



Good Practice Guide

Quality Laboratory Facilities

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Good Practice Guide

Quality Laboratory Facilities

Disclaimer:

This Guide describes how to apply a risk assessment to a quality laboratory facility and identify issues to be considered. The purpose of the quality laboratory is to support the execution of testing that assures the manufactured products meet the identity, strength, purity, efficacy, and safety as specified in an approved regulatory file. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The ISPE Good Practice Guide: Quality Laboratories Facilities aims to provide a baseline for the design of pharmaceutical quality laboratories supporting GxP regulated facilities producing pharmaceutical products. This Guide is intended to assist in the development of criteria for determining system impact and component criticality for a quality laboratory. It considers critical early planning decisions and questions, such as through-puts and the consequences of location. Guidance is provided on how to apply a risk assessment to a quality laboratory facility and identify issues to be considered.

Special Dedication to Tom Creaven

This Guide is dedicated to the memory of Tom Creaven, who was responsible for the Architectural Chapter until his passing at which time William Ferguson assumed the responsibility.

Tom Creaven's career spanned more than 25 years at Schering Plough and he was a Director of Global Engineering Services. He served as one of the company representatives to ISPE and was the main contact person for Schering Plough's Global Engineering Team. Tom was involved in a significant number of the projects for Schering Plough and had responsibility for the construction of laboratory facilities, office buildings, and manufacturing facilities. One of his last projects for the firm was the construction of a new cGMP Clinical Research Manufacturing Facility in Summit, N.J. This project was very successful and involved the use of modular construction to expedite the delivery of the facility. Tom was heavily involved in the remediation of the manufacturing site in Kenilworth to comply with the consent decree requirements. This led to the construction of new tablet manufacturing facility that at the time was state of the art when it was completed.

Tom was a licensed Professional Engineer in the state of N.J. and was an active member of ISPE for more than 20 years. He was a mentor to countless young engineers and a consummate professional who ensured that the firm paid attention to detail. Tom was an advocate for the ISPE Baseline Guides and promoted their use as a tool for engineering. Tom's legacy lives on today in the scores of junior colleagues that benefited from his training and guidance over the years, in addition to the friendships that he made with ISPE members, contractors, engineers, and other professionals. He is sorely missed by all.



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1 Background and Purpose

1.1 Background

Quality laboratories execute testing protocols to establish the stability baseline of materials and products, for initial material release, for in-process verifications, for final product release, and to investigate product complaints. The quality laboratory scientists develop and execute tests to guarantee the quality, integrity, and stability of pharmaceutical and animal care products and their components at each stage of a manufacturing process. Their analytical methods are defined in Standard Operating Procedures (SOPs). These methods are used to assure compliance to design and performance specifications prior to release of products to the market.

The quality control function is to verify the quality of the product and its components at each stage of manufacturing through a variety of diagnostic methods. The quality laboratory facility supports the scientists in executing these tests. The tests being performed verify that materials and products meet the necessary criteria to allow for the approval of materials at receiving, the movement of in-process materials from operation to operation and the final release for distribution. The quality laboratory is responsible for testing and release for both in house and outsourced manufacturing, packaging, and distribution. In addition, the quality laboratory supports the testing necessary for stability studies as well as clinical trial manufacturing, packaging, and distribution.

Quality operations are typically responsible for ongoing facility and utility monitoring. In addition, the Quality Control Department supports the commissioning and validation of new facilities in preparation for their release for use.

The application of this Guides' recommendations to a particular laboratory operation should be based on a risk assessment of the testing platforms being applied and the activities being performed. It should not be considered as a universal and generic code applied to all situations. The laboratory under consideration should be defined in concert with the laboratory management documenting their requirements and special needs. The design development team then participates in a joint venture risk assessment performed in concert with their scientific client to reach agreement on the characteristics of the facility to meet the agreed upon risk.

Quality control laboratories can be quite simplistic. Package testing laboratories can be an open room with no special considerations other than security of the samples being tested and verified. In-process control may be performed in rooms close to the physical operation. On the other hand, product testing may require, no to high levels of isolation, depending on the test being performed and the potency of the product being tested. Microbiology laboratories require levels of storage and isolation to protect the samples being tested and the individuals performing the tests. Microbiology laboratories have levels of isolation and safety equipment, including biological safety cabinets and a variety of enclosure containers, to provide containment of aerosols generated by many microbiological procedures. Different levels of isolation are provided depending on the biological compounds hazard level. The three elements of containment include laboratory practice and technique, safety equipment, and facility design.

The most important element to safety of the scientist is adherence to standard practices and techniques. Persons working with agents and materials must be aware of the potential hazards and must be trained and proficient in practices and techniques necessary for safely handling of such materials. The director or person in charge of the laboratory is responsible for providing and arranging for appropriate training of personnel and developing of the approved SOPs documenting these techniques and practices.

Each laboratory should develop an operations manual that identifies the hazards that will or may be encountered, and that specifies practices and procedures followed to minimize or eliminate exposures to these hazards. Personnel should be advised of special hazards and should be obliged to read and follow the necessary practices and procedures. A scientist, trained and knowledgeable in appropriate laboratory techniques, safety procedures, and hazards associated with handling the agents and materials to be tested must be responsible for the conduct of work with any agents or materials.

When standard laboratory practices are not sufficient, additional measures may be needed. The scientist or group trained and knowledgeable in appropriate laboratory techniques, safety procedures, and hazards associated with handling the agents and materials to be tested must be involved in the facility design and engineered features and safety equipment. In addition, it would be a best practice to have this team involved in the risk assessment process to be assured all are in agreement with the final facilities and safety equipment to be employed in the delivered laboratory. The design of the laboratory contributes to the laboratory workers' protection, provides a barrier to protect persons outside the laboratory, and protects persons in the community from agents that may be accidentally released.

1.2 Purpose

The purpose of the quality laboratory is to support the execution of testing that assures the manufactured products meet the identity, strength, purity, efficacy, and safety as specified in an approved regulatory file. It is important to note that a quality laboratory verifies product quality and does not affect product quality. When a quality test fails, i.e., the product fails to meet specifications, the material is quarantined, rejected, or subjected to further test procedures or rework.

The design of the quality laboratory should minimize or eliminate the risk of the facility contributing risk to patient safety through test function failure to detect an Out of Specification (OOS) product. This type of failure may be derived from laboratory conditions or because of a support system malfunction.

Regulatory initiatives and guidelines emphasize the principles of managing risk and the application of these techniques to pharmaceutical facility inspections and submission review. For a quality laboratory and its associated utilities and support systems, a documented risk assessment can identify those areas or systems having an impact on product quality and quality control functions, and provide a rationale for commissioning, verification, and qualification decisions.

1.3 Objectives

This Guide aims to assist project teams in the development of criteria for determining system impact and component criticality for a quality laboratory project. Using these requirements and design documentation, a review of the intended purpose of a laboratory area or the type of testing to be performed in a laboratory area may identify potential risks inherent in the design. Guidance is provided on how to apply a risk assessment to a quality laboratory facility and identify issues to be considered. Managing risk allows a consistent and science-based approach to decision making, across the life cycle of a product or project.

This Guide presents design guidelines focused on pharmaceutical quality laboratories within or part of a GxP regulated environment. Quality laboratories range across various functions, testing platforms, and product types.

This Guide aims to:

- Provide a baseline for the design of pharmaceutical quality laboratories supporting GxP regulated facilities producing pharmaceutical products for human and animal applications
- Assist in the interpretations of function, operation, or design for quality laboratories within the GxP regulatory environment
- Encourage and guide consistency in the baseline design and performance of quality laboratories
- Help to reduce costs in producing pharmaceutical products for human applications¹

¹ May also apply to animal applications.

1.4 Scope of This Guide

This Guide considers:

- Critical early planning decisions and questions, such as through-puts, as determinants of size and capacity, and the consequences of location, e.g., adjacent to or remote from manufacturing, centralized, or decentralized locations
- Identification and characterization of laboratories and support spaces
- The role of regulation via the GxPs and CFR 21 Part 11 [1]
- The parallel and controlling role of prevailing building codes and building regulations
- Prevailing critical industry and association standards related to systems and subsystems
- Systems necessary to support quality laboratory operations
- Various disciplines (e.g., architectural/HVAC/plumbing and fire protection/electrical), design philosophy, design approach, and appropriate alternatives
- Subsystems such as security, monitoring and instrumentation, and IT and electronic data capture
- Construction costs and their control

This Guide supports and references other ISPE Guidance Documents and provides associated examples. The relevant ISPE Guidance Documents should be consulted for regulatory expectations in a specific topic area.

1.5 Issues Which Define the Design of Quality Laboratories

Maintaining Good Laboratory Practice (GLP) is a prerequisite of an effective and efficient operation. This can be accomplished through:

- Security
- Product and people flow
- Environmental control and pressurization
- Monitoring
- IT systems
- Electronic data
- Documentation
- Sample storage and long term retention

Critical aspects for establishing a laboratory environment include:

- The tests being performed and the equipment to support those tests

- Providing the chemicals, solvents, and gases needed to support both the testing and the equipment
- Robust building utility systems, validated where needed, supporting an uninterrupted testing environment
- Flexibility to allow for the evolution of equipment and technology, products, and regulations

2 Concepts and Regulatory Philosophy

2.1 Introduction

This Chapter discusses aspects of quality laboratories that should be addressed when developing the Basis of Design (BOD) for sampling, storage, and analytical areas to help reduce risk and maintain the integrity of a sample and the test environment. The health and safety of laboratory personnel and control data are also considered during the BOD.

Meetings should be held with laboratory personnel to define the requirements for users and set the parameters for design. Laboratory design should consider:

- Physical and environment needs, utilities, equipment, and materials to support the measures and activities in testing a sample
- The space needed to conduct a test, as well as space for the orderly placement and storage of equipment and materials
- Benches and floor materials that are compatible with their intended use, cleanliness, and maintenance
- Mechanical, electrical, and plumbing needs to deliver the appropriate air changes, lighting and power, along with temperature and humidity control

Once the parameters for design are established, a design review should be performed as a risk assessment to ensure that the design meets regulatory, organizational, and user requirements.

2.2 Facility, Equipment, and Personnel

2.2.1 Facilities

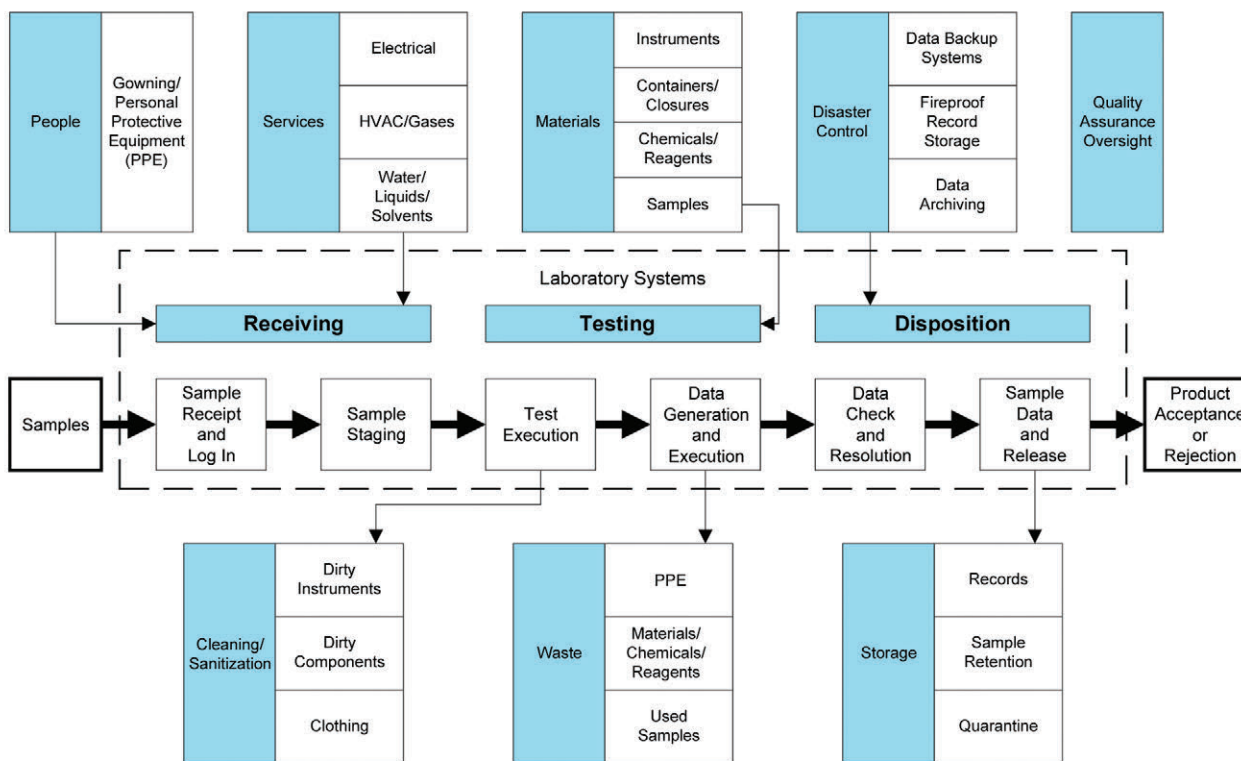
Quality laboratories are intended to support the testing and release of:

- Raw materials
- Active Pharmaceutical Ingredients (APIs)
- In process materials
- Finished product

Typically, quality laboratories also support stability testing of products. The day to day testing for manufactured products may be separated from ongoing stability testing, depending on an organization's philosophy.

Quality operations are typically responsible for facility and utility monitoring, and the testing of products along with their release for use. Laboratory operations can extend throughout an entire facility, including obtaining samples at off-site operations such as contract manufacturers, as well as on-site in receiving, manufacturing, packaging, and warehousing operations. Quality laboratories are normally responsible for the approval of the movement of materials from operation to operation. Quality laboratories are considered integral to facilities.

Figure 2.1: Laboratory Function Flowchart



Where the operations of the production process do not adversely affect the accuracy of the laboratory measurements and the laboratory and its operations do not adversely affect the production process, laboratory areas can be located in production areas. This applies particularly to laboratory areas used for in-process control. Considerations include:

- Control of biologicals, microbiologicals, and radioisotopes
- Special storage conditions for Drug Enforcement Agency (DEA) regulated compounds and finished product
- Handling of light sensitive ingredients and products
- Segregated testing areas for penicillin, cephalosporins, and other sensitizing products
- Handling of potentially hazardous compounds, e.g., biological or radioactive samples, or those which are highly toxic
- Effective handling of potent and toxic compounds
- Protection from a variety of drug products, solvents, and vapors
- Physical, chemical, and biological properties of samples to be tested
- Samples with low density and a high probability of becoming airborne, which may require containment and/or dust control
- Enclosures or rooms to protect personnel and sensitive instruments from vibration, dust, contaminants, noise, electrical or magnetic interference, humidity, etc.
- Suitable storage space for samples and records

- Monitored environmental conditions
- Security to control access to unauthorized personnel
- Traffic patterns and functional adjacencies
- Segregating dirty and clean operations and materials
- Protection of product, personnel, and equipment from contamination
- Temperature, humidity, and air flow requirements for:
 - Equipment
 - Instrumentation
 - Storage materials
 - Standards
 - Samples
- Layout, design, and construction materials for effective cleaning
- Sufficient space and organization to provide adequate segregation and prevent confusion to avoid mix-ups and cross contamination
- Sufficient space to allow for equipment cleaning, maintenance, and repair
- Regulatory guidance on sensitives, pesticides, and poisons

2.2.2 Equipment

The design team and laboratory personnel should focus on documenting instruments and equipment needed to support the testing program with the appropriate accuracy, range, and precision for a specified task. Specific conditions should be defined to assure equipment accuracy and operation during testing.

Storage needs should be defined for in-process samples. The flow of the process and personnel should be defined for placement of equipment. The design team should use this information to define the necessary utilities and appropriate access to the equipment with regard to set up, operation, cleaning, and maintenance.

This process should provide an understanding of:

- Equipment and instruments needed
- Special conditions demanded by the process/testing the equipment supports
- Equipment placement and process and personnel flow
- Special requirements such as clearance from moving parts and environmental demands
- The effect of building vibration on robots and other sensitive equipment
- Safety consideration for all equipment including robotic equipment

- Space for sample preparation
- Space for data recording
- Space and equipment access for set up, calibration, operation and cleaning
- Space for equipment and facility maintenance

2.2.3 Personnel

The design team and the laboratory personnel should document personnel requirements, the number of spaces needed to support the necessary number of analysts, as well as process space and with operational issues, e.g., potency, radioactivity, and power backup. This exercise should define and clarify the needs to support the testing programs with the appropriate spatial requirements to assure accuracy, range, and precision, as well as for analytical review and documentation. The design team should use this information to define the necessary bench space, write up area, and the equipment needed in support of this effort. This exercise should ensure that the support space provided meets the requirements of analysts. This process should provide an understanding of:

- Operational staff within the laboratory
- Administrative staff (typically housed outside the laboratory)
- Quality control staff not housed within the laboratory (samplers)
- Analytical evaluation and data entry space
- IT connections and support space
- Health and safety concerns
- Cleaning, setup, and maintenance
- Concerns with potent and/or toxic chemical, biological, and radiological compounds
- Adequate egress and flow pathway

2.2.4 Operation

Operational aspects considered during development of the BOD should define what the facility will support and how this will be accomplished. Aspects to consider include:

- Is the facility for finished product testing only?
- Is the facility supporting stability studies only?
- Is the facility supporting API manufacturing only?
- Is the facility supporting all three conditions, API, finished product, and stability studies?
- Is the facility running a monitoring program to be supported?
- What are the hours of operation?
- Number of personnel to be accommodated?

- Is there a particular driver which caused consideration for the project, e.g.:
 - Meeting current requirements?
 - Complying with increased regulatory requirements?
 - Providing infrastructure to allow for future expansion?
- Where is the facility to be sited?
 - What are the sites under consideration?
 - Is the laboratory to be in the vicinity of the manufacturing facility?
 - What is its proximity to available utilities?
 - What is its proximity of site services?
 - Where will the site entrance be located?
 - What is the distance to parking?
 - Will cafeteria services be provided?
 - What are the available environmental services?
 - What image is the building to portray?
- If there is an existing facility, will the scope include the transfer of its equipment (computers, test equipment, etc.) and personnel to the new area?
- If a transfer is planned, how will this be executed while keeping the existing laboratory in operation?

At the conclusion of this process, the team should be able to define the facility.

Table 2.1: Example – Potential Information in a Facility Definition

• This program will be for stability only with the following program elements: - Design and construction capable of supporting pharmaceutical and animal testing for drug products. - Qualification and validation requirements (where needed) are to be included in the building design. - Utilize building materials that conform to the image of the surrounding campus. - Design provisions incorporating future expansion. - Mechanical support will be from roof mounted equipment. - Compliance with all local codes, zoning ordinances, and Federal regulations.
• Office space will be provided for the directors and managers with cubicles provided on the laboratory floor for supervisors or team leaders.
• An in-house instrument laboratory will be provided for servicing malfunctioning instruments.
• The laboratory capacity is to accommodate the shift having the maximum number of analysts.
• Open desk positions will be programmed into space away from the equipment benches for analytical write up and stability work.

2.3 GMP Requirements

This Section provides a summary of the GMP requirements for quality laboratories and refers to 21 CFR 210-211 [2 and 3], ICH Q7 [4], the EU GMP [5], and other CGMPs. These regulations allow interpretation by users when assessing the needs of a project with an understanding of the products being handled and risks in handling the product and executing the testing. The regulations normally allow the design team to make appropriate decisions for the facility. The regulations provide requirements, but do not specify how they should be met.

2.3.1 *Quality Facilities*

Regulatory considerations that govern the physical facilities of quality laboratories include:

- Appropriate size, construction, and location to facilitate cleaning, maintenance, and proper operations
- Adequate space for orderly placement of equipment and materials to prevent mix-ups between components
- Personnel and materials flow to prevent contamination
- Defined and sufficient areas for specific uses with appropriate separations
- Adequate ventilation with appropriate temperature, humidity, and particulate content control

Regulatory considerations that govern the activities of quality laboratories include:

- Good Laboratory Practices (GLPs)
- Good laboratory safety practices
- Good documentation practices
- Standard Operating Procedures (SOPs)
- Validation of laboratory computer systems
- Methods validation
- Out of specification investigations
- Change control, deviation management, and Corrective Action and Preventative Action (CAPA) program
- Qualification, verification, calibration, and maintenance of equipment as necessary to be or remain fit for the intended use
- Personnel qualifications and training

2.4 General Laboratory and Support Space Characterizations

This Section considers a “centralized” approach for laboratories with laboratories designated for specific types of analyses.

2.4.1 Incoming Material and Component Sampling

Incoming materials and components used in the manufacture, testing, and packaging of pharmaceutical products should be subject to a scientifically justified sampling plan and identified, documented, sampled, inspected, and tested prior to release for use. Incoming materials and components include:

- Active Pharmaceutical Ingredients (APIs)
- Raw materials
- Gasses
- Excipients, solvents
- Primary packaging materials
- Secondary packaging materials
- Tertiary packaging materials
- Cleaning products
- Process water

GMP concerns that need to be addressed by a facility design relate to maintaining:

- Sample integrity
- Segregating materials
- Preventing contamination and cross-contamination

A risk assessment should be performed to establish appropriate flow, segregation, and protection of material, personnel, equipment, and waste.

Examples of operating approaches that should be considered during design of a QA laboratory include:

- Materials receipt and testing:
 - Materials should be logged and sampled in dedicated areas
 - Materials should be put in quarantine electronically or physically until released
 - The status of materials should be easily identified by electronic or physical means
- Tested Materials:
 - Materials meeting the established standards should be “released” for production

- Materials then should be moved to the designated released materials area in the warehouse
- Materials may not be physically moved if release and availability are administered through a computerized material control system
- Materials that do not meet their specifications should be rejected “in these cases, root cause analysis and CAPA procedures should be executed”

2.4.2 Sample Weighing

Workflow can be enhanced by providing central sample weighing. A room or area dedicated to this use would provide several weigh stations with appropriate ventilation for safe sample handling. Specific laboratories (e.g., microbiology) would have their own weighing area.

2.4.3 Sample Preparation

Typically, sample preparation is carried out in a centrally located area housing sonicators, shakers, centrifuges, carboys, and glassware. This area may be used for both raw materials and finished product analysis. Buffers may be prepared and stored for dispensing in this area. Storage cabinets should be provided for material, reagent, and solvent storage. “The integrity of the sample needs to be ensured.”

