic Packaging Systems and Their Materials of Construction
USP <661.1>	Plastic Materials of Construction
USP <661.2>	Plastic Packaging Systems for Pharmaceutical Use
USP <787>	Subvisible Particulate Matter in Therapeutic Protein Injections
USP <788>	Particulate Matter in Injections
USP <790>	Visible Particulates in Injections
USP <1031>	The Biocompatibility of Materials used in Drug Containers, Medical Devices and Implants
USP <1207>	Package Integrity Evaluation – Sterile Products
USP <1661>	Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact
USP <1663>	Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
USP <1664>	Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
USP <1787>	Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections
USP <1788>	Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions
USP <1790>	Visual Inspection of Injections

5.4 European Standards and Regulations

Standard/Document	Title/Description
Annex 1 of the European Union GMPs (EudraLex Volume 4)	Manufacture of Sterile Medicinal Products
British Standard/ European Standard BS EN 868-8:2009	Packaging for terminally sterilized medical devices. Re-usable sterilization containers for steam sterilizers conforming to EN 285. Requirements and test methods
EMA Guideline CPMP/QWP/4359/03 EMA/CVMP/205/04	Guideline on plastic immediate packaging materials
EMA Guideline EMA/CHMP/ BWP/187338/2014	Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission
EMA Guideline EMA/410/01 rev.3	Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products
European Commission Directive 2011/65/EU	Restriction of Hazardous Substances in Electrical and Electronic Equipment
European Commission Directive 2012/19/EU	Waste Electrical and Electronic Equipment (WEEE)
European Commission Regulation EC No. 1907/2006	Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
European Standard EN 556-1:2001	Sterilization of medical devices – Requirements for medical devices to be designated “STERILE” – Part 1: Requirements for terminally sterilized medical devices
European Standard EN 556-2:2015	Sterilization of medical devices – Requirements for medical devices to be designated “STERILE” – Part 2: Requirements for aseptically processed medical devices
German Standard DIN 58953-9	Sterilization – Sterile supply – Part 9: Use of sterilization container
International Electrotechnical Commission IEC 60601- 1:2005+AMD1:2012	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
International Electrotechnical Commission IEC 60601-1-2:2014	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests

5.5 European Pharmacopoeia (EP)

Standard/Document	Title/Description
EP 2.6.14	Bacterial endotoxins
EP 2.9.19	Particulate contamination: sub-visible particles
EP 2.9.20	Particulate contamination: visible particles
EP 3.1	Materials Used for the Manufacture of Containers
EP 3.1.3	Polyolefins
EP 3.1.4	Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations
EP 3.1.5	Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations
EP 3.1.6	Polypropylene for containers and closure for parenteral preparations and for ophthalmic preparations
EP 3.1.7	Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations
EP 3.1.9	Silicone elastomer for closures and tubing
EP 3.2.2	Plastic containers and closures for pharmaceutical use
EP 3.2.8	Sterile single-use plastic syringes
EP 3.2.9	Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders

5.6 Other International Regulatory and Pharmacopoeial Organizations

Country	Regulatory Organization
Australia	Therapeutic Goods Administration (TGA)
Brazil	National Health Surveillance Agency (ANVISA)
Canada	Therapeutic Products Directorate (TPD) • C.R.C. c. 870 Food and Drugs Act • Policy on the Canadian Medical Devices Conformity Assessment System (CMDCAS) – Quality Systems
China	National Medical Products Administration (formerly known as China FDA)
Japan	Japanese Pharmacopoeia

6 Appendix 2 – Example Training Procedures for Inspections

SUSs are typically delivered in cardboard boxes. Individual SUS units are usually double packed under vacuum, in plastic transparent over-pouches as secondary packaging. Protective foams are frequently used to safeguard the film from sharp components such as clamps, connectors or filters.

Recommendations for storage and handling of SUSs include:

- Follow shelf life and storage recommendations (environment, temperature, etc.) provided by the suppliers to minimize risk to the SUSs.
- Store the SUSs in their original box in the warehouse to minimize the risk of damage (as the number of products in each box is typically validated by the supplier with regard to specific design, weight, and constraints).
- When using cutters to open the cardboard box, take special precautions to avoid damaging the SUS.
- Organize a storage area in (or near) the production room, equipped with adapted shelves (with flat surfaces and no sharp angles), and use ergonomic transport carts for transfers. When SUSs are stacked on a shelf, care should be taken to the maximum quantity specified by the supplier (usually the same as in the original box) to minimize potential damage due to product/component weight.
- Pay special attention to single-use mixers and single-use bioreactors which may include impellers, stirrers, and sensors.

In creating the inspection procedures, the supplier can offer key recommendations. General inspection procedures may include:

- As a first step for all SUSs, check the cardboard box integrity and the certificate of release upon receipt
- Before unpacking the SUS, check the irradiation label and evaluate the over-pouch integrity to ensure it is under slight vacuum and free from damage
- Due to differences between SUS types, the procedures for the SUS itself should be based on component groups:
 - Packaging: check the over-pouches for creases, scratches, or tears.
 - Bag: check the bag for film damage (scratches or tears) and inspect the ports and sensors.
 - Container system: check suitability for bag installation and that the interior is clean, dry, and has no sharp areas. Suppliers should provide recommendation for hardware cleaning.
 - Tubing/connections: check the tubing for damage and missing clamps or cable ties. Ensure connections are properly tightened.
 - Filters and sensors: check for damage or improper installation.

7 Appendix 3 – Defective Products and Failure Risks

In an occurrence of failure, it is recommended to inform the supplier even when an official complaint or report is not required. The supplier can investigate the root cause, make recommendations, and develop a corrective action plan. In addition, the failure can be entered into the supplier CAPA system to support continuous quality improvement for the single-use product.

The supplier should provide to the end-user the procedure for complaint registration and the list of requested documentation. Product reference, batch number, and process descriptions should always be submitted to the supplier. Safety information about fluid contact and a certificate of decontamination are often requested before returning any defective products. The defective product should be evaluated and tested for damage or deviation that will support root cause analysis.

It is preferable to send the entire defective SUS (not only the part where the defect is located), arranged back to the originally received configuration with the original set of packaging (including over-pouches), to provide more information on where the failure may have occurred. For example, if damage/demarcation on the packaging and SUS correlate to the same location, this may indicate that damage occurred prior to installation.

If the defective product cannot be sent (e.g., due to contact with toxin or live virus), the complaint investigation and report would only be based on a batch documentation review. In this case, submitting pictures or videos with a thorough explanation can help support the investigation.

The reminder of this appendix provides a general overview of common factors that lead to SUS failures during use. Due to the broad variety of SUSs, the associated risks should be identified by the supplier and end-user and assessed in the context of the application; an adapted troubleshooting procedure can then be defined.

Detection of supplier defects (missing components, incorrect assembly, foreign particulates within the packaging, etc.) is part of the inspection procedure. Such observations should lead directly to a formal complaint.

During use, SUS failures are mostly related to leakages. The main factors that contribute to leakage are listed below, with suggestions for how to mitigate these risks:

- Improper handling during storage, transfer, and setup
 - Optimize storage conditions following the supplier's recommendation
 - Use ergonomic storage bin and transfer cart
 - Provide operational training
- Mechanical stress on film or welds
 - Optimize bag deployment method, minimizing manipulations and folds/creases
 - Follow supplier recommendations for pressure and flow rate
 - Optimize shipping condition

- Accidental puncture
 - Avoid use of sharp objects
 - Use a flat table to unpack the SUS, when possible
 - Control cleanliness of container, avoiding sharp edges or barbs
- Leakage on connections
 - Check the clamping on relevant lines
 - Follow supplier recommendations for operational pressure
 - Optimize the design to a specific application (reinforced tubing, strong connection systems, additional qualification work, etc.)

8 Appendix 4 – Additional Information for Risk Management Qualification Attributes

8.1 Attribute 1: Biocompatibility Testing

Biocompatibility testing is a core requirement for polymeric materials having product contact. Testing should follow USP <87> [22] and USP <88> [23] as follows:

- Documentation should be provided to show testing by a recognized laboratory meeting the requirements of 21 CFR Part 58 Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies [83].
- Results should be reported with actual reactivity scores, rather than with a simple “Pass”. The criteria for a passing result could be less than Grade 2 (mild sensitivity), where Grade 0 (no reactivity) is the desired result. Results for the following tests are expected:
 - Elution and agar diffusion tests per USP <87> [22]
 - > The elution test involves extraction of polymeric material using minimum essential media and placed on confluent monolayers of mouse fibroblast cells and examined after 48 hours for changes in cell morphology.
 - > The agar diffusion test involves placing portions of material on an agarose surface directly overlaying confluent monolayers of mouse fibroblast cells and examining after 24 hours for changes in cell morphology.
 - Systemic injection, intracutaneous, and implantation tests per USP <88> [23]
 - > Studies should be performed as Class VI plastics and with 70°C for the temperature of extraction.
 - Suppliers may choose to use alternative testing, such as ISO 10993-1 [26]; however, scientific justification for equivalency in testing results should be provided.

8.2 Attribute 2: Mechanical Properties

For mechanical properties, the expectation is that the supplier will supply the documented test results for the applicable properties of each single-use product. Refer to:

- ASTM F2097-16 Standard Guide for *Design and Evaluation of Primary Flexible Packaging for Medical Products* [84]
- BPSA 2015 Single-Use Manufacturing Component Quality Test Matrices Guide [68] for best practices and specific test references

8.3 Attribute 3: Gas Transmission Properties

The gas transmission properties of containers constructed of plastics should be provided according to the appropriate ASTM [2] methods:

- ASTM F1249-13 [85] for water vapor at dry conditions
- ASTM D3985-17 [86] for oxygen at dry conditions
- ASTM F1927-14 [87] for oxygen at controlled relative humidity

The conditions of the testing should be stated for the reported result(s), including thickness of the film tested, temperature of the test, oxygen partial pressure used on both sides of the film during the test, and relative humidity on the upstream side of the film during the test.

If the testing completed to provide reported values for the oxygen and water vapor transmission rates were not completely in accordance with the appropriate ASTM [2] method, then the differences between the test method and the ASTM [2] method should be clearly stated.

