Chapter 4

Validation

Objectives

This chapter provides an overview of validation practices and procedures typical of the biomanufacturing industry and will examine not only current concepts and practices in the validation field but also the historical events that precipitated the requirement of validated systems in pharmaceutical production.

After completing this chapter the student will be able to:

- Define and apply common validation terminology.
- Describe how equipment, process, and method validation fit into the overall quality system.
- Define the types of validation documents found in a biomanufacturing organization and their typical content and purpose.
- Explain the validation lifecycle.
- Describe how risk assessment and analysis are applied to validation activities in the biomanufacturing industry.
- Explain how a validation program is systematically established and the flow of validation requirements involved.
- Distinguish procedures and outcomes for Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).
- Describe the general methods for facility, equipment, and utility validation; analytical method validation; computerized systems validation; process validation; and cleaning validation.
- Summarize the change control and support processes.

Terms

Amendment: a controlled change, prior to execution, to an approved protocol

Calibration (Metrology): a process/program that demonstrates that a measuring device produces results within specified limits of those produced by a reference standard device over an appropriate range of measurements

Certification: documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are accept; personnel certification is proof that a person has achieved a certain level of qualification.

Change Control: a formal process that follows a predetermined procedure set out in a Quality Assurance document or Master Validation Plan for making changes to equipment, systems, or procedures that may change the parameters or affect expected outcomes

Current Good Manufacturing Practices (cGMP): guidelines defining acceptable manufacturing methods and facility standards that ensure safety, purity, and potency of a biologic, as applicable to APIs, per 21 CFR, subparts 210 and 211 and ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Commissioning: a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user or validation; this results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Control Chart: a statistical trending tool that graphically represents whether a process is either in- or out-of-control by depicting a variable compared to calculated upper and lower control limits over time

Design Qualification: a process to ensure that equipment and systems are suitable for their intended use; an example of design qualification parameters would be checking that the water system has sufficient capacity to serve the needs of the facility (including production, testing, steam generation, and autoclave operations)

Development Studies: studies that are performed prior to validation to determine the extent and scope of required validation testing; examples of development studies may include temperature mapping of autoclaves to identify cold regions as well as cleaning studies in dishwashers to identify hard to clean items

Deviation: any event occurring during validation of a system that is a departure or variation from a written procedure or acceptance criteria

Direct Impact System: a system that is expected to have a direct impact on product quality; these systems are designed and commissioned in line with Good Engineering Practice and are subject to Qualification Practices that incorporate the enhanced review, control, and testing against specifications or other requirements necessary for cGMP compliance

Indirect Impact System: a system that is not expected to have a direct impact on product quality but will typically support a Direct Impact System; these systems are designed and commissioned following Good Engineering Practice only

Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with approved design, manufacturer's recommendations, and/or user requirements

Installation Verification (IV): the verification or checkout that all equipment and/or systems are installed as designed and specified; the IV is performed during commissioning and as equipment and/or systems are installed over the life of the installation (construction) phase; all installation is verified and documented to reflect as-built conditions; IV is executed by making a complete field verification of all trade contractors' work and vendors' deliverables by performing line-by-line checks using purchase orders, design documents, P&IDs, specifications, electrical drawings, instrument & control drawings, testing procedures, SOPs, and all other available tools

Issued For Construction (IFC): the stage of design for specifications, drawings, and/or other design documents when the design document is deemed acceptable to use for construction

Limit of Detection (LOD): the lowest amount of analyte that can be detected in a sample but not necessarily quantified

Limit of Quantification (LOQ): the lowest amount of analyte in a sample that can be quantified with suitable precision and accuracy

Master Validation Plan (or Validation Master Plan): a document that pertains to the entire facility and describes which equipment, processes, systems, and methods will be validated and under what conditions; the Master Validation Plan should include a format for the IQ, OQ, and PQ protocols and include the types of information to be found in each document

Out of Specification Results (OOS): results of any measurement that differ from predetermined specifications

Operational Qualification (OQ): the documented verification that the system or subsystem operates as expected according to the manufacturer's specification and/or the user functional requirements

Operator Interface Terminal (OIT): a graphic display panel serving as the interface between an operator and a control system

Overkill Approach: a cycle that provides a minimum 12-logarithm reduction of a resistant biological indicator with a known D-value of not less than one minute; this approach assures a reduction of the bioburden that is substantially greater than a 12-log reduction; therefore only minimal information on the bioburden is required

Performance Qualification (PQ): documented verification that the system or subsystem performs as intended, meeting predetermined acceptance criteria under actual production conditions; establishes confidence through appropriate testing that the process is effective and reproducible

Precision: describes the closeness of agreement or degree of scatter between a series of analytical measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions

Process Validation: the scientific study of a process conducted in order to: prove that the process works as intended (process is under control); determine the process-critical variables and their acceptable limits; and set up appropriate in-process controls

Programmable Logic Controller (PLC): a specialized industrial computer used to program and automatically control production and process operations by interfacing software control strategies to input/output devices

Relative Standard Deviation (RSD): %RSD=Standard Deviation x (100%)/mean—it is the absolute value of the Coefficient of Variation

Re-Qualification (RQ): documented verification that the system or subsystem remains in a validated state; this can apply to a specific function or the entire operation of a system and/or equipment

Retrospective Validation: validation of a process or piece of equipment for a product already in distribution based upon accumulated and statistical reviews of production, testing, and control data; these reviews are primarily accomplished by graphic representation of the data in chronological order; the review is limited to quantitative results that are indicative of product quality

Second-Order Kinetics: chemical reactions that proceed at rates that are proportional to the square of the concentration of one of the reaction ingredients; reactions that proceed by second order kinetics decrease faster than reactions that proceed through first order kinetics

Stakeholders: departments with a vested interest in facility, system, and/or equipment validation

Steam In Place (SIP): the introduction of steam to sanitize or sterilize a piece of equipment without disassembling the equipment

Sterilization: an act or process, either physical or chemical that destroys or eliminates microorganisms

Terminal Sterilization: a process whereby a product is sterilized in its final container, permitting the measurement and evaluation of quantifiable microbial lethality

Turn Over Package (TOP): data package(s) consisting of critical data and documentation to support system validation; documentation of the design basis, fabrication, assembly, installation, and testing of equipment and facilities, which provides the basis for validation,

operation, and maintenance; the documentation package that is provided with each qualified system is typically supplied by the facility or equipment provider/installer

Validation Protocol: a written plan describing the process to be validated, including production equipment and how validation will be conducted; this includes the kind and number of samples and replicates, the tests to be used, and acceptance criteria for the test results; the validation protocol addresses objective test parameters, product and process characteristics, predetermined specifications, and factors which will determine acceptable results.

What is Validation?

Though it is important to note that organizations can be subjected to regulations from various governmental agencies throughout the world, this chapter of the text will focus primarily on United States regulatory agencies.

The Food and Drug Administration (FDA), the primary regulator of drug and biologic products marketed in the United States, has defined a number of important terms for the pharmaceutical and biopharmaceutical industries. These definitions can be found on the FDA web site (www.fda.gov) and in the relevant Code of Federal Regulations (CFRs) and guidance documents. One of the terms vital to the biomanufacturing industry is *validation*; it is defined by the FDA as:

> "The process of *demonstrating*, through *documented evidence*, that a process, procedure, piece of equipment, analytical method, or facility will *consistently* produce a product or result that meets *predetermined* specifications and quality attributes."

Note that the FDA explicitly calls for "documented" evidence. Therefore, biomanufacturing organizations must *prove* that the production process will consistently create a product that meets all of the specifications or quality attributes that have been established for that product. To accomplish this, organizations must ensure that:

- the facility, equipment, and utilities all perform as expected
- the analytical methods used in the quality control laboratory perform as expected
- each step of the production process contributes to a final product that meets all of the quality attributes and specifications

Validation is an external check on the performance of a system and ultimately the entire manufacturing process. If the process performs properly, it should produce a product that meets predetermined specifications. If it does not perform properly, a step in the process exists that is either inadequately understood or is not performing as designed.

Validation also forces the biomanufacturer to examine assumptions about equipment, materials, procedures, and the entire production process. For example, one can assume that material placed in an autoclave will be sterilized if the autoclave is working properly. But how can that person know that the autoclave is working properly or that it sterilizes the material to meet the necessary established standard if it *is* working properly? Validation demonstrates and documents that the autoclave is working according to its design specifications and that the autoclave cycles are sufficient to sterilize the material placed within. Furthermore, studies are conducted and experiments are performed to demonstrate that the system is working properly.

When principles of demonstration and documentation such as these are applied to the equipment, test methods, and production process used to produce a therapeutic protein, areas of uncertainty in the production process are eliminated, increasing the likelihood a product meets pre-defined specifications.

The validation of facilities, equipment, software, procedures, and processes used in

biomanufacturing is a time-consuming and expensive aspect but one that is essential to producing a safe and effective product; and given the importance of validation to both regulatory compliance and patient safety, validation activities permeate the entire biomanufacturing organization, including:

- top levels of management that establish the validation philosophy of the organization
- department heads that determine the needs and procedures
- the validation technician who actually performs the validation protocols and gathers the data in support of the validation activities

Changes in the field of validation have made the previous mindset "validate anything that moves and don't move anything that is validated" a thing of the past. The current approach is based upon a thorough understanding of the manufacturing process, a clear assessment of risks posed to patients and product by the manufacturing process, and a rigorous, scientific approach to validation based on the elimination or reduction of those risks. This relates to the approaches and efforts discussed in ***Operational Excellence***, ***Metrology, Quality Assurance***, and ***Quality Control*** chapters.

This chapter provides an overview of the validation process, beginning with key concepts and events that have shaped current validation practices. A description of the various documents and procedures used in the validation of facilities, equipment, processes, and analytical methods follows, with a brief discussion of issues associated with the validation of computerized systems, analytical methods, and equipment cleaning closing the chapter.

A validation example

As mentioned above, validation is a critical, time-consuming, and expensive aspect of the biomanufacturing process. To aid in understanding the complexity of the validation process, an organization producing a biopharmaceutical product in mammalian cells can be used as an example.

Since mammalian cells can potentially harbor viruses that could contaminate the product and infect patients, the organization will need to include a heat inactivation step in the production process. This will eliminate the risk of viral contamination and reduce the risk to patients taking the product. The design specifications for this heat inactivation step require that the process achieve and hold a temperature of 56°C for 60 minutes.

To accomplish this an autoclave will be used (Figure 4.1). Before proceeding, the following assumptions must be proven or validated:

1. Holding the process material at 56°C for 60 minutes will inactivate any and all contaminating viruses.
2. The container used for the virus inactivation allows all of the material in the container to achieve a temperature of 56°C.
3. The heating step can be maintained for 60 minutes.
4. Heating of the product to 56°C for 60 minutes does not impact the quality of the product.

Figure 4-1. Autoclave

More specifically, it must be *proven* that:

1) Heating a sample to 56°C for 60 minutes will, in fact, inactivate any potential viruses.
2) The entire sample within the container (this might involve thousands of liters at the manufacturing scale) is uniformly heated to 56°C .
3) The heating step can be maintained uniformly throughout the solution for a minimum of 60 minutes.
4) The heating step does not adversely affect the quality of the product (the half-life of typical microbial and viral proteins is approximately two minutes at 55°C).

A number of experiments must be conducted to test the heat inactivation of viruses. In all likelihood these experiments will be done on a smaller scale during the process development phase and not in the production facility. In the production facility it must be demonstrated that the process vessel can heat the entire sample according to the temperature and duration specifications mentioned above. Doing so may require temperature-mapping studies to ensure that all areas within the container achieve the desired temperature. Additionally, the mixing rate of the material needs to be documented to prove that as the solution is mixed it maintains its temperature.

This test will also need to be performed under a worst-case scenario, with maximum volume, lowest mixer setting, a partially-operable heater, or other mechanical issues that could affect product quality. This verifies that if specifications are met at the limits of the ranges, the specifications will assuredly be met at the normal operating range. Furthermore, it must be demonstrated that heating the product to 56°C has no effect on product quality.

The effort involved for this single scenario, one of many operations within a biopharmaceutical production process, proves that validating a complex biomanufacturing operation is a major

and ongoing task.

Validation begins with the design of the manufacturing process and continues with the specification and installation of the facilities and equipment used in the individual steps (e.g. buildings, air handling units, tanks, temperature control units, mixers, timers, and a control system); and is sustained as the equipment is operated and used in trial production runs. At the end of this process, the organization will have a body of evidence that demonstrates that each piece of equipment, each analytical method, each step of the production process, and each production run will consistently produce a product that meets its predetermined specifications.

Validation is not a one-time event. To ensure that the process, procedure, piece of equipment, or analytical method continues to operate in a "validated state," periodic revalidation is necessary at specified intervals or in the event of changes. In the above example, tests would be re-run periodically, with the autoclave operation validated as well. Furthermore, the proof (evidence) from this validation example requires a number of supporting documents. The purpose of this documentation is to meet regulatory requirements and assist the organization's efforts with quality, operations, process optimization, maintenance, troubleshooting, etc.

Documented evidence

The FDA's definition of validation establishes the standard for its implementation in the biomanufacturing industry (e.g., processes, procedures, methods, equipment, or facilities that are used to produce the product). It also describes how these must be validated—through documented evidence. Validation must *prove* that a process, procedure, piece of equipment, or analytical method performs as designed and *consistently* meets specifications. For example, it is not adequate to demonstrate only once that the cleaning procedure removes all traces of media, proteins, and cleaning fluid from a fermentation tank; it needs to be shown through repeated rounds of cleaning that the procedure performs as designed. This proves that the process works and that the limits of the process are understood.

Documenting the validation process is an essential aspect of demonstrating the production of a quality product. Improper documentation or the failure to investigate an Out Of Specification Result (OOS) during a validation test can result in a citation if the FDA conducts an inspection of a facility. Documentation must be thorough, accurate, and complete to ensure that the validation process is in compliance with governmental requirements. For example, a soft contact lens producer received the following FDA citation during an inspection:

> "Failure to validate with a high degree of assurance a process that cannot be fully verified by subsequent inspection and test, and to document and approve the activities and results of the validation, as required by 21 CFR 820.75(a). For example:
>
> > Your firm failed to adequately validate the terminal steam autoclave sterilization process.
> >
> > There was no validation protocol or procedure for the original sterilization validation.
> >
> > There was no evidence that the sterilization process validation had any established acceptance criteria prior to validation efforts.

The validation study documentation discussed the results of bio-indicators placed in the autoclave during the validation study, but the documentation did not establish if there were positive or negative controls utilized in the study.