2.4.4 General Testing Laboratories

These are the most common type of quality laboratory. General testing laboratories can be large with an open floor plan and equipped with island benches. Characteristics these laboratories may include:

- Multiple sets of High Pressure Liquid Chromatography (HPLC) equipment. HPLCs can be configured on bench tops or on specialty benches designed for instrument stacking. Another approach is to use specialty racking systems allowing for vertical stacking of components to conserve bench space. The racked instrument is moved in place and connected to services provided. If the racking system is equipped with wheels, the HPLC can be moved intact for servicing, maintenance, and recalibration.
- Preparation of mobile phase for HPLC. This area typically houses a walk-in fume hood that is used to mix and dispense mobile phase mixtures. An appropriate grade water service would typically be piped to this hood to facilitate operations. Dispensing cans may be stored on a properly grounded dispensing rack/shelf within this area. This area typically handles large volumes of solvents with appropriate storage cabinets for unmixed solvent and has containment should a spill occur.
- Gas Chromatography (GC) instrumentation on the bench top with dedicated gas delivery, usually from local cylinders in closets (cabinets for hydrogen).
- Fume hoods for safe solvent and reagent handling. Solvents may be stored under the hoods or nearby the hood in solvent storage casework. Common practice is to store solvents in a solvent storage cabinet across from fume hoods since the fume hood is the most flammable/dangerous portion of the laboratory. NFPA 45 [6] or equivalent local regulations should be referenced for guidance on handling solvents. Solvent storage cabinets should not be vented, as ventilation will cause the solvents mixed with the air to pass back and forth through the explosion limits. The need to ventilate solvent storage cabinets may be governed by regional laws.
- Acids and bases should be stored separately under hoods in cabinets dedicated to either acids or bases.
- General use gases (e.g., nitrogen) may be distributed from central system or local closets; reactive gases (e.g., hydrogen, acetylene) should be supplied from cylinders in local gas storage cabinets.
- Storage areas including freezers and refrigerators as needed should be alarmed if failure is critical.

- Ventilation should be provided as needed. “Point of Use Ventilation” requirements occur throughout a laboratory to ventilate equipment, capture fumes from solvent dispensing and storage, and to protect personnel from airborne particulates.
- Aisle widths should enable safe and unencumbered flow of personnel and materials.
- Island benches with flat surfaces and utility connections designed for use in conjunction with large equipment arrays.
- Space for temporary storage of solutions from sample analysis. This can be accomplished with shelving or cabinetry within the laboratory.
- Utilities to support the instrumentation (see Section 6.8.3 of this Guide)
- Conditioned electrical provided where needed.
- Failure-proof electrical power (UPS/generator). This is typically a UPS system of sufficient size to allow for the controlled shut down of equipment during a power failure. For environmental chambers housing long-term studies, a risk assessment should be performed and appropriate backup and alarming systems provided.
- ASTM, CAP, USP, WFI grade water may be provided by point of use polishing units. This may be more economical than distributing purified water from a centralized source.
- Write up desks for analysis of test data
- eLIMS with an adequate number of workstations to support the laboratory

2.4.5 Controlled Substances

When controlled substances are present, an area should be provided in the laboratory for storage and control of these materials that is sized appropriately to accommodate anticipated quantities. The storage area should be appropriate for the schedule of drugs as directed by the Drug Enforcement Administration (DEA) or other relevant authority. Schedules for a specific active material may be different when handled in a pure state versus a constituent of a drug substance at lower concentrations. (Drug schedules are included in Title 21 CFR Chapter II 1308.11 through 1308.15) [7] Schedule I and II substances require either a safe, or if quantities dictate, a vault with perimeter alarms. Schedule III, IV, and V Substances require only a wire cage or locked cabinet with controlled access and perimeter alarms. For specific design requirements, refer to Title 21 CFR Chapter II Subparts 1301.71 through 1301.76, Security Requirements [8].

Card key access tied to a monitoring system can help to restrict access to areas where these substances are used or stored. This provides a record, including times, of personnel entering and leaving the area. Security cameras hooked up to motion detectors also provides a video record of activity within the area. It may be beneficial to locate these areas on top floors or on restricted access floors within a given building. Monitoring and restricted access should form increasingly secure areas as persons pass from the least sensitive areas (main campus gates) to the most highly sensitive areas (highly restricted areas within a building). Organizations may eliminate signage at doors to sensitive areas to make them more difficult to find.

Extending partitions full height to the underside of structures, providing “hard lid” ceilings and placing fire-resistive plywood behind interior drywall on interior partitions are intended to make access to sensitive rooms more difficult and time-consuming. Organizations may provide a central storage or dispensing room that is managed full-time by an operator so that a limited number of personnel are responsible for substances distributed throughout a facility.

2.4.6 Glass Wash/Clean Glass Storage

The glass wash function is a central utility typically remote from the quality laboratory. The glass wash function is a validated process using qualified equipment, ensuring that the glassware is appropriately cleaned and will not compromise test results. This area should be sized for current and potential future capacity. Storage space and staging areas should be included for both clean and dirty glassware. Cabinets should be provided within the glass wash area to house glassware backup inventory. A large and deep sink should be provided for hand washing of glassware. For compendial testing, glass washers should be supplied with purified water for the final rinse cycle.

A fume hood and a solvent storage cabinet are usually included in a glass wash function because of the need for acetone to remove the markings from the glassware before washing. Additionally, washing detergents require storage as well as a position next to the washer for pumping into the washer during the wash cycle. Containment type pallets may be used to hold open detergent and to capture any spills from an open drum.

Glass wash equipment (e.g., glass washers and dryers, autoclaves, depyrogenation ovens) requirements for room and utilities design include:

- Adequate space for loading and unloading of carts into the washer
- Adequate space for carts that are in use or in storage; various types of carts are available for different load patterns, depending on the items being washed.
- Sinks for manual washing: a supply of purified water of appropriate quality for the final rinse step of the washing process should be provided.
- Drains equipped with back flow preventers/air breaks
- Washer/dryer selection, e.g.:
 - Closed systems that wash and dry glassware in one cycle may be available
 - Combined systems which are ventilated throughout the cycle provide dried final product which does not release moisture into the washer space
- Adequate ventilation should be provided to minimize the potential for growth of mold.
- Adequate space should be provided for dirty goods staging, washing, drying, wrapping and preparation, sterilization, and clean goods storage. These areas should be segregated and provide a one-way flow to prevent cross flows between clean and un-clean glassware, and to separate this 'wet' function from compromising the environmental conditions for other functions.
- In a standalone laboratory, the glass wash function is usually programmed next to the laboratory receiving area outside or across from the main laboratory. Cleaned glassware is delivered to the laboratory and placed in glassware storage cabinets within easy access to the laboratory personnel.

2.4.7 The Autoclave

Autoclaves sterilize bacterial enrichment media, equipment, glass ware, etc. Factors which should be considered when incorporating autoclaves into the laboratory design include:

- Supply of adequate steam for the number of autoclaves located on one steam feed line. Simultaneous use may challenge the system and cause autoclave cycles to abort.
- Steam supply of the quality needed for the function being supported

- Sufficient room exhaust to handle the condensation and noxious fumes generated by the breakdown of plastic and organic material in the waste container used to decontaminate waste. This may be achieved by using a canopy or other capture device above an autoclave.
- Purchasing of the GMP package usually offered on new autoclaves is recommended. These modified pressure vessels contain pre-drilled portals and sensory components that allow for easier validation studies.
- Autoclaves with appropriate sized chambers for loading should be selected to maintain efficient operation and minimize continuous use, providing adequate spare capacity.
- Sufficient space should be provided around autoclaves to accommodate maintenance, re-validation, repair, and modification when necessary.
- Sufficient space should be provided for parking carts and other devices used to transfer items to autoclaves.
- Skid proof flooring (especially if carts are used to load and unload the autoclave)
- Adequate space should be allowed for autoclave carts with wall/furniture protection against accidental damage from the carts

2.4.8 Sample and Records Retention

Sample retention is needed for pharmaceutical ingredients and finished product. The samples should be stored in a secured area that is environmentally controlled within the range of storage and humidity conditions consistent with product labeling for:

- Raw materials
- Active material
- Finished product

Storage should be sized appropriately for the number of samples retained. US regulations require that samples be retained for one-year after the expiration date. Samples from Over-the-Counter (OTC) products, exempt from bearing an expiration date, require three years retention after distribution under US regulations.

The storage area should be sized appropriately to accommodate securely the storage for the type of products, expiry, and twice the number of samples as needed by manufacturing protocol for each production lot. Specific requirements for sample retention can be found in, ICH, EMEA, WHO, and Title 21 CFR Chapter I Subpart 211.170, Reserve Samples [3], and the EU GMP [5] respectively. Sample retention storage may be located remotely to take advantage of lower construction costs in non-laboratory space. High density storage systems generate a smaller constructed footprint. If controlled substances are present, security requirements should be instituted in compliance with the regulations.

For stability studies, samples should be retained within the variety of environmental chambers needed for ongoing testing. These chambers may be located on the stability laboratory floor or depending on size, they may be found in close proximity to the laboratory or off the laboratory floor in less costly unfinished space.

In-process records and reference SOPs should be stored in secure files within a quality laboratory. These files may be kept in the sample receiving area where the sample is prepared for analysis and the associated paperwork is correlated with the appropriate sample.

Long-term records, engineering, qualification, and validation documents, and retained samples typically are stored in an area remote from the quality laboratory. Systems used to store retained documents and samples should be sized sufficiently to provide secure storage over their expected life. As long as extremes of Relative Humidity (RH) are avoided, then normal comfort conditions are considered adequate to store paper records for their usual life expectancy. A reception room may be planned in close proximity to the records retention area for accommodating visiting agency representatives.

2.4.9 Americans with Disabilities Act (ADA)[9] and Barrier Free Compliance

Laboratories should comply with local requirements for accessibility requirements as it relates to the building site and circulation. In the US, the requirements include parking spaces, curb cuts, ramps, and a clear path of travel allowing disabled individuals to park and access the building. Doorways and corridors should be sufficiently wide for wheelchair transport. Elevators should provide access to each occupied floor. Restrooms, drinking fountains, pay phones, and all public spaces should be designed for use by disabled persons. Signage and elevator call buttons should be equipped with raised Braille markings. Fire alarm systems should have both visual and audible signals.

Pharmaceutical and biotech organizations may be able to work with local and state jurisdictions to avoid having to design the laboratory and support areas incorporating lower sinks, bench tops, and wheelchair accessible fume hoods. Local authority may allow organizations to write a letter that is kept in its files stating that laboratory areas will be modified to accommodate physically disabled persons that they hire in the future on a case-by-case basis. (The rationale is that designing a laboratory to strictly comply with **all** aspects of the ADA could actually result in a hardship to those employees with no disabilities.) Additionally, there may be laboratories or areas within a building where the work is of such a nature that it cannot reasonably be performed by a person with specific disabilities. Wheelchair clearances are still required at all doorways, aisles between laboratory benches, and elsewhere.

2.4.10 Other Support Spaces

Other support spaces that require appropriate sizing and location are:

- **Stockroom:** this is typically located near the shipping/receiving area to facilitate receipt of items being delivered to the laboratory building. It is a central laboratory service for the storage of supplies and reagents used for routine testing.
- **Solvent Storage:** a centralized solvent storage area is important to assure continuing operations. Due to the need to store large quantities of solvents, this room is typically equipped with a fire suppression system and has containment to accommodate spills. Its location is typically away from the laboratory floor near the stockroom so as to share support personnel. A well-organized solvent storage operation can greatly ease the fire code limitations in multi-floor quality laboratories, due to its ability to provide solvent as a just-in-time service. This effectively limits the quantities of solvents kept on the laboratory floors.
- **Solvent Storage on the Laboratory Floor:** NFPA 45 [6] dictates solvent storage capacities within each zone of the building. Solvents kept on the laboratory floor are typically housed in flammable storage cabinets located in each section of the laboratory in proximity to the fume hood to provide local supplies yet limit solvent quantities in accord with local fire code requirements.
- **Environmental Chambers:** cold rooms and freezer rooms are used for storage of samples waiting testing as well as for storage of raw materials, reagents, microbiological samples, media, etc. Warm rooms (environmental rooms) are usually used for incubation of environmental monitoring or sterility test media. Rooms are used in lieu of individual refrigerators, freezers, or incubators where space needs and economy dictate. These rooms are commonly located near their respective laboratories or are distributed throughout the building. Having them near the laboratory allows for the dissipation of the heat produced through ventilation rather than having to deal with the added heat within the air conditioned lab. Depending on the criticality of loss, environmental rooms may be provided with redundant systems and appropriated alarming.

- **Shipping/Receiving:** shipping and receiving, when part of a quality laboratory facility, can offer many efficiencies of operation and consideration of testing of incoming materials. Alternatively, the area may be separate and a part of the facility warehousing.
- **Gas Cylinder Storage:** cylinder storage is usually outside the laboratory building with the gas cylinders in storage racks. A centrally-provided gas service, e.g., nitrogen, would be provided with a manifold allowing automatic switchover from empty to full cylinders and an alarm indicating when this has happened. Where they are used, interior storage systems need to be well ventilated.
- **Information Systems:** information technology will need rooms in the building to support servers linked to corporate functions, e.g., email, central computer access, and networking. For quality laboratories, the laboratory local area network, including the stability studies storage control systems usually needs secure space with an appropriate fire protection system.
- **Locker Rooms:** laboratories may provide for locker areas to store the personal effects of users that do not have a designated office space outside of the laboratory.
- **Personal Protective Equipment:** garment change areas are needed to put on garments before entering the laboratory. Personal protective equipment should include laboratory coat, gloves, and safety glasses during material handling. The change area location can be at the laboratory or at the entry to the laboratory facility depending on the personnel flow. A designated space should be provided for these functions rather than cause congestion by combining these with entryways and corridors. These areas should have storage systems for new garments, waste hampers for disposal of the garment wrapping, used gloves, and safety glasses along with hampers for the disposal of the removed garment.
- **Laboratory Waste Handling:** the waste product from testing should be considered during design development. Solvent handling and disposal, potent compounds, and other waste products have a major impact on laboratory operation. Laboratory drainage systems can be kept separate from other drainage systems. Where waste materials are hazardous, drainage systems may be constructed of “pipe within a pipe” systems so that they can be monitored for any leakage. To minimize solvent content on the laboratory floor, consideration can be given to removal of spent solvents from HPLCs via a piping system to the outside where the spent solvent is accumulated in a solvent storage/disposal container housed on a Resource Conservation and Recovery Act (RCRA) pad.

2.5 Speciality Laboratories

2.5.1 Aseptic and Sterility Test Laboratories

Aseptic and sterility laboratories usually house specific functions, including:

- Provision for gowning and airlocks, as appropriate
- Preparation and storage areas for samples and solutions (e.g., media, buffer solutions)
- Microbiology laboratories for testing for the presence of microorganisms in sterile products and enumerating and identifying microorganisms in non-sterile products. Compendial sterility testing usually is practiced in isolators to avoid the risk of false positive results
- Space for sterility testing, usually a clean room within a microbiological laboratory
- Environmental rooms

An appropriate environment should be provided to prevent impact on the integrity of the testing samples. The laboratory design should include isolation of the testing environment via a pass-through airlock and gowning area; alternatively, testing can be performed in a mini environment, e.g., a sterility testing isolator, within a standard laboratory.

Layout, equipment, and design issues for microbiology laboratories include:

- Space for incubators
- Laminar flow hoods
- An autoclave, with consideration of a pass through, to sterilize waste from the laboratory and to sterilize materials used in **microbiological and sterility** testing
- Dedicated refrigerators for **storing solutions**
- A -94°F (-70°C) freezer or **liquid nitrogen storage system** may be necessary for cultures.
- Support rooms to house the autoclave, refrigerators, and other frequently used equipment
- Purified water and carbon dioxide gas are usually needed. (Purified water may be obtained from a **local water polisher unit** dedicated to the suite.)
- Seamless work surfaces of stainless steel or epoxy construction
- Seamless floor finishes coved at the wall for cleanability
- Wall coverings finished with non-porous, water resistant materials
- Ceilings finished in washable water resistant material
- No floor drains is preferred, if floor drains are used they should be sealed

Contamination control, both for personnel and the laboratory environment, is considered a significant challenge to microbiology laboratory operations. Spatial and temporal separation of working procedures may be used to achieve control.

Organizational procedures for cleaning and disinfecting the microbiology suite should be established. Aseptic testing laboratories should be qualified and maintained to meet the appropriate area classification pertinent to the materials being tested.

2.5.2 **Biohazard Laboratories**

Biohazard or **biocontainment** laboratories should allow safe and efficient work with biohazardous materials. The objectives of a biohazard laboratory are to:

- Protect laboratory workers from accidental exposure to biohazardous materials
- Prevent cross-contamination of non-hazardous samples or non-contained areas of the facility with biohazardous materials
- Prevent release of biohazardous materials to the environment

In the biopharmaceutical arena, the term “biohazardous materials” includes organisms or products produced using recombinant DNA technology. For the types of laboratories discussed in this Guide, containment conditions will be dictated by the likely presence of production organisms and the nature of the work intended for the laboratory. Examples of production support laboratories requiring biocontainment include:

- Master/working seed production

- Inoculum preparation
- Upstream in-process laboratories
- Bioassay laboratories

Analytical testing involving samples or materials containing viable infectious or recombinant organisms should be performed in a biological containment laboratory designed to the appropriate biosafety level. In the US, the National Institutes of Health (NIH) and the Center for Disease Control (CDC) have defined biohazard levels based on the potential lethality of the host organism. The NIH Guidelines [10] were developed for processes involving recombinant DNA organisms; however, these guidelines are based on existing approaches to the containment of pathogenic organisms and are appropriate for vaccine production using hazardous non-recombinant production organisms. NIH has defined four physical containment levels for laboratories:

1. BSL-1
2. BSL-2
3. BSL-3
4. BSL-4

BSL-1, 2, and 3 are applicable to biological manufacturing facilities and associated quality laboratories. (General laboratory design and practice guides are available from NIH [10] and CDC websites [11].) For further information, see the ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities [12]. Similar guidelines apply to EU member states. Additional guidelines apply to operations involving oncogenic viruses these may be obtained from the National Cancer Institute [13].

GMP issues are the same as for other laboratories. In most cases, the dual objectives of personnel and product protection can be met by performing “open” processes in appropriately designed and installed Biosafety Cabinets (BSCs). Additional measures such as air lock entry and exit, decontamination equipment, and specialized HVAC design may be required for specific cases. Isolators/glove-boxes/Class III BSCs should be considered. Refer to NSF/ANSI 49-2011 [14] which governs the classification and testing of BSCs.

In addition to the design features relating to general and microbiology laboratories, biohazard laboratories design should consider:

- Segregating the laboratory from areas with unrestricted traffic flow. Cascading airflow from low-risk to high risk or airlocks as “sinks” or “bubbles” are considered beneficial in BSL-2 laboratories. Airlocks into these laboratories may have interlocked double entry.
- Room finishes and casework should be non-porous and resistant to chemical disinfectants.
- Entrance doors to the laboratories should be self-closing and interlocked.
- Spaces between and under benches, cabinets, and equipment should be accessible for cleaning and disinfection.
- Wall/ceiling penetrations should be kept to a minimum and sealed.
- Floor drains should be avoided if possible. If used, floor drains should be connected to the facility biohazard waste drain.
- For hand washing, a sink can be provided although the water being discharged should be to a biokill system. Non-aqueous hand wash eliminates the need for a sink.

- Include an autoclave in the general vicinity, preferably a pass through autoclave, for handling biohazardous wastes. All biowaste should be decontaminated before disposal or appropriately contained for off-site disposal via a contract biowaste hauler.
- BSCs for “open” operations. Class I or II BSCs are appropriate although Class II BSCs may be used, which provide a degree of product protection in addition to personnel protection. BSCs may be exhausted locally to the room (Class II, Type A) or exhausted via a ducted exhaust system (Class II, Type B1, or Type B2). Consideration should be given to clearance above BSCs to allow connection of an exhaust thimble and isolation damper to facilitate decontamination of the BSC. The room HVAC, system should not create drafts at the face of BSCs. BSCs should be located away from doors and general traffic flow to avoid drafts.
- Depending on hazard evaluations, consideration should be given to the use of isolators.
- Additional environmental protection (e.g., personnel showers, HEPA filtration of exhaust air, containment of other piped services, and the provision of effluent decontamination) should be considered if recommended by the agent summary statement, as determined by risk assessment, the site conditions, or other applicable regional or local regulations.

Design practices specific to **BSL-3** Laboratories include the following:

- HEPA filtered supply air
- Architectural finishes should be compatible with the cleaning agents that will be used in the laboratory. Users should provide cleaning lists so that compatible materials are selected. Aluminum may not be compatible with some cleaning agents. Wood products should be excluded from these laboratories. This includes finishes and hidden material, such as shims.
- Passage through two sets of doors for entry into the laboratory from access corridors or other adjacent areas is recommended. This is commonly achieved with a double door air lock/change room. Showers may be included, but are normally needed only if volumes in excess of 10 liters of biohazardous agent are used. The air lock entry should be negative relative to the adjacent space and may be designed as a “sink” (negative to BSL-3 laboratory as well). Doors should be interlocked such that both doors cannot be opened simultaneously.
- Hand washing sinks should be located near the laboratory exit. Typically, sinks are foot, elbow, or automatically operated. Non-aqueous hand wash eliminates the need for a sink.
- Water within BSL-3 laboratories should be discharged into a biokill system.
- An autoclave should be available, preferably within the laboratory containment suite. A double door pass-through autoclave is recommended. A bioseal should be provided.
- All biowaste should be decontaminated before disposal or properly contained for off-site disposal via a contract biowaste hauler.
- Vacuum lines are protected with HEPA filters and liquid disinfectant traps.
- Specialty gases and other utility connections should be accessible from outside the containment zone.
- Maintenance access to autoclaves and other support equipment should be from outside the containment zone.
- Circuit breakers should be located outside of the containment area.
- Light fixtures recessed in the ceiling and serviceable from above is considered preferable. An alternate approach may be a flush mounted, gasketed fixture.