8.4 Attribute 4: Compendial Physicochemical Testing

Physicochemical testing should be performed for components constructed of plastics, such as high-density PE, low-density PE, PP, PET, PETG, and poly(ethylene-co-vinyl acetate). Testing should follow USP <661> [20] or EP 3.1.3 [73] requirements set forth for these plastics. Testing should be applied to containers, connectors, tubing, fitting, etc. as appropriate.

Plastic container requirements of USP <661> [20] for polymeric containers are listed below, with additional specific tests according to polymer type:

- Infrared spectroscopy (IR) with multiple internal reflectance spectrum, range is specific to the plastic type
- Differential scanning calorimetry, range is specific to the plastic type
- Heavy metals
- Non-volatile residue
- Residue on ignition
- *In vitro* biological reactivity tests per USP <87> [22]
- Total terephthaloyl moieties
- Ethylene glycol

Table 8.1 details the plastic container property requirements of the EP [88] according to polymer type.

Table 8.1: Summary of European Pharmacopoeia [88] Testing Requirements

Polymer Type	Polyolefins ¹	Polyethylene without additives	Polyethylene with additives	Polypropylene with additives	Poly(ethylene-vinyl acetate) with
Reference EP Chapter	EP 3.1.3 [73]	EP 3.1.4 [89]	EP 3.1.5 [90]	EP 3.1.6 [91]	EP 3.1.7 [92]
Appearance of Solution	Yes	Yes	Yes	Yes	Yes
Acidity or Alkalinity	Yes	Yes	Yes	Yes	Yes
Absorbance	Yes	Yes	Yes	Yes	Yes
Reducing Substances	Yes	Yes	Yes	Yes	Yes
Substances soluble in Hexane	Yes	Yes	Yes	Yes	Yes
Additives	Not applicable	Yes	Not applicable	Not applicable	Not applicable
Extractable Aluminum	Yes	Not applicable	Yes	Yes	Not applicable
Extractable Chromium	Not applicable	Not applicable	Yes	Yes	Not applicable
Extractable Titanium	Yes	Not applicable	Yes	Yes	Not applicable
Extractable Vanadium	Not applicable	Not applicable	Yes	Yes	Not applicable
Extractable Zinc	Yes	Not applicable	Yes	Yes	Not applicable
Extractable Zirconium	Not applicable	Not applicable	Yes	Not applicable	Not applicable
Extractable heavy metals	Yes	Yes	Yes	Yes	Not applicable
Sulphated ash	Yes	Yes	Yes	Yes	Yes ²
Phenolic Antioxidants	Yes ²	Not applicable	Yes ²	Yes ²	Yes ²
Non-phenolic Antioxidants	Yes ²	Not applicable	Yes ²	Yes ²	Not applicable
Plastic Additive 22	Yes ²	Not applicable	Not applicable	Not applicable	Not applicable
Amides and Stearates	Yes ²	Not applicable	Yes ²	Yes ²	Yes
Notes: 1. Containers should confirm to the requirements of EP 3.1.3 [73] for Polyolefins, if constructed of the following materials: • Polyethylene • Polypropylene • Polymers of ethylene or propylene with up to 25% higher homologues (C4 to C10) or carboxylic acids or esters 2. If used in the composition of the material					

8.5 Attribute 5: Animal Origin Control

Animal origin control is a core requirement for polymeric materials having product contact. The single-use product should not contain or be derived from specified risk material as defined in EU Commission Decision 97/534/EC [27]. Any bovine material must be product originated from a BSE-free country as defined by 9 CFR Part 94 [93], Section 94.18.

If it does contain a stearate or other ingredient of animal origin, the processing conditions of the ingredient should meet the requirements of the EP 5.2.8 [94] and EMA “Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)” [95]. Relevant animal species within the scope of these requirements are cattle, sheep, goat, animals that are susceptible to infection with TSE agents, or susceptible to infection through the oral route other than humans and non-human primates.

The materials of concern associated with the animal species listed above are those used for the preparation of:

- Active substances
- Excipients and adjuvants
- Raw and starting materials and reagents used in the production (bovine serum albumin, enzymes, and culture media)
- Materials that come into direct contact with the equipment used in the manufacture of medicinal product – potential for cross-contamination
- Materials used in the qualification of plan and equipment where there is a risk of cross-contamination, e.g., media fills
- Other materials such as cleaning agents, softeners, and lubricants that come into contact with the medicinal product during routine manufacture

The following points should be established by the supplier:

- If the product, or the starting materials for the product, contain any material of animal origin. If animal products are used to process the product or the starting materials of the product, e.g., animal derived enzymes used to hydrolyze plant material, gelatin used to filter hydrophobic compounds, or animal products used in fermentation broths for recombinant processes.
- If there are any animal-based products which are used at the facility that may come into contact with the products during the manufacturing process, e.g., lubricants.
- If any of the cleaning materials used in the cleaning of the processing equipment are derived from animal origin.

If the answer is yes, the supplier should supply a signed and dated copy of a current certificate of suitability as issued by the European Directorate for the Quality of Medicines (EDQM) [96].

If the answer is no, for those products or processing materials where there is no certificate available, but they contain materials of animal origin, the suppliers should apply for a certificate of suitability for the materials supplied.

For all products, lubricants, cleaning agents, and product contact materials for which there is no certificate available or they use materials from TSE-relevant animal species, consideration should be given to all the necessary measures to minimize the risk transmission of TSE. The following questions should be answered:

- What is the Geographical BSE Risk categorization of the products of animal origin in accordance with the EP [88] descriptions below
 - Highly unlikely
 - Unlikely but not excluded
 - Likely but not confirmed or confirmed at a lower level
 - Confirmed at a high level
- What is the category of Animal Parts Used as Starting Materials based on levels of infectivity
 - High Infectivity (e.g., Central Nervous System (CNS) tissues): CNS tissues that attain a high titre of infectivity in the later stages of TSEs, and certain tissues that are anatomically associated with the CNS and will not be used in the manufacture of medicinal products
 - Lower Infectivity Peripheral Tissues: Peripheral tissues that have tested positive for infectivity and/or PrPsc (PRion Protein SCrapie) in at least one form of TSE
 - No Detectable Infectivity (e.g., cleaning materials, starting agents, processing materials such as lubricants): Tissues that have been examined for infectivity, without any infectivity detected, and/or PrPsc, with negative results

8.6 Attribute 6: Total Organic Carbon Analysis

Although TOC is a non-specific test, it is a means for testing consistency in a process. Performed during qualification, this value can serve as a baseline for subsequent testing which may include incoming acceptance testing. As part of qualification, there may not be an acceptance criterion.

TOC analysis should be conducted consistent with USP <643> [97], but other methods may be utilized if the methods are described. TOC should be reported in mg/L units.

As with the other qualification tests, the test material used should be representative of the component supplied; for instance, if the component is supplied gamma irradiated, then the test material should be gamma irradiated.

8.7 Attribute 7: pH and Conductivity

Although pH and conductivity are non-specific tests, they are a means for testing consistency in a process. Performed during qualification, this value can serve as a baseline for subsequent testing which may include incoming acceptance testing.

Specific applications may have a pH range requirement, but for most products when rinsed with carbon dioxide free water, the pH should be no less than 5 and no higher than 8.

Specific applications may have a conductivity requirement, but for most products when rinsed with pharmacopeial grade WFI, the conductivity should not be more than double the conductivity of the water quality being used for testing.

As with the other qualification tests, the test material used should be representative of the component supplied; for instance, if the component is supplied gamma irradiated, then the test material should be gamma irradiated.

8.8 Attribute 8: Extractables and Leachables

The extractables testing approach described in this section is intended to create a design space for use of the intended materials. This approach does not rely on typical testing per USP <381> [19] and USP <661> [20]. As such, the exaggerated conditions used for any extractable testing done by the supplier would define the conditions within which the intended material could be used.

The design space would be defined by such variables as pH range, temperature range, contact time, and/or solvent. The components used for an E&L study should include pre and post sample treatment. The post-treated sample should use the same treatment steps, including gamma irradiation for sterilization as intended to be supplied as components to the end-user.

To support an E&L evaluation, the supplier would be requested to perform and/or provide the following information:

- Extractable testing that supports the design space, which involves testing using:
 - Polar (e.g., WFI, water) and non-polar (organic) solvents (e.g., isopropanol, hexane)
 - Media/buffers with low and high pH
 - Media/solvents of varying temperatures (e.g., 20°C or ambient and 80°C or reflux temperature)
 - Media/solvents of varying ionic strengths (e.g., NaF/KCl)
 - Varying extraction times (e.g., 2, 4, and 8 months)
- Leachable testing that supports the design space, which involves testing using:
 - In use exposure times of up to thirty days at ambient and elevated temperature (e.g., 40°C) (USP [13] testing would address short exposure times)
 - Analysis of extractables/leachables is expected to be performed, at minimum, with GC-MS, High Performance Liquid Chromatography (HPLC)/UV-Visible (or MS), and Inductively Coupled Plasma Mass Spectrometry (ICP-MS, or other heavy metal analysis technique)

Copies of actual extractables/leachables study reports should be provided by the supplier.

All data should be expressed in ppm and/or mg/in² (e.g., for bag) or mg/in length (e.g., for tubing) or mg/unit (e.g., filter) depending on the design of the single-use component.

Any extractables that exceed pharmacopeial limits (such as ICH Q3C(R6) [98] Class 1 solvents and USP <467> [99]) should be identified.

Refer to the following documents related to the use of plastics in pharmaceutical applications and providing guidance on the testing and detection of extractables in SUSs:

- FDA Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Documentation* [79]
- EP 3.2.2 [100]
- EMA Guideline on *Plastic Immediate Packaging Materials*, Reference Numbers CPMP/QWP/4359/03 and EMEA/CVMP/205/04 [60]

- ICH Q1A [101]
- ICH Q3A, Q3B [102, 103]
- ICH Q3C [98], EP 5.4 [104], USP <467> [99]

Tables 8.2, 8.3, and 8.4 provide examples of testing methods and extractables from filters and containers. The quantities detected are indicative of levels and will depend on the methods used and materials tested.