There was no documentation that the sterilization validation results were acceptable and approved."

The FDA pays particular attention to an organization's validation strategies and testing during an audit. The above citation specifically cites the lack of documented evidence and predetermined specifications (acceptance criteria), two critical aspects of validation. Additionally, the company failed to document its use of controls; and the FDA maintains that if something is not documented it did not occur.

As evidenced above, documentation is an important step in the validation process. Below is an example of established documentation guidelines in an environment that follows the FDA's cGMPs (Table 4-1). These particular guidelines for recording written data, taken from the International Society for Pharmaceutical Engineering (ISPE), are required to ensure documentation integrity and prevent misinterpretation of information.

Table 4-1. Standards for recording and entering written data

2.1	Use black indelible ink.
2.2	Do not use correction fluid or other correction mediums.
2.3	Do not use ditto marks or arrows.
2.4	Write legibly.
2.5	Record data while performing an operation (not after).
2.6	Review acceptability of data before signing. If unacceptable, explain what action will be taken.
2.7	Fill in all spaces. Mark unused spaces as "N/A" or line with initial and date.
2.8	Correct entry errors with a single line through the error; initial and date each correction.
2.9	Initial/sign and date each entry or page.
2.10	Identify where the original copies of all documentation are kept.

The need for validation

How did the FDA and other similar government agencies around the world arrive at their regulations on validation? There is an historical basis for these validation requirements, resulting from various accidents and incidents that affected human health and safety. These accidents and the causes behind them were thoroughly investigated by government agencies and independent sources. Based on the investigation findings, governmental regulations were established to prevent similar incidents from occurring in the future.

In the case of the pharmaceutical and biopharmaceutical industry, many of the FDA's regulations are the result of tragic, or potentially tragic, incidents involving medicines and drug delivery devices. In the area of regulations that address process and equipment validation requirements, two major events are examined: one case known as the Cutter Incident and another case of *Pseudomonas* contamination in Large Volume Parenterals (LVPs, or injectable medicines). These incidents illustrate how assumptions that have not been proven through rigorous scientific study can have a fatal impact.

The Cutter Incident

The development of an effective vaccine to prevent polio was a significant accomplishment in the fight against the infectious disease. In 1955 the vaccine was introduced, with more than 10 million children in five countries inoculated during the first year that the vaccine was available.

A number of companies were recruited to produce the batches of vaccine necessary for this massive vaccination effort, including Cutter Laboratories. In April, 1955, during this mass vaccination drive, public health officials in California noticed an increase in reported cases of polio. A subsequent investigation showed that over 200,000 people had been inoculated with a vaccine prepared by Cutter Laboratories that inadvertently contained the *live* polio virus instead of an *inactive* virus.

Vaccines are often prepared from either attenuated (weakened or modified to render them inactive) or whole-killed infectious agents. In the case of the polio vaccine, the live virus was prepared and then inactivated by treating it with formaldehyde. This inactivation was assumed to proceed with first order kinetics**,** meaning that the rate of inactivation was directly proportional to the concentration of live virus. With first order reactions, knowing the concentration of live virus and the rate at which the inactivation by formaldehyde occurs, it can be predicted when the entire virus is inactivated. The inactivation in this case, however, was actually proceeding by second order kinetics, meaning that the rate of virus inactivation varied with the square of the virus concentration. The practical effect of this mistaken assumption was that the viral inactivation reaction slowed much faster than predicted. What was assumed to be a batch of completely inactivated virus actually contained virus that had not been inactivated and thus was still capable of causing disease. Instead of inoculating children *against* polio, the vaccine was actually *causing* the disease. As a result more than 200 children developed permanent paralysis and ten died.

Large Volume Parenterals (LVP)

Solutions that are injected into the body are known as parenterals and ensuring that these solutions are sterile is a major concern for the organizations that produce them. Parenterals, and other heat stable medicines, are typically sterilized by a process called terminal sterilization. In terminal sterilization, the final packaged product is sterilized using any of a number of methods. This includes autoclave sterilization, which uses high temperatures and pressures to kill any microorganisms present.

A second example of the importance of validating assumptions occurred in 1971, when parenteral solutions used in burn wards were incompletely sterilized and thus contaminated with live *Pseudomonas spp.* bacteria. Patients with severe burns were administered these solutions, with a large number of patients developing infections—more than 50 deaths resulted. Consequently the products were recalled, and the responsible production facility was closed. During the FDA investigation of the manufacturer, it was determined that both the positioning of materials within the autoclave and the time and temperatures used to sterilize the solutions had not been tested on the actual material. When the product was packaged, air was trapped between the metal crimp used to seal the container and the rubber bung that was inserted into the vial. The trapped air had served to insulate residual *Pseudomonas* bacteria that were then able to survive the autoclave conditions used.

FDA response

Both the Cutter polio vaccine and the incorrectly sterilized parenteral solutions demonstrate the consequences that can occur when assumptions are made concerning manufacturing processes. Often it is assumed that what occurs on a small scale will also occur at the manufacturing scale (thousands of liters). Instances such as these have led to the requirement for validation in the pharmaceutical and biopharmaceutical industry; not just validation on small scale processes but on manufacturing processes as well.

The case of the large volume parenteral solutions also demonstrated a serious defect in the then accepted reliance on quality control testing to determine product reliability and safety. Today the practice of producing a product and *then* testing to ensure it meets its specifications is not accepted by regulatory agencies or the organizations that produce the product.

With any product it is impossible to guarantee that it conforms to specifications in its entirety unless every sample is tested, which is clearly unfeasible. As an alternative, guiding principles have been developed in what is known as Good Manufacturing Practices (GMPs). The aim of GMPs is to ensure that the process itself will produce a product that meets the quality specifications. By relying on the process to achieve quality standards, validation of the process and its individual steps and equipment becomes an essential part of producing a quality product.

The lessons from the Cutter Incident and the *Pseudomonas* contamination incident led to expanded validation requirements. In 1976 the FDA proposed changes to the GMPs, focusing on various types of sterilization processes used in the pharmaceutical industry and the need to validate those operations. Regulatory documents were written to include terms such as *validation*, *qualification*, and *protocol*. Along with sterilization processes, the FDA began examining ancillary and supporting systems in the pharmaceutical industry, including filtration operations, environmental controls, water systems, and aseptic processing operations.

In the more than 30 years since the introduction of validation requirements in the GMPs, validation activities have grown into both costly and time-consuming exercises. These activities, at their best, provide confirmation of a well-defined design and development process. These requisite validation activities, however, place an enormous burden on biopharmaceutical organizations in terms of time, capital, employee training, and employee sensitization.

The industry approach of “validate anything that moves but don’t move anything that’s validated” is an approach that contributes to this burden. This approach essentially discourages innovation and continuous improvement efforts. It also contributes to the perception that validation is a "necessary evil" rather than a value-added activity. For these reasons this approach is being replaced with more effective and efficient approaches over time. One of the alternative approaches is based on identifying the critical process parameters that affect product quality and safety and understanding the risks posed to the product when those parameters are not met. This risk-based approach, proving more efficient and effective, is being embraced by more pharmaceutical organizations and regulatory agencies.

In September 2004, the FDA published its guidance *Pharmaceutical cGMPs for the 21st Century:*

A Risk Based Approach. The FDA's objective was to propose a more scientifically rigorous quality system, which integrates quality, safety, and risk-management considerations. For industry, risk-based validation represents an efficient and effective combination of scientific rigor, quality assurance, and business savvy.

The Validation Lifecycle

As mentioned above, validation is not a one-time event. Validation is a lifecycle that begins with the conceptual design of the manufacturing process or facility (see the ***Facilities Chapter 2***) and ends with system retirement. The intent of the lifecycle approach is to ensure that:

- validation activities and requirements are taken into account at the earliest stages of the design process
- construction and installation activities are leveraged and used to reduce repetitive validation activities
- activities that support the manufacturing process, such as analytical methods, training programs, and computer systems, are adequately validated
- the need for periodic maintenance, changes to the manufacturing process, and revalidation activities, are adequately addressed

The result from using the lifecycle approach should be a continuous effort aimed at establishing a solid foundation for follow-on validation activities and the leveraging of design, construction, and installation activities to facilitate regulatory compliance. As illustrated in Figure 4-2, the commitment to validation efforts must be made early and accepted by the entire manufacturing facility.

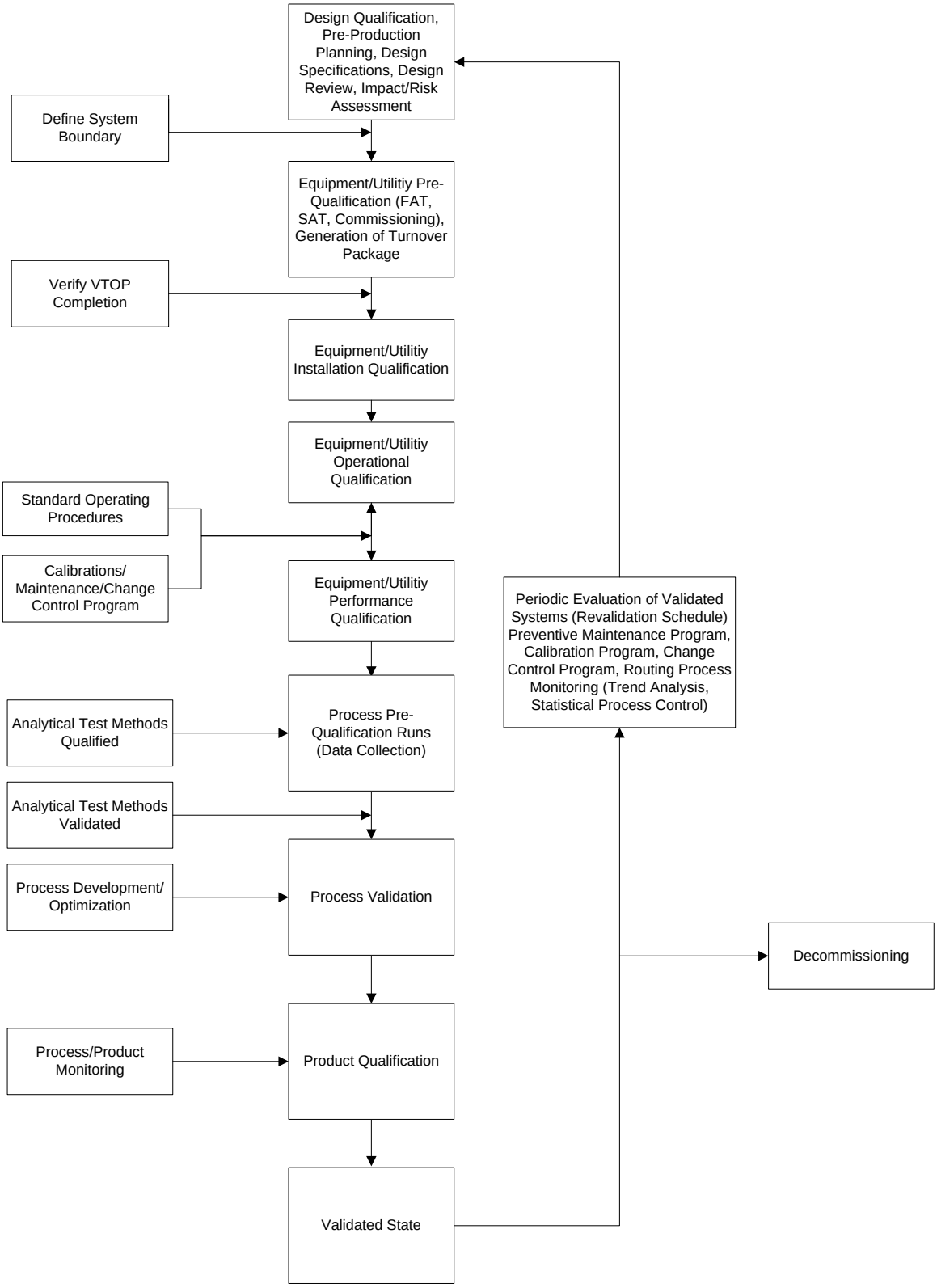

Figure 4-2. The validation lifecycle and its relationship to the process

The Validation Program

Validation policies

Any quality validation program should begin with the organization's Quality manual or policies. The manual is a high-level document that not only provides a general view of the organization's philosophies but also presents its philosophy toward validation, which guarantees product quality and fulfills regulatory requirements. It does not, however, provide specific detail of how to perform those validation activities.

Corporate validation policies are developed based upon an organization’s Quality manual. Consider the relationship between documents such as the United States Constitution and the Bill of Rights. The Constitution makes high-level statements, while the Bill of Rights provides specific details. An organization’s Quality manual would be similar to the Constitution—its validation policies the Bill of Rights. When these policies are developed, an appropriate amount of time and resources must be allocated to allow for adequate validation of all facility equipment and utilities, test methods, and processes.

Figure 4-3 illustrates how the organization's validation documents relate to each other. The amount of detail included in each document increases with each lower row in the chart. Not represented in the chart are documents generated as part of the risk assessment process or detailed validation protocols. Later sections will describe the various documents.