- A ducted exhaust system to provide directional airflow that draws air into the laboratory, i.e., the laboratory should be at negative pressure (between .03 and .08 inch w.g.) relative to the surrounding areas. Mounting the exhaust fan at the discharge point on the roof should assure that the exhaust ducting is negative throughout the system. The exhaust air should be discharged to outside and dispersed away from occupied areas and air intakes and not recirculated to any other area of the building. Supply and exhaust fans should be electrically interlocked to prevent the laboratory from becoming positively pressurized if the exhaust system fails. HEPA filtration of the exhaust is not needed although many organizations elect to do so.
- Depending on hazard evaluations, consideration should be given to isolators.
- Additional environmental protection (e.g., personnel showers, HEPA filtration of exhaust air, containment of other piped services, and the provision of effluent decontamination) should be considered if recommended by the agent summary statement, as determined by risk assessment, the site conditions, or other applicable regional or local regulations.

2.5.3 Potent Compound Laboratories

The potency of highly potent compounds needs categorizing via Occupational Exposure Limits (OEL), Occupational Exposure Bands (OEB), or Exposure Control Limits (ECL) (see Chapter 4 of this Guide). Advances in instrument precision now allow detection of smaller quantities of these materials.

The design team and client group should determine the facility design philosophy. Typically, this philosophy would follow the types and levels of controls used in the respective manufacturing areas and would include definition of:

- The primary containment boundary: defines the containment device, the level of open operations, and the nature of the exhaust (local versus general). For extremely hazardous substances, a glove box may be needed.
- The secondary containment boundary and protection: defines airlocks and personal protective equipment, etc.

Quality laboratories normally would handle relatively small quantities of these materials. The level of containment and its facility design would reflect both the nature of the controls in the manufacturing area and the quantities being handled along with the method of handling (hydrated, etc.) within the laboratory.

The OELs needed could be achieved by Personal Protective Equipment (PPE), containment at the source or a combination of the two approaches. Containment at the source may be preferred or mandatory. For example, in the UK, the Control of Substances Hazardous to Health Regulations (enacted in 1988) [15] require that *“so far as reasonably practicable, the prevention or adequate control of exposure of employees to a substance hazardous to health shall be secured by measures other than the provision of personal protective equipment.”*

Highly potent compounds (such as those which may be categorized in Operator Exposure Band (OEB) 4 and 5 PPE) may require laboratory coats to be fastened, gloves, and safety glasses during material handling. Gown up may be needed in containment areas. Disposable laboratory coats or impervious suits, as well as double disposable gloves may be used. A designated change area of sufficient size to facilitate good laboratory decontamination practices will be needed, and should be located as close to the entrance/exit as possible.

2.6 Specialty Compound Laboratories

Some compounds that do not have severe OELs, such as hormonal compounds, penicillins, cephalosporins, and radio isotopes require similar segregation to that used for potent compounds. Materials control, gowning procedures, and facilities should be similar to those specified in Section 2.5.3 of this Guide. These facilities typically are dedicated to the specific compound type.

2.6.1 *Radioisotope Laboratories*

Radioisotope laboratories for **low- and intermediate-level radioactive substances** differ from normal testing laboratories because of the regulatory aspects of dealing with radioactivity. In general, there are two areas that should be considered:

- Protection of the public: care should be taken to ensure that the public is not exposed to radioactive materials. Design features to accommodate this responsibility include:
 - Minimal movement of radioactive substances
 - Appropriate shielding and security with restricted access to areas where radioactive substances are stored and used
 - Control of radioactive waste
 - Exhaust air should be suitably treated to prevent ambient contamination. Filtration of exhaust air may include carbon beds, lead shielding, and radiation detectors, and should be matched to the type of radio-isotopes used in the laboratory.
 - Laboratory personnel should wear monitoring badges or similar devices at all times within the laboratory to ensure that exposure limits are not exceeded.
- Protection of personnel: in addition to design features intended to protect the public, design features should include:
 - Adequate space to carry out the necessary activities shielding should be provided to ensure worker safety
 - All surfaces in the laboratory should be easy to decontaminate

Laboratory planning for radioisotope laboratories is similar to planning of other laboratories and should include these considerations:

- The design should assure these laboratories are at negative pressure relative to the surrounding areas.
- Airflow should be toward areas of higher radioactive load.
- Appropriate ventilation devices should provide safe working conditions.
- Air should not be recirculated in these laboratories.
- The combined radioactive exhaust from the building should be placed to ensure no entrainment to any other building.
- Filtration of exhaust may include carbon beds and should be matched to the type of radio-isotopes used in the laboratory.

Ventilation devices, such as fume hoods, should have similar characteristics to those for other laboratories with the following exceptions:

- Where radioactive substances are used, the fume hood exhaust system may be manifolded only to the exhaust systems for laboratories not to general area extracts.
- The fume hood exhaust duct should be marked/labeled at frequent intervals to alert personnel working on a building exhaust system.

- The fume hood work bench should have suitable strength to support any necessary shielding materials.
- The linear face velocity for fume hoods typically is in the range of 80 to 120 linear feet per minute (lf/min) (0.41 m/s to 0.615 m/s).
- Emergency power should be provided to fume hood exhaust fans.

Laboratory finishes for radioisotope laboratories are similar to those for biohazard or potent compound laboratories, including:

- Walls and ceilings should be washable and have sealed joints.
- Flooring should be impervious and have coved joints with walls.
- Laboratory furniture, including cabinets, shelving, sinks, and utility fixtures should be washable.

Utilities provisions:

- A remotely operated hand sink should be located near the laboratory exit door.
- Drain lines from the laboratories should be suitably labeled at frequent intervals to alert personnel (e.g., maintenance personnel).

It is anticipated that the individual quantities of radioactive substances to be handled in a quality laboratory will be relatively small. The aggregate quantity of these substances should be managed to minimize the total radioactive load within the radioisotope laboratory suite.

2.6.2 Cold Laboratories

Specific QC activities may require procedures be performed in a cold environment, either because the product or sample is temperature sensitive or because the test should replicate processing conditions. Working cold rooms (as opposed to storage cold rooms) should meet life/safety issues, such as a “**man-in box**” alarm, in addition to providing the appropriate environmental conditions for testing, such as low-pressure column chromatography for a protein biologic. Cold laboratories may have an increased risk of mold growth if the relative humidity in the area is not controlled.

It is recommended that cold laboratory is discussed thoroughly with the quality department. These areas are arduous to work in, create additional safety operating procedures, and are expensive to design and build. A chromatography refrigerator may be used in place of a cold laboratory.

Cold or environmental rooms typically are generally pre-engineered and supplied as modular units complete with condensers and evaporator/fan units. Considerations that apply to cold laboratories include:

- Cold laboratories should be fitted out with utilities, casework, and instrumentation in support of the activities to be conducted. The heat load from equipment should be accounted for in the mechanical design.
- If the cold room is supplied with a raised floor, ramps will be needed for rolling carts or equipment
- Data ports should be provided for remote monitoring of equipment outside the cold environment. Fire alarms and other emergency messages should be audible within the room. A telephone or intercom may be useful.
- Large view panels should be provided so that on-going operations may be monitored from outside the cold space.

Regulations require that fresh air is introduced into cold laboratories or cold rooms that will be occupied for significant lengths of time by personnel. Appropriate dehumidification equipment should be provided as a part of the environmental chamber to control humidity or dew point of the incoming outside air. Uncontrolled dew point will lead to high relative humidity in the cold laboratory as well as increasing frost build up on cooling coils. Penetrations into the cold laboratory should be adequately sealed to prevent exterior humidity from entering the cold laboratory causing water buildup within the laboratory. Sealed light fixtures should be specified during design to eliminate the possibility of condensate buildup within the fixture. Defrosters should be used in window panes to keep them clear of moisture during operation.

Cold rooms should have several inches of insulation within the panels that make up the floor, walls, and ceiling. The flooring transition should be considered. The cold room floor panel can be recessed into the slab² so that the transition is smooth and level or the flooring panels can go on top of the slab, in which case, there should be a short ramp either outside or inside the cold room to make up any difference in floor height. Placing the cold room on top of the slab is generally more flexible, as the room can be moved anywhere. Recessing the unit avoids a short ramp, which can be more challenging than a level transition. Additionally, insulation should be considered beneath raised slab areas above grade to avoid condensation forming below the floor deck and damaging areas in ceiling or spaces below.

Cold room condenser units can be remotely located on a rooftop or in a mechanical space. This will require longer piping runs from the unit to the environmental room, but the heat load from the condenser usually is less of a problem. Where a condenser is situated directly on top of a cold room (e.g., in the ceiling or interstitial space), local heat exhaust for that unit is recommended to be directly above the condenser and sufficient to remove that heat load. Vibration isolation should be considered to dampen out the vibration of condensing units, which may have a significant effect on tests being performed in a cold room.

Stainless steel benches and shelves, hard polymeric, or suitably sealed natural stone usually work well in cold laboratory environments and are easy to clean. Wood and plastic laminate laboratory furniture should be avoided in cold environments. A wide range of standard finishes and options are available, from which choices can be made based upon compliance requirements. "Deli doors" or double glazed glass doors incorporating heated seals similar to those on the freezer units at supermarkets may be convenient. They can be placed in wall panels for quick access to sample or media storage racks, or equipment carts, to allow access without having to enter a cold room.

Cold laboratories used for bio-molecule analysis, as in the case of the biopharmaceutical industry, should be equipped with temperature monitoring probes linked to an alert system for temperature deviation detection and notification to responsible personnel. Quality control protein and DNA analysis conducted in a cold room can be adversely affected by undetected temperature drifts which are not corrected rapidly. In general, cold rooms and laboratories should be monitored and alarmed as needed.

² Slab is a term used in engineering and architecture for "the concrete floor of a building." The cold room is typically a modular system with insulated panels for the walls, floor, and ceiling that is typically placed on top of the slab. When this approach is used, access to the cold room is made by ramps to account for the elevation from the slab to the floor of the cold room. The slab of a building may be undercut or pocketed so that the floor of the cold room sits within this concrete floor cavity; therefore, eliminating the need for the ramps. The am

3 Laboratory Process and Equipment

3.1 Introduction

Understanding the path that a sample travels, both physically and experimentally, helps to establish a logical workflow. The laboratory design and workflow, along with the placement of equipment and instrumentation, should support easy and clearly defined transitions for samples, from the point of receipt, through testing and data review, to long term storage.

Laboratories may not require all spaces to be physically located within the laboratory (e.g., environmental chambers for stability studies). The layout should be determined on a case-by-case basis.

A list of equipment to be utilized within a laboratory should be developed early so that design considerations are known during the development of the Basis of Design (BOD) and in the detail design.

This Chapter is not intended to provide information covering all possible testing scenarios.

3.2 Areas Supporting General Laboratory Processes and Procedures

A sample entering the laboratory should be taken to a dedicated sample receipt area. Responsibility for the integrity of the sample within the quality laboratory begins at the dedicated sample receipt area. This area should be designed to support clerical items (e.g., labeling materials, computers, and logbooks) needed by laboratory procedures to initiate and assure sample traceability.

As the sample enters the testing phase, auxiliary areas should support the testing process, including:

- Areas for storage of samples
- Areas for sample preparation before testing
- Storage equipment, e.g., refrigerators, freezers, and desiccators
- Workstations for documentation activities

Light-resistant containers may be needed depending on the chemical, physical, and microbiological characteristics of samples. Data and telephone lines for computers and telephones, as well as printers and other office supply equipment should be provided. Ease of access to cable trunking for maintenance and future interfacing should be considered.

Adequate desk and bench space should be provided, allowing the correct use of computers and note books to prevent clutter.

When establishing a laboratory workflow, the location of storage areas should be considered. These areas may be located outside the laboratory footprint because of spatial constraints. As a large volume of material used for microbiological analysis is temperature sensitive, sufficient space in either walk-in refrigerators or several stand-up refrigerators should be provided.

Cabinets (preferably fire-proof) should be provided for the retention of laboratory notebooks, hardcopy data, and electronic data.

Cabinets should be provided for the storage of glassware.

A secure room, refrigerator, freezer, and desiccator should be provided for storage of reference standards.

Storage cabinets for solid reagents, organic liquid solvents, acids, bases, and hazardous waste should be suitably installed and segregated from other areas, and should be conducive to workflow and safety considerations.

For microbiology laboratories, test tubes and large flasks are frequently recycled; requiring washing and autoclaving. Glassware washers and autoclaves should be evaluated for their capacity to handle large volumes and heavy work load schedules to accommodate potentially high demands.

3.3 Functional Area Equipment Allocation

Quality laboratories can serve a variety of functions; common functions include:

- General release testing
- Stability testing
- In-process testing
- Testing requiring sterile conditions
- Microbiological testing
- Testing of potent compounds

Each function will have unique instrumentation needs. Isolation of activities is considered good practice to prevent cross-contamination and optimize workflow.

Table 3.1 provides recommendations for the grouping of instrumentation associated with various types of testing. The groupings are further delineated by the various testing activities (i.e., physical testing, chemical testing, microbiological testing, or sample preparation).

Table 3.1: Example Laboratory Equipment

					Power Requirements					
No.	Equipment	Comments	Space/ Unit	Space Type	Normal	Clean	Gen.	UPS*	UPS Time	Power Load
3.5.1 Chromatography Equipment										
1	High Performance Liquid Chromatography (HPLC)	Includes autosampler, pump, detector, data acquisition device, etc.	10 linear feet (lf)	Bench		x				12 amps/ 110V
2	Gas Chromatograph (GC)	Includes autosampler, gas supply, data acquisition device	14 lf	Bench		x				12 amps/ 110V
3	Ion Chromatograph (IC)	Includes autosampler, data acquisition device, etc.								
4	Thin-layer Chromatography (TLC) Detection Box		2 ft	Bench						12 amps/ 110V
3.5.2 Spectroscopy Equipment										
5	Infrared Spectrophotometer		10 lf	Bench		x		x		10 amps/ 110v
6	Ultraviolet-Visible Spectrophotometer		5 lf	Bench						12 amps/ 110V
7	Near-Infrared Spectrophotometer		4 lf	Bench						15 amps/ 110v
3.5.3 Other Analysis Equipment										
8	Mass Spectrometer	Portable equipment needs gas cylinders and vacuum pump	8 lf	Bench/ Floor		x		s		20 amps/ 220V, 110V
9	Atomic Absorption Spectrophotometer		12 lf	Bench/ Floor						
10	Polarimeter		3 lf	Bench		x				10 amps/ 110V
11	Total Organic Carbon (TOC) Analyzer		5 lf	Bench		x		x	30 min	5 amps/ 110V
12	Autotitrator		3 lf	Bench		x		x	30 min	5 amps/ 110V
13	Karl Fisher (KF) Titrator		3 lf	Bench		x		x	30 min	5 amps/ 110V

Table 3.1: Example Laboratory Equipment (continued)

					Power Requirements					
No.	Equipment	Comments	Space/ Unit	Space Type	Normal	Clean	Gen.	UPS*	UPS Time	Power Load
14	Melting Point Apparatus		1 lf	Bench	x					2 amps/ 110V
15	Viscometer		1.5 lf	Bench	x					110V
16	Moisture Analysis									
17	Sieve Balance		1.5 lf	Bench	x					110V
18	Hardness Tester		2 lf	Bench						
19	Thickness Tester		2 lf	Bench						
20	Disintegration Tester		2 lf	Bench	x					5 amps/ 110V
21	Ro-tap Sieve Shaker		4 lf	Floor	x					110V
22	Tapped Density Tester		1 lf	Bench	x					110V
23	pH Meter		1.5 lf	Bench	x					110V
24	Conductivity Meter		1.5 lf	Bench	x					110V
25	Computrac		3 lf	Bench	x					
26	Friabilator		3 lf	Bench						110V
3.5.4 Dosage Form Specific Equipment										
3.5.4.1 Solid Dose										
27	Dissolution Bath	Includes autosampler	4 lf	Bench		x				15 amps/ 110V
3.5.4.2 Aerosol										
28	Cascade Impactor		4 lf	Bench						110V
29	Dose Delivery Analysis		4 lf	Bench						110V
30	Waste Spray Station		10 lf	Bench						110V
3.5.4.3 Microbiological										
31	Autoclaves	Varies in size, check equip specs	6 lf	Bench/ Floor						110V / 220V
32	Incubators	HEPA filtered	4 lf	Floor	x					30 amps/ 220V
33	Refrigerators-Biosafety		4 lf	Floor	x		x			10 amps/ 110V
34	Laminar Flow Hood		10 lf	Floor	x					5 hp motor
3.5.5 General Laboratory Equipment										
35	Loss on Drying (LOD) Oven		3 lf	Bench	x					

Table 3.1: Example Laboratory Equipment (continued)

					Power Requirements					
No.	Equipment	Comments	Space/ Unit	Space Type	Normal	Clean	Gen.	UPS*	UPS Time	Power Load
36	Vacuum Oven		1.5 lf	Bench	x					20 amps/ 110V
37	Manifold and Vacuum Pump			Bench / Floor	x					5 amps/ 110V
38	Muffle Furnace		1.5 lf	Bench	x					20 amps/ 110V
39	Water/Steam Bath		3 ft.	Bench	x					10 amps/ 110V
40	Desiccator		1 lf	Bench	N/A					
41	Balance – Top Loader		2 lf	Table		x				5 amps/ 110V
42	Balance – Analytical		3 lf	Table		x				5 amps/ 110V
43	Freezer 68°F (20°C)	Available in 110V or 220V	4 lf	Floor	x		x			10 amps/ 110V
44	Refrigerator 39.2°F (4°C)		3 lf	Floor	x		x			10 amps/ 110V
45	Heat Plate Stirrers		2 lf	Bench	x					15 amps/ 110V
46	Shakers		4 lf	Bench	x					2 amps/ 110V
47	Media Mate		4 lf	Floor	x					
48	Sonicator	Samples and mobile phase	4 lf	Bench	x					5 amps/ 110V
49	Centrifuge – Refrigerated Tabletop		2 lf	Bench	x					5 amps/ 110V
50	Centrifuge – Large		3 lf	Floor	x					30 amps/ 220V
51	Glasswasher/Dryer		2 lf	Floor	x					20 amps/ 110V
52	Stability Chambers with Deionized Water (DI) Supply		4 lf	Floor	x		x			30 amps/ 220V
53	Turbidimeter		1.5 lf	Bench	x					110V
54	Microscope		3 lf	Bench	x					110V
55	Fume Hood		4 lf, 6 lf, 8 lf	Bench/ Floor	x					110V/ 220V/ 5 hp motor
56	Glove Box		3 lf	Bench	x		x			110V / 220V

Table 3.1: Example Laboratory Equipment (continued)

					Power Requirements					
No.	Equipment	Comments	Space/ Unit	Space Type	Normal	Clean	Gen.	UPS*	UPS Time	Power Load
57	Safety Equipment	Fire extinguishers, fire blankets, eye-wash								
58	Sterility Test Isolator									
59	Biosafety Cabinet		4 lf, 6 lf	Floor	x					20 amps/ 110V
60	CO ₂ Manifold		3 lf	Floor						
61	-94°F (-70°C) Freezer	Available in 110V or 220V	4 lf	Floor	x					20 amps/ 110V
62	N ₂ Generator		3 lf	Bench	x					3 amps/ 110V
63	Zero Air Generator		3 lf	Bench	x					1 amp/ 110V
64	Hydrogen Generator		3 lf	Bench	x					12 amps/ 110V
65	CO ₂ /N ₂ Incubator		3 lf	Floor	x					7 amps/ 110V
66	Platelet Incubator		4 lf	Bench	x					2 amps/ 110V
67	Isotemp Gravity Convection Oven	Available in 110V or 220V	2 lf	Bench	x					15 amps/ 110V
68	Controller Pump									
69	Transfer Pump									
70	Orbital Shaker Incubator		2 lf	Bench	x					12 amps/ 110V
71	Image Analyzer									

**Note: UPS requirement for instrumentation is dependent on laboratory program.*

Terms and abbreviations used within this table:

Space/Unit: Amount of linear feet allocated to the unit. It is assumed that the unit will fill the entire depth of the bench if a bench-top unit.

Space Type: Location where the unit is operated.

Power Requirements:

Normal: Standard electrical supply.

Clean: Electrical supply that is isolated or otherwise controlled for spikes.

Gen.: Refers to the need for back-up power supplied by an auxiliary source in the event of a power failure.

UPS: Uninterrupted Power Supply.

UPS Time: The amount of time power is supplied by the UPS.

Power Load: Electrical specifications for unit.

Qual. Req.: Qualification requirements.

4 Hazard and Safety

4.1 Introduction

This Chapter addresses requirements for the use, design, and engineering of barrier or isolator technologies in quality laboratories. Functions, design, engineering, and operation of equipment and technologies that are used to protect the health and safety of the operators and the product during its final testing prior to release are considered. The use of the risk assessment (see Chapter 5 of this Guide) assists in determining the need for and type of microenvironment.

Traditionally, operators have been protected using PPE. PPE limited the time that operators could spend in a processing area, and equipment cleaning meant significant downtime. Organizations, such as OSHA, encourage the use of potent compound containment rather than relying on PPE.

Scientists and manufacturing personnel incur increased risks for occupational exposure to compounds during manufacturing and quality testing.

4.2 Occupational Exposure Limits

Understanding OELs is fundamental to the safe handling and storage of compounds. The OEL concept is used to quantify the toxic effects of compounds. It is a measure of the health effects of long-term occupational exposure to a compound. The OEL is the maximum concentration of a chemical (in air) to which personnel may be exposed for an eight hour work day, over a 40 hour work week, over a 40 year lifespan, resulting in no measurable adverse health effects.