Table 8.2: Examples of Extractables from Single-Use Components after 50 kGy Irradiation

Test	Compounds Identified	Concentration
Fourier-Transform Infrared (FTIR) spectroscopy on ethanol extracted Non-Volatile Residue (NVR)	Acrylates (derived from membrane surface modification)	NVR < 0.5 mg
GC-MS on ethanol extract	2-Ethylhexanoic acid	0.56 ppm
	1,3-Di-tert-butylbenzene	0.52 ppm
	2,4-Di-tert-butylphenol	0.12 ppm
	Lauryl acetate	0.13 ppm
	Lauryl acrylate	0.64 ppm
Test	Fatty Acid Derivatives Identified	Concentration
GC-MS on derivatized ethanol extract	Ethanedioic acid, dibutyl ester (oxalic)	0.16 ppm
	Propanedioic acid, dibutyl ester (malonic)	0.10 ppm
	Dodecanoic acid, butyl ester (lauric)	0.23 ppm
	Butanedioic acid, butyl ester (succinic)	0.17 ppm
	tetradecanoic acid, butyl ester (myristic)	0.09 ppm
	Hexadecanoic acid, butyl ester (palmitic)	0.61 ppm
	Octadecanoic acid, butyl ester (stearic)	1.23 ppm
	1,4-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	2.24 ppm
Test	Compounds Provisionally Identified	Molecular Weight
LC-MS on ethanol extract	2-Ethylhexanoic acid	144.21
	Lauric acid	200.32
	Myristic acid	228.37
	Palmitic acid	256.42
	Stearic acid	284.48
Note: Identity and quantities of compounds in ethanol extracts from a polypropylene filter capsule with modified polyvinylidene fluoride membrane		

Table 8.3: Identified Extractables from Membrane Filter Cartridges from Several Manufacturers

	Water Extract	Ethanol Extract
Volatiles	2-Methoxy-2-propanol	2,3,4-Trimethylpentane
Semi-volatiles	No peaks	Low molecular weight aliphatic hydrocarbons 1,3-Di-tert-butylbenzene 2,4-Di-tert-butylphenol 1-Tridecanol Lauryl acrylate
Non-volatiles and heat-sensitive compounds	No peaks	Irgafos 168® antioxidant and its degradants
Organic acids	Oxalic acid	Myristic, Palmitic, and Stearic acid
Inorganic elements	Na, Fe, Zn, and K <10 ppb; Ca 53 ppb	Na, Al, K, and Ca no higher than for the negative control

Table 8.4: Identified Extractables from Polyethylene Bioprocess Containers with Ethyl Vinyl Alcohol Interlayer

	Water Extract	Ethanol Extract
Volatiles	2-Methyl-2-propanol Butanal Hexanal 2-Octanone	2-Methylpentane Hexane Trimethylpentane 3-Methylheptane 1-Octene Octane
Semi-volatiles	No peaks	Low molecular weight oligomers of polyethylene 1,3-DTBB 2,4-DTBP 2-Octanone 1-Heptadecanol 1-Octadecanol
Organic fatty acids	Oxalic acid 0.07 ppm	Succinic, palmitic, and stearic acid all below 0.06 ppm
Inorganic elements	Na, B, Mg, K, Ca, and Ba all at ppb levels	B 8.3 ppb

Toxicity of E&L

Some chemicals may be considered unacceptable at almost any concentration in pharmaceutical products (such as ICH Q3C(R6) [98] Class 1 solvents); determination of toxicity of extractables or leachables is otherwise a function of the actual concentration of leachables in the final drug product, the dose size and regimen, mode of delivery, patient population, and risk/benefit assessment.

Extractables identification and quantification are used to then determine the potential concentration of potential leachables in the final drug product after considering further processing.

The concern with leachables is not limited to toxicity of the leachable to the patient. A leachable also may affect the function of various functional elements of the process. As an example, it has been reported that residual silicone from silicone tubing has been shown to significantly suppress post-use bubble points of sterilizing grade filters, resulting in false integrity test failures.

Using Supplier Documentation for E&L

Supplier extractables data is a starting point for general information on E&L for single-use components. Data is generated using model extraction solvents under exaggerated conditions of your choice, with preference given to, but not limited to, the use of polar and non-polar solvents, low and high pH, ambient and elevated temperatures. Given the specificity of each product and diversity of E&L, as well as production or use conditions, an assessment of the data should be performed to confirm if it is representative of the actual process. Supplier documentation may be sufficient for certain applications where risk is low (such as short-term exposure, no drug product contact, or position in the process stream). The component used for an extractables study should be the same as that intended to be supplied for use, using the same pretreatment steps, including gamma irradiation for sterilization.

8.9 Attribute 9: Chemical Compatibility

Chemical compatibility is the measure of resistance exhibited by a specific contact material (plastics, valves, connectors, etc.) to a specific chemical (e.g., acids/bases) or contact with heavy metals (e.g., carbon steel, 316 stainless steel). Chemical compatibility charts provide supplier-based recommendations for the use of the product contact material with specific tested chemicals/heavy metals.

Testing by the supplier covers the evaluation of the contact material's physical properties (weight, dimension, appearance) for resistance to the chemical reagents. The physical characteristics of thermoplastics and elastomers are sensitive to temperature, therefore recommendations for chemical compatibility should indicate temperature limits or temperature test setting for chemicals tested. Pressure and chemical concentrations should also be included in the compatibility charts since they affect chemical compatibility.

Testing methods for chemical compatibility testing are driven by ASTM D543-95 [105] and ISO 175 [106].

Note: In-house evaluation should be performed if chemicals used with the contact materials are not provided on the chemical compatibility charts or if the contact environment (temperature, pressure, etc.) during manufacturing is outside of the test limits.

8.10 Attribute 10: Protein Adsorption Studies

Currently, there are no broadly accepted standards for protein adsorption studies; however, such testing is necessary for understanding the impact that a polymeric system may have on the biochemical processes they are in contact with. This section intends to define an expectation rather than defining specifications.

Consideration should be given to utilizing one of two large molecular weight commercially available products for testing, insulin and heparin. These compounds are readily available, as are methods for detecting these compounds.

Alternate but equivalent methods could also be used, such as the use of bovine immunoglobulin or bovine serum albumin measured by direct quantitative amino acid analysis. In such studies, more than one temperature for storage and multiple time points should be used. It is also crucial that the surface area to volume ratio is presented in the data. For more information, refer to Burke et al., 1992 [107].

For the test results to be meaningful, the testing should be performed on components that are assembled in the manner suitable for delivery and sterilized in the manner used for components delivered for use.

Understanding that protein adsorption will occur, such as adsorption of proteins onto surfaces such as borosilicate glass, studies are expected using model proteins at more than one temperature point and at multiple time points to understand the kinetics of the adsorption; the adsorption is not only a function of the material such as ultralow density PE, but also the physical characteristics of the surface, which could be altered by the sterilization technique. Because it is useful to understand the differences, studies for the polymeric system should be performed side by side with stainless steel and glass systems. Additionally, such comparison studies would form a baseline for understanding variations that occur from laboratory to laboratory.

8.11 Attribute 11: Endotoxin Testing

Endotoxin testing per USP <85> [48] and EP 2.6.14 [74] is a requirement for single-use products with product contact and which need to be sterile and pyrogen free, per the intended application. USP <85> [48] and EP 2.6.14 [74] utilize Limulus Amebocyte Lysate (LAL) testing to demonstrate the absence of pyrogens (for the purpose of this Guide, endotoxins and pyrogens are considered equivalent terms).

For the test results to be meaningful, the testing should be performed on components that are assembled in the manner suitable for delivery and sterilized in the manner used for components delivered for use.

The supplier can also provide a statement indicating the systems and processes in place to reduce or control endotoxins. The statement should indicate that assembly occurs in a classified environment with appropriately gowned personnel, or that a visual inspection process is used for particulates. Periodic testing should be performed to demonstrate that the process successfully produces material that meets the endotoxin requirements. The document should indicate the frequency of the testing.

In the absence of other requirements, the material should pass USP [13] WFI endotoxin standards when tested with USP WFI.

8.12 Attribute 12: Sterilization (Irradiation)

Robust evidence/data should be provided by the supplier to support the sterility claim (SAL) for the single-use product. Sterilization validation should be based on ANSI/AAMI/ISO 11137 [51].

The sterilization validation package should include:

- Validation performed per ANSI/AAMI/ISO 11137 [51] methods
- Method used to establish minimum sterilization dose (e.g., Method 1, VD_{max}^{25} , etc.)
- Demonstration of adherence to method used
- Dose setting/dose substantiation
- Pre-sterilization bioburden determination (per ISO 11737-1 [108])
- Verification dose experiment (per ISO 11737-2 [109] for sterility testing)
- Auditing of sterilization dose (demonstration of continued process effectiveness)
- Frequency each testing is performed

For selection of the single-use product used for validation, justification/documentation should include:

- Product family definition/matrixing
- Product that represents the product family (e.g., master, equivalent, or simulated product)
- Criteria for defining the product family
- Plan for maintaining product family
- Determination and adequacy of SIP selection

Bacteriostasis/fungistasis testing is required by USP <71> [110] for sterility testing, in order to:

- Validate the sterility test to be used for verification dose experiments (tests of sterility)
- Demonstrate if the product material itself does not inhibit growth (pre or post-sterilization)
- Demonstrate that product bioburden can be detected in the sterility test

Robust data to support supplier's sterility shelf life claim should be provided. Refer to ANSI/AAMI/ISO 11607-1 [111] which distinguishes between a sterile barrier system and protective packaging:

- Sterile barrier system: Minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at point of use
- Protective packaging: Configuration of materials designed to prevent damage to the sterile barrier system and its content from time of assembly to the point of use

Validation testing to support sterility shelf life should be performed from date of sterilization and includes:

- Real time aging
- Accelerated aging (refer to ASTM F1980 [55])
- Physical and functional testing and/or sterility testing
 - Physical testing is performed to substantiate the microbial barrier
 - Functional testing is performed to evaluate the ability of the package to maintain sterility/integrity over time
 - Sterility testing per USP <71> [110] for evidence of bacterial ingress
- Leak testing
 - Pressure decay per ASTM F2338-09 [112]
 - Seal integrity-peel per ASTM F88/F88-M-15 [113]
 - Transportation/shipping integrity
 - Visual inspection per ASTM F1886-98 [114]
 - Dye penetration per ASTM F1929-98 [115]

8.13 Attribute 13: Container Closure Integrity

Container closure integrity validation demonstrates the effectiveness of the sterile boundary or closure system against microbial ingress by means of a specific challenge. At a minimum, the closure system should be qualified by at least one of the container closure integrity test methods listed below (as appropriate for the container design):