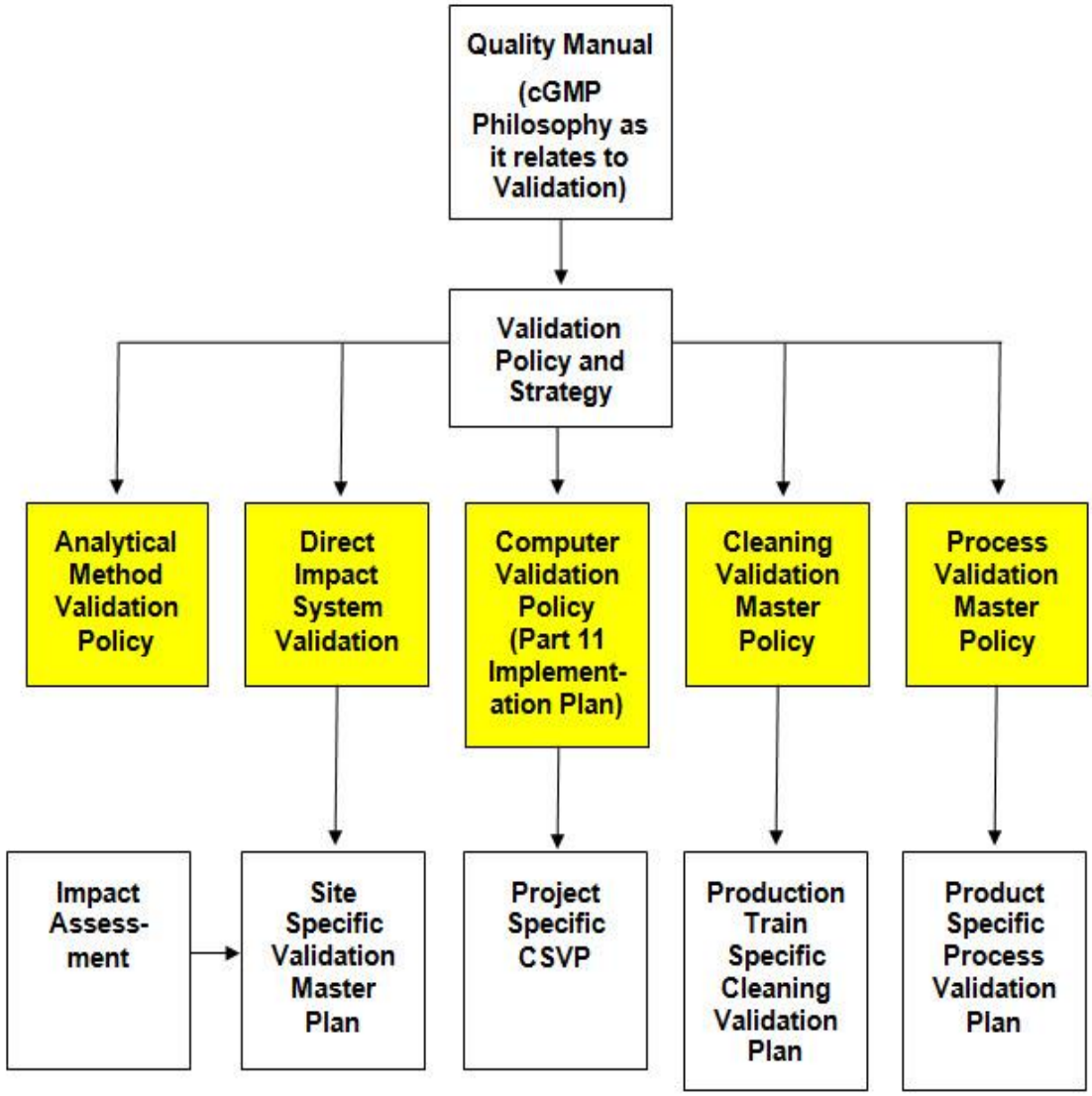

Figure 4-3. Hierarchy of validation documents within an organization

Validation Policy & Strategy document

Below the organization's Quality manual/policies is the Validation Policy & Strategy document. This document is used to identify the specific responsibilities for the validation department. This includes the generation or acquisition of required documentation, along with the execution of equipment, process, procedure, or analytical method validation. Typically the validation department does not decide specifics independently. These decisions are made by a team of individuals representing different departments in the organization, such as manufacturing, engineering, quality control, quality assurance, and validation. The team performs an organized and well thought-out risk assessment to decide upon the type of activity necessary for a given piece of equipment or process. This risk assessment process, as described in a later section, defines those aspects of the equipment, facility, or process that pose the greatest risk to product quality and patient safety. These are oftentimes referred to as critical process parameters.

Validation Master Policies

Increasing in specificity, Validation Master Policies are developed for those areas that require focused validation activities. These include validation of:

- the analytical methods used to determine the purity or identity of raw materials, process intermediates, or final product
- systems that have a direct impact on product quality
- computer systems
- cleaning systems
- the overall manufacturing process

The validation of these areas is addressed specifically in the CFRs due to their potential impact on product quality and patient safety. These Validation Master Policies establish the process, team make-up, and approvals necessary for the development of the Validation Master Plans for each of these areas, as well as periodic revalidation activities in response to changes to manufacturing or unit operations.

Validation Master Plans

Validation Master Plans include specific information on individual areas and individual pieces of equipment within a facility. The plans also include specifics on the type and extent of activities as they relate to each area or equipment type. The development of individual Validation Master Plans proceeds through a risk assessment process to identify those specific items within an area that require qualification or validation. This includes identifying systems and system boundaries; determining the potential impact of those systems on product quality; and determining the activities necessary to adequately document the performance of the system. The development of the Validation Master Plan is discussed in a later section of this chapter.

Validation Master Plans, whether they pertain to equipment, facilities, or analytical or computer systems, will generally include the following:

- Revision History: a log providing a detailed reason for the revision to the document
- Introduction: a brief paragraph providing a high-level overview of the company and its intention to satisfy cGMP requirements within the context of the scope of the VMP
- Purpose: the intended achievements of the document. The purpose should be written as an overview and should not contain overly detailed information.
- Scope: a clear definition of the boundaries of the document (e.g. subjects that the document does and does not address)
- Overview: a brief description of the facility, product, etc., and the intended operations and or process. All activities within the scope of operations should be briefly discussed in this section of the document.
- Definitions/Abbreviations: a description of the key terms and abbreviations in the document
- References: all applicable reference materials used in the generation of the document; references may include internal corporate policies and Standard Operating Procedures (SOPs), drawings, validation plans, or industry-accepted publications, articles, and papers.
- Description: a more detailed explanation of the facility, process, or similar designation; the description should provide sufficient detail to ensure that individuals with a cursory knowledge will comprehend the facility, process, or similar designation defined by the document.
- Validation Program: an outline of the intended validation approach employed by the plan, including the validation rationale or philosophy; critical validation documents, such as Turnover Packages (TOPs), Installation Qualifications (IQs), Operational Qualifications (OQs), Performance Qualifications (PQs), final reports, deviations, amendments, and addenda will be identified and described in the validation program. Each validation document will be clearly described, and appropriate SOPs will be referenced.

  The validation documents' sequence of execution and approval mechanisms should also be clearly defined within the Validation Program section, defining the responsibilities of all plan signatories. Additionally, the responsibilities of contractors and miscellaneous non-signatory groups can be defined. Finally, the Validation Program section will briefly describe the revalidation plan and references to the appropriate SOPs or policies.
- Validation Requirements: clear identification of the specific validation requirements; in order to group like systems, equipment or processes, this section may be subdivided as necessary (e.g., Utility Systems, Process Systems, etc.).

- Support Programs: identification of critical ancillary programs required to ensure facility systems and equipment remain in a validated state. Typical support programs will include, but are not limited to, commissioning, calibration/metrology, preventive maintenance, document control, change control, drawing control, SOPs, training, environmental monitoring, and high purity system monitoring; each of the identified support systems will include a brief description and references to applicable SOPs.

The documents described here, beginning with the organization's Quality Manual and continuing through the Validation Master Plan, represent the overall policies and activities that are needed to satisfy qualification and validation requirements for an organization's facilities and operations from conceptualization to retirement. Additional validation documents, such as the validation requirements matrix, individual system validation plans, and validation protocols are developed in response to a thorough understanding of the manufacturing process and an analysis of the risks posed to patient safety, product quality, and regulatory compliance.

A Risk-Based Approach to Validation

Risk analysis

Risks are a constant companion of every activity in which one engages as well as every decision one makes. From deciding on which foods to eat to arranging travel, risks are ubiquitous. In daily life one continuously makes decisions based on perceived risks and benefits though rarely engages in the type of scientific scrutiny and examination of risks as demanded by industry.

Risk Analysis (RA) is a formal analytical activity that has traditionally been used in high-risk fields such as aeronautical or nuclear engineering. Increasingly, biomanufacturers are using RA to identify, assess, and manage risks related to the product, patient, and workers. As mentioned earlier, the FDA has suggested the use of risk-based approaches in its pharmaceutical cGMPs for the 21st century in an effort to support innovation without compromising product quality.

The idea of risk analysis is to first identify and then ideally eliminate those risks. However, not all risks can be eliminated entirely. In those cases ways in which to reduce and manage those risks must be found. For example, the daily drive to work or school is a risky activity. It is difficult to eliminate the drive, so procedures or devices that will help mitigate those risks are developed. Devices such as seat belts and air bags and procedures such as obeying the traffic laws can reduce the consequences of our risky behavior.

The entire lifecycle of a drug or biological product is a story of risk. There are risks to patients, to capital, and to the company developing the product. When elimination of these risks is not entirely possible, ways of risk mitigation have to be identified. In the biomanufacturing industry, risks to product quality and patient safety must be identified. It is the manufacturer's responsibility to ensure that the patient receives products that are safe, effective, easy to use, and affordable. Individuals in production, Quality Control (QC), Quality Assurance (QA), Engineering, and other groups in the organization share the goal of consistently manufacturing products of required quality and safety standards at the least possible cost to the manufacturer. With the entire organization working to producing a safe and effective product, the patient benefits.

Validation is essential to product quality; however, the traditional view of validating *everything* does not add value to the product. In fact, it can have the opposite effect since it adds costs without explicitly addressing those activities that can have a major impact on product quality. Systematic and scientific examination of the risks to product quality that are posed by the manufacturing process allows the organization to address those risks through validation activities.

The risk analysis process typically consists of four stages:

1. systems identification
2. definition of system boundaries
3. Systems Impact Assessment (SIA)
4. risk assessment

Systems identification

A system is a set of engineering components that have a defined operational function (e.g., tanks, piping, instrumentation, equipment, facilities, computer hardware/software, etc.). During the systems identification stage, a comprehensive list of all systems in the manufacturing operation needs to be created. This list is typically broken out by functional area. For example:

- facility, equipment, and utility systems
- analytical equipment systems
- computerized systems
- cleaning systems

Each system within a functional area needs to be clearly defined (e.g., chilled water system, clean steam system, WFI system, HVAC to process areas, biowaste system, filling line system, autoclave, etc.). Once defined, each system is given a unique identification number. The Validation Master Plan will then refer to those systems by their identification number to eliminate confusion.

Definition of the system boundaries

Once the systems have been identified, the boundaries (limits) of the system need to be defined. A system boundary is a limit drawn around a system to logically define what is and is not included in the system. For example, Figure 4-4 depicts a Piping & Instrumentation Diagram (P&ID) of a tank with its associated piping. Notice the boundary line indicating the limits of this particular tank system. The system boundaries will determine which components are to be evaluated together during the systems impact assessment.

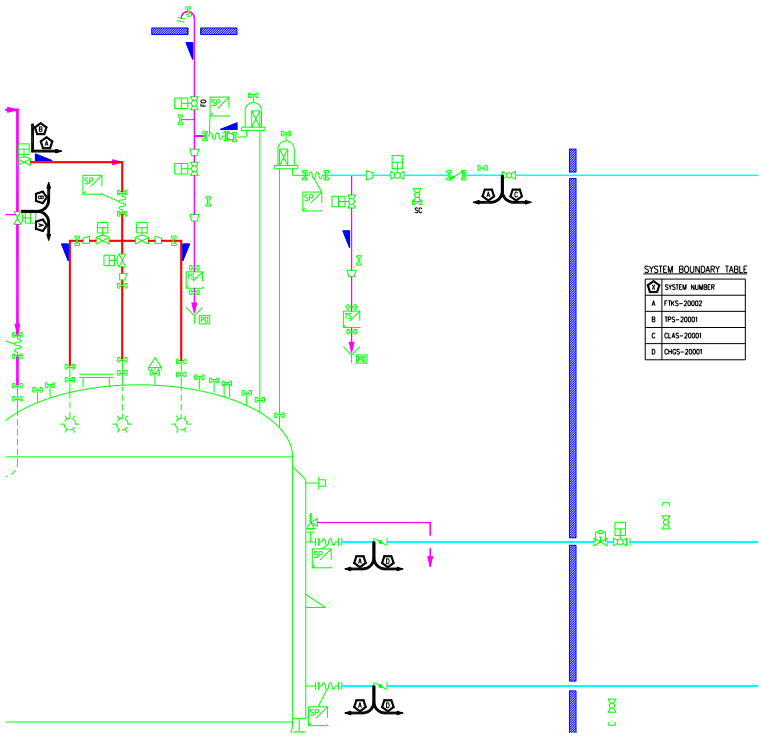

Figure 4-4. P&ID showing a tank and its associated piping with a boundary limit to indicate where the tank system begins

Systems Impact Assessment (SIA)

Once the systems of a biomanufacturing operation are identified and their boundaries determined, the impact that the particular system will have on product quality must be determined. The Systems Impact Assessment (SIA) is a process to determine which systems should be subject to qualification, which evaluates the impact that a system has on product quality. This is a high level assessment made within the organization. Each identified system is then categorized as one of the following:

- **Direct Impact (DI) system**
- **Indirect Impact (ID) system**
- No Impact (NI) system

The assessment is usually conducted by a multi-disciplinary team consisting of representatives from engineering, validation, operations, quality assurance, etc. The SIA will document all of the process systems and provide a rationale as to why they are classified as DI, ID, or NI systems (and whether they should or should not be qualified).

With the traditional approach toward validation, every system is qualified and validated. With the risk-based approach, qualification activities are limited to **Direct Impact Systems (DI**). An Indirect Impact (ID) system does not have a direct impact on product quality but supports a DI system. For example, the potable water system has no direct impact on product quality. However, it provides input to the purified water system, a DI system. It is therefore an ID system. The performance of the potable water system has a potential to affect the performance of the purified water system and thus product quality. The interfaces between DI and ID systems need to be carefully assessed as well.

In those instances where a system can be considered both a DI and ID, the requirements of the DI take precedence to ensure compliance with the cGMPs. In other words, systems that could be classified as either DI or ID should be treated as DI. The final output of this assessment shall be approved as part of the Validation Master Plan (VMP) by technical, QA, and other representatives.

Risk assessment

At this point the systems have been identified and defined and their potential impact on product quality has been determined. The process of risk assessment and management can now proceed. In this case the following risks are the most important (ranked in order of importance):

1. patient safety: risk of a patient being physically harmed
2. product quality: risk that the product quality profile (identity, strength, quality, or purity) will be negatively impacted
3. compliance: risk of a regulatory enforcement action (e.g., FDA, EMA, etc.) or the delay of a product approval

These risks are managed through formal procedures designed to minimize product/process risks, while preserving product/process benefits. The risk management process can be divided into four basic elements (Figure 4-5):

Risk Assessment: the identification and characterization of risks; includes analysis and evaluation of the nature, frequency, and severity of identified risks and assesses the risk-benefit balance for products

Risk Control: the process of making decisions about acceptable risk levels and risk mitigation; the level of risk control should relate directly to the significance of the risk; design engineering and validation efforts should focus on risk mitigation.

Risk Communication: the sharing of information about risk and risk management among affected parties

Risk Review: the periodic review of the risk management process designed to verify that risk management is current with project changes and experience; evaluate the effectiveness of risk management tools; and reassess risk-benefit balance.