The process of developing these limits for Active Pharmaceutical Ingredients (APIs) includes:

- Gathering data on the API and review its mechanism of activity
- Determining if the OEL can be established by analyzing the potential for primary carcinogenic effect
- Identifying risk factors
- Reviewing dosage range and mode of administration
- Classifying the API based on American Industrial Hygiene Association "Performance-Based Occupational Exposure Limits" [16]

For each substance and compound to be worked with in a quality laboratory, understanding the short and long-term exposure limits and hazards helps in the selection of the appropriate measures to be taken to minimize the possibility of exposure. Considerations include:

1. Acute versus chronic exposure:
 - A single brief exposure
 - Repeated long-term exposure over time
2. Route of exposure:
 - Ingestion

- Inhalation
 - Absorption
 - Injection
3. Physical properties of the compound:
- Controlling fumes
 - Controlling particles
 - Controlling oxygen access
 - Controlling humidity
 - Controlling temperature
4. Nature of hazard:
- Does the compound affect the cardiovascular system?
 - Does the compound affect the central nervous system?
 - What are the appropriate first aid measures?
 - Are the symptoms or injuries permanent or temporary?
5. In-use:
- Open system
 - Closed system
6. In storage:
- How will the compounds be manipulated?
 - In what quantities?
7. Material and personnel flow:
- Where are the compounds delivered?
 - types of containers/packaging
 - method of disposal
8. What is the laboratory process flow:
- Can handling and transport of the materials be minimized?
9. Gowning and PPE

10. Equipment cleaning

Considerations for containment include:

- Separating personnel and material via directional airflow
- Providing decontamination showers or misters in personnel airlocks
- Evaluating paperless technologies
- Monitoring environmental conditions:
 - RH
 - Temperature
 - Pressure/directional airflow
- HEPA air filtration on supply and exhaust
- Maintaining the appropriate air change rates
- HEPA filter replacement technologies designed to protect the maintenance staff as well as the environment
- Containment and management of effluent
- Ensuring ergonomic issues are closely considered

The Environmental, Health, and Safety (EHS) Department or Safety Officer should assess risks to employees. It is considered good practice that an Environmental Engineer and/or Chemical Engineer provide substance classifications and a Hazardous Materials Master Plan along with a chemical summary list. This information is used by the laboratory staff to determine SOPs and by the facility design team to ensure that the room classification is correct with respect to building codes and systems design.

The goal is to ensure that adequate and correct information is gathered and ready for use before the laboratory is designed, constructed, and occupied. This includes Material Safety Data Sheets (MSDSs), hazardous material reports and all pertinent regional and industry guidelines and regulations applicable to the design and/or use of the laboratory. Once the answers to these questions are analyzed, proper equipment and systems can be established.

4.2.1 *Isolators*

Isolator technologies come in a variety of designs. Their primary function is to create microenvironments that contain or protect products and maintain the health and safety of the operators. Detailed design guidance and recommendations are given based on the type of microenvironment necessary. Additional factors to consider prior to the selection of a specific technology include:

- Risk assessment
- Schedule
- Budget
- Reliability

- Availability
- Flexibility

Isolator systems can be used for aseptic processing activities or containment of potent compounds or simultaneously for both asepsis and containment. Open isolators (aseptic isolators) use positive airflow and allow for continuous or semi-continuous ingress/egress of materials, while maintaining a level of protection over the internal environment. Closed isolators (containment isolators) use negative pressure, and are capable of levels of separation between the internal and external environment.

An understanding of the laboratory macro-environment and in particular, the HVAC system, is critical in the selection of the micro-environmental technology. In addition, familiarity with regulations concerning the specific hazardous compounds being used is assumed, including:

- BMBL for biological hazards [17]
- NFPA for chemical hazards [18]
- NRC for radiological hazards [19]
- USDA for agricultural hazards [20]

Integral isolator systems associated with particulate-generating steps, such as fill, tablet, and mixing systems, avoiding the challenge of structural, ergonomic, access, MEP, and service integration involved with mating unrelated systems. Such systems require intense cooperation between multiple vendors to provide an integrated system.

Powder containment rooms offer alternatives to isolator systems. These rooms act much like biological safety cabinets, drawing room air over the process zone and away from workers and deliver the air back to the room generally requiring an inflow of fresh air around 10% of the system airflow to help control the airflow direction.

Regardless of the engineered control that is chosen to minimize exposure, every technology needs proper implementation and training.

Similar to production facilities, the primary and (if necessary) secondary means of containment or isolation can be determined. The following are exposure control elements that can be considered in designing quality laboratories:

1. Fume hood or Class III safety cabinets deemed adequate given the nature and severity of the hazard
2. Isolators with glove ports
3. Docking ports installed at these isolators so that protective outer packaging can be removed before use within the protective environment
4. Breathing air as back-up precaution to primary containment
5. Toxic or potent compound put into solution may be safe to handle outside a Class III safety cabinet or isolator
6. Exhaust stream from the hoods and isolators, and perhaps the room may require treatment before release:
 - Fumes may require chemical adsorption media, carbon, or water filtration.
 - Particulates may have to be removed by filtration.

7. Recessed ceiling sprinkler heads used to minimize dust and microbial accumulation in BSL and bio-clean room facilities. It also maximizes the ease to apply surface disinfection or sanitization solutions by a mop or sponge application.
8. Once the isolator or hood is used – how will it be cleaned?
9. What is the nature of the laboratory waste and how will it be collected and/or disposed of?
10. If the laboratory is the means of containment, is an airlock or gowning/degowning vestibule needed?
11. Room pressurization levels and airflow requirements should be established.
12. In the event that there is an exposure:
 - What will you do?
 - What procedures and response measures are in place?
13. As with all spaces, appropriate signage should be in place to identify the hazards present.
14. When there may be a conflict between GLP/GMP requirements and safety requirements – both GxP and safety requirements should be considered.
15. What would be the impact of equipment failure?

4.2.2 Pressurization for Barrier or Containment

The need to provide a contained environment is the key reason to consider isolator technology. The techniques for creating a contained environment within an isolator is similar to those used for facilities although the air quantities are generally smaller and can be controlled at greater precision at a lower cost.

Barrier systems may be designed as positive pressure: to protect the product, or negative pressure: to protect the operator. The pressure in the local environment can similarly be surrounded by positive pressure as a means of providing isolation.

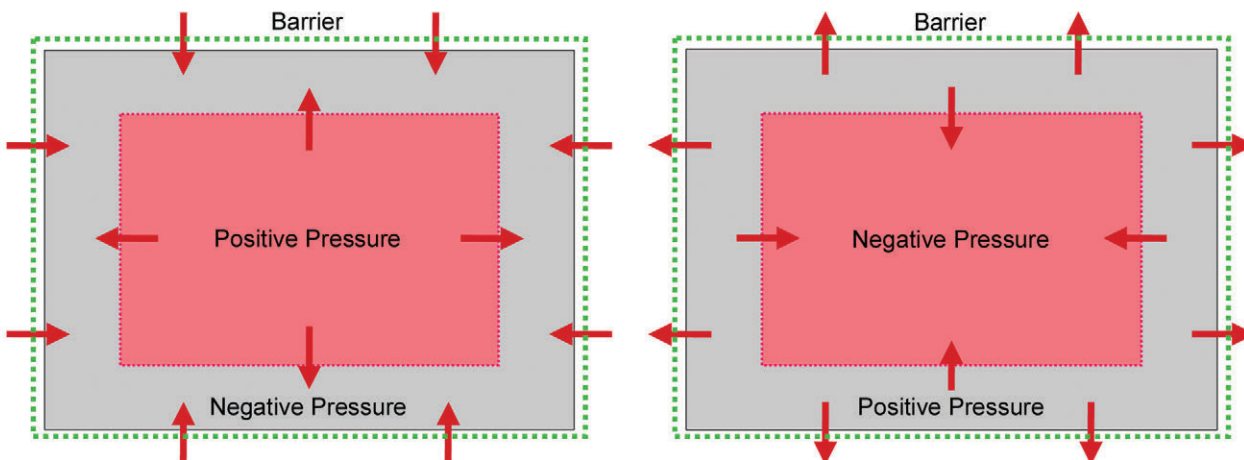
The design should consider the primary objective and design the area pressurization accordingly, see Chapter 8 of this Guide on HVAC.

This technique is useful for handling processes that are designed to protect product or process from contamination from personnel or ambient conditions. Typical applications would include:

- Aseptic processing
- Tissue and cell culture
- Filling and capping operations
- Some packaging applications

In selecting or designing an isolator application, it is important to determine whether a barrier, containment, or combination environment is needed. Different configurations are specified according to the application.

Figure 4.1



4.2.3 Highly Potent and Highly Toxic Compounds

Genetics and biochemistry promise new generations of small-molecule and protein products, gene therapies, viral vectors, personalized targeted solutions, and more complex delivery and dosage forms. Several of the APIs in newly-developed therapeutic agents for treating cancer and other chronic diseases are so potent that they are formulated in microgram doses.

Organizations define their primary segregation objectives, understand which ones are absolutely essential, and then interpret secondary segregation. Risks involved are looked at in at least two perspectives – regulatory risk and business risk. Regulatory risk addresses issues of contamination, cross contamination, and mix-up, whereas business risk addresses operator safety, deflagration, and loss of production.

Controlling contamination needs the dynamics of handling the product to change, as the handling of the tablets can create enough particulate to breach the airborne threshold level. Sample preparation where the potent compound is subdivided and solutions are prepared for testing is the operation with the highest risk, as these steps involve open containers and manual manipulation of the form.

4.2.4 Biohazard Laboratories

Biohazard laboratories are classified by the NIH/CDC Guidelines [10] as Biological Safety Level (BSL) 1, 2, 3, and 4. Only the first three are applicable to biological manufacturing facilities, and hence to their quality laboratories. General laboratory design and practice guides are outlined and discussed in detail in the NIH Design Policy and Guidelines for Research Laboratories, and in the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL) [17] available on the NIH and CDC websites. Refer also to the ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities [12]. Similar guidelines apply to EU member states. Additional guidelines apply to operations involving oncogenic viruses (National Cancer Institute) [13]. For further information on BSL-2 and BSL-3 laboratories, see Chapter 2 of this Guide.

In most cases, the dual objectives of personnel and product protection can be met by carrying out “open” processes in appropriately designed and installed BSCs. In specific cases, additional measures such as air lock entry, decontamination equipment, and specialized HVAC design are needed. Barrier isolators/glove-boxes/Class III BSCs should be considered. Refer to NSF/ANSI 49-2011 [14] or local equivalent which governs the classification and testing of BSCs.

4.2.5 *Physical Hazards*

Some chemicals, gasses, and support systems present physical hazards that should be addressed in the scope development and design phase of the project. Internal storage of pressurized or liquefied gases also present potential asphyxiation risks. Prevention and/or detection should be considered during risk assessment. In some cases, the chemicals and gasses can create explosion hazards if not properly handled and stored. If addressed early on, systems can be engineered to minimize the impact on the facility and personnel.

Building regulations are generally primarily concerned with fire. Flammable substances, oxidizers, and organic peroxides present additional risks that require management.

The International Fire Code (IFC) [21] designates the use as an IFC category H3 for flammable liquids, oxidizers, and organic peroxides that pose a physical hazard. Flammable liquids used in open containers or with very low flash points ($< 73^{\circ}\text{F}/< 22.8^{\circ}\text{C}$) and boiling points ($< 100^{\circ}\text{F}/< 37.8^{\circ}\text{C}$) are considered a deflagration hazard, H2.

The EHS Department, Safety Officer, Environmental/Chemical Engineering team should be involved in establishing the nature and severity of the hazard present based upon each chemical, compound, and gas to be used. For further information regarding highly potent and highly toxic compounds, see Chapter 4 of this Guide. A study of the solvent loading, storage, and use on the testing floor needs to be conducted to determine the loading and subdivision of the laboratory to meet fire codes as well as to have adequate storage facilities for back up supply as well as waste. The emergence of the International Building Code (IBC) [22] has allowed a more consistent analysis of hazards from jurisdiction to jurisdiction. The IBC establishes building uses that affect construction type and allowable building height and area. The use of toxic and flammable substances is more fully addressed in the companion International Fire Code. However, many jurisdictions or state fire marshal's offices may choose the National Fire Protection Association's reference code 1 (NFPA 1: Fire Code) [23].

A careful analysis of the use of the chemicals in a facility may allow keeping them below exempt amounts allowed by the code. The definition of the areas where exempt amounts are stored or used is defined as a control area. Amounts of toxic and highly toxic materials may be large, requiring the definition of the facility as H4. However, flammable liquids may be used in small amounts for cleaning, dryers, and instrumentation. For further information see the International Building Code (IBC) [22].

A differentiation between explosion and deflagration is important because the code addresses each differently. A deflagration is rapid oxidation and moves at a subsonic speed. Non-exempt amounts should be placed in an H2 use. An explosion or detonation moves at a supersonic speed. Non-exempt amounts should be placed in a H1 use area. This has important considerations for the building design because the subsonic deflagration can be vented. H2 uses require deflagration analysis; venting that release deflagration pressures, and interior walls that resist the deflagration pressures. The IBC allows a pressure resistance of up to 216 psf (1.5 psi) for these interior walls which pose a structural challenge with expensive solutions. H1 uses are rare and strong consideration should be made to store and use these materials in a separate facility.

A control area can be an entire building, a floor or any demarcation desired by the designer; depending on the amounts of exempt materials. The areas designated should be defined by rated construction. Usually the fire barrier is rated one hour; on the fourth level and above this rating becomes two hours. In addition, only four control areas are allowed per the first floor, this number diminishing as the height of the level increases.

Note: the floor of a control area usually needs a two hour floor (see the International Building Code (IBC) [22]. Establishing a suitable building use needs proper definition of the hazard in order to assure a safe and cost effective solution. Wherever possible, laboratories are designed as a non-hazardous occupancy classification to avoid additional building code restrictions and requirements. The code assigns toxic and highly toxic materials to a Hazard Level H4 for materials that pose a health hazard. The IBC definitions of toxic and highly toxic may be considered simple when compared to the exposure control bands typical to a pharmaceutical facility. However, the IBC code does not impose a penalty on construction type for toxic and highly toxic H4 uses. H4 has allowable heights and areas similar to F-1 Moderate Hazard Industrial, or S-1 Moderate-Hazard Storage uses depending on the construction type.

Chemicals such as isopropyl alcohol (IPA) or toluene and other organic solvents present a unique challenge as their vapors are heavier than air. These fumes can roll down a work surface and accumulate at the floor level. Room exhaust should be placed low in the room at floor level to prevent vapor accumulation, and electrical outlets, switches, motors, lighting, and fixtures should be explosion-proof to avoid being a potential source of ignition. Sources of heat are kept away from these chemicals. Standard operating procedure in a quality laboratory that handles these types of substances should require that they are handled in the fume hood. Where large quantities are to be mixed, stored, and dispensed for general use such as the pre mixed mobile phase for HPLC analysis, design this area to have the appropriate safeguards for mixing, storing, and dispensing.

Hydrogen gas also presents an explosion hazard. As much as possible, this gas should be used in as small a quantity as practical and in a closed system, or within a hood to contain the gas. Hydrogen in the quality laboratory is likely used for flame ionization detectors for GCs. The hydrogen is usually supplied from a cylinder inside a cylinder cabinet designed for this gas located adjacent to the instrument. Alternately, hydrogen generators may be used, directly piped to the instrument with an automatic shutoff in case of a leak. Hydrogen sensors connected to an alarm system can be placed within the room to detect rising levels of hydrogen gas.

Some flammable/combustible chemicals are not extinguished, but rather spread or are actually ignited by sprinkler water. Should materials of this type be used in a laboratory, active wet sprinklers should be avoided. An alternative type of automatic fire suppression system should be provided- such as a dry chemical or gaseous suppression. Foam or other types of extinguishers also may be provided within the room. Fire Department officials and/or the Local Fire Marshal should be involved in the discussions regarding what types of systems to employ as well as response measures to be taken in the event of an accident. Risk assessments should address the specific hazards and risks of the materials, use, and operations. The information from the risk assessment should be used in determining the appropriate fire protection and prevention methods. Local codes and authorities having jurisdiction also will influence the design criteria.

Personnel with pacemakers should be careful not to enter Nuclear Magnetic Resonance (NMR) suites where they might enter the equipment's magnetic field or gauss line limits. Non-ferrous material also should be employed as much as possible in proximity to this equipment. Signs, SOPs, and proper training should be used to educate and inform personnel regarding the hazards specific to NMR equipment.

Exposure to radiation is another hazard. Low level radioisotopes should be relegated to alcoves or isolation laboratories – certain materials should only be handled in radioisotope hoods. Other types of equipment, such as some X-ray units may require lead linings behind drywall or shielding within the room.

4.2.6 Signage

Signage at the entrance and within the laboratory should alert personnel to the potential hazards within a laboratory. This is important both to scientific personnel and to maintenance and outside support personnel.

5 Risk Assessment

5.1 Introduction

The purpose of quality testing is to assure manufactured products meet the identity, strength, purity, and safety as specified in an approved regulatory file. Testing also is performed in a quality laboratory to establish the stability baseline of materials and products, for initial material release, for in-process verifications, and to investigate product complaints.

Typically, when a quality test fails, i.e., the product fails to meet specifications, the material should be quarantined, rejected, or subjected to further test procedures or rework. Conversely, risk to patient safety may exist when a test function fails to detect an Out of Specification (OOS) product. This type of failure may be derived from laboratory conditions or because of a support system malfunction.

Regulatory initiatives and guidelines emphasize the principles of risk management and the application of these techniques to pharmaceutical facility inspections and submission review. For a laboratory and its associated utilities and support systems, a documented risk assessment can identify those areas or systems having an impact on product quality and quality control functions, and provide a rationale for commissioning, verification, and qualification decisions.

The ASTM Standard E2500 [24] and the ISPE Baseline® Guide on Commissioning and Qualification [25], promote the application of risk-based assessments to determine the impact or risk of a given system on product quality. Assessments can be used to determine a qualification plan for any applicable systems.

Note: a quality laboratory verifies product quality and typically, does not affect product quality. The criteria for determining system impact and component criticality as defined by the ISPE Baseline® Guide on Commissioning and Qualification [25] cannot be directly applied to a quality laboratory.

A risk assessment should be employed to develop appropriate criteria for determining system impact and component criticality for a quality laboratory project. Additional guidance on determining impact criteria can be found in the ISPE GAMP Good Practice Guide: Validation of Computerized Laboratory Systems [26]. However, this GAMP guidance focuses primarily on the impact to data quality and integrity.

Guidance is provided on how to apply a risk assessment to a quality laboratory facility and identify issues to be considered when conducting the risk assessment. A risk assessment is an element of an overall risk management strategy. Risk management allows a consistent and science-based approach to decision making, across the life cycle of a product or project. For further information on how to conduct and document a risk assessment, see ICH Q9 [27].

Risk assessments should be performed prior to, or during, the detailed design stage for a new or renovated facility as part of the enhanced design review or at design qualification, see the Baseline® Guide on Commissioning and Qualification. [25]

Using requirements and design documentation, a review of the intended purpose of a laboratory area or the type of testing to be performed in a laboratory area may identify potential risks inherent in the design. For example, a test area may not be adequately segregated from manufacturing or sample receiving to prevent cross contamination. An assessment also may reveal that a laboratory space is insufficient for the planned storage or staging of samples and reagents for testing, potentially leading to inadequate storage conditions or mix up. While in the design phase, appropriate mitigation of the identified risks can be made; therefore preventing the potential for quality issues. When employed early in a project, risk mitigation through design changes can be more cost effective and have less impact on project schedules.

The criteria used to assess risk and the risk assessment itself should be documented. This provides a traceable rationale for both design qualification, where needed, and the development of impact assessment criteria and the verification strategy for a project.

5.2 Regulatory Review

A review of regulatory guidance documents for requirements of laboratory systems is as follows:

- CFR Section 211.160 [3] states that “The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.”
- The current good laboratory practice regulations, 21 CFR Part 58.61 [28] impose similar requirements stating that “equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and standardized.”
- EudraLex Volume 4 – Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use (2008 Edition) [5] states that “Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.”
- ICH Q9 – Quality Risk Management [27]. This document contains a systematic approach to quality risk management, including risk assessment. ICH Q9 is a guidance document meant to help the industry. It is recommended that ICH Q9 be consulted prior to determining any laboratory risk assessment strategy.

5.3 Assessing Risk

A risk assessment has been defined as a “methodology, conducted during the scope and design development of the facility, to determine, analyze, and manage potential risks to product quality in the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment [29]. For the quality laboratory facility, this definition can be extended to include the potential risks to corporate reputation and profits and also the potential risks to personnel or sample safety. While these are not considered to be regulatory risks, they are still risks to consider when determining the verification strategy. To accurately perform a risk assessment for the quality laboratory, there should be an understanding of the purpose of these facilities and the functions contained within.

There are many different types of samples which can be sent to a quality laboratory for many different types of testing. The types of samples and testing which are expected in a given laboratory facility should be understood in detail, prior to conducting the risk assessment.

A risk assessment of the intended use and function of a laboratory, utility, or support system should determine potential risk to a quality function or outcome, which could result in the erroneous generation of an OOS test result or release of an OOS product.

To arrive at meaningful conclusions, the assessment procedure needs a thorough understanding and review of what can fail, the consequences of that failure or subsequent failures on the QC function, and an analysis of the control systems or procedures in place that will detect or prevent the failure. For example, the risk associated with loss of power should be considered. Many different areas of a laboratory facility could be affected or compromised in the event of a power failure. Potential risks, such as loss of HVAC in controlled areas, affects on analytical equipment related to power loss and restart, restricted electronic security access, sample, or personnel safety related to specialty containment systems, should be understood. Identification of these types of risks will help in the planning for backup and emergency power and also will help to determine the level of testing needed for such systems.

It is not the intent of this Guide to define how to conduct a risk assessment or which risk assessment method to use as there is a lot of guidance already in existence; however, an example of an FMEA approach is provided.

In FMEA, each risk has two primary elements, the probability of a given failure occurring, and the severity of the failure if it occurs; these two elements together define each risk. In addition, it may be beneficial to include the ability to detect the risk or hazard. Typically, all three elements are used in the quantitative analysis of risk. Quantitative risk may be referred to as the Risk Priority Number (RPN).

RPN = Probability × Severity × Detectability

Before performing a risk assessment, the organization should establish criteria for assessing the risk, including what level of risk is acceptable, and what level of risk needs remediation or mitigation actions. The level at which risk becomes unacceptable to the organization may be defined by RPN. It is important to note there is no industry or regulatory standards defining the acceptability levels for risk. Organizations should define a scale and acceptable ranges. The rationale for defining the acceptability of risk should be documented. The risk assessment can be used as an impact assessment to determine the degree of testing for the laboratory systems, including how the system should be verified.

High risk systems are usually those which come in contact with the samples and can affect test or data validity.

Medium risk systems are usually those which are not expected to have a direct impact on samples or affect test/data validity, but typically will support a high risk system.

Low or no risk systems are those which support the facility, but are not expected to have any impact on samples or affect test/data validity. For further information on how to develop an appropriate verification strategy, based on the results of the risk assessment, see Chapter 11 of this Guide.