- **Helium leak test:** Helium is used as a tracer gas for detection and measurement of leakage across a package seal and is detected by mass spectrometry (ASTM E498-95 [116], ASTM E499-95 [117]).
- **Liquid ingress test:** A liquid tracer (i.e., dye, radionucleotide ions) is exposed to the test seal and requires submersion of the package in the liquid tracer or filling the package itself with liquid tracer followed by submersion of the package in water or other suitable solvent. Migration of the tracer across the seal is determined either visually (with dyes) or by other analytical means appropriate to the type of liquid tracer used (ASTM E165-02 [118]).
- **Vacuum decay test:** Containers are placed inside a chamber where a vacuum is applied. Once the chamber reaches a steady vacuum level, the vacuum is monitored to detect any leak from the test container into the vacuum chamber (ASTM F2338-09 [112]).
- **Pressure retention test:** Container pressure retention is measured over time inside the container by using a pressure measuring device (e.g., absolute or differential pressure transducers or gauges).
- **Tensile test:** Used for seal quality including checking connection strength, closure coring, intravenous bag port connection strength, and residual seal force. Test samples are stretched at a constant rate to a predefined load. The goal of the test is to confirm the ability of the test sample to withstand a stress without breaching the boundary or compromising the integrity of the system (ASTM F88/F88-M-15 [113]).
- **Compression test:** Used to test plastic tube or bag seal quality and strength. Test samples are compressed at a constant rate to a predefined load. The goal of the test is to confirm the ability of the test sample to withstand a stress without breaching the boundary while the content is pressed against the seals.
- **Microbial challenge tests:** Per liquid immersion or aerobiology methods (USP <71> [110]).
- **Residual seal force:** Established for specific vial/stopper combinations while considering the nature of the stopper (e.g., rubber composition), vial, cap, and process conditions experienced before, during, and after the closure is created (e.g., washing and sterilization). The goal of the test is to confirm the compression levels on the closure (e.g., crimped stopper on vial) once the crimp is in place. This testing is required in addition to component closure integrity qualification for all final finished products.

Test sample sizes for the above assays should be representative of the lot sizes being requested.

For additional information, refer to USP <1207> [63], USP <1> [119], and ASTM E432-91 [120].

8.14 Attribute 14: Particulate Testing

Particulates, both loose visible and non-visible to the extent defined by USP [13], can contaminate or adulterate the product if there are no intervening steps between use of the component and fill/finish. Therefore, polymeric materials should be free from particulate matter.

Particulate testing should be performed for polymeric materials having product contact per USP <788> [49], EP 2.9.19 [75] and EP 2.9.20 [76], as a starting point. The potential to shed particles into the process due to the intended application will require additional qualification, including additional information concerning sub-visible particles and the composition of any particulates found.

USP <788> [49] utilizes light obscuration particle testing, and the methodology is appropriate for large volume parenterals for single dose infusion.

EP 2.9.19 [75] allows for the use of both light obscuration and the microscopic methods.

For the test results to be meaningful, the testing should be performed on components that are assembled in the manner suitable for delivery and sterilized in the manner used for components delivered for use. Results should be presented as actual data, and not simply as “Passed”.

In addition, a statement should be provided by the supplier indicating the systems and processes in place to reduce or control particulates. The statement should indicate that assembly occurs in a classified environment with appropriately gowned personnel, or that a visual inspection process is used for particulates. Periodic testing should be performed to demonstrate that the process successfully produces material that meets the particulate requirements. The statement should indicate the frequency of the testing.

8.15 Attribute 15: Calibration of Embedded Instrumentation

For single-use products that have embedded instrumentation providing data utilized for controlling and monitoring processes, documentation should include:

- Traceable calibration certificates (per instrument) that comply with international standards such as National Institutes of Standards and Technology (NIST) [121] and United Kingdom Accreditation Service (UKAS) [122] and include the calibration expiration date
- Verification that the instruments can be independently calibrated pre and post-use
- Calibration procedures, including a specific calibration range and loop tolerance details of the integrated instrument (element, indicator, etc.)
- Data regarding the shelf life and whether the instrument can be recycled
- Data regarding the stability of the embedded instrumentation to withstand cleaning and sterilization processes
- If required, technical verification regarding connectivity of the instrument to end-user control systems

9 Appendix 5 – Case Study: 2000 L Single-Use Bioreactor – Evaluation and Implementation

Steve Comer and Edward Stevens, GlaxoSmithKline
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9.1 Summary

GlaxoSmithKline's biopharmaceuticals clinical manufacturing facility in Upper Merion, PA was renovated to install single-use bioreactor (SUB) systems and establish a new global manufacturing platform strategy for scale-out at 2000 L. The latest advances in 2000 L SUB technologies were assessed through a comprehensive selection process based on qualitative and quantitative attributes of three suppliers. Quantitative results were compared to performance of an existing 1200 L scale stainless steel bioreactor.

GlaxoSmithKline first installed the selected 2000 L SUB technology in one of two similar existing cell culture suites. This approach minimized plant downtime and provided the opportunity to apply lessons learned in a subsequent phase for installation of two 2000 L SUBs in the second cell culture suite. The design included a hybrid approach using stainless steel and single-use systems for large-scale media prep and transfer operations.

9.2 SUB Technology Selection

Initial qualitative evaluation determined which SUB vendors would be selected for a more extensive quantitative evaluation. Results of comprehensive qualitative and quantitative evaluations were summarized in a weighted scoring system for a decision on the selected supplier.

9.2.1 Qualitative Evaluation

The SUB selection team implemented the following qualitative evaluation criteria for the 2000 L SUBs:

- Ergonomics and ease of operation, including the bag installation.
- Flexibility and options available in the bag design, including agitation and sparging choices.
- Industry and commercial experience of each vendor, including gathering third party experiences and references.
- Scale down-representation of different SUB sizes available to allow process development and transfer to production scale
- Vendor supply chain robustness, including lead times for standard and custom bags
- Vendor support and experience at the local level and at other sites in GlaxoSmithKline's international network.

9.2.2 Quantitative Evaluation

GlaxoSmithKline evaluated SUBs from three established vendors at capacities ranging from 200 L to 1000 L scale and compared the results to their existing 1200 L stainless steel bioreactor.

Quantitative evaluations involved hands-on testing in non-GMP areas at the Upper Merion site. Testing included measurement of blend time at full and partial volumes, as well as mass transfer capabilities. Cell growth and product titers were compared to the existing 1200 L stainless steel bioreactor using a platform cell line.

A third-party consultant modeled the SUBs at the 2000 L scale using computational fluid dynamics.

9.2.2.1 Bioreactor Blend Time

Bioreactor blend times were tested to collect imperial data. The testing was determined by measuring the time required for a bolus of acid to be dispersed throughout the vessel. Replicate tests were conducted over the range of operating speeds. Measurements were made both at the lower tangent line and just below the liquid surface.

Figure 9.1: Example Blend Time Based on Whole Volume Is Plotted Here – Volume Uniformity of 1 Means 100% Mixing

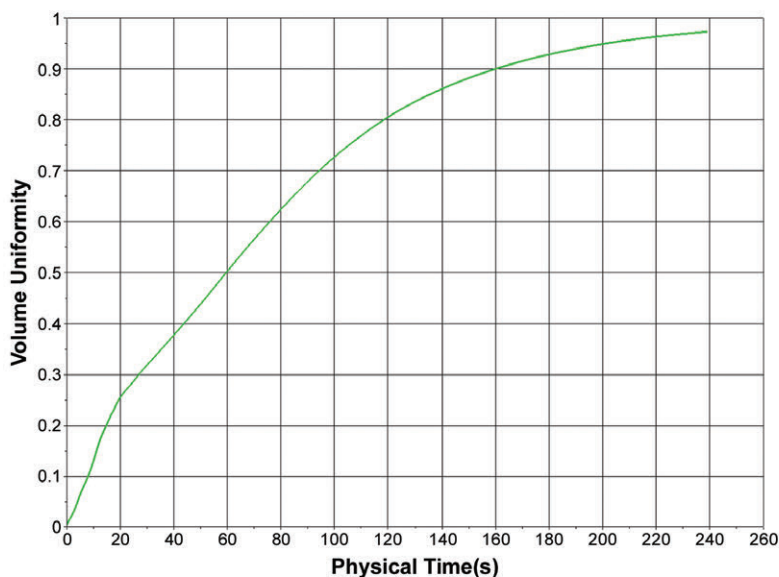
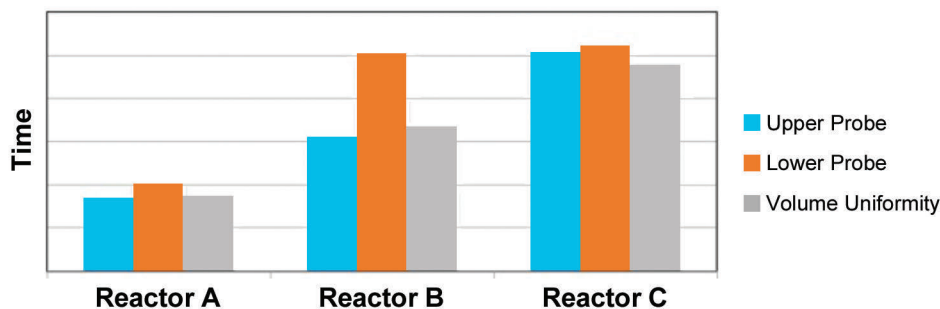


Figure 9.2: Blend Time Results – Reactor A Shows the Best Performance and Reactor C the Lowest



9.2.2.2 Oxygen Mass Transfer Coefficient (kLa)

kLa was determined by monitoring the increase in dissolved oxygen in the vessel contents while sparging in air. The tests were conducted over a range of operating conditions by varying the agitator power input and gas sparge rate. Dissolved oxygen was measured both at the lower tangent line and just below the liquid surface level to assess spatial variation.

9.2.2.3 Carbon Dioxide (CO₂) Stripping

CO₂ stripping experiments were conducted over the range of gas rates (superficial gas velocity) and agitator speed (energy dissipation rate). The pH was monitored and its change versus time analyzed as a CO₂ saturated solution was stripped via air sparging. These measurements were also made both at the lower tangent line and just below the liquid surface level.