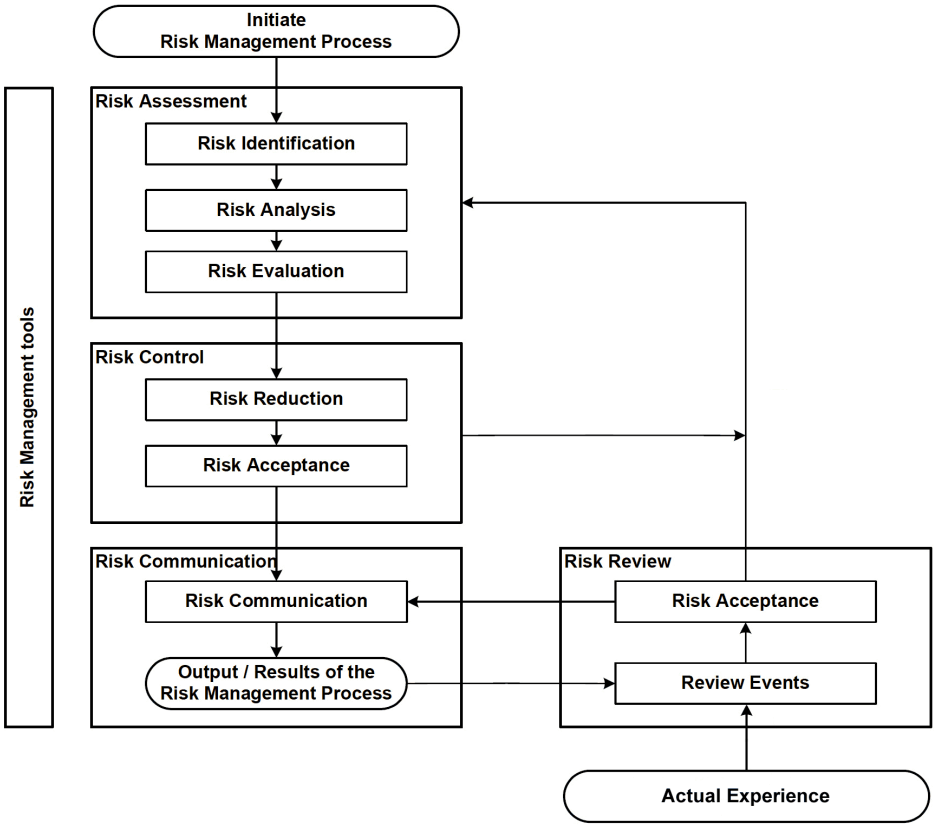

Figure 4-5: Risk Management Process Flow Diagram

The emphasis placed on each element will vary from case to case. However, all elements should be considered. It is important to realize that risk management is an iterative process that should be continuous throughout a product or project lifecycle. New knowledge, equipment, or technology may require that adjustments be made, as appropriate, to further improve risk control and/or the risk-benefit balance.

Definition of validation scope as required by risk assessment

At the conclusion of the system impact assessment and risk assessment exercises, a validation scope matrix (or validation requirements matrix) is created and included in the Validation Master Plan. Table 4-2 identifies the individual systems and the types of qualification activities (IQ, OQ, PQ) required.

Table 4-2. Validation scope matrix

REQUIREMENTS ***SYSTEM NAME/ System Identification number***	*IQ Required*	*OQ Required*	*PQ Required*	*Classification*
Potable Water PW-1621	-	-	-	NI
Instrument Air IA-2648	-	-	-	NI
Clean Air CA-6248	X	X	X	DI
Oxygen O2-7500	X	X	X	DI
Water For Injection WFI-7200	X	X	X	DI
Clean Steam PSG-7300	X	X	X	DI
HVAC AHU-01	X	X	X	DI
CIP Skid CIP-7700	X	X	-	ID
Autoclave AHU-01	X	X	X	DI
Glass Washer GWD-0500	X	X	X	DI
Portable Tank CIP Station (PTCIP-01)	X	-	-	ID
Portable Tank SIP Station (PTSIP-01)	X	-	-	ID

The validation scope matrix shows systems, their System Impact Assessment classification (DI= Direct Impact system, ID= Indirect Impact system, NI= No Impact system) and their qualification requirements based on the SIA.

Definition of individual validation plans as required by risk assessment

The Systems Impact Assessment and risk assessment exercise generates the validation scope matrix. The next stage is to develop individual validation plans for each system listed in the validation requirements matrix, corresponding to the level of qualification listed in the matrix.

Table 4-3 provides an example of an individual validation plan developed for a chromatography skid with control software. The purpose of this document is to define the various aspects of the equipment that need testing and to qualify each particular piece of equipment. This validation plan does not specify how the components are to be tested; that information will be specified in the individual validation protocols.

Table 4-3. Chromatography skid validation plan

System: Typical Chromatography Skid with Control Software
Separate IQ protocols are developed for each chromatography system. The IQs will ensure that the system has been installed per design specifications and manufacturing requirements. The IQ will include verification of all critical installation functions as identified in Documentation Requirements Scope Matrix.
The OQ portion of the validation will consist of Software/FRS/SDDS Documentation, Functional Testing, Sequence of Operation Testing, and Alarm Testing. Tests will include:
Sequence of Operations Testing
Verify that the chromatography system's sequence of operations function as specified.
Control System Verifications
Verify that the control system functions as specified. Testing will include security verifications, data entry/boundary limit verification, and OIT display verifications.
Data Integrity Testing
Verify that the chromatography skids satisfy requirements with respect to data integrity, trending, archival, and retrieval.

Table 4-3. Continued

Alarm/Interlock Verification
Confirm that the alarms and interlocks function as specified.
Pump Performance Testing
Confirm that the pumps operate as specified over the required operating range or range of intended use.
UV Detector Linearity Test
Verify that the chromatography skid UV detector is linear within the specified tolerances over the intended range of use.
Step Gradient Test
Confirm that the chromatography skid control's stepped gradients are within the specified tolerances over the intended range of use.
Linear Gradient Test
Confirm that the chromatography skid control's linear gradients are within the specified tolerances over the intended range of use.
Cleaning Procedure Verification
Verify that cleaning procedures for the chromatography skid are in place and run to completion (Cleaning Validation will be handled separately in this example).

The development of the Validation Master Plan, risk assessment, validation requirements matrix, and individual validation plan establishes the validation test plan. This is based on the regulatory requirements, risk analysis, and user requirements and not on the capabilities of the system. Systems such as the chromatography skid may have additional functions, but if the user will not be utilizing these functions there is no need to test them.

Considering the validation strategy for this chromatography skid, once a validation test plan based on risk analysis is performed, the same analysis can then be performed for similar systems in the facility. Validation test plans based on the results of detailed risk assessments are then compiled into a list of all necessary tests to be performed at different qualification stages. This list is an integral part of the Validation Master Plan.

Validation of Facilities, Equipment, and Utilities

This section will examine how the above concepts and documents are applied to specific areas, such as the validation of new or updated facilities, specific equipment, and utilities. Later sections will cover validation of analytical methods, computer systems, and cleaning.

For a new or upgraded facility, commissioning and facility validation is the foundation for assuring success in further manufacturing process validation. Before a manufacturing process is validated, an acceptable facility and the utilities and equipment to support its manufacturing operations must be in place. Facility qualification and validation activities will establish and provide documentary evidence that:

- The premises, supporting utilities, equipment, and processes have been designed in accordance with cGMP requirements; this constitutes **Design Qualification (DQ)**.
- The premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications; this constitutes **Installation Qualification (IQ).**
- The facilities, supporting utilities, and equipment operate in accordance with their design specifications; this constitutes **Operational Qualification (OQ).**
- The facilities, utilities, or equipment that can affect product quality perform as intended, meeting predetermined acceptance criteria; this constitutes Equipment Performance Qualification (PQ).
- A specific process will consistently produce a product meeting predetermined specifications and quality attributes; this constitutes Process Validation (PV); it can only be initiated once the facility has been validated (IQ + OQ + PQ).

Stages of qualification/validation

Qualification stages begin with the design of the facility, equipment, or process then progress through the ability of the facility, equipment, and process to produce a product meeting the predetermined product specifications. The completion of the required qualification and or validation stages for equipment/systems "cements" that equipment or operation in a validated state. Any changes to the equipment or operation from that point forward may require re-validation. The following section outlines the various stages of qualification/validation.

Formation of a project team

The first stage involves establishing a project team that has adequate skills appropriate for the size and complexity of the project. This is essential to the project launch. The selection of representatives from the various groups in an organization will be based on the project scope, resource requirements, and key stakeholders. Stakeholders can include staff with process, engineering, validation, and/or QA experience/responsibilities.

To ensure timely and cost-effective project completion, it is essential to have excellent communication, planning, and coordination among project team members. Fundamental project management issues that challenge project leaders include:

- organizing these teams
- establishing roles and responsibilities
- determining levels of authority
- monitoring performance
- taking corrective actions

Requirements phase

At the outset of the project, each team member must specify to the team his/her requirements for individual aspects of the facility, equipment, utility, and systems. These aspects must address function, throughput, operability, and applicable compliance standards. This enables the development and assessment of specific engineering options. These requirements are usually formalized in a detailed User Requirement Specification (URS) document.

Design Qualification

The functional design of the system or equipment must be confirmed as being correct and appropriate for the requirements of the URS. This confirmation can be made by detailed comparisons of the functional design with regulatory requirements, company procedures, manufacturer's documentation, and the URS in a formal DQ protocol.

Essential to the DQ is early involvement of the QA department to ensure clear understanding of the project's scope, facility, processes, and equipment. Early involvement of QA by means of a design review or similar approach should provide clear communication of the regulatory requirements that affect the project. This can also ensure that that effective procedures and practices to satisfy regulatory requirements are established upfront for inclusion in the project. This design review can be conducted in parallel with the impact assessment if required.

Risk assessment/impact assessment

Once the DQ is complete, a risk analysis or impact assessment can be conducted. As discussed in the risk assessment section, it is the function of the facility, equipment, or utility that determines the level of commissioning and qualification needed. Developing the commissioning and validation scope is normally accomplished by conducting a risk analysis or impact assessment. The impact of a system on product quality is evaluated and the critical components within those systems are identified. As discussed earlier, the Systems Impact Assessment classifies individual systems according to the potential impact they can have on product quality. It will separate systems and equipment into two classifications: those that have Direct Impact or Indirect Impact on the product and those that do not affect the product in any way.

Decisions concerning the extent of validation can be made using impact analysis based upon GMP requirements or relevance. This is a major opportunity for streamlining validation. This assessment should be performed by those with the appropriate skills and experience necessary to make an informed decision based on a comprehensive understanding of the product, process, and nature of the facility systems and components.

A typical biopharmaceutical company can expect to qualify and validate the following for a new or upgraded manufacturing facility:

- critical process support utilities (e.g. HVAC, compressed air, specialty gases, clean steam, and purified water systems)
- process equipment design, installation, and operation

As DQ is the final step to formally review and document the proper system design. The protocol must enable the reviewers to verify that all quality-critical attributes and other essential technical attributes of the system have been incorporated into the design. When the DQ report is approved, the system is ready for fabrication and construction.

Construction

Prior to initiation of construction, all of the expected deliverables are identified with the service provider as part of the bidding process. The validation group assembles a documentation requirements matrix for each system prior to the system construction bid. This allows the vendor to identify the documentation requirements prior to initiating construction and to choose suppliers that can deliver.

Vendors must be contractually obligated to provide documentation deliverables such as material certifications for product contact surfaces, welding information, operation and maintenance manuals, P&IDs, shop drawings, cut sheets/data sheets and instrumentation calibration data sheets; filter certifications; schedules for construction and testing of equipment; and any related quality documents. The key is presenting requirements at the beginning of the process so the vendor can begin assembly of the required documentation into a **Turnover Package (TOP)** upon award of the contract.

Validation planning

A project Validation Master Plan should be developed in the early stages to define the overall validation philosophy and methodology to be used throughout the project. This allows the project and validation managers to plan resource and scheduling requirements and ensure that design engineer specifications and detailed designs are suitable for validation.

The VMP should be a structured, detailed plan (as described previously) and should assign responsibilities for developing and executing validation program activities. Creation of a detailed plan will provide a first look at an anticipated testing execution schedule and timeline.

Commissioning

For the pharmaceutical industry, commissioning is defined as follows:

> "A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user or validation that results in a safe and functional environment that meets established design requirements and stakeholder expectations."

Plant commissioning efforts address the foundation of the manufacturing facility and are a vital element in the process of turning the facilities over to operations. It ensures that all building and process systems are designed, installed, functionally tested, and capable of operation in conformance with the design intent. Commissioning incorporates a systematic method of testing and documenting of systems and equipment at the conclusion of project construction but prior to equipment validation.

"Commissioning execution" typically occurs between physical completion and turnover to either the operational user or the validation team and involves activities such as system inspection (visual testing), adjustment and regulation, testing (individual system tests), and performance testing (combined system tests or sequence of operations testing). Commissioning also includes various activities designed to prepare equipment for startup and validation, such as installation of filters, alignment of motors, lubrication, and instrument calibration.

When possible the commissioning activities should be well documented in order to "leverage" the test data forward as part of IQ/OQ testing. This can help save time, efforts, and cost later. For example, testing of the control loop on the dissolved oxygen control for a bioreactor is required as part of the risk assessment process and validation requirements matrix. This testing can be done as part of the commissioning process and, if appropriately documented and reviewed, used to satisfy OQ testing requirements (as long as the initial testing is referenced in the OQ documentation and verified again by validation and QA).

When equipment is ready to be delivered to the facility, the equipment manufacturer will notify the project team of the impending completion and schedule the Factory Acceptance Test (FAT). The FAT should be performed whenever possible, as it can significantly reduce overall project timelines if performed properly. All of the FAT documentation can be used to support commissioning and Site Acceptance Testing (SAT). Additionally, issues raised during the FAT are much easier for the equipment provider to address if the equipment has not yet been shipped and installed at the site.

FAT ensures that specified equipment performs to the manufacturer's designs and that certification is supplied to confirm correct performance. At this stage all safety and quality-critical items should be examined and documented, and all of the defined documentation requirements should be assembled into a Turnover Package (TOP). The TOP should be reviewed and any anomalies addressed. Operational FATs can contribute to the OQ effort. Pre-delivery inspection and testing of major system components before delivery to the site can also contribute to the IQ effort.