User requirements should be defined for the facility infrastructure and systems, and for each type of laboratory functionality that will be contained within the facility (e.g., analytical testing, microbiological testing, or stability studies) in order to conduct an assessment. Organizations should determine a standard for creation of user requirements. User requirements may be generated on a system by system basis or captured in more general terms for an entire facility. After systems have been classified, it may be prudent to revisit the user requirements for high risk systems with more detail added as appropriate.

Questions to be asked in determining user requirements may include:

- What functions will occur in each laboratory space?
- Are there regulatory requirements governing any of these functions?
- What are the types and volumes of samples expected?
- What equipment will be located in the area and how will its operation affect the laboratory environment?
- Does the system produce data evaluated to accept or reject product?
- Does the system produce in-process data evaluated to move from step to step in the manufacturing process?
- Does the system produce data evaluated to establish regulatory stability?
- What are the expected uses of, and the associated criticality of, the utility or support systems?
- What protective devices are necessary for product protection?

- What protective devices are necessary for personnel protection?

User requirements should be used as the basis for facility design and for assessing the verification requirements of the facility, utilities, and equipment. Depending on the system or functionality being evaluated, these user requirements can originate from scientific, quality, engineering, maintenance, automation, or information technology functions. User requirements should capture all regulatory requirements for systems and functions, as well as operating, safety and equipment parameters, and maintenance requirements.

It is important to remember that this Guide focuses on the utilities and equipment related to the laboratory facility. While a risk assessment also may be useful for determining the verification strategy for laboratory equipment and instrumentation, it is outside the scope of this Guide.

Once user requirements are defined and a preliminary design of all systems has occurred, each system should be individually and collectively evaluated for risk. Regulatory and business risks, as well as safety risks should be considered. While business and safety risks do not require verification, they can be important risks to be assessed as part of the laboratory project.

Risk assessment is not a onetime activity. When there is a change to either the user requirements or the design, the risk should be re-assessed with respect to the change to ensure that the verification strategy is still appropriate.

Risk assessment, risk management, and quality control principles are applied in all industries to improve efficiencies, increase reliability, comply with applicable regulations, reduce costs, and improve safety. For further information on the commissioning and qualification process for quality laboratories and the types of activities and deliverables to consider when developing a verification strategy, see Chapter 11 of this Guide.

6 The Project Execution

6.1 The Laboratory Design Process

Quality laboratories are an integral part of the pharmaceutical manufacturing process. Responsibilities range from establishing product stability to testing of the incoming packaging components, raw materials, and providing final product release. Quality laboratories establish and confirm that all components supporting the product meet specifications, assuring safety to patients.

Laboratory design involves:

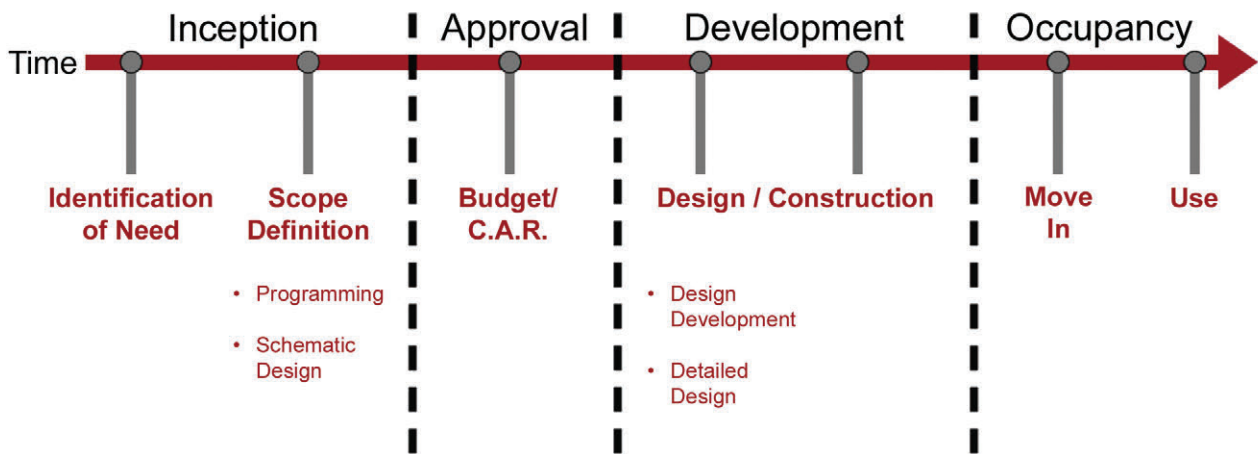
- The formation of teams to conduct the process
- The implementation of project management tools, including scheduling, budget management, management of the project scope and client expectations, and change management
- A knowledge of the stages of design and the evolving definition of the facility
- The understanding of the basics of architectural design for a regulated environment
- An understanding of the basics of laboratory layout and functionality
- An understanding of the process of quality control and stability testing

As with the manufacturing process, the design of laboratories needs an understanding of and attention to the protection needed for both the product and the personnel.

The laboratory design process provides the mechanism for designing a new laboratory or renovating an existing laboratory. The design phase of a project is where the team members execute their responsibility to effectively influence and determine the outcome of that project. User representatives should share their unique vision of their laboratory with the design consultant. The programming process should identify clearly the purpose and scope of a project. Detailed design should further define and refine building layouts. The result of these efforts is a common understanding of the facility and the establishment of a collaborative working relationship for the duration of the project.

Figure 6.1 shows the major stages of a facilities project. Once the facility need has been identified, the scope for the facility can be defined. For quality laboratories, this defines the services to be provided and the activities necessary to perform those services. For example, a small API manufacturing site may require only a few laboratories for raw materials, in-process, and API testing. Alternatively, a larger site could include all these activities plus product testing, package/component testing, and stability testing.

Figure 6.1: Major Project Stages



6.1.1 Programming

Programming (also called concept development) encompasses the series of activities that lead to the determination of the scope and design criteria for a facility. It is the foundation of a project and is the information gathering stage where client groups should be interviewed, industry standards discussed, and specific laboratory layout requirements determined. Programming is the first opportunity for the owner's representatives as team members to share their vision with the design team leader and other project team members. User requirements should be defined during programming.

Scheduled team meetings should be arranged, in which input is presented from quality personnel and various support groups, including:

- Quality Operations
- Site EHS
- Regulatory and Analytical Sciences
- Facility and Utilities Services
- Information Systems
- Operational Services
- Financial Services
- LIMS and Automation

6.1.2 Schematic Design

Schematic design defines an overall plan for a laboratory facility. Information should be compiled for individual laboratory layouts, their adjacencies to support, office and public spaces, corridors, materials, and personnel flows. The engineering efforts at this stage focus on general utility distributions and the definition of unique utility requirements. At the conclusion of programming and schematic design, the design team should have adequate information to:

- Describe the proposed laboratory facility in text and with floor plans

- Diagram personnel and materials flows
- Forecast a project schedule
- Determine a project order of magnitude cost
- Provide to management the first-pass cost analysis, the project scope associated with this cost analysis, and sufficient documentation to set the stage for agreement and concurrence

The programming process allows the design team to document the room requirements in the form of room data sheets. The room data sheet is a tool that documents the requirements of each space planned for the laboratory facility. It also explains the need for the space provided and defines the specific area under consideration as well as its size. It identifies:

- The equipment and furnishings to be installed along with the electrical, mechanical, and plumbing needs
- The details for scientist and product protection
- Materials of construction and finishes
- Ventilation requirements
- Lighting requirements and power conditions
- Temperature and humidity requirements for product considerations as well as personal comfort
- Communication and data requirements
- Special condition needs for the defined space such as fume hoods, solvent storage space ventilation, showers and eye washes, and containment devices
- Signage

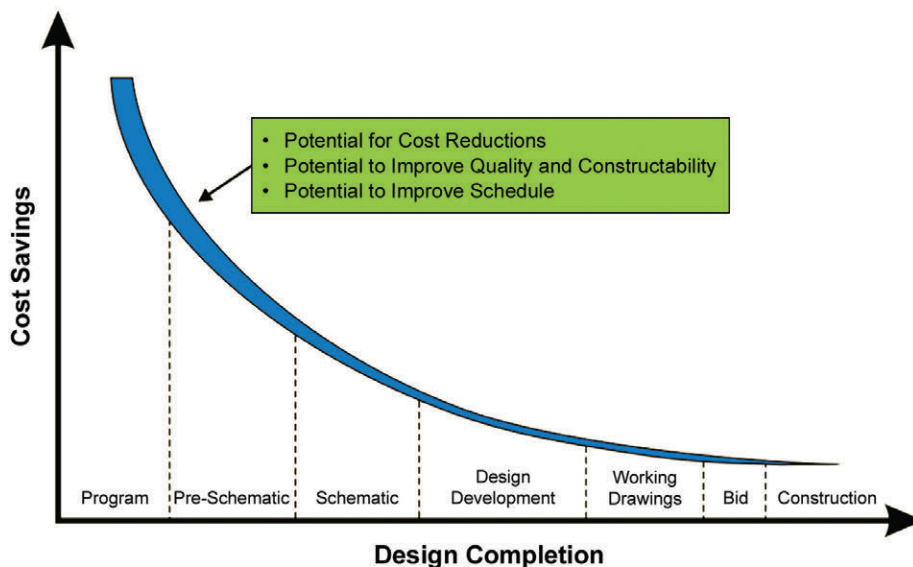
The room data sheets detail spaces for all elements of the developed scope of work supporting the recommended floor plan. Using these sheets, the design team should have an understanding of the appropriate scope and space requirements including the specific procedures being performed in each of the defined spaces. The room data sheets, along with the written scope of work, should be submitted to the client team for review and approval.

Programming through schematic design is the process of developing the Basis of Design (BOD). It is an iterative process, gathering information that is restated in descriptive terms, giving the client a document that can be easily read, revised if necessary, and approved. This document summarizes the concepts, technical criteria, and performance criteria for the laboratory under consideration. With the programming phase completed, the project team has the basis to secure end user concurrence. Management approval of the BOD gives the team permission to proceed to detailed design. The approved BOD is the document of reference for the duration of the project. At this stage, the approved scope should be frozen in order to limit future changes and control project cost.

6.1.3 Change Management

Change management is important throughout a facilities project. Project change may be controlled using a well-defined BOD. Figure 6.2 (and later in Section 6.8 (Figure 6.6)) shows a graph which emphasizes the fact that changes to the project are most effective when they occur in the early stages of programming and design development. As the project proceeds, design nears completion and construction elements are in place, a change can have a significant and negative effect on cost and time to completion. An extended time to completion can have a significant effect on the corporation if the new laboratory space is needed in support of increased requirements due to a new product introduction.

Figure 6.2: Cost Savings vs. Design Completion



6.1.4 Design Development

Design development provides the detailing for all spaces, including utility locations, selection of laboratory furniture elements, and utility distributions throughout the building. Significant client interaction is desirable during this stage to assure that laboratory utilities are provided in sufficient quantity and at the correct locations for the laboratories to productively support the intended operations.

Detailed design leads to the compilation of construction documents; those that are used to build the facility.

6.2 The Project Team

The project team should include:

- Representatives from the quality department(s): to provide access to quality management and scientific functions for the determination of scope and functionality issues. They are ultimately responsible for the creation of a facility that meets the needs of the quality function. The nomination of one individual to be the focus for communication with the client quality department has proven to be very beneficial to the success of the project.
- Representatives from site-related functions: Environmental, Health, and Safety (EHS), facilities, information systems, maintenance and engineering and automation
- Representatives from the compliance group
- Representatives from the group responsible for validation
- A project manager: this person has the responsibility for managing the project, including fiduciary responsibility to the organization for management of the assigned funding for the project.
- Representatives from the architectural and engineering firm(s) responsible for the design
- Representatives from the construction management or general contractor who will build the facility

Individuals from each of these groups should have specific assignments with clearly defined responsibilities.

Strategic individuals participate in the entire process. Other individuals participate on an as-needed basis when the design process is concentrating on a specific area requiring a special discipline. The project team should be empowered with establishing the execution strategy along with the decisions needed to reach consensus. They should have decision-making authority for the process along with conflict resolution responsibilities.

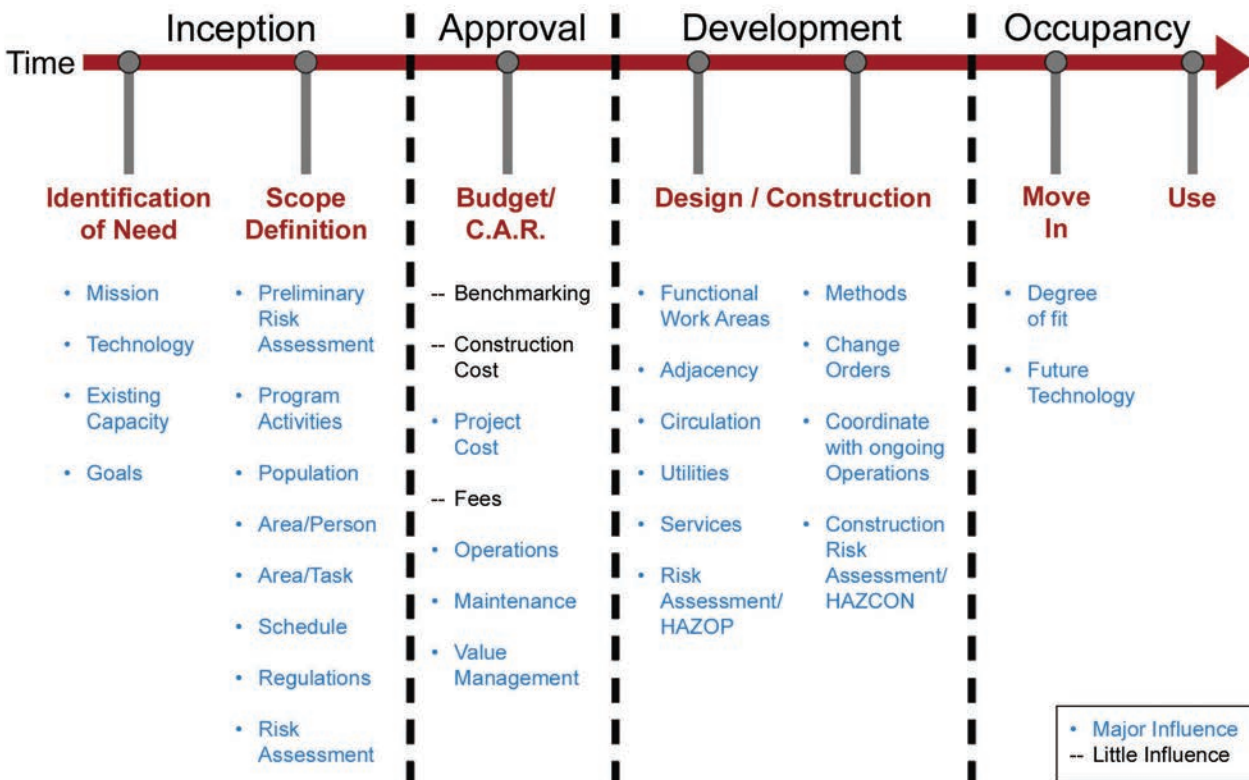
For every facility project, there are two clients:

- Those who work in the facility – the scientists, technicians, and their management
- Those who work on the facility – EHS, site facilities management, information systems, maintenance and engineering, automation

These individuals will interact with the facility for many years. Figure 6.3 depicts (with bullets) the extent of these client impacts. The success of a facility may be determined by their collaboration during the design. Their participation should be empowered by their respective management and should be considered as an important part of their overall job responsibilities.

Involvement of the constructor (construction management firm or general contractor) is important during the design. These professionals will review the evolving design and make comments on constructability issues as well as offering advice concerning less costly ways of building the project. As shown in Figure 6.2, the earlier constructability issues are identified, the more positive the impact on project schedule and budget.

Figure 6.3: Project Information Milestones with Client Impacts



6.2.1 The Programmer

The programmer (usually a designated individual from the architectural firm) should employ varied tools along with proven techniques to develop a detailed description of the project.

To achieve an acceptable program (or conceptual design) that will continue for the life of the project, the programmer should gather information through a series of interviews. The programmer's task is to facilitate the documentation of the vision, needs, objectives, and goals of the various participants. Design information should be verified to define the scope of work, while minimizing and eliminating assumptions. This input should uncover the possibilities, opportunities, and potential alternatives leading to the proposed design solution. This gathering of suitably defined design information and its documentation should guide the design development team throughout the project. The programmer's leadership, organizational skills, and laboratory design experience should give the client assurance that the design team will understand the needs, goals, and expectations of the project.

The design process should seek to balance the ideal against the practical, i.e., what is needed in the design and what design aspects would be "nice to have." The programmer should provide information and guidance so the client can make any difficult choices. The programmer should offer advice as to what works and more importantly, what does not work.

The end result should be an agreed-upon document that summarizes the facility needs, performance, area layouts, and vision of the project that serves as the foundation for the design development and construction execution phases. The importance of a thorough and descriptive laboratory program is highlighted by the broad-based use of this document and the need to have it focused and well defined. The program document is a compilation of user requirements and a presentation of the conceptual design.

6.2.2 Communication

Communication is fundamental to the collaboration necessary for the successful completion of a facility project. By experience, each team member will have a different professional vocabulary, separate and different from the project vocabulary. It is important for all team members to "speak the same language." Thus, some corporations mandate a team-building session before starting a project. These exercises can be helpful in getting team members to learn how to communicate with each other. Collaboration is dependent on the communication between team members. The project manager has the responsibility to assure proper and sufficient communication during the project.

Some teams create a list of basic rules of conduct that is useful for assuring smooth operations throughout the project. An established communications protocol between the design team, the owner, client, and the constructor can be helpful to overall project conduct and control.

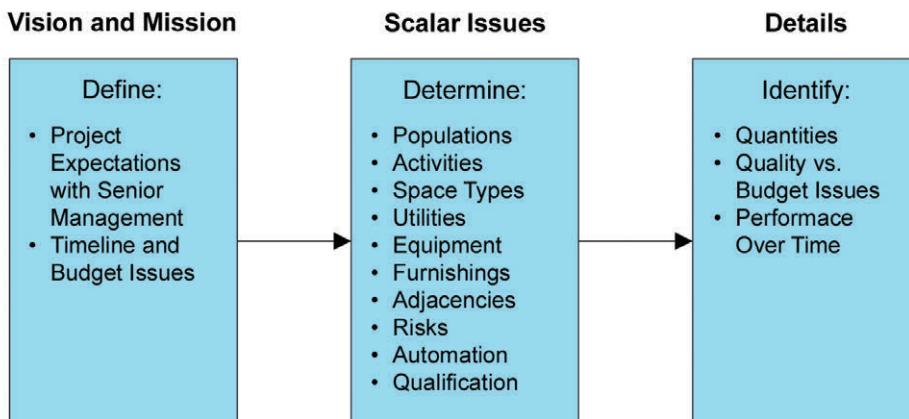
6.3 The Basis of Design

The primary goals of laboratory design include:

- Foster the best science
- Encourage and maintain safety
- Plan the layout for dynamic activities
- Create the ability to manage change easily
- Design for flexibility and growth

Figure 6.4 shows that facility design seeks to translate a management vision into documentation that closely captures the details necessary to create a building that manifests that vision.

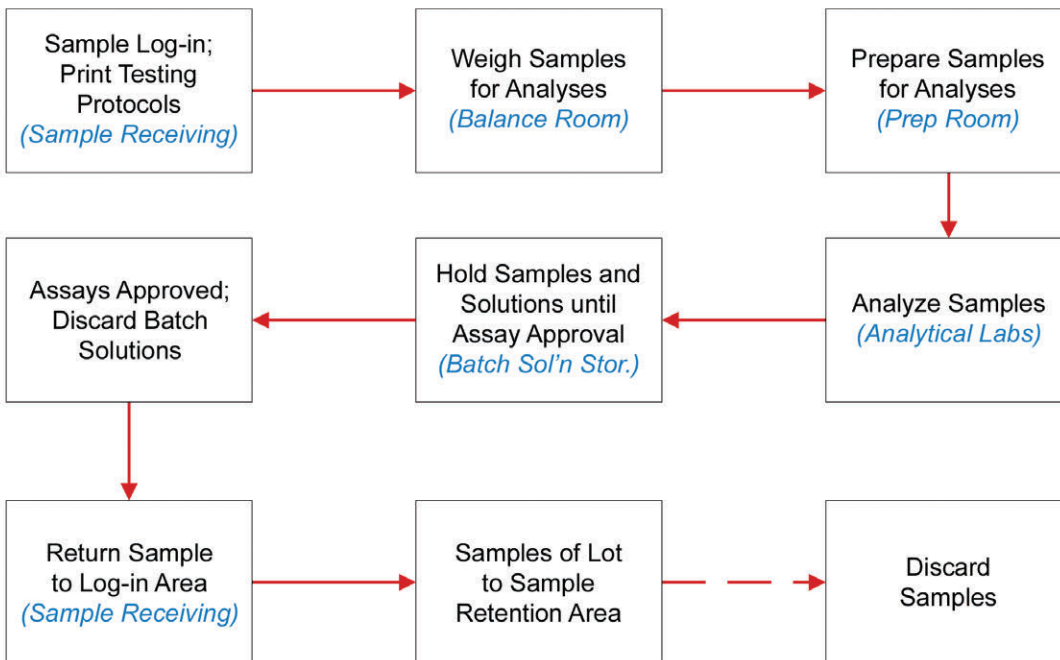
Figure 6.4: Vision to Design Details



This emphasizes the importance of the interaction of the project manager and designers with the management that sponsors the facility design. Successful designs may have the assignment of a client spokesperson as the principal contact for the determination of the scalar and quality details to define a productive, cost-effective building. Typically, this spokesperson is a quality operations manager who is well-connected to both the science and the management who oversees it. This person manages the vision and the acquisition of the scalar and detail information that defines the design.

Quality laboratories should have a process flow. The process flow is characterized by the design team so that the functions needed to accommodate the mission of the facility can be identified. Figure 6.5 provides a sample flow diagram for a relatively small quality operations department for a manufacturing site. Note that the sequence of activities permits definition of laboratories that will execute the activities. The notes written in blue identify spaces suggested by the flowchart activities.

Figure 6.5: Process Flow for a Quality Laboratory



Creation of a work flow diagram should identify space types and indicate relationships between spaces that require closeness of proximity to encourage optimal productivity. The flow diagrams also should assist in the identification of support spaces. Spaces will be determined by the product mix within the responsibility of the quality organization and the testing needed.