9.2.2.4 *k*L_a and CO₂ Results

The results were obtained and correlated for the tested volume. These correlations were used to extrapolate to the 2000 L scale. Significant differences were observed between the different systems tested. The greater differences were seen for the oxygen mass transfer, lesser differences for the CO₂ stripping. The sparger design was determined to be a contributing factor for the differences observed. One system tested outperformed the stainless-steel control system.

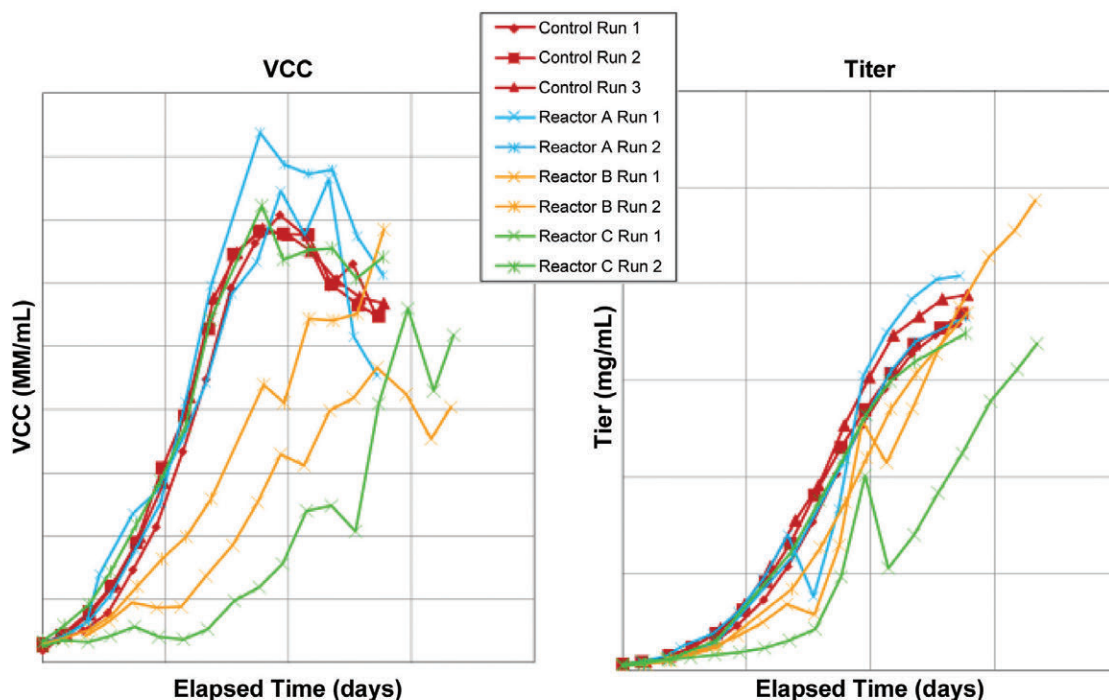
9.2.2.5 Computational Fluid Dynamics (CFD)

CFD modeling was performed to predict the performance of the three mixing vessel designs at the 2000 L scale. This involved breaking each SUB into 3 – 5 million units with a mesh size of 1 – 2 cm and then modeled. This solved for the time accurate mixing behavior of each vessel by introducing a virtual tracer into the mesh at a location comparable with the experimental data and then comparing tracer concentrations and mixing times with the experimental data.

9.2.2.6 Cell Performance Testing

Cell performance was tested in the three SUBs using an established CHO cell process. All three SUBs used the same media lot and seed pool to eliminate these factors as potential variables. The testing evaluated cell growth and viability, titer, metabolic profile and product quality in each SUB. Results were compared to historic performance in the 1200 L stainless-steel bioreactor. Reactor A was comparable or better than the stainless-steel system. Reactor C consistently underperformed. Reactor B underperformed during one run due to a pH probe failure.

Figure 9.3: Viable Cell Count and Titer Performance versus the Stainless Steel Control



9.2.3 Vendor Comparison Overview

The score card below illustrates the weighted ranking system that was used to objectively evaluate each SUB platform. Three factors receive the highest weight factor: cell performance, mixing/kLa and vendor supply chain. Vendor support had the lowest weight factor.

Figure 9.4: Assessment of Vendors Using a Weighted Scoring System

SUB Rankings				
	Weight	Reactor A	Reactor B	Reactor C
Cell Performance and Comparison	5	5	3	3
Mixing/kLa	5	5	5	2
Computational Fluid Dynamics (CFD)	3	5	3	2
CFD 2000L	3	5	2	2
Vendor Supply Chain	5	3	5	3
Ergonomics and Ease of Operation	3	5	3	3
Turn Down Ratio	3	5	1	5
Industry Experience at 2000L	3	2	5	5
Third-party Feedback	3	5	5	3
Scale Down Representation	3	5	3	5
Controls and Source Code Access	3	3	1	5
Vendor Support	1	3	5	3
Weighted Score		173	139	133

Legend:

Advantage	5
Acceptable	3
Improvement Required	1

Weighting:
5 = High
3 = Medium
1 = Low

In some cases, a reactor received multiple scores for the same criteria. Reactor A vendor support, for example, received a 5 for US support but a 1 for UK support. Total weighted score for Reactor A was considerably higher than the scores for the other two SUB systems, and was chosen as the technology for installation in the Upper Merion clinical manufacturing facility.

9.3 Installation of 2000 L SUB in an Existing GMP Facility

9.3.1 Overview of the Existing Facility

GlaxoSmithKline's first 2000 L SUB was installed in Building 38 (UM-38), a multi-product clinical manufacturing facility in Upper Merion PA.

Figure 9.5: GlaxoSmithKline's Multi-Product Clinical Manufacturing Facility in Upper Merion, PA

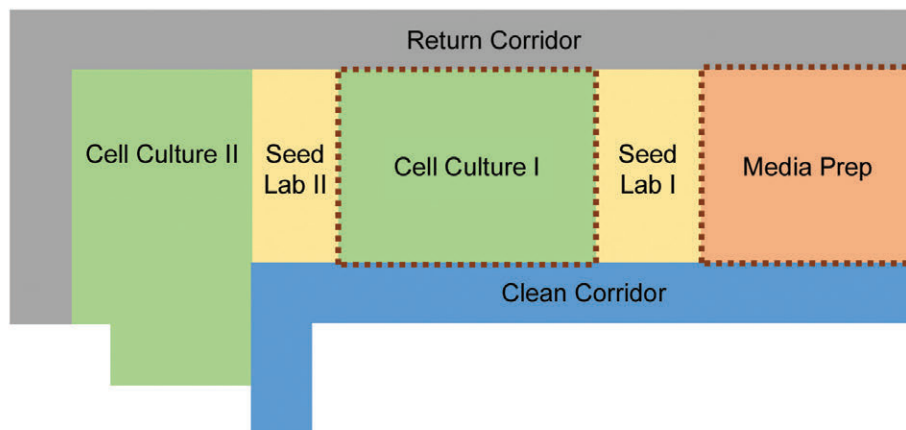


UM38 has GMP clinical operations on three floors, with process utilities at the basement level. The first floor includes microbial fermentation, with purification, media and buffer prep, wash area, laboratories and offices. The second floor includes two independent but similar mammalian cell culture suites, including a dedicated seed scale-up lab for each suite. Cell culture operations share a media prep area and wash area. Clarified harvest from the cell culture operations is transferred to the third floor, which includes two independent purification suites, supported by a shared buffer prep area and wash area. These three levels of GMP clinical production share distribution of WFI and clean steam from the basement level.

The floor-to-floor height of each production level is 16 ft., with 2 ft. of supporting steel, providing a clear height of 14 ft. below steel. Process operations on these floors typically have a 9 or 10 ft. ceiling, with distribution of process piping, utilities and ductwork in the remaining space above the ceiling. High hat areas provide higher ceiling elevations in specific locations that need to accommodate larger equipment.

A 2000 L SUB was installed in one of the two cell culture suites. The media prep area was also renovated to install single-use mixing systems.

Figure 9.6: Mammalian Cell Culture Operations at UM-38 On the Second Floor



The cell culture operations on the second floor have unidirectional flow with operators and clean materials entering each process area through the clean corridor. Operators and waste materials leave the areas through the return corridor.

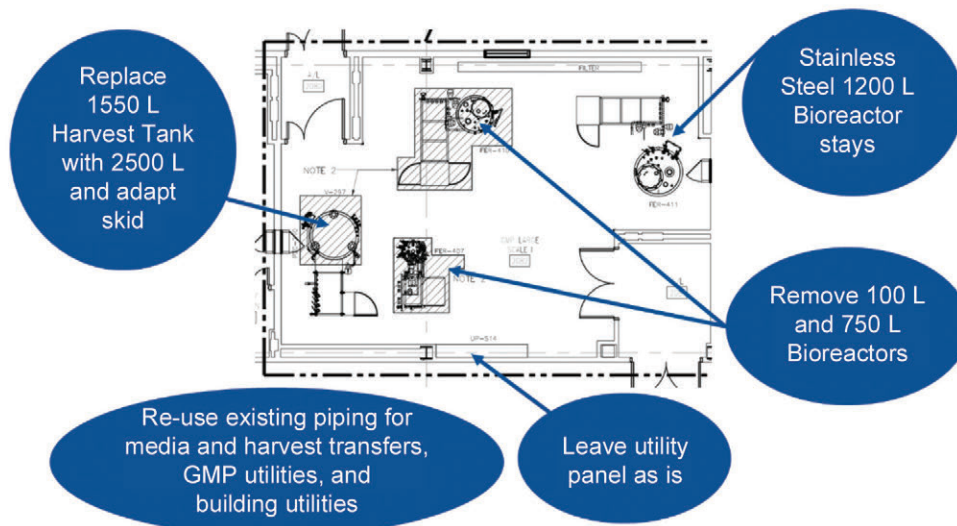
9.3.2 Construction Access

Renovation of Cell Culture I and Media Prep was completed while maintaining existing operations in Cell Culture II. The return corridor was used during this renovation for construction access. Entry airlocks from the clean corridor were sealed with plastic sheathing. These soft barriers deterred construction personnel from entry into the clean corridor, but still allowed emergency egress in this direction.