The development of Standard Operating Procedures (SOPs), Preventive Maintenance (PM) procedures, and user training can also be conducted early—during the commissioning phase of the project. It is always good practice to have future operators/technicians assist in the commissioning and validation efforts in order to begin familiarizing them with the systems they are to operate.

When commissioning activities are complete, there is normally a phased project turnover of the system or equipment to the end-users or validation team, along with the commissioning documentation (e.g. drawings, design documents, fabrication quality manuals, test procedures, factory acceptance protocol, site acceptance protocol, calibration data, inspection records, and Operation and Maintenance [O&M] manuals).

Installation Qualification and Operational Qualification (IQ/OQ)

IQ and OQ are regulated activities that are part of final qualification activities before Performance Qualification or Process Validation begins. Commissioning and qualification testing are interrelated, and testing performed during commissioning may be used to support qualification activities.

The Installation Qualification (IQ) begins as the equipment is delivered and installed. The IQ ensures that a piece of equipment is installed correctly. For example, installation can involve ensuring that the equipment has an electrical supply of the correct voltage and amperage or that a water supply is of a particular level of purity and pressure, using a properly sized water line. These and other related installation needs are checked and verified during the IQ stage. IQ protocol execution should tie in closely with the construction schedule so that as sections or systems are completed they are inspected, with the results documented in the IQ protocol.

In addition, the IQ process will ensure that the final TOP provided from the vendor(s) contains all documentation and software as required in the validation documentation requirements matrix. For the controls side of the IQ, the software must be appropriately annotated so that a trained controls engineer will be able to troubleshoot or modify the programming if required later.

Once the results of the IQ execution have been completed, the OQ execution can begin. OQ protocol execution should tie in closely with the commissioning schedule; as sections, systems, or equipment are completed they are tested, with the results documented in the OQ protocol. As part of equipment or system IQ/OQ activities, computer-related functionality may also be validated as part of combined or individual protocols. During the OQ it must be demonstrated that the equipment or system operates as intended.

Typical testing that occurs during the Operational Qualification should include:

- documenting the version of the software that is being tested and any revisions to the software that occur during testing (e.g. changes made as a result of failed tests)
- sequence of operation testing (testing all control functionality of the equipment/system)
- alarm testing
- power outage testing
- Standard Operating Procedure and logbook verification (verify that the operational SOPs are indicative of operation of the equipment and system-redline document(s) as required)

Qualification protocols are normally required to be written for "direct impact" systems. These are individual documents describing the system under consideration, documentation deliverables, testing plans, acceptance criteria, and forms for recording the test results. This is to ensure that a system is installed and operates in accordance with predetermined specifications.

IQ and OQ protocols can be combined into one document, or the protocols may be kept as separate individual documents. After IQ and OQ protocol executions are complete, approval by the original protocol signatories is required before the Performance Qualification (PQ) can proceed. For this approval review, a summary report can be written at the end of the OQ stage to summarize the IQ/OQ results and provide data analysis. It can also be written at the completion of PQ.

Performance Qualification (PQ)

PQ is the final qualification activity before Process Validation (PV) begins. Only "direct impact" systems will be subject to PQ. The PQ integrates procedures, personnel, systems, and materials to verify that the utility, environment, equipment, or support system produces the required output. This output may be either a product contact utility (clean compressed air, purified water, etc.) or an environmental system such as HVAC.

At this stage of the qualification exercise, the commissioning activities have been completed—IQ and OQ are complete; all deviations or snag items from IQ/OQ have been resolved; pertinent SOPs have reached final draft stage and/or approval; and training in these areas is complete and documented. OQ and PQ protocols can be combined into one document, or the protocols can be kept as separate individual documents. On completion of the construction phase, individual systems and process areas are reviewed to satisfy compliance with the project objectives and regulatory requirements.

Final report

Following all IQ/OQ/PQ tests, a final report will be written summarizing the testing performed at each step and the results achieved for each test. The report will describe any deviations or failures to meet the acceptance criteria, along with the subsequent investigation and resolution(s) to the deviations.

Typically, the report will be reviewed by senior validation personnel, the system owner (operating department), and the QA department. The signature of the responsible individual(s) from QA will constitute acceptance of the report, and the system will be released for use in the production.

It is important to recognize that once a system is validated through the DQ/IQ/OQ/PQ process, it is considered "locked in" and cannot be changed without a formal change control process (described in a later section). This locked-in, validated state applies to equipment, processes, procedures, computer systems, and analytical methods.

Related programs/Process Validation (PV)

Related programs are undertaken to provide assistance and information in support of the qualification activities. For example, these programs can include Environmental/Health/Safety, SOPs, training, preventive maintenance and calibration, and cleaning validation. The activities within these programs can be addressed and managed through the VMP or through independent plans and programs referenced within the VMP.

Commissioning and qualification of facilities, equipment, and utilities are the foundation for Process Validation. Process Validation includes consideration of the suitability of the physical plant and materials used, as well as the performance and reliability of equipment and systems. It is normally addressed separately from the facility qualification plan.

Plant release and start-up

Once IQ/OQ/PQ are complete, planning for the plant start-up can begin. The facility and systems are considered acceptable for use following the review of the validation documentation. This document concludes that the validation has met all the requirements set forth in the approved validation plan and that all deviations incurred during this validation have been identified, documented, and resolved. Authority to release and use the facility is granted by the QA department.

Tasks for plant start-up include planning for the transfer of the technology to the intended users, training personnel, handling logistics of raw materials, determining finished product distribution, and ensuring that technical and business systems are in place. If any problems occur during the commissioning, qualification, and validation process, it is usually due to the lack of start-up planning at the project's scheduling stage.

Periodic review, change control, and revalidation

To verify compliance with procedures and policies, validated systems should be subjected to ongoing operational audits. Review of a previously validated system is recommended to identify possible trends in the system's performance. This periodic review should be conducted according to an SOP and in accordance with schedules established and documented in QA audit plans.

The frequency of audits should be based on system importance relative to regulated operations. Upon completing the evaluation, a report on the findings should be issued and should include all actions recommended and the corresponding supportive documentation. If

system revalidation is necessary, the result of this periodic review will determine the need and degree.

Change control is essential to the successful management of a system and should be in place when the system enters into service. Once a system is validated and becomes operational, changes will occur during its operational lifetime that may impact its validation status. If a change is deemed to have a potential effect on the system's validation, appropriate re-qualifications and/or re-validation measures should be executed, documented, and approved. Change control maintains functionality as the system evolves and provides an audit trail that helps maintain the system in an operating and validated state.

Validation of Analytical Methods and Equipment

Validating the equipment used in the manufacturing process is a critical aspect of biopharmaceutical production. No less important is validation of the analytical laboratory methods and equipment used in the QC process. Analytical systems comprising equipment and methods may need to be fully validated, or in some cases only qualified. For example, all analytical assays used to generate data for Process Validation need to be qualified for their intended use (at the least). However, to initiate Process Validation, all bulk-release and in-process assays need to be fully validated with specified acceptance criteria. Analytical method validations are performed to confirm that the method(s) to be used on a qualified analytical instrument meet the specifications for the intended use.

Analytical equipment qualification

Before an analytical method can be qualified or validated, it is necessary to qualify the analytical instruments that will be used for the method. To ensure the reliability and confidence in the data generated, analytical instrument qualification is a prerequisite to analytical method validation. The Analytical Equipment Validation Master Plan ensures that fundamental qualification requirements are defined and satisfied by identifying not only the criteria by which all analytical instruments are assessed but also the guiding principles for instrument qualification. As with process equipment, analytical instruments and their respective control system require assessment of risks posed to patients and product; this is to determine which aspects require qualification (as described in Risk Analysis).

Typically two types of analytical instrument configurations exist in most biomanufacturing firms: stand-alone analytical instruments and laboratory computerized systems. Stand-alone analytical instruments are systems, which fall into the definition of an analytical instrument and are not associated with a computerized system. Laboratory computerized systems are systems which fall into the definition of both an analytical instrument as well as a computerized system.

The process of qualifying laboratory instruments, as with any other piece of equipment, follows the lifecycle approach (Figure 4-6). Qualification activities begin with initiation of the instrument into the program. Requirements, testing plans, and acceptance criteria are then developed as necessary and implemented based on specific IQ, OQ, and PQ protocols. Upon completion a final report is prepared and signed by the various departments, allowing the analytical equipment to be used to qualify and validate (if necessary) the analytical method.

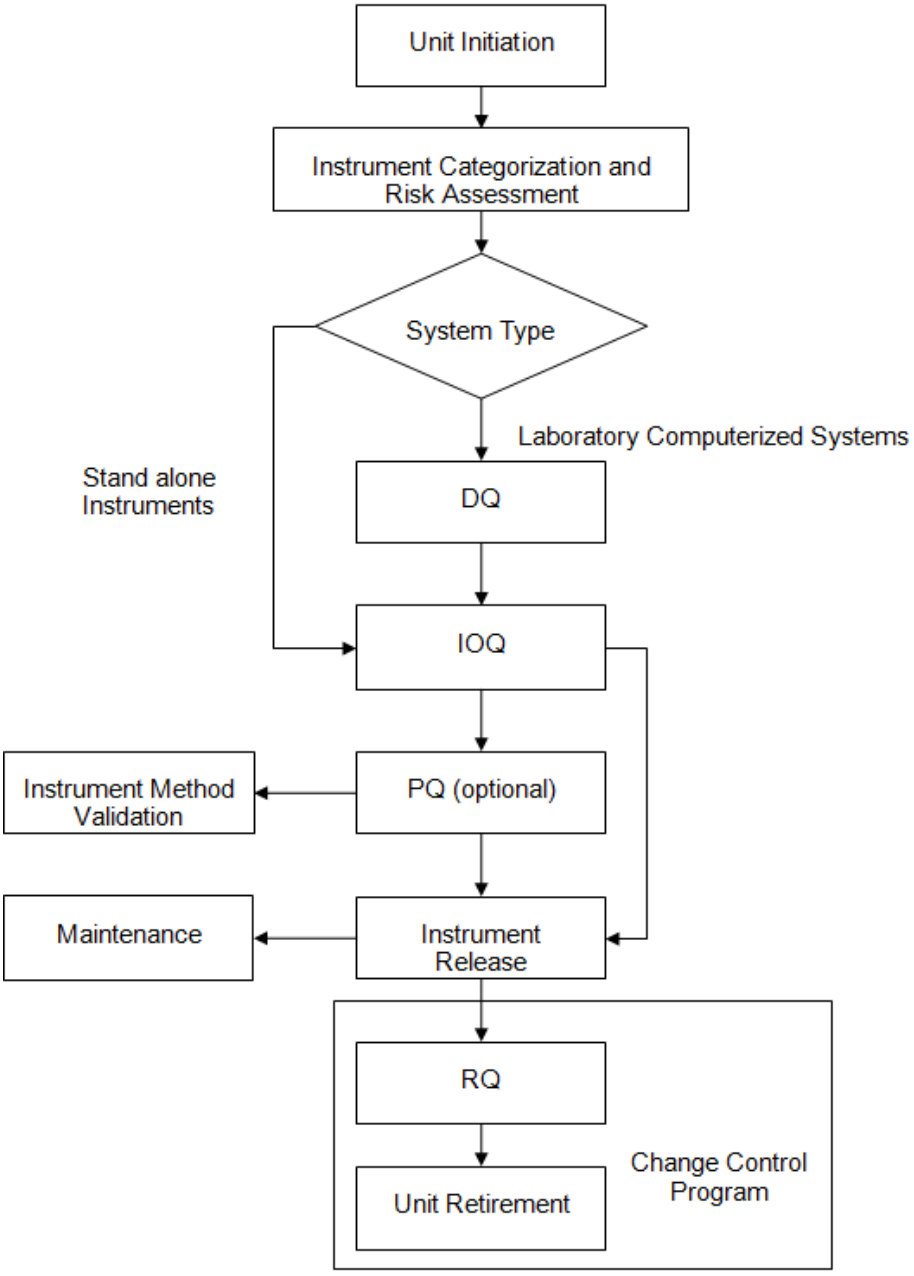

Figure 4-6. Analytical instrument validation lifecycle flow chart

Analytical method qualification

Qualification of an analytical method involves a distinct set of experiments performed prior to the method's use for cGMP clinical product testing. Qualification demonstrates that the method performs as expected *before* it is formally validated. Methods requiring qualification should be defined in a Validation Policy document to determine the scope of analytical methods to be addressed.

Analytical methods must be developed for a defined, intended use. The nature of the samples and specific analytes to be tested, the procedures, and the outcomes should be documented before qualification activities begin. These methods should be developed with sufficient reliability, sensitivity, and specificity to assure they produce meaningful results. These factors should be consistent with the specifications of the product being analyzed. Prior to starting Method Qualification, the method development must be appropriately documented in a development summary report, which should be reviewed and approved by the validation group.

Also prior to initiation of Method Qualification, a corresponding SOP should be drafted and modified as corrections and changes are identified. The final, approved version must be ready prior to Method Validation. The experiments to be executed during qualification are determined primarily by the purpose of the method. In addition, the technology and or the phase of product development may be considered when planning a qualification study. A formal protocol is not required. However, a written study plan can be used for the execution of qualifications.

Pre-specified acceptance criteria are not required during Method Qualification. Nevertheless, a qualified method should be capable of providing results consistent with proposed product specifications. Justification of the method’s suitability should be provided whenever these criteria are not met. Table 4-4 indicates the performance characteristics that should be addressed during the qualification for the intended use of the method.

Table 4-4. Method performance characteristics

Performance Characteristic	Intended Use of Method				
	Purity	**Impurity Detection**	**Impurity Quantitation**	**Identity**	**Content**
Repeatability Precision	+	+	+	+	+
Intermediate Precision	+	+	+	+	+
Accuracy	+		+		+
Specificity	+*			+*	
Linearity	+		+		+
Range	+		+		+
LOQ	+		+		+
LOD		+	+		

*Specificity may be determined with an orthogonal method during method development. Reference to such should be made in the Qualification Technical Report. For quantitative purity/impurity methods, specificity may also be derived from the accuracy evaluation.

Other tests that do not fit these categories must have qualification approaches appropriate to the method and its intended use. Rationale for the performance characteristics tested should be documented in the Qualification Technical Report.

Following are the various procedural factors that must be considered during Method Qualification:

- Execution of qualification experiments should be distinct from other method development activities.
- Qualifications must be carried out with samples representative of those to be tested during cGMP production; a traceable representative sample is required for all qualification studies.
- A reference standard should be incorporated in qualification experiments when available. This may not be necessary for process impurities assays.
- Appropriately calibrated and maintained instruments must be used during qualification studies.