The compilation of a space list follows earlier activities. Table 6.1 shows the initial space list from this flow chart example. Key to the listing of the spaces was the determination of the activities and their sequence, since each of the spaces effectively supports the activities. Discussions with the quality team members should determine the sizes of these spaces. Subsequent design efforts will refine the final sizing and numbers of spaces, along with further defined needs and intents of each space. The designer will incorporate this space list data into a more comprehensive list that will further define the needs and intents for each space. This becomes the program summary.

Table 6.1: Preliminary Space List by Type

Space Identification	Space Activities
Sample handling	Sample receiving, log-in, dispensing
Materials weighing	Weigh room with balances in weigh enclosures
Sample preparation	Fume hoods for sample solution and analytical solutions prep
Sample analysis	General testing: physical properties
Sample analysis	Chromatography: GC, HPLC
Sample analysis	Spectroscopy: AA, UV/Vis, NMR
Sample analysis	Microbiology: prep lab, incubator room, microbiology lab
Sample solution storage	Cart marshalling area in lab
Sample solution discard	Alcove in physical properties lab
Sample storage	Stability storage in stability chambers
Sample storage	Sample retention

6.3.1 Zoning

Zoning of the laboratory areas for supervisor's offices, technician's workstations, laboratory benches, and potential sources of hazardous fumes and materials, affects the overall workplace safety and operational efficiency. These spatial relationships reflect the type of work and the support needed to maintain a productive environment, and to maintain sample integrity. Office, support, and technical areas that are not related to direct interaction with the laboratories need not be close to the laboratory. Cubicles, write-up areas, support, and technical areas directly related to laboratory use should be in close proximity to the laboratory for efficiency and communication.

As equipment becomes more sophisticated, analysts may spend less time in the laboratory, as data can be analyzed remotely. This results in more of a focus on the efficiency of the office work environment. Issues such as perimeter offices, the provision of natural light and outlook, as well as visual access to the laboratory areas may be important. Shared open workstations may provide a productive solution for analyst write up space.

Support areas to the laboratory include locker rooms, gowning and toilet facilities, cafeterias, offices, off-line testing laboratories, and mechanical and electrical support spaces. The overall layout of the facility should account for the potential impact these spaces have on materials, product, and personnel flows into and out of these spaces.

The arrangement of spaces within a building involves the determination of adjacencies, both horizontal and vertical. This activity is called **blocking and stacking**. Successful iterations of the building layout should optimize the flow of personnel and materials so as to encourage efficiency, productivity, and safe practices. The designer should offer layout alternatives for the client groups to review, consistent with their understanding of the facility needs. The client group and the project manager should decide on a final iteration that will sufficiently support the quality operation into the future. It should be understood that alternatives in building layouts will have their own costs, and that differences in these costs may affect final layout selection.

6.3.2 Equipment List

An equipment list should be compiled for a facility. This list identifies all equipment with its location, power requirements, and special needs. The sample list in Table 6.2 has been reduced to fit the page. These lists may be very large and include great amounts of detail. The engineering design depends significantly on an accurate accounting of equipment to assure the proper utilities with their attendant capacities will be provided for each laboratory and support space.

Table 6.2: Sample Equipment List

Preliminary Equipment List			Project Name: Client												Project Number:						
															Date:						
Room Name							Electrical								Mechanical						
Equipment Description	Size L × W × H	Qty	F/L	New/Exist.	Floor/Bench	Other	Volts	Amps	Phase	Watts	EP	Conn.	Plug Type	Other	Vent	Gases	Water	Drain	Other		
Lab Name																					

The Basis of Design (BOD) encompasses all project elements needed for review and approval. These elements are combined into one package that can be reviewed and approved by the project team and aligned with the perceived business needs. The BOD typically includes:

- Project execution plan
- Scope of work
- Project location with reference to the overall site
- Project location within the specific site building
- Process/personnel flow diagram
- Summary of spatial requirements
- Equipment list
- Floor plans

- Schedule
- Order of magnitude cost estimate
- Building code analysis
- Environmental impact
- Risk analysis
- Construction execution and operational interference plan

The preliminary cost estimate included within the BOD usually is the first iteration for the project. It fosters the first cost/benefit exercise for management. The preliminary estimate may require a reassessment of the facility requirements and a revisiting of the space list.

6.4 Design Development

The BOD documentation should be the agreed-upon scope for the facility. It is at this point that the footprint and layout of the building should have been ascertained and the general sense (i.e., building capacity, quality levels, amenities, etc.) of the intended design understood. The scope and its budget estimate should be reviewed by client management and agreement reached, or alternately, the project scope should be modified to accommodate the project budget. This is a major milestone from which design development begins the official documentation phase of a project.

Design development involves:

- Compiling the architectural detailing for all spaces, both inside and outside of the building
- Determining laboratory casework layout and equipment locations within the laboratories
- Defining quantities and locations of all laboratory utilities
- Determining utility routing inside and outside the facility and the utility capacities

These activities should be performed in an iterative manner, with increasing refinement, until construction documents are complete.

Construction funding may be sought during the design-development phase. With increased definition as the design evolves, increasingly greater accuracy may be expected from the project cost estimate.

It should be emphasized that communication with the client group continues throughout the project design via ongoing project team meetings. Client representatives should review each design iteration with representatives from quality operations.

6.5 Construction

During construction, project meetings typically should be held weekly or biweekly at the construction site. The quality operations representative also should attend these sessions. This will allow the client and the quality department represented to maintain connection with the facility. In addition, it is important that quality operations representatives visit the construction site regularly to understand the evolving translation of the written design to a physical structure. While architects and engineers have the ability to imagine the built facility from drawings, quality operations management, and staff likely will not. Use of 3D now allows users to see the design at early stages.

6.6 Commissioning and Qualification

Commissioning quality laboratory facilities begins at the programming stage. This is the time when the extent of the impact of relevant GMP regulations and company standards are defined for the facility. The subsequent design accommodates the necessary controls and area definitions such that the intent of the regulations are embraced and achieved. Attention to fulfilling the regulatory requirements continues through design, construction, and commissioning. When the facility is turned over to the client, the building systems will be working as intended.

6.7 Budgeting

Construction costs can vary greatly. Examples of this can be seen when comparing the average cost of a fume hood intensive chemistry laboratory to a biology laboratory or a very complicated, process intensive, CGMP pilot plant laboratory that is designed to handle potent compounds. Each of these laboratories fall under the heading of “laboratory building,” but the finishes, infrastructure, and support systems are very different and have a different impact on the overall facility cost. While this section deals with cost, the owner, design professional, and the constructor should ensure that safety, both during construction and within the new laboratory, is the primary concern.

The development of a project budget for a laboratory facility should be done by an experienced organization. The development of a baseline budget or estimate of a new laboratory facility varies greatly with the type and use of the facility. This is not the case when building other types of facilities where there is little variation in the type of materials or design. A good case in point would be an office building where a reliable order of magnitude can usually be obtained by applying a cost-per-square-foot standard or by comparing similar facilities.

Although laboratories may seem extremely similar, each is unique. Each laboratory has:

- Specific expectations from users regarding programming, finish quality, amenities, and projected longevity
- Different demands for mechanical and process systems
- Issues that will impact site development and construction costs

These variables (and others to be discussed in more detail) can significantly affect the construction and project costs.

6.7.1 Budget Components

The cost of a laboratory facility is typically detailed and arranged by Construction Specification Institute (CSI) codes. They usually include the cost for the actual construction (bricks and mortar) plus a number of other costs, including:

- Land acquisition
- Planning and feasibility studies
- Architectural and engineering design fees
- Specialist consultants (sound, environmental, traffic, etc.)
- Permits and legal fees
- Construction, including materials, equipment and labor
- Field supervision of construction
- General conditions and requirements

- Insurance and taxes
- Owner's general office overhead
- Furniture, Fixtures, and Equipment (FF&E) not included in construction
- Inspection and testing
- Start-up, commissioning, and qualification
- Moving costs
- Audio visual, data, and telecommunications
- Contingency

In addition, design activities also would include an estimation of operating costs. Operating costs over the project life cycle include:

- Rent, if applicable
- Operating staff
- Laboratory equipment and supplies
- Labor and materials for repairs and changes for adjustments after start-up
- Labor and materials for maintenance and repairs
- Periodic renovations
- Insurance and taxes
- Financing costs
- Utilities
- Owner's other expenses

The magnitude of each of these cost components depends on the nature, size, and location of the project as well as the management organization, among many considerations. In general, an owner is interested in achieving the lowest possible overall project cost that is consistent with its business objectives.

It is important for design professionals and construction managers to realize that while the construction cost may be the single largest component of the capital cost, other cost components are not insignificant. Life cycle analyses are typically conducted to assist owners in making good decisions.

In most construction budgets, there is an allowance for contingencies or unexpected costs that may arise during construction. This contingency amount may be included within each cost item or be included in a single category of construction contingency. The amount of contingency applied to a particular project is based on several factors, including:

- Historical data and experience with the type of project

- Phase of the project and level of completeness of the design drawings
- Anticipated changes
- Schedule pressures
- Site conditions, including costs due to local ordinances pertaining to zoning, etc.

6.7.2 Influences

The influences that can have an impact on the construction costs of a laboratory facility can be grouped into three categories:

1. External
2. Internal
3. Project approach

External influences are those that the facility owner or designer will not have control over. These influences will vary from location to location and year to year and include:

- Local market conditions – these are usually driven by the specific dynamics of supply and demand and the labor force in the area where the construction is proposed.
- Material Costs – energy prices may remain elevated, making the energy-intensive process for making steel more expensive. In addition to higher energy costs, there is a growing global demand for steel and raw materials that has elevated market prices.
- Energy Cost – operations and transportation.
- The value of currency – As the local currency drops against other currencies, imports will become costlier.
- Regulatory changes – continued pressure from outside regulatory agencies to look at laboratory operations.
- Local Authority Having Jurisdiction (AHJ) regarding construction

The facility operator or designer has some control over internal influences. These influences will vary from project to project as a result of the type and application of the laboratory, the type of materials that are being handled and the amount of flexibility that the end user needs. These influences include:

- The facility program – the type and number of laboratories, the blocking and stacking of like functions in the building
- The number of fume hoods in the laboratory
- Flexibility of utilities in each laboratory
- Classification of laboratories for the handling of hazardous materials, i.e., Biosafety Level 2 (BSL-2), Biosafety Level 3 (BSL-3), and Potent Compounds
- The level of finishes needed
- Classifications of laboratories for cleanroom applications

There is a potentially enormous impact on reducing first cost and life cycle operating costs by minimizing the number of environmentally classified spaces and reducing the level of classification perceived to meet the requirements of the laboratory. The use of barrier isolator systems offers an economical alternative.

The project approach can influence the cost and outcome of a laboratory project. These influences are more easily controlled by the facility owner and designer, and include:

- Schedule – speed to market influences and the need to work premium hours to meet the project milestones
- Project Delivery – design/bid/build, design/build, fast track, turnkey, etc., each of these project delivery choices can influence the cost of a laboratory project

6.8 Cost Control During Construction

6.8.1 Construction Management

6.8.1.1 Introduction

The successful execution of a construction project begins before the first bid packages for equipment or trade subcontracts, particularly when the project is for a laboratory facility. This section considers the construction planning necessary during the design phase to help to ensure a successful project delivered under budget, on time, and either meeting or exceeding quality demands.

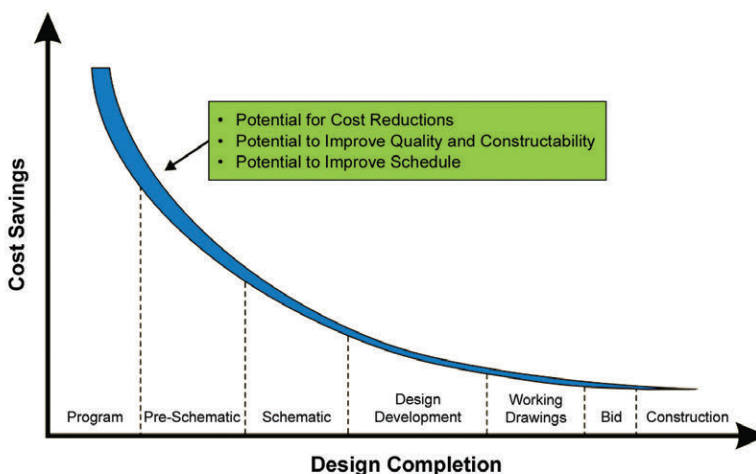
For a pharmaceutical or a biotech organization, where a project is for a QA/QC laboratory, a chemistry laboratory, a biology laboratory, a vivarium space, BSL2/3, or a combination of these spaces; the early-on construction planning process should be identical.

This Section discusses the influences and variances in the design and construction of laboratories and to make all parties involved (end users, owner engineering/facility teams, designers and constructors) aware of the impact on construction of their decisions.

6.8.1.2 Why Early Involvement

Constructors should be involved early-on in the design process. As described in the influence curve in Figure 6.6, the greatest ability to positively influence the outcome of the project at the lowest cost is during the planning and design phase.

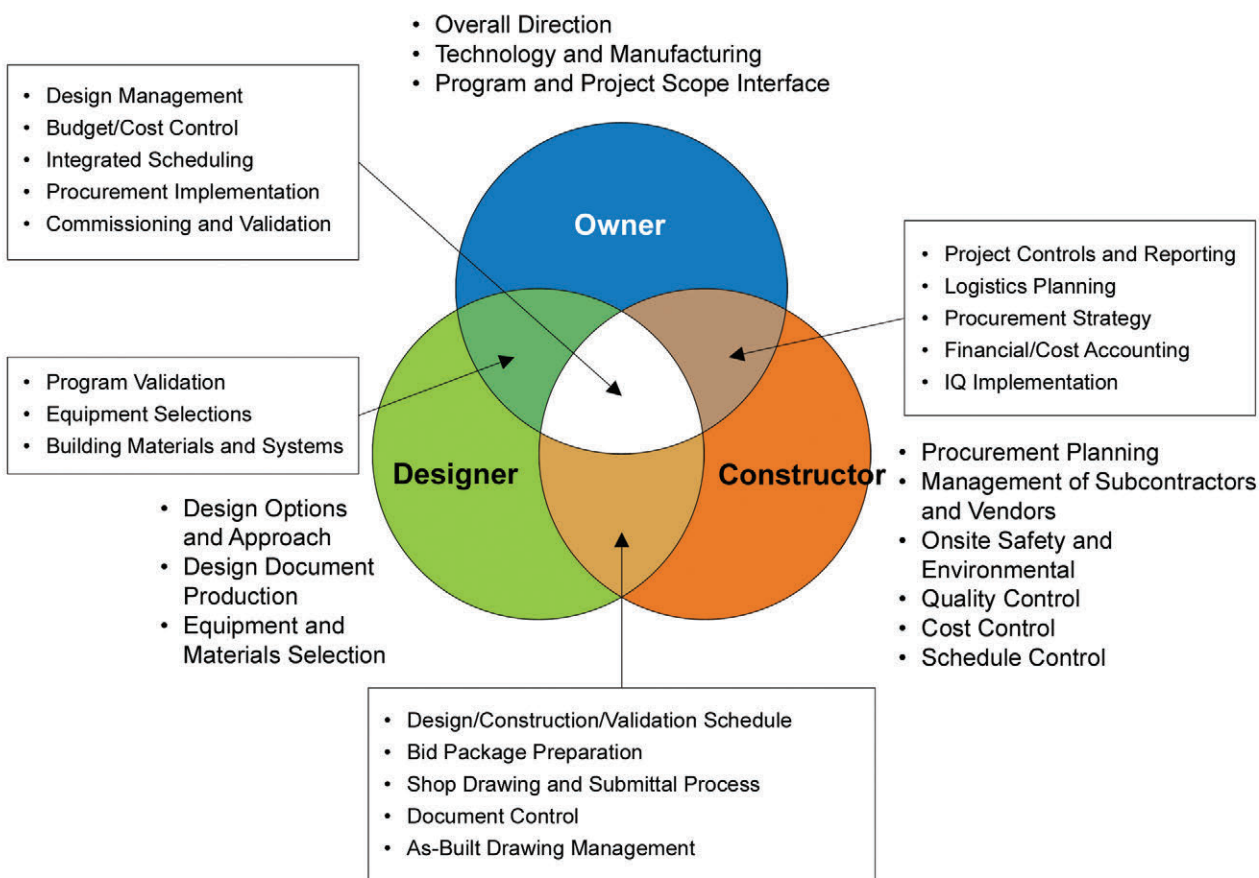
Figure 6.6: Cost Influence Curve



Once the project moves out of design and into construction, changes can involve redesign and re-bidding of packages, which also negatively impact the schedule, and can increase the project cost. Planning all aspects of the project early on and working together as a team helps to ensure that once the project is bid, it is the project that will be built.

The ability to positively influence the successful execution of laboratory facility capital projects is also dependent upon the close cooperation of the three basic teams involved: the owner, the designers, and the constructor. Each of these teams have their own areas of expertise and responsibility for the project, but there are many areas of overlap which have to be identified and coordinated throughout the life of the project see Figure 6.7.

Figure 6.7: Project Team Member Overlaps



There are several areas in which two teams have overlapping responsibilities; the central area shows where all three teams overlap, including:

1. Design management
2. Budget/cost control
3. Integrated total project schedule
4. Procurement plan and packages
5. Commissioning/qualification/validation

Team building with these three organizations early within the project timeline is considered essential to the successful execution of a project.

6.8.1.3 *Total Integrated Project Schedule*

A capital project involves more than the typical design and construction schedules. The project schedule should incorporate all components of the project in order to give a true picture of the status of the project. Critical path items tend to differ from project to project and from phase to phase within the project, but decisions and actions made during the life of the project have implications on other components. The schedule is largely driven by the date when the quality organization needs to begin work in the laboratory space.

By developing a total integrated project schedule during the planning and early design phase, critical paths can be identified and strategies developed to address these. Among the important early milestones should be internal funding dates and local and agency permitting dates, which have a direct influence on deliverables due from the designer and contractor.

Once the project begins, design deliverable dates should be reflective of the procurement strategy the team has agreed upon:

- The bidding schedules of equipment and trades should reflect the execution strategy of the team, as does the construction schedule with its dozens and dozens of sub-schedules.
- The commissioning and qualification schedule and sub-schedules should reflect the strategy needed to meet regulatory needs.
- The move-in schedule reflects how the end users will inhabit the facility to facilitate their research efforts.

These may be interdependent upon each other, a change in procurement that will have an effect on the commissioning and subsequently the move-in will be accurately reflected, allowing the team to develop the right strategies to bring the end date back in line.

6.8.1.4 *Start-Up, Commissioning, and Qualification*

The commissioning and qualification of a laboratory facility is critically important. During design and construction, the quality lead, regulatory compliance, facilities representatives, and project lead collaboratively work to assure that the laboratory facility will be commissioned and qualified efficiently with the least re-work. This can only be accomplished when properly planned, designed, procured, and installed to ensure compliance.

With this in mind, the planning should incorporate the following:

- Commissioning should be integrated into the design deliverable packages, the procurement/bid packages with all of the inspection and “paperwork” requirements, and the construction schedules.
- Within the master schedule, a very detailed sub-schedule calls out all of the start-up, commissioning, and qualifications efforts needed with special emphasis places on critical path requirements.
- Secure an agreed upon commitment from the vendor with regard to their internal fabrication schedule to assure that the availability of the equipment will be on time and that they have a plan and the resource in place meet the Factory Acceptance Test (FAT) schedule.
- Develop an FAT and Site Acceptance Test (SAT) strategy that includes who is responsible for what, which members of the team will perform which inspections, and what is each team member specifically responsible for on the inspections. The level of quality needed would also be included.
- The constructor has to develop and implement procedures to manage a host of activities that have impact on the start-up, commissioning, and qualification efforts to follow, including:

- Quality control
- Punch list execution to support early start-up activities
- System completion focus
- Turn over package development
- System certification requirements

6.8.1.5 *Safety*

When designing and building any laboratory facility, safety is the primary concern – for the end users, for others on the campus, and for personnel constructing the facility. Safety requirements for the quality staff should be incorporated into the design documents, and safety requirements for the trades should be built into the construction bid packages, and reinforced throughout the construction.

Primary tools for this are the logistics plan(s) and the Hazards of Construction Risk Assessment (HAZCON) developed to accurately reflect how the project will be executed. The safe and efficient movement of personnel, materials, and equipment is considered fundamental, and can change with the phase of the project. These plans should be included in the bid packages so that the trades know what is expected of them for parking, laydown, delivery schedules, etc. These are developed in conjunction with the site security and safety teams to ensure that personnel follow the appropriate protocols.

6.8.1.6 *Procurement Strategy*

As the team develops the execution strategy for the project, the procurement strategy should begin development. Working closely with the design team, the appropriate quantity of design packages should be developed with the schedule as to when they are needed to bid so as to meet the construction schedule. The goal of the procurement strategy is relatively simple: manage risk through the right procurement plan. This is achieved by procuring the following from the most qualified contractors:

- Schedule commitment
- Logistics/security plan
- Safety and environmental program
- FAT, SAT and systems start-up requirements and training for operators
- Commissioning/qualification/documentation support
- Cost model/control
- Contract type and terms

The aim is to get the best value for the investment allocated, and the procurement strategy should emphasize this.

6.8.1.7 *Value Management/Constructability*

Value Management (VM) (also known as value engineering) and constructability efforts are lost when performed after the project is bid in order to bring the project back to budget. VM is valuable when performed early on and continuously during the planning and schematic phases, because the emphasis there is on systems, which is where the real values are found. As the team goes through the design review meetings, ideally the areas of discussion should center around:

- Air distribution/exhaust methods
- Structural system selection
- Mechanical system diversity
- Systems redundancy
- Solid/liquid waste disposal
- Emergency power requirements
- Serviceability/flexibility
- Floor/wall material finishes
- Decontamination methods
- Concrete mix and placement methods (for BSL3/4 facilities)
- Ease of maintenance and repair

VM/constructability meetings are great opportunities to bring the team even closer together. They should include end-users, engineering/facility staff, maintenance staff, designers, and constructors, and may include specialty trades where appropriate. The meetings should identify, confront, and resolve design issues, and reduce re-work. They should provide the team with options and alternatives to be reviewed early on when an elimination of a wall or HVAC line involves erasing a line on paper. They should include specific deliverables, whether an action plan, benchmark information, estimate or schedule impact or whatever. This provides information for the team to make informed decisions that will positively impact the project.