9.3.3 Suite 1 Renovation

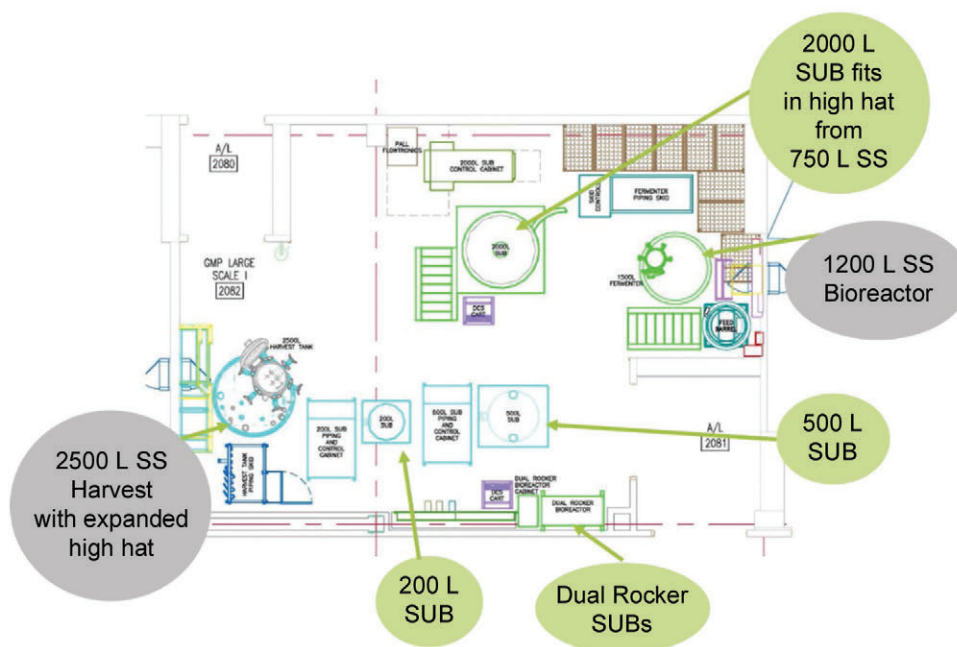
The existing cell culture suite had 100 L, 750 L, and 1200 L stainless steel bioreactors, and a 1500 L stainless steel harvest tank. The 1200 L bioreactor remained for ongoing comparisons of performance in a stainless steel and single-use bioreactors. The harvest tank was replaced with a larger 2500 L system to accommodate the new 2000 L SUB.

Figure 9.7: Renovation Plan for Cell Culture Suite I



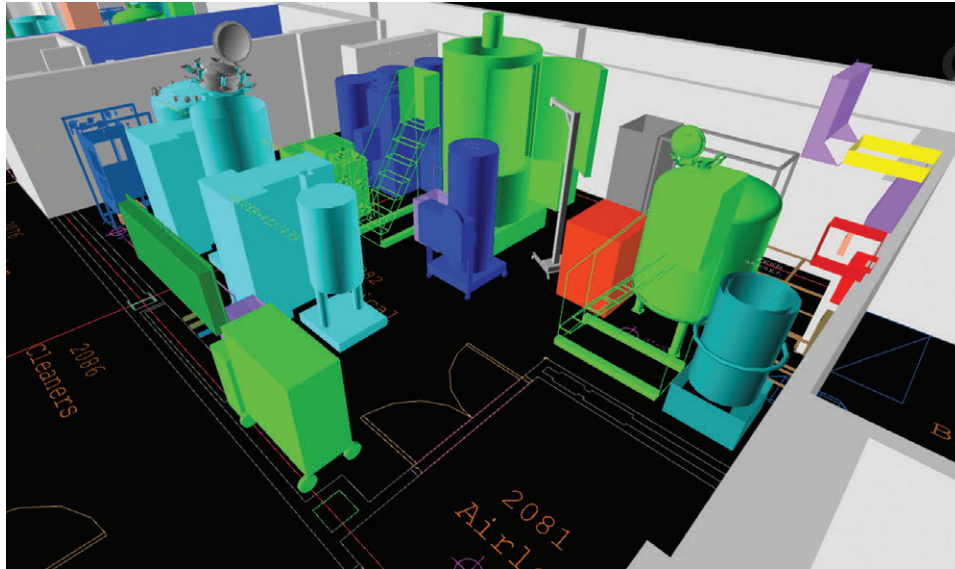
The 2000 L SUB was installed in the previous location of the 750 L bioreactor. This location was chosen because the existing high hat area was able to accommodate the larger SUB with minimal modifications to the ceiling and no impact to existing mechanical systems above the ceiling. The new 2500 L harvest tank aspect ratio was chosen to work within the existing high hat area elevation. The existing high hat width was expanded to accommodate a wider tank.

Figure 9.8: Renovations implemented in Cell Culture Suite I



This model was used later in the design phase to determine lengths for single-use process tubing.

Figure 9.9: 3D Model for Renovations Implemented in Cell Culture Suite I



Renovations to the media prep area included removal of the 640 L and 1100 L stainless steel mix tanks and installation of single-use mixing systems for 50 L, 200 L, 650 L, and 1500 L media prep.

9.3.4 Stainless Steel and Single-Use Hybrid Approach

A hybrid approach was used for the 1500 L media prep operation. Powder additions to the top of the 1500 L mixing station would have required significant modifications to install a high hat in the ceiling, as well as additional footprint for platform access. A floor mounted stainless steel inline powder-liquid mixing system, typically used for much larger scale operations, was integrated with the 1500 L single-use bag. This eliminated the need for ceiling modifications, minimized floor space requirements and provided a more ergonomic design for powder additions.

Transfers of media from the 1500 L media prep to the 2000 L SUB were designed to use the existing stainless steel media transfer line, with minimal modifications to the existing system.

Existing systems for cleaning and sterilization of equipment and piping made this hybrid approach possible with minimal impact to the facility.

9.3.5 Project Schedule

Design and installation of single-use systems in the two areas was completed twenty-four months after the single-use technology was selected. Equipment was specified and procured early to minimize risk of construction delays. Equipment for the hybrid system was set up and tested in an existing non-GMP space prior to installation in the media prep area to minimize risk of delays in system start-up. Media prep construction was completed first to allow this area to support the existing operations in Cell Culture II.

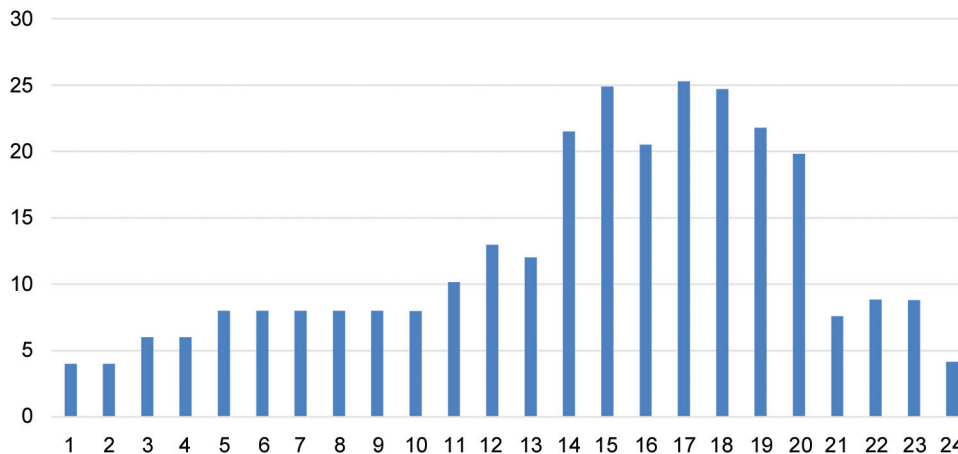
Figure 9.10: Overall Project Schedule



9.3.6 Project Support

GSK internal support for this project included personnel from engineering, technology, manufacturing operations, quality, validation and calibration departments. Staffing peaked at twenty-five people during construction and validation. Generation of new protocols for validation of single-use systems created greater demands for personnel than normally expected with stainless steel systems, where existing protocols could be leveraged.

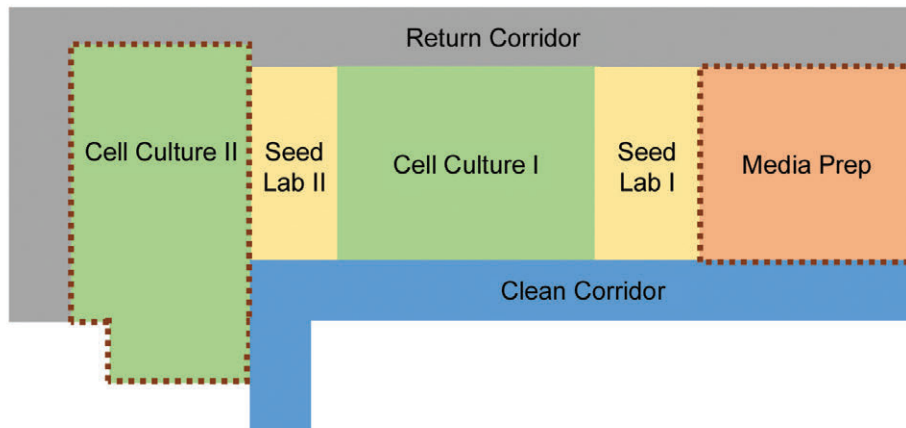
Figure 9.11: GSK Project Support Staff for Engineering Through Validation



9.3.7 Phase II Renovations

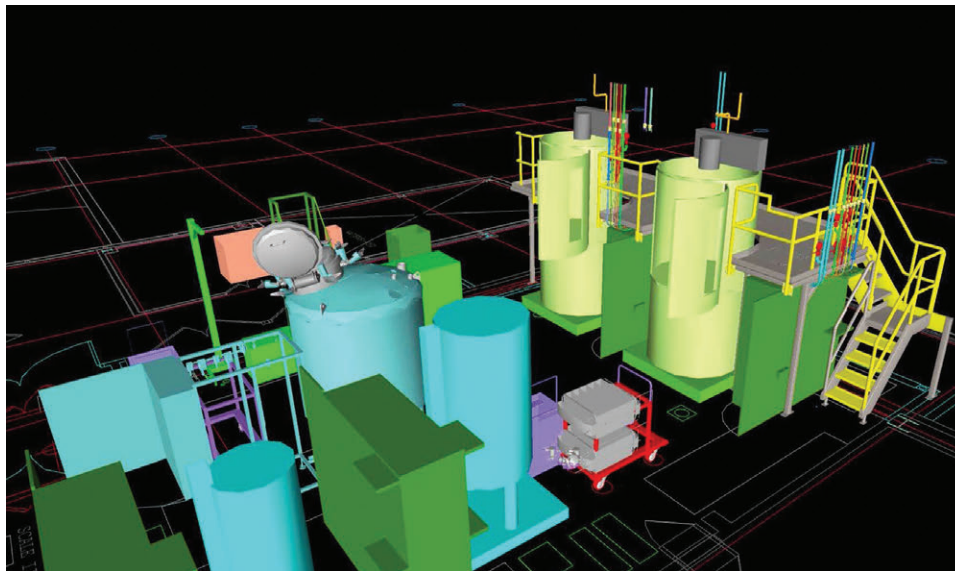
A second phase of renovations was completed to install two 2000 L SUBs in Cell Culture II. This renovation also required a second renovation to the Media Prep area to install a second 1500 L media mixing station to accommodate the increased bioreactor capacity.