- System Suitability data must be collected from all method runs executed during the qualification.
- All data required to satisfy System Suitability Acceptance Criteria should be compiled during the qualification; the average, standard deviation and/or CV (as appropriate) of any quantitative System Suitability Criterion should be reported; a summary of any qualitative Acceptance Criteria should be documented as well.
- Performance factors that are potentially relevant to method suitability but are not specified in the SOP may also be collected and reported; examples of relevant types of performance factors include, but are not limited to, % purity, retention time, tailing factors, resolution, peak areas, peak height, and peak width.
- Attachments should detail suggested experiments for qualification of common methods; if a specific method is not covered or another approach is employed, the scientific or technical rationale for the experiments executed must be documented in the Qualification Technical Report.
- Qualification of each performance characteristic does not require an independent experimental run to be executed; data obtained for one parameter may be used in the evaluation of others.

At the completion of all testing for a Method Qualification, a summary report is generated that contains, at minimum, the following:

- a method purpose (indicating the intended use and the nature of samples qualified)
- methods and materials used in the qualification
- a summary of performance characteristics tested
- appropriate data documenting each of the performance characteristics
- a summary of the system suitability data and observed statistical variations
- discussion of any variations, exceptional conditions, or out-of-trend data encountered during the qualification and any impact to the study or method
- justification for revision of the SOP or further method optimization (if appropriate)
- a conclusion stating the observed accuracy and variability of the method and general conditions under which this performance was observed

For any analytical method there are several parameters that must be established for the method. Examples of some of the parameters that must be determined for the method include:

- selectivity or specificity of the method
- demonstration of the linear range or validation of curve-fitting algorithms
- Limit of Detection (LOD) of the method
- Limit of Quantification (LOQ) of the method
- the precision of the method (precision is covered in ***Chapter 3 Metrology***)

The selectivity or specificity of a method refers to the method's ability to detect the analyte in question in the presence of similar compounds. For example, when performing an analysis of endotoxins, the method should only detect endotoxins and not other carbohydrates that could also be present in the sample. Selectivity is of particular concern with antibody-based methods such as the Enzyme-Linked Immuno-Sorbent Assay (ELISA).

With any antibody-based method, a concern is cross-reactivity between the antibody and extraneous material that may be present in the sample. A method that has poor selectivity will give rise to frequent false positives, meaning the method falsely indicates that the substance being assessed is present. False positives will generate a number of Out Of Specification Results (OOS) that must be further investigated.

Along with selectivity, the analytical method range must be demonstrated as linear. This means that the output from the technique (e.g., absorbance measurement, color change, peak height) is directly proportional to the amount of the substance present; the proportionality constant does not change with increasing concentration of the analyte. Very few analytical techniques are linear at all possible analyte concentrations and most have only a limited linear range. Above or below this range the relationship between output and substance may curve away from a straight line, complicating attempts at quantification.

In some cases curve fitting algorithms are available that can extend the range of the analytical method beyond the linear range. But as with other aspects of the method, it will be important to validate the curve fitting equations or software. For other methods it is important that the analytical determinations measurements fall within the linear range to generate accurate numbers. In this case the linear range must be determined for the technique and the method performed so that the analysis falls within that linear range. This may require diluting samples so that the concentration of the analyte falls within the linear range. Figure 4-7 illustrates a linear range.

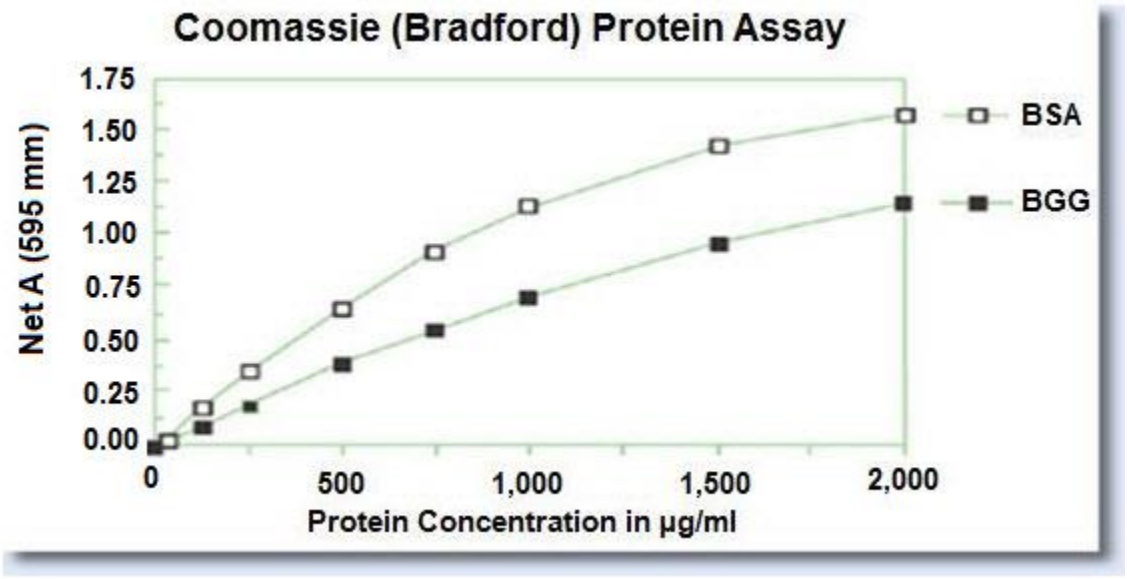

Figure 4-7: **Example of linear range**

Two additional parameters that need to be established for the validation of an analytical method are the Limit of Detection (LOD) and Limit of Quantification (LOQ). These values establish the lower limit at which we can *detect* the analyte of interest (LOD) and the lower limit at which we can accurately *quantify* the analyte of interest (LOQ).

Knowing the LOD is important, as the results of the analysis cannot state that there was nothing there. Instead the report indicates that nothing was detected over the LOD. Consider a method for determining if an analyte might contain heavy metals such as lead (Pb), cadmium (Cd), chromium (Cr), and/or other potential contaminants of raw materials. If the LOD of the method being used is 1ppb (part per billion, 1pg/ml) and the analysis does not detect any heavy metals in the sample, the analytical report states that the sample contained less than 1 ppb heavy metals. Because of the LOD of the method, it cannot be reported that our sample contains zero levels of heavy metals only that it contains less than the LOD.

Similarly the LOQ provides the lower level at which the analyte can be quantified. The presence of the analyte might be detected at a lower level, but because of various background fluctuations (including instrument and reagent variability) it is possible that an accurate quantification of the analyte cannot be made. Typically the LOQ is based on the signal-to-noise ratio between the analyte and background fluctuations, along with the precision of the analytical method. For example, a given method may have an LOQ based on a 10:1 signal-to-noise ratio. This ratio is determined by comparing the signals from samples containing known low levels of the analyte with those of blank samples. Levels of analyte that give a reading 10 times the background level and fall within the precision specifications (i.e., <10% of the Relative Standard Deviation or RSD for the method) establish the LOQ for a given method. Commonly the precision and signal-to-noise level of a method are related—the higher the precision required, the higher signal-to-noise level and higher level of quantification required.

USP methods or other methods that have been previously validated are fairly straight forward to validate since information about the specificity of the assay, linear range, and limits of detection are probably known. Newly-developed methods might require more extensive developmental testing to define the parameters of the assay.

In addition to the LOD and LOQ, the sampling and preparation method must be capable of recovering all of the analyte from the sample matrix. One must consider the sample matrix as well as all the components found in the sample other than the analyte. In biopharmaceutical production one can be dealing with complex media components and possible biological fluids that could interfere with the ability to quantitatively recover the analyte from the matrix.

A typical method for performing recovery studies is by adding ("spiking") known amounts of the analyte to a representative sample matrix and comparing the amount actually recovered versus the amount added (e.g., if 5 µg of a therapeutic protein is added to a sample but only 2.5 µg are detected using the analytical method). Thus the recovery is only 50 percent. When performing future analyses, the amount detected during the analytical method must be multiplied by the recovery factor.

An example of how recovery studies are applied to analytical methods is demonstrated by swabbing studies. Swabbing is commonly used to test for residual cleaning fluids or process fluids (Figure 4-8). A clean swab is wiped across a surface and submitted to the analytical laboratory. In the case of cleaning fluids, a typical analysis performed on the swab sample would be Total Organic Carbon (TOC). This would indicate the presence of any residual proteinaceous process fluids that contain organic carbon.

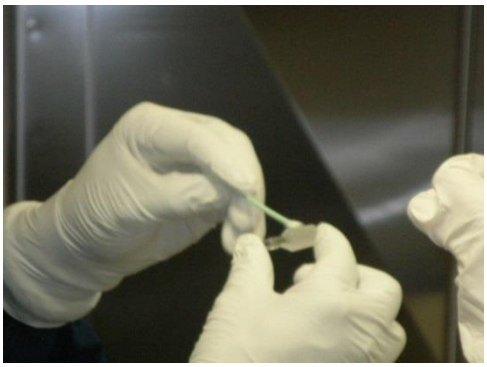

Figure 4-8. Swabbing

The ability to recover any residual detergent is going to be related to the swabbing procedure. To ensure that swabbing is consistent, SOPs (and in some cases templates that define the swabbing area) are used so that any recovery variation based on the swabbing technique is limited. Often the results of methods applied to swabbed samples are adjusted to reflect known recovery limitations of swabbing samples.

The precision of an analytical method needs to be determined in the process of validating that method. Precision refers to the variability of test results when the test is performed on multiple portions, or aliquots, of a homogenous sample. The quality laboratory's validation plan or SOP will specify the precision requirements, most often as Percent Relative Standard Deviation (%RSD).

The nature of the material being analyzed, as well as the available analytical methods, will determine the precision requirements. Simple raw materials or conventional pharmaceutical material can have RSD requirements of less than two percent. More complex biological

materials can result in a greater variation in the precision of the method. This is due to the complexity of the sample matrix or analysis method.

Many factors affect precision. To separate or distinguish factors responsible for methods variation, regulatory guidance suggests breaking precision into areas that include **repeatability** (or method precision) and **system precision**. Repeatability, or method precision, is the inherent variability due to the analytical method. Typically method precision is determined by analyzing six aliquots from the same homogenous sample using the same equipment, reagents, and analyst. Day-to-day variability in the method can be determined by having the same analyst prepare fresh reagents and analyze samples on different days using the same equipment. Equipment variability, analyst variability, and even laboratory variability can also be determined in a similar manner. System precision is the overall precision of the analytical method, taking into account items such as variation in reagents, equipment, and analyst technique.

Control charts can be used to monitor the analytical method's precision and provide early detection of any adverse trends in the analytical results. For example, a trend in greater variability while running duplicate samples could indicate issues such as degradation in a reagent, the need to make new solutions, or equipment that might need maintenance. An additional item pertaining to analytical laboratory methods is **robustness**, or the ability of the analytical method to tolerate small but deliberate variations in the method parameters yet remain unaffected. Robustness studies lead to the identification of critical variables within a procedure and reveal how those variables interact.

Small measurement errors, temperature fluctuations, or concentration changes may or may not affect the method's performance. Defining how these changes affect the method will not only lead to increased understanding of the method's critical factors but will also help define the method's SOP and training requirements for performing the method. For example, if it is important for a particular method that the incubation temperature be within 0.5°C of 37°C , then laboratory analysts can be trained on this critical parameter and monitor it accordingly. However, if temperature is not important to the performance of the method, then specifying temperature can be omitted from the SOP for the method.

Computerized Systems and Software Validation

In both manufacturing and biomanufacturing, production operations are becoming increasingly automated and the implementation of computerized devices for plant operation is increasing. The growing use of both automated, computerized control and data-logging systems has necessitated the development of validation protocols for both the hardware and software used in these systems. Title 21 CFR Part 11 is devoted to electronic records and electronic signatures and specifically calls for:

> "the validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records"

Personnel must be familiar with software and validation processes. Computerized Systems Validation (CSV) applies to computerized systems involved in managing GMPs Good Laboratory Practices (GLPs) and Good Clinical Practices (GCPs) data.

Validating computerized systems can result in a very complex and involved validation effort. CSV practices are not just internal to an organization—they extend to suppliers as well. Suppliers must assure quality and integrity in all aspects of their product.

Computerized System Architecture (CSA)

Computerized systems are validated as a series of layers, with each layer dependent on lower layers for services. Together these layers are referred to as Computerized System Architecture (CSA). Figure 4-9 illustrates a CSA.

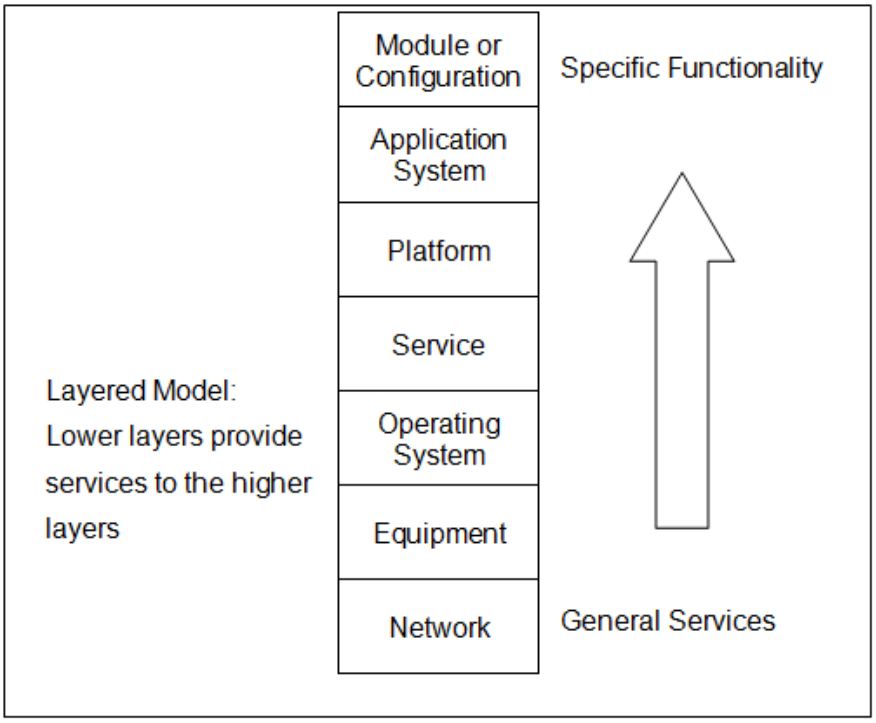

Figure 4-9. Computerized Systems Architecture (CSA)

The CSA layers are as follows, listed from lowest to highest:

- network: services for data exchange among computers, including network cabling, connection establishment, routing, transport, error handling, and network management; examples include cabling, routers, switches, encryptors, etc.
- equipment: computer hardware and the infrastructure (power, air handling, etc.) that support the computer; examples include file servers, controllers and I/O cards, spectrophotometers, etc.
- Operating System (OS): basic set of software services and commands that are bundled with hardware; examples include Windows, DeltaV Programmable Interface firmware, barcode scanner firmware, etc.