6.8.1.8 *Planning Deliverables*

Deliverables provided at the end of pre-construction include:

- Constructability reviews
- Value engineering reviews
- Conceptual cost analysis report
- Conceptual schedule analysis report
- Integrated project execution plan
- Integrated project procedures manual
- Site logistics plan
- Clean build plan
- Prefabrication strategy and plan
- Construction sequencing plan

- Construction permitting plan
- Cash flow projections
- Construction cost estimates
- Procurement plan with bid package preparation
- Project schedule
- Site specific environmental, health and safety plan
- Integrated quality assurance plan and construction QA dossier
- Integrated start-up, commissioning, and validation plan

7 Architectural

7.1 Introduction

This Chapter provides project architectural concepts for consideration when designing a laboratory facility that supports the quality functions of products being manufactured and distributed for human consumption. The concepts presented are global in nature and do not take into consideration local code issues or organizational cultural considerations.

The primary architectural goals are:

- To design and construct a facility that meets all requirements for a quality testing laboratory
- To comply with all local codes, zoning ordinances, and Federal regulations (disability and applicable GMP regulations)
- To incorporate commissioning and qualification requirements (where needed) into the building design
- To select appropriate building materials
- To consider design provisions for future expansion of the laboratory
- To develop an agreed-upon project schedule and budget range
- To align with corporate standards/expectations

7.1.1 *Laboratories in the Scope of This Guide*

Laboratories supporting the manufacturing of regulated compounds as well as their process development and improvement are many and varied. This Chapter discusses design considerations for each type of quality laboratory as well as issues and concerns that apply to all laboratories. This discussion will focus on the following areas:

- Incoming material inspection and testing laboratories
- In-process and off-line intermediate testing laboratories
- Final release and stability testing laboratories
- Sample storage and records retention areas
- Other support areas such as solvent storage, materials storage, waste handling

7.1.2 *Intended Use*

This Chapter of the Guide is intended to assist and guide a user in the conduct of the laboratory design process as well as the process of making decisions in architectural layouts, finishes, adjacencies, and other components of the design for new and renovated laboratories. Benefits and drawbacks of various options are reviewed to allow the user to make the most appropriate determination, selection, and decision for their particular situation.

This Chapter is intended to provide information which may be used as a basis for making decisions.

7.2 Laboratory Design and Organization

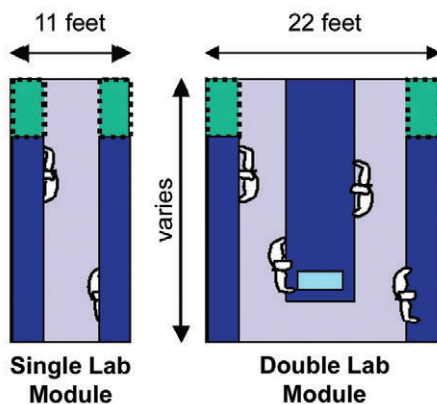
Several of the basics of laboratory design are discussed. Considerations of each of these topics will permit the quality organization to determine the attributes for their laboratories.

7.2.1 Open versus Cellular Laboratories

Scientific activities performed in laboratories may be hazardous or use hazardous materials. Typically, these spaces would tend to be smaller discrete rooms so as to suitably contain these operations. Alternately, there are activities such as HPLC analysis that are not intrinsically hazardous. When an HPLC is applied to analyzing materials that are relatively non-hazardous, these analyses could be conducted in a very large laboratory that can house many such units. Thus, the room size may be much larger to accommodate many HPLC instruments.

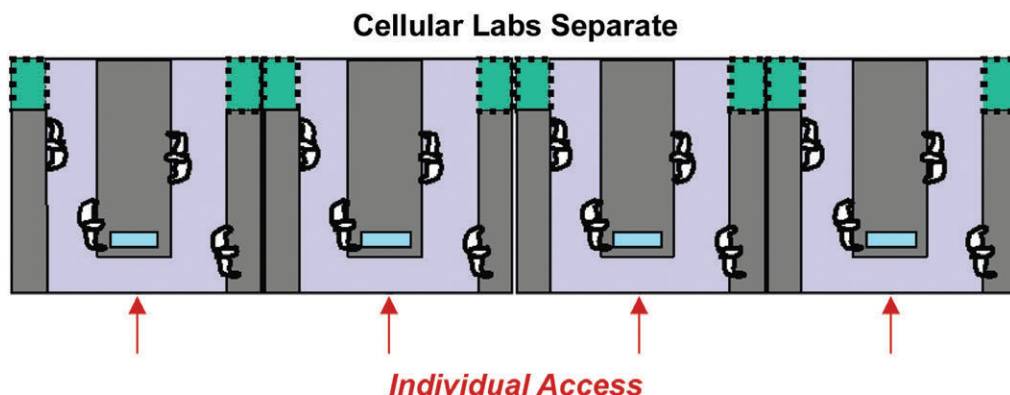
Laboratory size is usually formed as a multiple of a basic unit, called the laboratory module. The creation of a laboratory module permits standardization of the building structure and thereby simplifies the overall design. Within the standard module, there will be fixed aisle widths and fixed laboratory casework depth. Figure 7.1 shows a standard laboratory module and a double laboratory formed of two units. The latter may be sufficient for a four person laboratory, and with the appropriate casework, would work well for a variety of laboratory types. For either of these spaces, a single entry normally would be used.

Figure 7.1: Laboratory Module



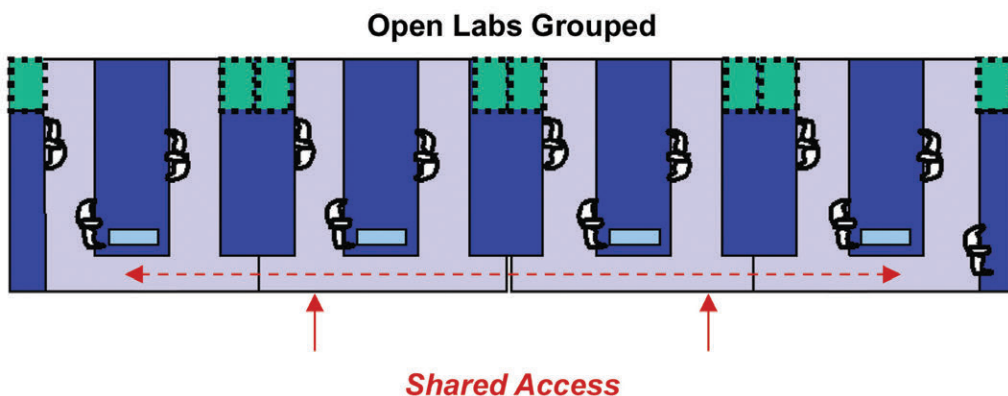
Cellular laboratories would be smaller enclosed spaces similar to those shown in Figure 7.1. These laboratories would house the more hazardous operations such as chemistry or research involving the use of radioactivity. On a laboratory floor composed of cellular laboratories, there would be several laboratory spaces or discrete rooms, each with its own entry. Figure 7.2, provides an example.

Figure 7.2: Cellular Laboratories (Separate)



Open laboratories, as shown in Figure 7.3, are not segmented (i.e., no walls at the module boundaries) like cellular laboratories. They are large, open rooms with a limited number of entrances. In these laboratories, the use of hazardous materials or operations is limited.

Figure 7.3: Open Laboratories (Grouped)



There are characteristics to each of these laboratory types. Table 7.1 lists these properties.

Table 7.1: Comparison of Cellular and Open Plan Laboratories

Cellular Lab	Open Plan Lab
Good contamination control	Less costly to build
Good environmental control	Less costly to change
More dense utilities	Quicker to change
Increases accumulation of chemicals and supplies	Capacity to absorb growth
Worker safety	Reduced redundancy
Staff retains defined work space	Simplified circulation
Can foster competition, sense of enterprise	Encourages interaction
Proven track record	Team oriented
	Foster experimentation with work flow
	Greater sense of openness
	Can be noisier

Laboratories supporting chemical analysis are well supported by the open plan concept. The larger space enables easier characterization of workflow thereby promoting greater operational efficiency.

7.2.2 Casework Types and Flexibility

Laboratory casework is the furniture of laboratories. The arrangement and type of casework can make tremendous impacts on the conduct of science in the laboratories. This casework can vary from permanently installed units to completely flexible units that can be moved in accord with the scientists' needs. There can be a sizeable impact on project cost depending upon which type is selected. Some of these casework types can be combined, thereby imparting elements of flexibility within a fixed arrangement.

Utilities can be supplied to the work area – normally a bench – in many ways. Therefore, it is important to determine how laboratory activities are to be conducted prior to selecting the style of the casework. For example, if the activities require a large, uninterrupted work surface, utilities are routed in a manner to support the activities without getting in the way. The selection of the proper casework is made with reference to the activities that the laboratory will support.

Following is a brief explanation of the four basic types of laboratory casework. Note that three house utilities in a central core. Pictures of each casework type are shown in Figures 7.4 to 7.9.

Fixed casework is the most common type and is suitable for routine work stations. Within the quality laboratory, there are areas that serve a need that is unlikely to change significantly over time. Therefore, fixed casework would be the best choice as well as the most economical. Attributes of fixed casework are:

- Floor mounted storage provides very good stability
- Full storage capacity available under the work surface
- Very good load capacity with the ability to further strengthen load bearing if necessary
- A service chase or wall from which utilities are supplied
- Can be used with other casework types
- Lowest initial cost
- Difficult to make changes in configuration

See Figures 7.4a and 7.4b for examples of fixed casework.

Figure 7.4a: Fixed Metal Casework with Conventional Storage Cabinetry and Reagent Shelf over Bench



Used with permission from Kewaunee Scientific Corp., www.kewaunee.com

Figure 7.4b: Fixed Metal Casework with Movable Cabinetry Under



Used with permission from Kewaunee Scientific Corp., www.kewaunee.com

C-Frame casework provides flexibility because the lower cabinetry is suspended from a frame assembly, the C-Frame. Attributes of C-Frame casework are:

- Cabinetry can be changed in accord with changing laboratory activities
- The service chase is part of the C-Frame structure
- Ability to remove cabinets assures access to utility chase
- Can be used adjacent to fixed casework
- Frequently supplied with wheels for ease of reconfiguring
- Load capacity is only marginally less than fixed casework
- Less cabinet storage capacity under the bench top
- Space under cabinets can collect debris
- Difficult to create large expanses of surface for large arrays of equipment
- Higher initial cost than fixed casework

See Figures 7.5a and 7.5b for examples of C-Frame casework.

Figure 7.5a: C-Frame Casework with Movable Storage Under

Used with permission from Kewaunee Scientific Corp., www.kewaunee.com

Figure 7.5b: C-Frame Casework Designed to Move About Lab; Suspended Casework in Background

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Suspended casework provides a different type of flexibility. The major difference is that suspended casework has a structural core that provides the strength to mount cabinets and/or shelving both below and above the bench top. Further, all pieces can be mounted at various heights to suit either staff preference or equipment setups. Attributes of flexible casework include:

- Needs greater analysis and characterization of laboratory activities to specify the initial setup of casework
- Most adaptable of casework with a fixed utility core

- Components can be stored to allow changeover at any time
- Most ergonomically friendly
- Can be used adjacent to fixed casework
- Load capacity is only marginally less than fixed casework
- Less cabinet storage capacity under bench top
- Space under cabinets can collect debris
- Difficult to create large expanses of surface for large arrays of equipment
- The structural/utilities core becomes an anchor within the laboratory; this restricts movement of equipment to within connectivity with this core.
- Higher initial cost than fixed casework

See Figures 7.6a and 7.6b for examples of suspended casework.

Figure 7.6a: Suspended Casework with Raised Backsplash and Reagent Shelving



Used with permission from Kewaunee Scientific Corp., www.kewaunee.com

Figure 7.6b: Suspended Casework with Reagent Shelving

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Though not a type of casework, overhead service carriers have created a revolution in laboratory layout and design. Provision of services from above has eliminated casework as an anchor within the laboratory. The only deviation from this “ultimate” flexibility is the need for drains when water is necessary. For laboratories designed with these carriers, sink services are commonly located at the perimeter, allowing the center of the laboratory to be freely adaptable. Attributes of overhead service carriers include:

- Allows freedom of layout for casework in the center of the laboratory
- Eliminates routing of utilities to island bench or utility column locations
- Encourages experimenting with equipment layouts, thereby allowing optimization of activities
- Potentially the least expensive option, especially when tables rather than cabinetry are used for equipment setups
- Can be used adjacent to any of the three other casework options. Overhead service carriers can augment casework in a laboratory creating a flexible zone for experimenting with equipment setups

A schematic is shown in Figure 7.7. See Figures 7.8a and 7.8b for examples of overhead service carriers.

Figure 7.7: Schematic of Overhead Service Carrier

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Figure 7.8a: Combination Fixed-Suspended Casework with Overhead Service Carrier



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Figure 7.8b: Overhead Service Carrier with Tables Under



Photo courtesy of Earl Walls Associates, a studio of HKS, <http://hksinc.com>

Figure 7.9: Utilities from Overhead Service Carrier Configurations

Used with permission from Dow Diversified, www.dowdiversified.com

7.2.3 Utilities and Utility Placement

Utilities distribution design may include or be influenced by:

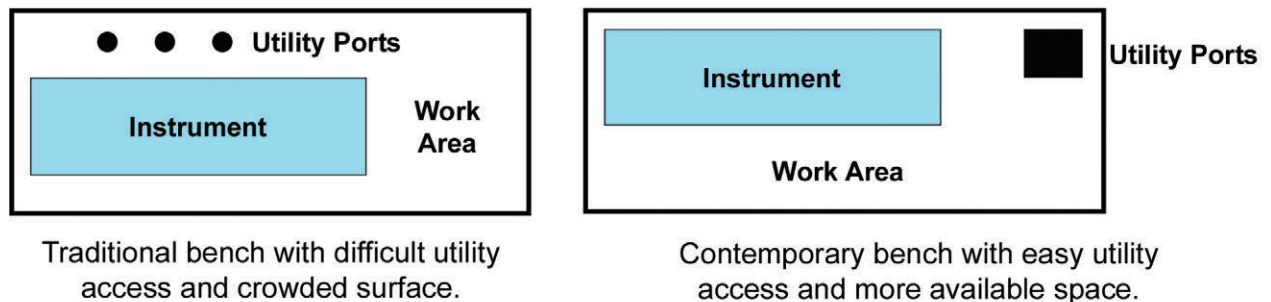
- Utilities redundancy
- Ventilation devices used
- Environmental cleanliness of the laboratories
- Future flexibility and capacity
- The need for Uninterruptible Power Supply (UPS) and generator backup

- Facility and site networking requirements
- Gas bottles/cylinders vs. central distribution
- Sinks and drains
- Safety showers
- Purified water type, distribution, and level of independence from the rest of the plant
- Floor drains: none. Sealable floor drain design if necessary.
- Maintenance access to services and exhausts (e.g., the roof)
- Exhaust fans and ductwork
- Reliability
- Technology changes
- Emissions planning
- Energy efficiency
- Operating costs
- Performance
- Regulatory concerns
- Safety
- ROI

Concealed connections and distribution is a common trend in contemporary laboratories with maintenance friendly accessible service areas or panels that provide good access to service chases.

The location of the utilities within the laboratory is usually considered important to the quality staff. As these utilities are connected to benches, their location can either help or hinder analytical operations. As shown in Figure 7.10, significant bench space can become available with the proper placement of utilities.

Figure 7.10: Utility Placement on the Bench



For alternatives for locating utilities, see the figures in Section 7.2.2 of this Guide.

7.2.4 **Materials Storage and Handling**

Materials storage is a significant issue in laboratory design. Regulations tightly limit solvent quantities and handling, which frequently becomes a controlling issue in the number and locations of storage spaces in a facility. However, other types of substances may escape the scrutiny that solvent storage receives. Designers should be proactive about providing space for proper storage of materials. Following are guidelines offered for storage of various substances in or near the laboratory:

- Solvents: store under hood or in solvent storage cabinets; organic vapors are heavier than air; therefore, provide exhaust at floor level if venting is mandated.
- Oxidizers: store in a separate cabinet; note that these are not normally used in significant quantities.
- Acids: typically stored under the fume hood.
- Reactive gases: stored outside in ventilated area. In-use cylinders may be placed in cylinder storage cabinets in or near the laboratory and fed to the laboratory use point(s). Most gases are heavier than air. Storage areas should be vented at both floor and ceiling levels.
- Hydrogen: Always stored and used in a drafted area, vented at ceiling level. Hydrogen is explosive in air from four to 75% by volume, making it a potent explosion hazard. Fugitive emissions should be scrupulously removed. Detailed design recommendations can be obtained from the National Safety Council as well as from the National Fire Protection Association and other agencies.
- Other gases: store cylinders in ventilated area. Gases provided to laboratories may be routed from local cylinder closets located in a corridor near the use points. Gases that are consumed in large quantities (e.g., nitrogen, carbon dioxide) are usually distributed from a central building source.

Quality laboratories generate a large quantity of solvent waste. Following is commentary on waste handling:

- Consideration should be given to disposal of laboratory chemicals and reagents. In all probability, a high percentage of these chemicals are Resource Conservation and Recovery Act (RCRA) or otherwise regulated and should be disposed of in a regulatory compliant manner. Since the majority of chemicals used by the laboratory are not consumed in the analytical process, provisions should be made for collection and accumulation of waste chemicals until such time they may be removed from the laboratory to temporary storage awaiting removal by a licensed waste hauler. These satellite accumulation areas should be designed with adequate ventilation and spill containment and accommodate segregated storage of reactive materials.
- Waste flow should not contaminate the process it is derived from nor serve as a source of contamination to other areas.

Types of laboratory waste can be broadly classified as the following:

- Innocuous non-product laboratory waste is generated outside the process area where product exposure is not a concern. Examples are packaging materials and paper products. These materials require no special treatment or handling.
- Product-contaminated laboratory waste is generated within the laboratory area and includes any disposable material that comes in contact with the product. Handling of product-contaminated waste should be controlled by procedure (SOP).

- Hazardous or regulated laboratory waste includes materials that have specialized storage or disposal requirements. Examples include biological hazards, combustibles, potent/toxic materials, and sharps (needles). Hazardous or regulated waste should be handled, collected, and stored in a manner which addresses safety, health, and environmental concerns and which complies with all applicable codes and regulatory requirements. Note that increasing use of engineering controls to handle potent/toxic compounds and other hazardous materials means less danger of human exposure, product contamination, and environmental controls.
- Packaging waste: discarded packaging labels require special handling to reconcile product runs and confirm control and tracking.

The typical quality laboratory utilizes several hundred different chemicals and reagents in its day-to-day operation. In most cases, the storage, handling and disposal of chemical inventory adds a level of complexity to the overall design in terms of life/safety issues and regulatory compliance. In order to address these issues, the designer should develop an understanding of laboratory operation and the chemical inventory. The chemical inventory should be identified, quantified, and evaluated to determine the impact of its storage, handling and disposal requirements on building design. Only then can the necessary design criteria be established to assure compliance with State and Local Building Codes, National Fire Protection Association (NFPA), and the Resource Conservation and Recovery Act (RCRA).

7.3 Architectural Finishes

Architectural finishes maintain performance qualities consistent with the necessary level of protection. This may require regular maintenance procedures. Alterations or repairs should be able to restore the qualities of the original finish. In general, the less disruptive and involved the repair effort, the better the finish will serve both to maintain architectural requirements and meet the needs of the laboratory operation.

Finishes should be cleanable and robust, non-shedding, and able to withstand the traffic while keeping the need for maintenance, repair, or replacement within acceptable limits. Generally, floor finishes should be non-slip and impervious. Non-friable and easy to clean surfaces should be specified for ceilings. Non-porous and easy to clean surfaces should be used for walls. The table shown as Table 7.2 is a brief review of materials that have been found to be acceptable and are commonly used in the industry. These materials are typical and not meant to be specific.

Finishes resistant to chemicals inherent in the samples or testing procedures, as well as cleaning and/or sanitizing agents, including solvents that can damage many types of finishes should be used. Other products or materials used in production may have particular agents that will stain surfaces. Certain finish systems may be more susceptible to attack than others. Additionally, floor tiles should not be used where there is a potential for bacterial contamination.

Table 7.2: Summary of Typical Laboratory Finishes

	Floors	Walls	Ceiling	Doors	Casework
Incoming Materials and Component Sampling	sealed concrete, VCT tiles	dry wall, painted CMU	none, suspended	painted hollow metal	metal with epoxy top
Sample Prep	VCT, vinyl sheet, epoxy	dry wall, painted CMU	suspended	painted hollow metal	metal with epoxy top
Sample Weighing	VCT, vinyl sheet, epoxy	dry wall, painted CMU	suspended	painted hollow metal	metal with epoxy top
General Testing	VCT, vinyl sheet, epoxy	dry wall, painted CMU	suspended	painted hollow metal	metal with epoxy top
Aseptic/Sterility Testing	vinyl sheet, epoxy with coved base	epoxy-coated dry wall or CMU	mylar-coated and sealed tiles	painted hollow metal	metal with epoxy top
Biohazard	vinyl sheet, epoxy with coved base	epoxy-coated dry wall or CMU	epoxy-coated dry wall	painted hollow metal	metal with epoxy top
Potent Compound	epoxy with coved base	epoxy-coated dry wall or CMU	epoxy-coated dry wall	painted hollow metal	metal with epoxy top
Hazardous Materials	vinyl sheet, epoxy	epoxy-coated dry wall or CMU	suspended	painted hollow metal	metal with epoxy top
Radioisotope	epoxy with coved base	epoxy-coated dry wall or CMU	epoxy-coated dry wall	painted hollow metal	metal with stainless steel top
Cold Labs	sealed concrete or prefab panels	sealed concrete or prefab panels	prefab panels	prefab, insulated powder-coated steel	metal with epoxy top
Controlled Substances	VCT, vinyl sheet, epoxy	dry wall, painted CMU	suspended	painted hollow metal	metal with epoxy top

7.4 Laboratory Design Checklist

Issues to be considered in the design of quality operations laboratories:

- Flexible or fixed furnishings
- Work surface materials. Wet laboratory versus dry laboratory
- Maintenance requirements
- Visual access to laboratory: large expanses of windows for visual communication
- Utility distribution

- Resource constrained activities
- Shared areas or equipment
- Analysis and documentation methods
- Alarms and monitoring
- Instrument logs, data ports, qualification, and calibration
- Structure – vibration control and isolation
- Specific areas with greater air filtration
- Redundancy/AHU separations (zoning)
- System and component commissioning versus validation
- Glass wash/autoclave sterilization, media/buffer preparation
- Uninterrupted power supply – house system versus localized batteries
- Refrigerator, freezer, incubators
- Phone and data port distribution and networking
- Waste management and handling
- Cost implications capital and operational
- Aesthetic considerations
- Product testing requirements (type, duration, number of tests)
- Personnel (and shift)
- Life safety/code compliance and egress requirements
- Productivity
- Efficiency
- Expansion
- Equipment requirements
- Bench height requirements
- Meeting requirements
- Food and coffee room locations
- Garmenting requirements
- Commissioning and qualification requirements

7.5 Organization of Quality Laboratory Spaces

The quality laboratory is a secured access facility that supports pharmaceutical stability testing, incoming material testing, in process control, final release for raw materials, and finished products manufactured for human consumption.