Figure 9.12: Phase II Renovations for Cell Culture II and Media Prep



Unlike the first renovation, which focused on minimal renovations to the facility, this phase required significant modification to Cell Culture II to expand the area into the return corridor.

Figure 9.13: 3D Model for Phase II Renovations in Cell Culture II



A platform was provided around the two 2000 L SUBs based on lessons learned from Phase I. This provided greater access to the top of the bioreactors for installation of filters and media transfer connections. The platform provided a clear height of 6 ft. 8 in. below the platform, which enabled operator access around the back of the bioreactors and also provided the ability to install control systems under the platform. Overall height of the area above the 2000 L SUBs is 13 ft. 9 in., just below the 14 ft. elevation at the bottom of building steel.

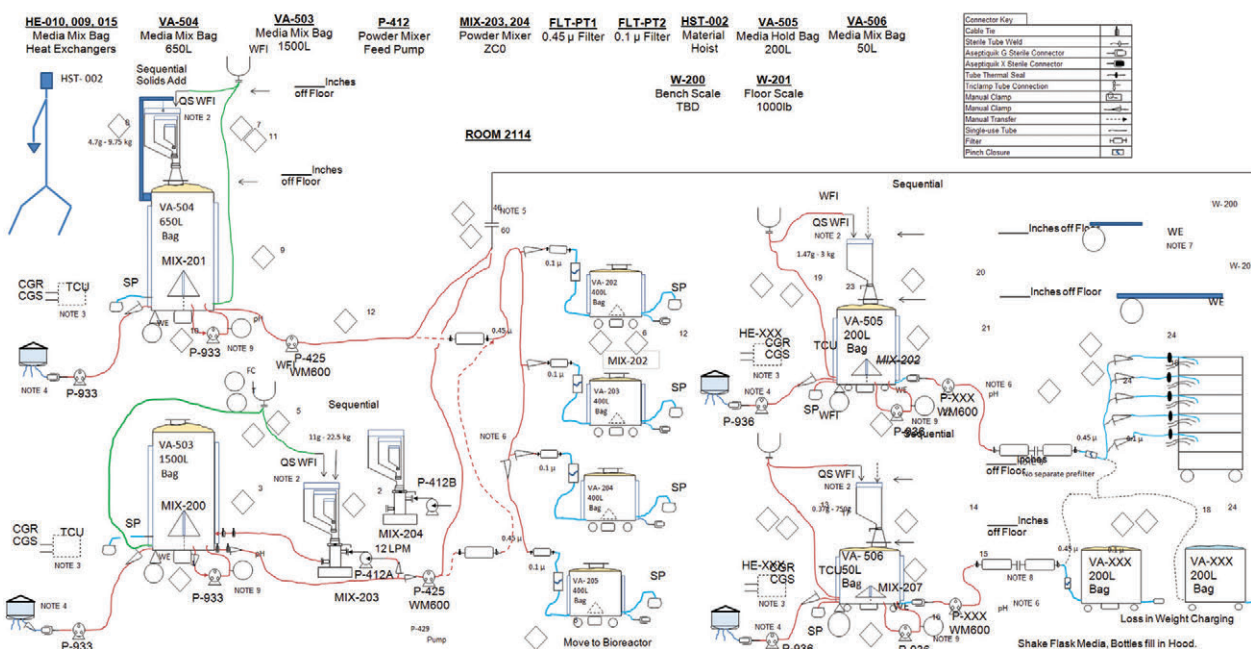
9.4 Project Risks and Mitigation – New Technology

Changing from stainless steel operation to disposable technology introduced new risks such as potential leaks due to manual connections and improper handling of bags. In addition, new disposable systems needed to be created to move product within the plant. Working with disposable technology is a long-term relationship with your suppliers and relies on the robustness of their supply chain in addition to increased inventory management.

To mitigate these risks, water and engineering batches were conducted to train equipment operators in unpacking and loading the bags and in making the aseptic connections between disposables. A Failure Mode and Effects Analysis (FMEA) was conducted to assess equipment and operational SOP's, identify risks and generate a mitigation plan.

A detailed process flow map was created to show both major pieces of process equipment and the disposable systems needed to connect the equipment. The map showed tubing types, sizes and connectors needed and helped organize and consolidate the inventory of unique items required. The goal was to not have a specific tubing set for each process step but instead common ones that could be used in multiple areas.

Figure 9.14: Media Process Flow Map Indicating All Hose Requirements



9.5 Vendor Supply Chain

The vendor relationship and supply chain are critical to a successful conversion to single-use technology. Tubing sets can be generic and can be sourced from multiple vendors to ensure continuity of supply. Bags for SUBs are proprietary and the SUB vendor supply chain is critical to business success. Items to consider for vendor supply chain include: bag film source, any bag component and connectors, back-up bag manufacturing and irradiation sites and bag shipping protocols. Any single points of failure should be identified jointly with the vendor and a mitigation plan prepared.

In addition to the vendor supply chain, the internal supply chain needs to be able to forecast bag usage to plan appropriate inventory levels, taking into consideration bag expiry and space required for storage.

9.6 Application of Lessons Learned for Future Single-Use Renovations

As this project was conducted in two phases, the second phase provided an opportunity to apply learnings from the first phase to the second so as not to have the same issues. After Action Reviews (AARs) were conducted with the various groups involved in the project (Operations, Validation, Engineering, Quality and the equipment vendor). The feedback included what went well and what did not along with ideas for improvement. We found the results could be divided into three high level buckets – Communication (60%), Documentation (30%) and Installation (10%), which included site acceptance testing and validation. These results were then turned into measurable actions and applied to the next phase.

Specific AAR themes:

- Project schedule – get buy in from all parties involved, communicate details early and often in the project and make sure the schedule is easy to follow. Keep everyone involved and engaged throughout the project.
- Documentation – projects of this nature require extensive amount of both internal documentation and exchange of documents between vendors. A common portal site was used to keep track of external documents. Internal documents need to be carefully staggered during the project to ensure both timely delivery and not overwhelm reviewers and approvers.
- Installation – initial estimates for disposable supplies needed for start-up and validation activities were low, substantially more supplies were needed than planned.

In addition to the AAR, a retrospective safety review of the first phase was conducted and updates to the equipment and installation plans were prospectively made for the second phase.

9.7 Conclusions

GlaxoSmithKline has successfully installed 2000 L SUBs in their existing clinical manufacturing facility and has observed cell titer and product yields that are comparable to their 1200 L stainless steel bioreactors. Single-use technologies, though appearing inherently simpler than stainless steel systems, present new challenges with operator training and a long-term dependence on the SUB vendor and their extended supply chain.

Installation in an existing facility presented some challenges with limitations in height and room adjacencies, but use of stainless steel and single-use hybrid process design enabled the design team to overcome these challenges. Existing infrastructure with ability for steam in place and clean in place made the hybrid approach possible.

9.8 Acknowledgements

- GSK Team
 - SUB Selection Team
 - Operations
 - Process Development
 - Validation, Engineering
 - Quality
- Hargrove Team
 - Process and Facility Design
 - Project Management and Planning
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11 Appendix 7 – Glossary

11.1 Acronyms and Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ADI	Average Daily Intake
AET	Analytical Evaluation Threshold
ANSI	American National Standards Institute
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials
bDtBPP	bis(2,3-di-ter-butylphenyl)phosphate
BPE	Bioprocessing Equipment
BPOG	BioPhorum Operations Group
BPSA	Bio-Process Systems Alliance
BSE	Bovine Spongiform Encephalopathy
BSL	Biosafety Level
BTEC	Biomanufacturing Training and Education Center
CAPA	Corrective Action Preventative Action
CCS	Container Closure System
CDER	Center for Drug Evaluation and Research (US FDA)
CFR	Code of Federal Regulations
CIP	Clean-In-Place
CMDCAS	Canadian Medical Devices Conformity Assessment System
CNS	Central Nervous System
COA	Certificate of Analysis
CPP	Critical Process Parameter
DECHEMA	Gesellschaft für Chemische Technik und Biotechnologie/Society for Chemical Engineering and Biotechnology (Germany)
DO	Dissolved Oxygen
DOE	Design of Experiment
E&L	Extractables and Leachables
EDQM	European Directorate for the Quality of Medicines
ELSIE	Extractables and Leachables Safety Information Exchange
EMA	European Medicines Agency (EU)
EPDM	Ethylene Propylene Diene Monomers
FAT	Factory Acceptance Test
FDA	Food and Drug Administration (US)

FMEA	Failure Mode and Effect Analysis
FTIR	Fourier-Transform Infrared
GC-MS	Gas Chromatography–Mass Spectrometry
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HMI	Human Machine Interface
HPLC	High Performance Liquid Chromatography
IC	Ion Chromatography
ICH	International Council for Harmonisation
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectroscopy
ID	Inner Diameter
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
JP	Japanese Pharmacopoeia
kGy	kiloGrays
LAL	Limulus Amebocyte Lysate
LC-MS	Liquid Chromatography–Mass Spectrometry
LC-UV	Liquid Chromatography–Ultraviolet
MBT	Mercaptobenzothiazole
MS	Mass Spectroscopy
NEC®	National Electrical Code®
NIBRT	National Institute for Bioprocessing Research and Training
NIH	National Institutes of Health
NIST	National Institutes of Standards and Technology
NVR	Non-Volatile Residue
OINDP	Oral Inhalation and Nasal Drug Products
OPC	Open Platform Communications
OTR	Oxygen Transfer Rate
P/V	Power input per unit of volume
PCM	Process Contact Material
PDA	Parenteral Drug Association
PE	Polyethylene
PET	Polyethylene Terephthalate
PETG	Polyethylene Terephthalate G