- service: general-purpose services designed to support a variety of platforms and applications; examples include Oracle, LDAP, DHCP, SecurID, RSLinx, etc.
- platform: sets of software tools and services, database schemas, and application interfaces for a related class of services used to build specific, integrated application systems; examples include SAP, Trackwise, etc.
- application system: systems of hardware, software, and procedural components designed to support a specific business process; examples include CCDARTS, Clintrial, Manufacturing Execution and Control System, etc.
- module or configuration: data, configuration parameters, and user-defined procedures used to modify the behavior of the application; examples include a Trackwise quality record type, an EDMS document type, etc.

Computerized systems that consist of multiple layers are normally validated at the highest layer's requirements.

Key elements of Computerized System Validation

User Requirements Specification (URS)

The purpose of the URS is to document the expectations for the operation and performance of a computerized system. A business group can create a URS to communicate requirements to the technical manager. Typically a URS would only be appropriate at the platform, application system, and module or configuration layers of the CSA; it is most useful prior to vendor selection. At a minimum, URS documents will be considered for revision upon system upgrade.

Functional Requirements Specification (FRS)

The purpose of the FRS is to enumerate a set of requirements that will satisfy the needs of the requesting business group and the needs of the system owner in order to comply with quality Computerized Systems practices. Typically an FRS would only be appropriate at the platform, application system, and module or configuration layers of the CSA. At a minimum, FRS documents will be considered for revision upon system upgrade.

Vendor audit

The purpose of a vendor audit is to verify a vendor's level of compliance with applicable regulations and assure that their deliverables are developed in an acceptable fashion. Typically a vendor audit would only be appropriate at the platform, application system, and module or configuration layers of the CSA.

Validation plan

The purpose of a validation plan is to identify the CSV activities and approvals required for one or more computerized systems to be implemented under HGS validation policy. The validation plan contains the decisions regarding the validation documents to be created for a computerized system and the justification and approval for those decisions.

Configuration Specification (CS)/System Detailed Design Specification (SDDS)

The purpose of a CS is to describe the *configuration* of a computerized system in a manner that addresses the requirements within an associated FRS. A CS is appropriate for a configurable system at all layers of the CSA.

The purpose of an SDDS is to describe the *design* of a computerized system in a manner that addresses the requirements within an associated FRS. An SDDS is appropriate for a custom-built system at all layers of the CSA.

At a minimum, CS/SDDS documents will be considered for annual revision for the systems that were subjected to change controls throughout the year.

Commissioning protocol

The purpose of a commissioning protocol is to provide documented verification that establishes confidence that hardware and software components are installed and satisfy appropriate user and functional requirements. Commissioning protocols may be used to reduce testing within qualification protocols and shall be referenced in applicable sections of the qualification protocols. A commissioning protocol is appropriate at all layers of the CSA.

Installation Qualification (IQ)

The purpose of an IQ is to provide documented verification that establishes confidence that hardware and software components of a computerized system are installed as intended and satisfy all applicable specifications. An IQ is appropriate at all layers of the CSA. In some cases an IQ shall include the transfer or migration of data from the test environment, previous versions, or other systems.

Operational Qualification (OQ)

The purpose of an OQ is to provide documented verification that establishes confidence that the hardware and software components of a computerized system operate as intended and satisfy functional requirements. Typically an OQ would only be appropriate at the platform, application system, and module or configuration layers of the CSA. SOPs for the operation and administration of a computerized system shall be drafted prior to OQ execution.

Performance Qualification (PQ)

The purpose of a PQ is to provide documented verification that establishes confidence that the hardware and software components of a computerized system perform as intended under actual production conditions and satisfy appropriate user requirements. Typically a PQ would only be appropriate at the application system and module or configuration layers of the CSA. If SOPs for the operation and administration of a computerized system are required, they shall be approved prior to PQ execution.

Rollout Qualification (RQ)

The purpose of an RQ is to provide documented verification that establishes confidence that the production computerized system or subsystem is installed as intended; satisfies all applicable specifications; operates as intended; and satisfies functional requirements. An RQ is employed when previous qualification protocols are executed against a validation environment. An RQ incorporates testing from a computerized system's IQ and OQ and is executed against the production environment. Typically an RQ would only be appropriate at the application system and module or configuration layers of the CSA.

Requirements Traceability Matrix (RTM)

The purpose of an RTM is to document the decisions for which requirements shall be tested within the qualification protocols of a computerized system and to document the justifications and approval for those decisions. Typically an RTM would only be appropriate at the platform, application system, and module or configuration layers of the CSA.

Final Report (FR)

The purpose of an FR is to summarize the CSV activities performed and approvals received for a computerized system. An FR is required if a computerized system's validation plan requires qualification protocols. An FR is appropriate at all layers of the CSA.

Decommissioning plan

The purpose of a decommissioning plan is to assess the impact of taking validated computerized systems off-line, ensuring essential information is accurately transferred to a new system (when required) and that any backup or archival data may be accurately and completely recovered. A decommissioning plan is appropriate at all layers of the CSA.

Table 4-5 illustrates the key elements of the CSV as they relate to the CSA.

Table 4-5. Necessity of CSV Documentation and its applicability within the CSA

	Initiation	URS	FRS	Vendor Audit	Validation Plan	CS / SDDS	Commissioning Protocol	IQ	OQ	PQ	RQ	RTM	FR	Decommissioning
Module or configuration	NA	A	A	A	A	A	A	A	A	A	A	A	A	A
Application system	R^1	A	A	A	A	A	A	A	A	A	A	A	A	A
Platform	R^1	A	A	A	A	A	A	A	A	NA	NA	A	A	A
Service	R^1	NA	NA	NA	A	A	A	A	NA	NA	NA	NA	A	A
Operating System	R^2	NA	NA	NA	A	A	A	A	NA	NA	NA	NA	A	A
Equipment	R^2	NA	NA	NA	A	A	A	A	NA	NA	NA	NA	A	A
Network	R^2	NA	NA	NA	A	A	A	A	NA	NA	NA	NA	A	A

Legend:

A: applicable at this level of the CSA; created if necessary per a validation plan

NA: not applicable at this level of the CSA

R^1: required for computerized systems at the service, platform, and application system layers of the CSA within applicable departments

R^2: required for computerized systems at the network, equipment, or operating system layers of the CSA on which validated computerized systems rely

Process Validation

The FDA recently published a revised guidance for Process Validation that conveys its current thinking and is consistent with basic principles first introduced in the 1987 guidance. This guidance also provides recommendations that reflect some of the goals of the FDA's initiative entitled *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*, in particular with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.

The FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical manufacturing require that drug products be produced with a high degree of assurance that they possess all the attributes they are intended to possess (21 CFR 211.100[a] and 211.110[a]). Effective process validation contributes significantly to assuring drug quality.

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- quality, safety, and efficacy are designed or *built* into the product
- quality cannot be adequately assured merely by in-process and finished-product inspection or testing
- each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes, including specifications

Process Validation is defined as the collection and evaluation of data (from the process design stage throughout production) that establishes scientific evidence that a process is capable of consistently delivering quality products. Process Validation involves a series of activities taking place over the lifecycle of the product and process. The FDA guidance describes the process validation activities in three stages:

- Stage 1–Process Design: The commercial process is defined during this stage based upon knowledge gained through development and scale-up activities.
- Stage 2–Process Qualification: During this stage the process design is confirmed as being capable of reproducible commercial manufacturing.
- Stage 3–Continued Process Verification: Ongoing assurance that the process remains in a state of control is gained during routine production.

Before Process Validation efforts can begin, process development and characterization must be completed. Process characterization can be summarized as follows:

- typically performs at small-scale within non-GMP labs as part of developing (and locking) process
- determines effect of controllable parameters on various outputs
- defines key roles of individual process steps
- defines critical, key, and non-key parameters (Figure 4-10)
- uses a Design of Experiments (DOE) approach (Figure 4-11) in Upstream and Downstream processes
- provides data to further support Batch Record Ranges (NOR) and Proven Acceptable Ranges (PAR); defines “Design Space.”
- paves the way for Process Validation/Commercial Process

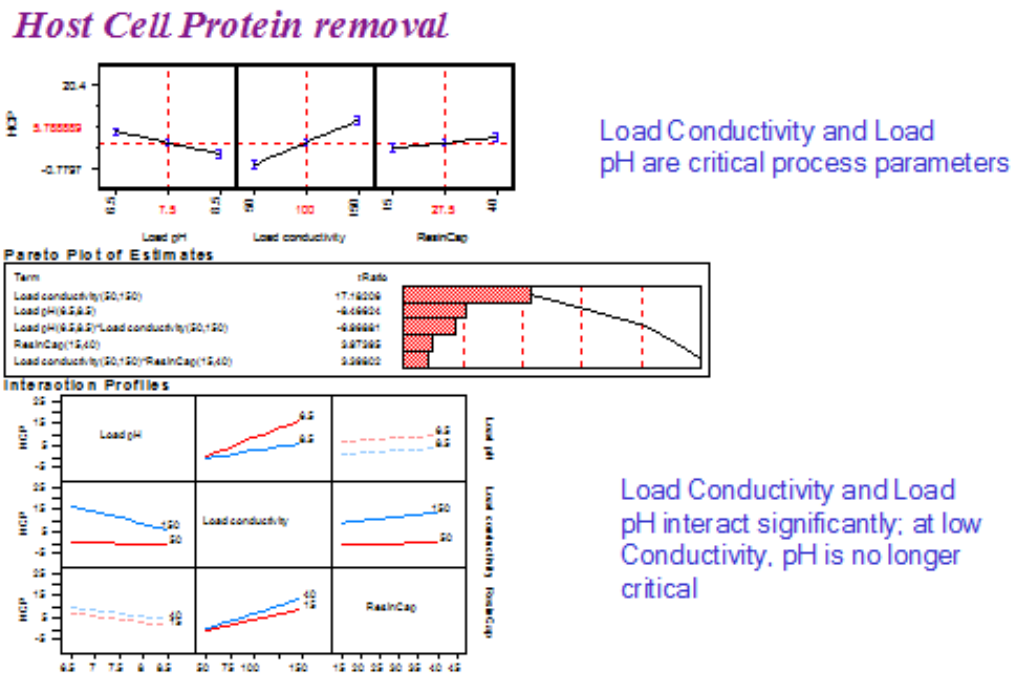

Figure 4-10. Example process characterization of an Anion-Exchange step

Run Order	Load PH	Load Cond mM NaCl	Bed Height cm	Flow Rate cm/hr	Resin Cap g/L
1	6.5	150	28	300	15
2	6.5	50	28	100	15
3	6.5	150	13	300	40
4	8.5	50	13	300	40
5	6.5	50	13	300	15
6	7.5	100	20.5	200	27.5
7	8.5	50	28	300	15
8	8.5	150	13	100	40
9	6.5	50	13	100	40
10	6.5	150	13	100	15
11	8.5	50	28	100	40
12	8.5	150	28	300	40
13	7.5	100	20.5	200	27.5
14	8.5	150	28	100	15
15	8.5	50	13	100	15
16	6.5	150	28	100	40
17	8.5	150	13	300	15
18	6.5	50	28	300	40

Figure 4-11. Example of Design of Experiments for process characterization of an Anion-Exchange Chromatography step

Once the process has been fully characterized and all critical, key parameters and non-key parameters have been identified *at commercial process scale,* Process Validation can proceed. Where process development and characterization was *experimentation*, Process Validation is *verification.* All Process Validation (verification) work is protocol-driven. Documentation is critical and is comprised of:

- technical reports
- campaign summaries
- Process Validation Master Plan (product specific)
- Process Validation protocols
- study plans
- sample plans
- Process Validation reports

Process Validation-related documents are approved by a cross-functional team, including representatives from Process Development, Analytical Development, QA, Manufacturing, Regulatory Affairs, and others as needed.

Process Validation work consists of many separate studies (not just Conformance Lots) and includes small- and large-scale work; for small-scale work, qualification of the scale-down model is critical. Validation is an ongoing effort, continuing post-approval with process monitoring and Statistical Process Control (SPC) of the commercial process.

Upstream validation studies can include:

- scale-down qualification: verifying that the process operates the same at small-scale as it does at large-scale
- media stability: verifying growth promotion for maximum hold duration
- stability of in-process intermediates at varying temperatures and maximum hold times
- cells at limit/end of production: verifying that genetic consistency is maintained throughout maximum doublings at varying process parameters
- conformance lots-cell culture and harvest process: demonstrating that the commercial process, when executed as specified in batch records, consistently produces in-process intermediates and Bulk Drug Substance (BDS) that meet all established specifications

Downstream validation studies can include:

- scale-down qualification: verifying that the process operates the same at small-scale as it does at large-scale
- column lifetime: verifying resin performance for maximum allowable duration and maximum number of process cycles
- column cleaning: verifying cleaning procedures

- buffer stability at all temperatures and vessels used in the process for maximum allowable hold duration
- sanitization/storage buffers and verifying effectiveness
- reprocessing (if applicable): verifying consistency of product after reprocessing
- small molecule clearance: verifying small molecule removal at each step
- conformance purification and bulk fill verification: demonstrating that the commercial process, when executed as specified in batch records, consistently produces in-process intermediates and Bulk Drug Substance (BDS) that meet all established specifications

Cleaning Validation

Cleaning validation is accomplished by performing pre-approved qualification protocols that include **development studies** (CDEV) and validation (CVAL); each are applied where appropriate. Protocols are generated, reviewed, and approved prior to execution. These protocols indicate the proposed tests and acceptance criteria.

Cleaning validation limits

Any cleaning validation program is based upon scientifically developed limits to evaluate product residual reduction and detergent reduction to pre-determined acceptance limits. Regulatory agencies determine basic cleaning limits, while higher limits can be set by an individual organization based upon process/product requirements. Several analytical methods can be used to assess cleaning efficacy, including:

- Total Organic Carbon (TOC)
- conductivity
- endotoxin level(s)
- bioburden
- proprietary product-specific assays

In addition a visual inspection is performed to verify the system under consideration is “visibly clean.” Table 4-6 is an example of cleaning acceptance criteria.