PP	Polypropylene
PPAR	Pharmaceutical Process Analytics Roundtable
ppb	parts per billion
PPC	Primary Packaging Component
ppm	parts per million
PQRI	Product Quality Research Institute
PrPsc	PRion Protein Scrapie
QbD	Quality by Design
QRM	Quality Risk Management
QT	Qualification Threshold
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (EU)
RPM	Revolutions Per Minute
SAL	Sterility Assurance Level
SAR	Structure-Activity Relationship
SAT	Site Acceptance Test
SCT	Safety Concern Threshold
SOP	Standard Operating Procedure
SUB	Single-Use Bioreactor
SUS	Single-Use System
SUT	Single-Use Technology
TDI	Total Daily Intake
TOC	Total Organic Carbon
TPE	Thermoplastic Elastomer
TIR	Technical Information Report
TSB	Tryptic Soy Broth
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of Toxicological Concern
UKAS	United Kingdom Accreditation Service
UL	Underwriters Laboratories
URS	User Requirement Specification
USP	United States Pharmacopeia
UV	Ultraviolet
VVM	Gas volume flow per unit of liquid volume per minute
WEEE	Waste Electrical and Electronic Equipment (UK)
WFI	Water for Injection
WHO	World Health Organization

11.2 Definitions

Absorption

Assimilation of molecules or other substances into the physical structure of a liquid or solid without chemical reaction.

Acceptance Criteria

The criteria that a system or component must satisfy in order to be accepted by a user, customer or other authorized entity.

Active Ingredient

Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.

Adsorption

Adherence of molecules in solution or suspension to cells or other molecules – or to solid surfaces, such as chromatography media.

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.

Antioxidant

Compound that slows the rate of oxidation reactions.

Aseptic

Free of pathogenic (causing or capable of causing disease) microorganisms.

Autoclave

An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g. filter assemblies, glassware, etc.).

Bioburden

The concentration of microbial matter per unit volume. Microbial matter includes viruses, bacteria, yeast, mold, and parts thereof.

Bioreactor

A closed system (flask, roller bottle, tank, vessel, or other container) capable of supporting the growth of cells, mammalian or bacterial, in a culture medium in which a biological transformation takes place.

Bovine

Of, relating to, or from a cow: *such as Bovine Blood: blood from a cow.*

Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values of a quantity realized by a reference standard.

Certificate of Analysis (COA)

A batch-specific document that is used to list test methods and results, including applicable specifications, acceptance criteria, and a final batch disposition.

Change Management (ICH Q10 [42])

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes.

Chromatography

Method of highly selective molecule separation using columns to purify proteins and other chemical products.

Closed Process (*ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18])

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.

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.

Conductivity

A measure of flow of electrical current through water.

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).

Containers

A receptacle for holding and/or transferring material.

Corrective and Preventive Action (CAPA)

A quality system defined by 21 CFR Part 820.100 [123]; the policies, procedures, and support systems that enable a firm to assure that exceptions are followed up with appropriate actions to correct a defined situation, and with continuous improvement tasks to prevent recurrence and eliminate the cause of potential nonconforming product and other quality problems.

Decontamination (FDA 2004 Aseptic Processing Guidance [16])

A process that eliminates viable bioburden via use of sporicidal chemical agents.

Dilution

Lowering the concentration of a solution by adding more solvent.

Elution

Washing out; removing adsorbed material with a solvent or buffering agent.

Endotoxins

Cell wall debris (lipopolysaccharide) from Gram-negative bacteria.

End-User

The pharmaceutical customer or user organization contracting a supplier to provide a product.

In the context of this document: The pharmaceutical organization applying the single-use assemblies or components to produce a pharmaceutical drug substance. The end-user typically purchases the single-use assemblies from a supplier but can also build the single-use assemblies by purchasing single-use components and building its own assemblies.

Enzyme

A protein capable of producing chemical reactions (biocatalyst). Enzymes are involved in practically all biochemical reactions.

Excipient (ICH Q6B [124])

An ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

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.

Failure Modes and Effects Analysis (FMEA)

Method of reliability analysis intended to identify failures, at the basic component level, which have significant consequences affecting the system performance in the application considered.

Functionally Closed Process (ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition) [18])

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.

Gamma Irradiation

A physical means of sterilization or decontamination also known as “cold process” (temperature of the processed product does not significantly increase) that uses electromagnetic radiation of very short wavelengths. Gamma irradiation kills bacteria by breaking down bacterial DNA and inhibiting bacterial division.

The most common source of gamma rays for irradiation processing comes from the radioactive isotope Cobalt 60 which is manufactured specifically for the gamma irradiation process.

Genotoxic

Substances which damage or modify deoxyribonucleic acid (DNA).

Glycosylation

Adding one or more carbohydrate molecules onto a protein (*a glycoprotein*) after it has been built by the ribosome; a posttranslational modification.

Hydrophilic

Having a strong affinity for water; attracting, dissolving in, or absorbing water; readily absorbing moisture; having strong polar groups that readily interact with water. Its opposite, hydrophobic.

Hydrophobic

The extent of insolubility; not readily absorbing water; resisting or repelling water, wetting, or hydration; or being adversely affected by water. Hydrophobic bonding is an attraction between the hydrophobic or non-polar portions of molecules, causing them to aggregate and exclude water from between them.

Integrity Test

In the context of this document: A test primarily done by the supplier as part of the release criteria. The end-user may also conduct the test prior to the use of the product. The test can be applied to single-use assemblies or to filters.

For single-use assemblies: The test is done to check the structural and mechanical integrity of the assembly. The test confirms that there are no leaks in the single-use assembly. The end-user should consider doing the test prior to use in critical applications.

For filters: It is typically a non-destructive and non-contaminating test used to determine if a filter can retain material of a specified size.

Intermediate

A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance.

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.

Migration

Release of substances (leachables) from the plastic component into the content of the container under conditions which reproduce those of the intended use.

Moiety

One of the portions into which something is divided; a component, part, or fraction. In chemistry, a specific section of a molecule, usually complex, that has a characteristic chemical effect or pharmacological property.

Monomer

The basic subunit from which, by repetition of a single reaction, polymers are made. For example, amino acids (monomers) condense to yield polypeptides or proteins (polymers).

Open Process (*ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [18])

A process that is exposed to the environment and therefore requires environmental conditions to mitigate the risk of contamination from the environment.

Packaging

All operations, including filling and labeling, which a bulk product has to undergo in order to become a finished product.

Parenteral Drug

A parenteral drug is defined as one intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion.

Particulate

Usually a solid particle large enough to be removed by filtration. Nonfilterable solids are usually referred to as colloids.

Perfusion

A method of cell culture that differs from batch or fed-batch methods in those cells are maintained in a relative steady state of cell concentration and productivity. Perfusion involves physical retention of cells and includes a system in which waste (spent) medium is continually replaced with fresh medium. Perfusion cultures are characterized by relatively high cell densities.

Peristaltic Pump

A type of positive displacement pump that operates by pulsations of flow caused by passing rollers over flexible tubing. Operating pressure limited by tubing tolerance.

Physicochemical

Of or relating to chemistry that deals with the physical and chemical properties of substances.

Polyethylene (PE)

A thermoplastic material that varies from type to type according to the particular molecular structure of each type, i.e. its crystallinity, molecular weight, and molecular weight distribution.

Polyolefin

The polyolefin polymer is probably one of the most economical and widely used classes of thermoplastics, including such materials as PB, PP, and PE.

Polymeric Materials

A natural or synthetic material whose molecules are linked in a chain.

Polypropylene (PP)

A plastic material used to make pipe; thermoplastic member of polyolefin family of plastics; lightest plastic known; polypro is a relatively inert material and contributes little in the way of contamination to pharmaceutical water.

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.

Process Contact Surface (ASME BPE [125])

A surface under design operation conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g., WWFI, CIP, pure steam, process gases), or components (e.g., stoppers) and where there is a potential for the surface to affect product safety, quality, identity, strength, or purity.

Proximal Material

All packaging materials other than the Primary Packaging Component (PPC), such as ink, adhesive, label, carton, protective packaging materials, etc.

Quality Risk Management (ICH Q9 [28])

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

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.

Quality by Design (QbD) (ICH Q8 [29])

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Risk Assessment (ICH Q9 [28])

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Management (ICH Q9 [28])

Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

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.

Single-Use Components

The single-use parts that may be used individually or as a subset of a single-use system (SUS).

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.

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

Sterile

Absence of life; usually refers to absence of viable microorganisms.

Sterilization

The act or process, physical or chemical that destroys or eliminates all forms of life (e.g., microorganisms). Despite being stated as an absolute, the action of sterilization is stated in terms of probability.

Supplier

An organization or individual internal or external to the user associated with the supply and/or support of products or services at any phase throughout a systems lifecycle.

In the context of this document: An organization that builds and supplies single-use components or assemblies to other organizations in the supply chain to satisfy the requirements of the end-users.

Supply Chain

In the context of this document: The organizations that are linked in the distribution and manufacture of materials used to build single-use assemblies which are applied by the end-users to produce pharmaceutical drugs. The supply chain starts at the raw materials for the single-use components and continues until the single-use assembly is utilized by the end-user for the production of pharmaceutical drug substances/products.

Support Equipment/Systems

In the context of this document: 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.

Technology Transfer (ICH Q10 [42])

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement

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, Structure-Activity Relationship (SAR), and any qualification data (if available).

Toxicology

A science that deals with poisons, their effects, and the problems involved.

Tubing Set

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

Ultrafiltration

Filter technology similar to reverse osmosis that is capable of filtering colloids and large molecular weight organics out of the water. The filter capability of ultrafiltration filters to 0.005 µm particle size. Ultrafiltration also will remove organic material down to about 1,000 – 10,000 molecular weight.

User Requirement Specification (URS)

A description of the requirements of the facility in terms of product to be manufactured, required throughput and conditions in which the product should be made.



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