Table 4-6. Example cleaning validation limits

Requirement	Upstream	Media Prep	Downstream	Buffer Prep	Glasswasher
Visible Inspection	No visible residue	No visible residue	No visible residue	No visible residue	No visible residue
TOC Swab	≤ 5000 ppb	≤ 5000 ppb	≤ 1000 ppb	≤ 1000 ppb	≤ 1000 ppb
TOC Rinse	≤ 5000 ppb	≤ 5000 ppb	≤ 1000 ppb	≤ 1000 ppb	≤ 1000 ppb
Conductivity	≤ 5µS/cm @ 25°C	≤ 5µS/cm @ 25°C	≤ 5µS/cm @ 25°C	≤ 5µS/cm @ 25°C	≤ 5µS/cm @ 25°C
Bioburden Rinse	≤ 300 CFU/100mL	≤ 300 CFU/100mL	≤ 300 CFU/100mL	≤ 300 CFU/100mL	≤ 300 CFU/100mL
Endotoxin Rinse	≤ 0.250 EU/mL	≤ 0.250 EU/mL	≤ 0.250 EU/mL	≤ 0.250 EU/mL	≤ 0.250 EU/mL

Product cleanability

All products produced in a facility need to be tested for their relative cleanability. The products and the method used to evaluate the cleanability need to be tested under approved method validation protocols. Cleanability is assessed for all product contact surfaces. From the results, the relative cleanability of the products is defined. Each new product will be assessed using the prescribed test method protocol and placed in its relative order of cleanability. Product cleanability will be used to determine validation requirements.

Product introduction

Validation requirements for products should be directly linked to the product cleanability matrix. The relative cleanability of the product in relation to the preceding worst case product will dictate the validation requirements. Introduction of an easier to clean product, following a validated and more difficult to clean product, is considered a better case cleaning scenario.

Cleaning processes

Most organizations validate three processes for cleaning equipment and systems: automated cleaning (Clean in Place or Clean out of Place), semi-automated cleaning (SOP-driven, using mechanical methods), and manual cleaning. Each of these processes requires the same evaluation of effectiveness.

Dirty Hold Time

Validation of the Dirty Hold Time (DHT) provides a window of time to clean soiled equipment/systems using the validated cleaning processes. DHTs provide operational flexibility to strategically stage cleanings, accommodating manufacturing schedules while assuring cleaning within defined limits.

Clean Hold Time

Validation of the Clean Hold Time (CHT) defines the maximum timeframe a cleaned system/equipment may be held clean and used before a re-cleaning is required. The CHT affords operations the flexibility to use cleaned equipment for manufacturing over a defined period of time. Once performed, the validated clean hold time for a system/equipment applies to all products for which the equipment's Dirty Hold Time has been validated. Since validation of the CHT assumes the equipment under consideration is within the established clean limits, CHT may be performed prior to validation of the DHT.

Cleaning training

To ensure the cleaning validation program is consistent, routine periodic training is required for both rinse sample and swab sample collection. The goal of cleaning training is to ensure that cleaning samples are collected, submitted, and controlled in a consistent manner. To ensure consistency, operators/technicians are trained to collect both rinse and swab samples according to approved procedures.

Analytical equipment and method validation

Cleaning validation limits rely substantially on the use of analytical instruments. As a result, analytical instruments methods may require analytical method validation to ensure instrument methods are precise, robust, and repeatable.

Document hierarchy

To capture specific cleaning validation activities, cleaning validation documents are organized by sub-types. Figure 4-12 identifies the basic documentation hierarchy (this excludes any required SOPs).

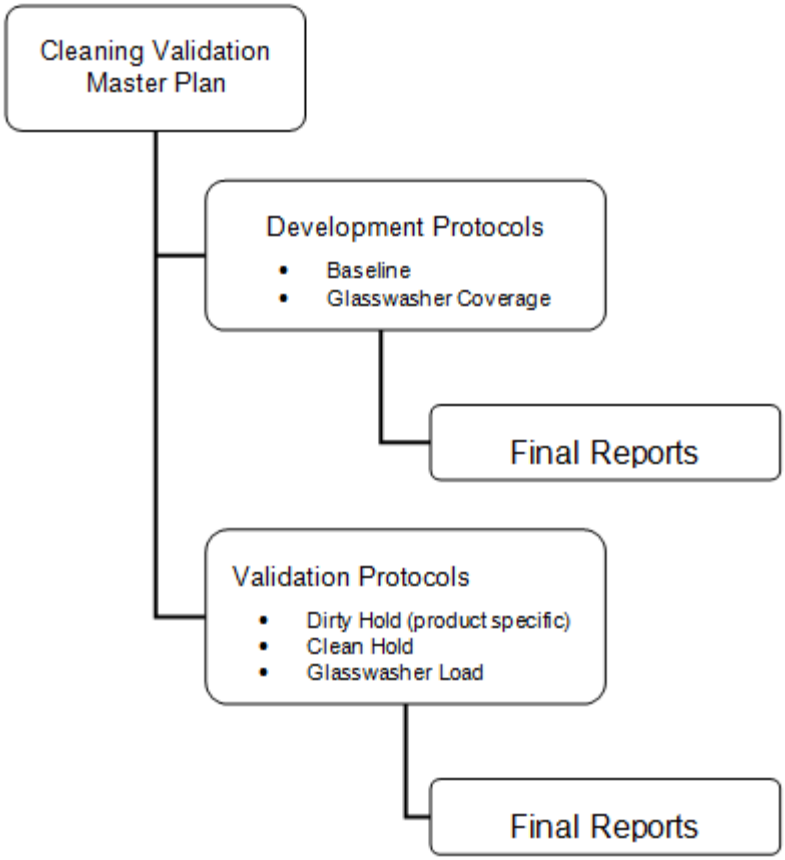

Figure 4-12. Cleaning validation document hierarchy

Cleaning validation protocols

Cleaning validation protocols are developed and executed for all products defined as requiring cleaning validation (typically in the Cleaning Validation Master Plan). Final reports shall accompany the completion of each protocol. Any **deviations** from approved procedures or acceptance criteria encountered during the execution of validation protocols need to be resolved prior to approval.

Development protocols

Development protocols are used in the early stages of cleaning validation to collect initial data associated with equipment. Examples of typical development protocols are baseline and glasswasher coverage studies. These protocols collect data that may be used to optimize the cleaning processes or to benchmark equipment cleanliness prior to product introduction.

Validation protocols

For a given product, validation protocols verify and document that the equipment and cleaning process under consideration satisfy the validation limits. Dirty and Clean Hold Time and glasswasher load configurations are examples of cleaning validation protocols.

Standard Operating Procedures (SOPs)

Where appropriate, SOPs supporting execution of cleaning validation activities ensure consistent and reliable instructions. The SOPs provide specific details to ensure that validation activities in support of validation protocols are repeatable by trained personnel. All SOPs used in support of individual validation protocols need to be referenced with their respective protocols.

Validation execution sequencing

Execution of the cleaning validation protocols is performed subsequent to facility/equipment qualification/validation activities. Generally utility support systems are qualified first, followed by the process systems. Once the process systems have been qualified, cleaning validation development protocols can be executed. At the completion of development protocol execution, the cleaning validation protocols can be executed. Validation will be considered acceptable when the following deliverables have been successfully completed and approved:

- development protocol(s) and final report(s)
- validation protocol(s) and final report(s)

Change Control and Re-validation

An old axiom states: “Change is the only constant.” This certainly applies to biomanufacturing operations. Because of the regulated nature of the biomanufacturing and pharmaceutical industries, changes—whether to procedures, documents, or equipment—must be controlled and evaluated for possible effects on product quality.

Change control, the term used to describe the process of evaluating operational changes, is particularly important with validated systems. Substantial changes, or changes that could potentially affect product quality, may require re-validation to comply with governmental regulations.

Changes are either unplanned or planned. **Unplanned changes** are frequently the result of equipment failure or malfunctions. In these cases changes must often be implemented quickly to get manufacturing operations running again. Examples include failures of pumps, valves, mixing elements, and probes. Unplanned changes to validated systems are defined as necessary to the continued operation of the validated system.

Often equipment types that are most prone to failure have been identified, and suitable (identical) spares are kept on hand. In such cases replacement of the failed piece with an identical model will be documented in the production or equipment logs. In this case the potential impact to product quality is low; however, an investigation into the equipment failure and its potential impact on product quality will be initiated. For example, if a pump failed during a time-critical operation and its replacement caused a delay in the procedure, product quality could have been compromised.

Unlike unplanned changes, **planned changes** require a thorough assessment of the change on the process. These types of changes are often implemented with the goal of improving the manufacturing process. For example, increasing the size of the bioreactor used to grow cells may help increase yield; however, the effects on upstream and downstream processes, such as harvest or chromatographic product capture, need to be evaluated before a change is made. In addition, the regulatory impacts of the proposed change will need to be addressed.

Some changes might require simply documenting the change in an annual report to the regulatory agency, while others could have significantly more impact on regulatory reporting, requiring **amendments** to the New Drug Application, NDA or Biological License Agreement (BLA). Significant changes to the manufacturing process could even require new studies on product quality, including product stability studies or possibly even new clinical trials.

An area that can change often in biomanufacturing operations is that of updating written documents, particularly SOPs. New SOPs may need to be created, or existing ones may need to be modified. SOP changes, however, cannot be made without adhering to the change control process. Typically this starts with submission of a Document Change Order (DCO) that specifies:

- the type of change requested
- why the change is being requested
- the person/persons requesting the change
- any regulatory impact from the change

After a review by the requestor's supervisor, the DCO is forwarded to the Quality Assurance team, which decides if the change is warranted. The QA team issues revision numbers or new document numbers depending on the request. Once the new document or revision is created, it will be forwarded to the various impacted departments for review and approval. The QA team grants final approval. The document control group will then issue the new revision or document to the impacted departments.

Tracking the thousands of documents (and versions of such) used in a biomanufacturing operation can be a daunting task. In large operations a dedicated document control department ensures that current versions of SOPs and other documentation are used. As new versions are implemented, older/out-of date versions are collected to make sure that only the current, approved version is used.

Out-of-Specification Results and Failure Investigations

At some point in the validation of a piece of equipment, method, process, or facility, a laboratory analysis will reveal an Out-of-Specification Result (OOS). When this occurs, the written specification is not achieved. The OOS's cause may be that the material analyzed does not meet specifications, which results in a full-scale investigation of the reason for the failure. The failure investigation (root cause analysis) will involve various departments within the organization: production, facilities, QA, QC, etc. Other causes for an OOS could include sample collection and laboratory errors. SOPs and protocols will describe the collection of samples, such as where and how they are to be collected.

For example, a cleaning validation study may require that rinse water be collected for Total Organic Carbon (TOC) analysis (Figure 4-13). This analysis will detect residual cleaning material or process material. If the sample collection vial or sample collection port is contaminated, then it is likely that the laboratory analysis will return an OOS for the rinse water. This will trigger an investigation to determine the cause, which can be costly in terms of both time and money. If the person collecting the sample guarded against contamination, an OOS and subsequent investigation could be avoided.

Figure 4-13. Analysis of rinse water for residual cleaning agents or process materials

Document control procedures are used to ensure that the latest version of all documents is made available and that all changes are tracked through a process called Management of Change (MOC). Past versions of documents are stored so that a history of changes can be reviewed if necessary. Along with hard copy versions of documents, electronic versions are backed up and stored in a secure location.

Check Your Knowledge

1. Define the following key terms:

    a. Validation
    b. Lethality/accumulated lethality
    c. DQ
    d. IQ
    e. OQ
    f. PQ
    g. Linear range
    h. LOD
    i. LOQ
    j. Control chart
    k. Master Validation Plan
    l. Validation protocol
    m. Retrospective validation/concurrent validation
    n. Change control

2. Ongoing production activities require a significant amount of _____.

3. Laws and regulations are _____, but guidance documents are not.

4. Which of the following is NOT an International Society for Pharmaceutical Engineering (ISPE) guideline for recording written data?

    a. write legibly
    b. record data after performing an operation
    c. fill in all spaces, marking unused ones with N/A or a line
    d. initial/sign and date each entry or page

5. In the Cutter Incident, the vaccine was assumed to proceed with:

    a. terminal sterilization
    b. traceable processes
    c. first-order kinetics
    d. second-order kinetics

6. Products or results must meet which of the following quality attributes? Select all that apply:

    a. identity
    b. robustness
    c. efficacy
    d. documentation
    e. consistency

7. Which government regulation states that at least one test shall be conducted to verify the identity of each component of a drug product?

    a. 21 CFR 600.3 (p)
    b. 21 CFR 600.3 (r)
    c. CFR 211.137 (a)
    d. CFR 211.84 (d)

8. The Process Qualification phase occurs before the Operation Qualification phase.
    a. True b. False

9. _____ involves the processes used to document that equipment is installed properly.

    a. DQ
    b. IQ
    c. OQ
    d. PQ

10. What is the term used to describe the time of exposure to a combination of temperature and pressure required to cause a selected reduction in the survivorship of a Biological Indicator population?

11. Once a system is validated through the DQ/IQ/OQ/PQ process, it cannot be changed without going through a formal _____ _____ process.

    a. control chart
    b. change control
    c. documentation change
    d. documentation control

12. The _____ establishes the lower limit at which we can accurately quantify the analyte of interest.

    a. LOD
    b. LIQ
    c. LRO
    d. LOQ

13. _____ is commonly used to test for residual cleaning fluids or process fluids.

14. What term refers to the variability of test results when the test is done on multiple portions, or aliquots, of a homogenous sample?

    a. reproducibility
    b. consistency
    c. precision
    d. accountability

15. Which type of validation strategy relies on historical data?

    a. retrospective validation
    b. retroactive validation
    c. concurrent validation
    d. co-current validation

Activities

1. Using the Internet, library, or other resources, research a pharmaceutical or biopharmaceutical incident (such as the Cutter Incident) that resulted in tragic results to the health and safety of the public. Write a one-page report describing the incident and how it could have been prevented.
2. An SOP for calibration of a pH meter calls for a two-point calibration at pH 4 and pH 7. You notice that a single point calibration at pH 7 produces the same result from pH measurements of your buffer solutions and allows you to take a longer break. Is it okay to do the one point calibration when the SOP calls for a two-point calibration? How would you go about changing the SOP to allow for a one-point calibration?
3. With a group of your fellow students, discuss potential problems with swabbing and final rinse sampling. Then generate a list of ideas on how to address such problems. Present your report to the class.
4. Select an electronic device, such as a home theater system or toaster oven, and write a protocol describing the IQ, OQ, and PQ for using the electronic device in or around your home.