The quality laboratory usually operates on similar shifts as the manufacturing plant (when associated with one). For 24/7 operations, usually there are three shifts per day with the potential for a lighter shift schedule on weekends. Quality laboratory capacity should be designed to accommodate the maximum number of analysts on a shift, usually the daytime shift. Open desk positions are typically programmed in space away from the benches for analytical write up.

Office space is usually provided for quality laboratory directors and managers with cubicles provided for laboratory supervisors or team leaders.

Centralized vs. Decentralized Quality Laboratories

Activities within a quality organization may be centralized, decentralized, or a combination of both. The selection of one or more of these modes is a function of how the workflow is organized.

Centralized quality laboratories have specific functions for each laboratory. Following a workflow analysis, specific areas can be defined in accord with the testing needed for the materials determined by the manufacturing plant product mix. A sample work flow diagram was provided as Figure 6.5. From this workflow, the spaces in Figure 7.11 were defined for the specific quality organization laboratory activities. These spaces are grouped by analytical technique or generalized laboratory activity. The microbiology laboratories might constitute a suite devoted to those analyses.

Figure 7.11: Centralized Quality Laboratories

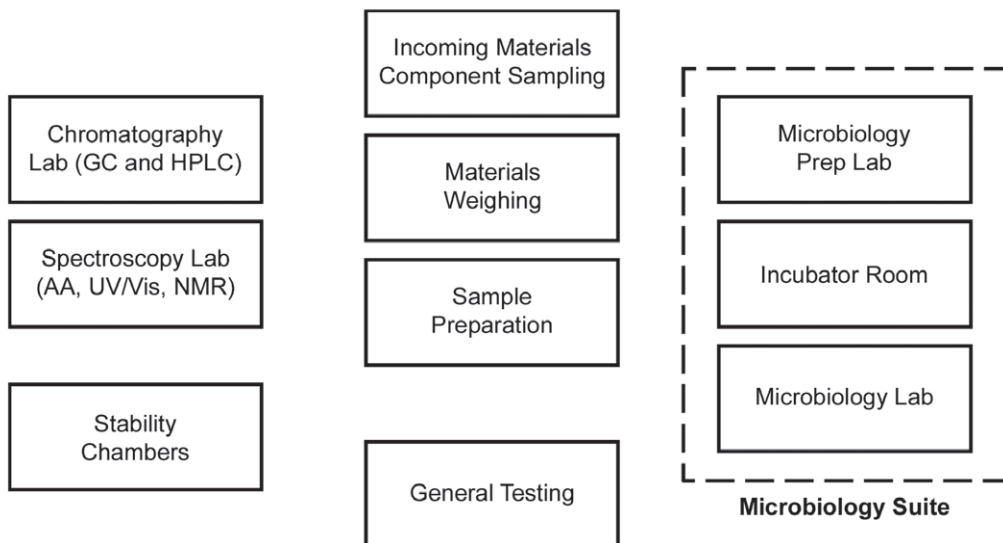
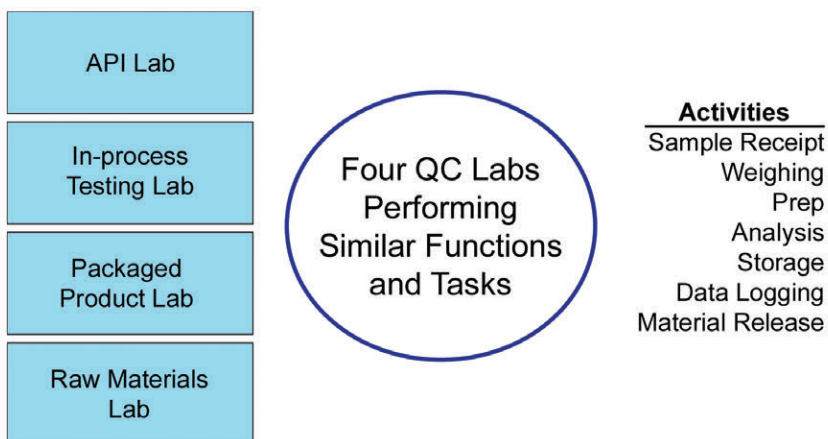


Figure 7.12 provides a schematic of how decentralized quality laboratories might be arranged. In this case, each laboratory has responsibility for performing testing related to a certain material or function. The laboratory name indicates what material(s) are tested.

Figure 7.12: Decentralized Quality Laboratories



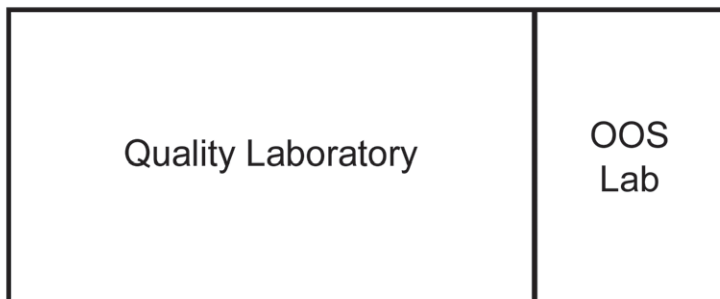
There are benefits and drawbacks to both centralized and decentralized quality laboratories; however, overall productivity and cost benefits accrue from the centralized mode. Within this type of organization of laboratory spaces, the evolution of analytical capabilities is more easily implemented and networking among analysts is greatly improved since there is a degree of analytical homogeneity within each laboratory. In addition, these laboratories are more likely found to be open laboratories (see section 7.21 of this Guide). One recent design included laboratories that were composed of eight modules. The dimensions of these laboratories were 35 feet by 88 feet (10.7 m by 26.8 m). These laboratories were committed to the most heavily used analytical techniques, those of dissolution testing and HPLC.

Additional laboratory space may be needed for Methods Development/Validation (MD/V) and Out-Of-Specification (OOS) testing. The methods development/validation activities may be centralized at one site for an organization or located at the manufacturing site. The centralized approach has benefits when an organization has multiple manufacturing sites for the same products. For this case, the method is developed and validated at the central location and the appropriate technical transfer and qualification activities applied to bring the methods to the sites where they are to be used. Out-of-specification testing is present at each manufacturing site.

For both MD/V and OOS, a discussion of overall facility workflow should help locate these functions in the building. Methods development typically uses more sophisticated and different types of instruments to fully test and validate the new or updated methods. Thus, MD/V may be located on a separate floor or wing of the facility. The MD/V function does not usually get involved with routine analysis. In addition, MD/V laboratories usually have used mixed casework – fixed and flexible with some overhead service carrier.

Analysis of OOS materials can confound routine quality activities, essentially disrupting workflow and causing inefficiencies. A solution to this situation is to create a parallel workflow and space to accommodate OOS testing, and thus retain overall testing efficiency. As shown in the schematic in Figure 7.13, space has been allocated adjacent to the quality laboratory to offload the OOS testing. This OOS laboratory would house instruments that would enable a quick and thorough resolution of the OOS problem. It should be sized appropriate to the projected OOS capacity. When not being applied to OOS testing, this space also can be used for other special testing requirements. The decision to separate the OOS laboratory in this manner should be assessed by a risk/benefits analysis.

Figure 7.13: Quality Laboratory with Separate Out of Spec Testing Lab

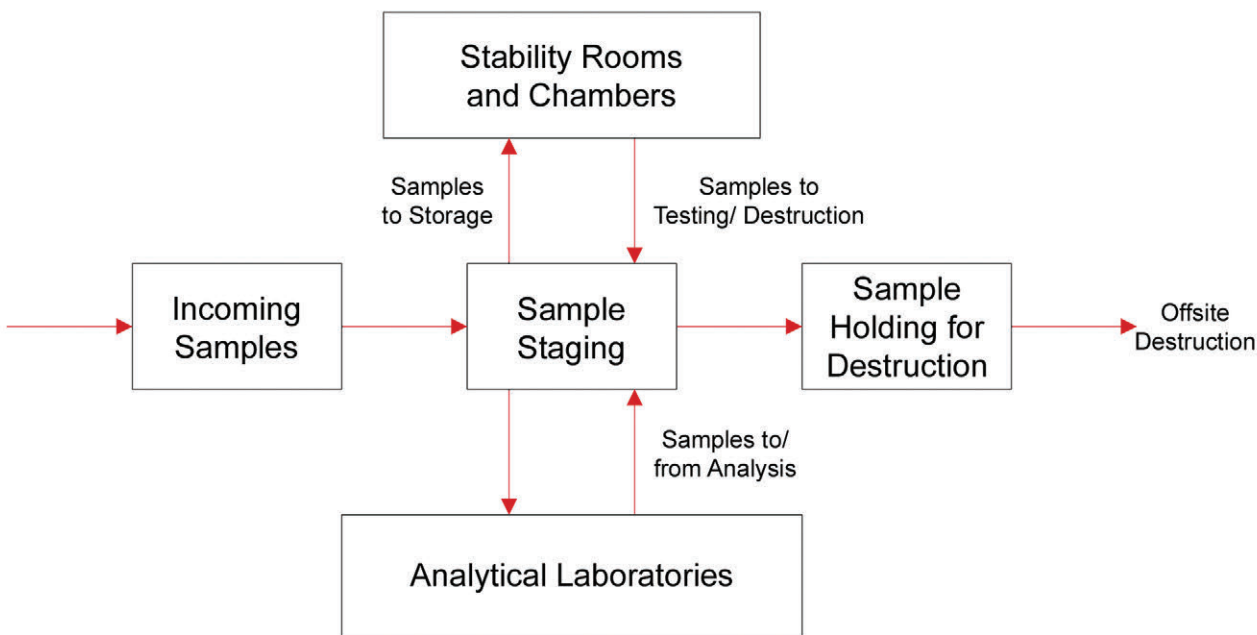


According to 21 CFR 211.166 [3], *"there shall be a written testing program designed to assess the stability characteristics of drug products."* Stability testing is conducted on both API, formulated, and packaged product. Tests are run on statistically relevant samples from multiple lots to assure proper characterization.

Stability operations share the same testing capability as previously described for quality laboratories. In addition, they need controlled environment chambers to allow storage of stability samples at various conditions of temperature and/or humidity and/or light intensity. These chambers may be small, similar to a refrigerator or freezer, or may be a large room. Each chamber is typically operated at one set of conditions, e.g., 98.6°F (37°C) and 75% RH. There are usually many chambers due to the need for determining stability at several conditions. These spaces are usually under control of a dedicated computer system that constantly monitors performance and will alarm should any chamber deviate from the set points. Electrical power backup with UPS is normally provided for this control system. Where chambers provide humidification, deionized or RO water is typically provided to minimize the possibility of fouling the humidification system.

A flow diagram depicting stability operations is provided as Figure 7.14.

Figure 7.14: Typical Stability Operations Flow Diagram



Laboratories servicing the stability organization would be quite similar to other quality laboratories.

8 HVAC

8.1 Introduction

This chapter addresses the Heating, Ventilation, and Air Conditioning (HVAC) systems that can be considered for Quality Laboratories.

This Chapter discusses criteria related to the cost effective and efficient design of HVAC systems serving quality laboratories such as:

- HVAC systems reliability
- HVAC diversity
- HVAC segregation
- Classification of areas
- Assessment of appropriate risks (HVAC equipment redundancy, emergency power, critical room HVAC parameters)
- Commissioning and qualification

The HVAC system provides comfort, health, and safety to the laboratory occupants and in specific cases protects the sample from contamination.

The laboratory exhaust system removes air from the space. This exhaust system serves equipment located within laboratory that is intended to further isolate workers from potential hazards. This often includes containment units known as chemical fume hoods, biological safety cabinets, isolators, and glove boxes. Additionally, laboratory rooms often require exhaust specialty provisions such as canopy hoods, chemical storage area exhausts, and bench type snorkel exhausts to remove heat, moisture, flammable fumes, and vapors.

The laboratory ventilation system provides conditioned replacement air for the air being removed by the exhaust. The number of fume hoods, the need for specialty spaces, the size of these spaces, the configuration of the furnishings, and the testing and instrumentation requirements, as well as the storage needs, all have an impact on the ventilation system.

Designers should be familiar with laboratory operations and industrial HVAC, along with sustainable design and construction practices, and be aware of local, national, and international codes, standards, and regulations. Codes and standards addressing industrial and environmental hygiene are of particular importance.

For further information on risk assessment as it applies to HVAC Systems see Chapter 5 of this Guide.

For further information on HVAC system design see the ISPE Good Practice Guide: HVAC [30].

8.1.1 *Safety and a Safe Work Environment*

The design and operation of the ventilation system contributes to the safety of the personnel in the laboratory. The HVAC design should support desired safety and industrial hygiene design criteria. Laboratory equipment or Personal Protective Equipment (PPE) used to isolate hazardous laboratory operations from personnel may affect the HVAC design and can include:

- Point of use extraction devices

- Glove boxes
- Isolators
- Fume hoods
- Bio-safety cabinets
- Ventilated enclosures

8.1.2 Effective and Efficient Operations

The HVAC design should identify options where there are significant operational or capital cost differences and rank them against a total cost of ownership model that accounts for:

- Inflation
- Utility impact
- The cost of capital
- Option life span
- Estimated maintenance costs for each instance

Within an effective and efficient HVAC design, selection or rejection of options in mechanical design and controls should be based on these considerations. Typical key decisions include a comparison of the initial costs against the life cycle costs of a variable air volume system, heat recovery systems, and control system strategies.

8.1.2.1 Environmental Conditions

The HVAC system should provide an environment which allows scientists and technicians to concentrate on their work without distraction by the room conditions, drafts, and noise. Equipment can operate over a wide range of environmental conditions with consistent test results, so the limiting factor would be provision of conditions for human comfort.

Worker comfort can also influence the results by promoting good work practices (e.g., workers not touching their skin while performing tests). In some situations sweat and particulate can affect tests.

Maximum and minimum room temperatures and humidity should be within national or local health guidelines. See the ASHRAE Standard 55 (Thermal Environmental Conditions for Human Occupancy) [50] and the ISO Standard 7730 (Ergonomics of the Thermal Environment) [51]. Conditions should be adjusted for workers in protective clothing to assure their comfort.

A range of 30% to 60% RH is recommended for worker comfort where occupancy is continuous. However, as some facilities will have 100% outdoor air systems, the need and cost of comfort dehumidification and humidification (where humidity will not affect the product) should be assessed.

Very low humidity can lead to:

- malfunctions or problems in some office, packaging, and electronic equipment
- rises in the potential for static discharges

- increases in dust clinging to surfaces
- increases in particulate generation from dry skin
- increased susceptibility to infection for occupants

High humidity can lead to:

- added moisture in the product sample
- condensation on exterior windows
- increased corrosion in furniture and equipment
- microbial growth on surfaces, in concealed spaces and in building materials
- malfunctions or problems in some office, packaging, and electronic equipment
- increased susceptibility to infection for occupants

8.1.3 *Ergonomics and Workflow*

Typically, quality laboratories have extensive equipment inventories and required support spaces. HVAC design should account for:

- Specific ventilation requirements of equipment
- Heat emitted by the equipment into the laboratory

User workflow and ergonomic designs may compete with efficient mechanical design. Successful HVAC design is a collaborative effort between all stakeholders during the bases of design, risk assessment and design development.

8.2 User Requirements

User requirements are a front end requirement for developing the appropriate scope and criteria for a laboratory facility (see Chapters 3, 4, and 5 of this Guide). From a customer perspective, asset realization, where a delivered facility meets the customer's needs in terms of efficient operational throughput, is a key measure of project success. Other factors which are considered contributions to a successful project include:

- Process
- Quality
- Safety: product protection/operator protection
- Operations
- Maintenance

8.2.1 Process

A database of the equipment to be installed in the laboratory should be developed (see Chapters 2, 3, and 4 of this Guide). This database should include the most restrictive environmental requirements (temperature, humidity, cleanliness, isolation, or barrier, etc.) for operation of the equipment or for performing the tests associated with the equipment, e.g., equipment for microbiological testing may require an ISO 5 (Grade A) laminar airflow and a controlled temperature environment.

Other environmental requirements also should be noted, e.g., a scale may require a vibration free mounting surface with no direct airflow onto the scale.

The database also should include utility requirements, heat emitted, and demands for ventilation such as air flow (constant, start-stop, or variable) to allow integration of equipment with the HVAC systems. Where heat emitted figures are not available, the power requirements can provide useful information for a designer.

8.2.2 Quality

Where environmental conditions can impact a test result, qualifying/monitoring may be a requirement if a determination has been made that the lack of environmental control may give negative test results.

It may be appropriate to apply the same controls as used in an equivalent manufacturing environment such as:

- Change rooms
- Airlocks
- Door interlocks
- Differential pressure regimes
- Air filtration

Typically, HVAC zones and equipment are segregated by the design team into systems/areas which require either qualification or commissioning.

8.2.3 Safety: Product Protection/Operator Protection

User requirements, as defined in Section 8.2 of this Guide, are a front end requirement for developing the appropriate scope and criteria for a laboratory facility (see Chapters 2, 3, and 4 of this Guide). Defined user requirements capture key data that will impact the facility by defining the areas of concern assuring the team that they are taking into consideration product safety and operator protection in the HVAC system.

8.2.4 Operations

User requirements identify the planned operating pattern for the laboratory, e.g., the shifts per day and working days per week, and define the allowable downtime, together with the maintenance strategy. This information, together with information on the products and processes to be performed (e.g., exposure risks and associated control strategies) can be used to establish redundancy requirements. It also can ensure that the HVAC design allows for system maintenance without affecting the laboratory operation, e.g., if hazardous materials are being handled then duplex fan systems with UPS/generator backup systems may be needed.

8.2.5 Maintenance

8.2.5.1 Importance

Maintenance is a requirement to ensuring the reliable operation of the quality laboratory. Quality operations laboratory facility failures can affect factory throughput directly. Maintenance schedules should be developed and the requirements of each HVAC component should be understood and incorporated. Well planned maintenance can reduce or eliminate unplanned events, including equipment and controls failures which can render a facility inoperative.

8.2.5.2 Reliability

Reliability of a system can be calculated by multiplying the reliability of each individual component. Reliability is a function of both the weakest link and the total number of links which are less than 100% reliable.

If a utility is 99% reliable, the equipment mechanical systems are 95% reliable, and the controls are 98% reliable, the overall system is 92% reliable. This means that the utility may have unplanned events 8% of the time (potentially 29 days out of an average year). Appropriate maintenance can significantly improve reliability; however, elimination of all unplanned events is considered impossible or impractical for a given system.

Redundancy may be used as a remedy for failures, e.g., having N+1 or standby capacity; however, the additional equipment adds to costs.

There are several techniques used to monitor system performance, e.g., vibration monitoring of equipment. For further information, see the ISPE Good Practice Guide: Maintenance [32].

In regard to reliability, HVAC design can depend on the:

- Requirement for the facility to operate continuously
- Planning for or availability of offsite quality testing facilities
- Availability for planned maintenance shut-downs
- Sensitivity of a process to an outage
- Strength and performance of a predictive maintenance group

8.2.5.3 Cost

The cost of maintenance personnel, equipment, and parts can be evaluated against the sensitivity for facility down time. Generally, the cost for unplanned outages is significantly higher than the cost of maintenance, so appropriate staffing, out-sourced functions, and stock levels can be estimated using facility management good practices.

8.2.5.4 Access

Physical access to devices should be incorporated into the design of the facility. In clean or classified space, it is considered good practice to locate devices that need maintenance outside of the envelope, in mechanical equipment or technical spaces. Other successful planning techniques include providing safe and ergonomic access to control valve stations and terminal devices.

For maintenance, HVAC systems typically require regular access to:

- Lubrication points

- Drive belts
- Electronic assemblies
- Interface panels
- Actuators, testing ports, and filters

Major components which need less frequent maintenance and access include:

- Control valve stations
- Motors
- Fan
- Louvers and dampers
- Coil sections
- Drain pans
- Drain piping
- Drain clean out fittings
- Strainers
- Fire dampers
- Automation power supplies

8.2.5.5 *Equipment*

Equipment selection can influence maintenance requirements, e.g., selection of an airflow monitoring station that requires frequent calibration will cost more over the life span than a device which requires infrequent or occasional reference checks. When equipment selections are based on economy, a complete study should reference the manufacturer's information on the frequency of maintenance (e.g., equipment calibration, cleaning, alignment, inspection, tightening, and failure rates).

8.2.5.6 *Monitoring*

Monitoring devices can consist of remote and local data gathering technology, SCADA, web based I/O, on-board diagnostics, and visual/video surveillance. The general goal of monitoring technology is to reduce the overall dependency on personnel, and increase the reliability by automating the comparison of real-time data versus accepted criteria to detect or predict failure and pre-failure conditions.

General monitoring input/output devices can be:

- Thermal
- Pressure
- Level

- Position
- Acceleration
- Air or water flow

Monitoring data points can be expensive and are dependent on reliability. An evaluation of monitoring should include a factor for the maintenance of or the failure of the monitoring system itself. In general, critical monitoring of single point failures, and monitoring that supports predictive failure is generally worth the cost of the points.

8.3 HVAC Design Parameters

HVAC design parameters should be identified during the development of the user requirements as defined in Chapters 2, 3, and 4 of this Guide. The user requirements should define the conditions to be met allowing for the appropriate selection of components to ensure that the HVAC system will perform as required.

8.3.1 HVAC Design Criteria

This section is not intended as a design instruction guide for engineers. Existing design guides are available and should be utilized as necessary (see the ISPE Good Practice Guide: HVAC [30]).

8.3.1.1 Space Loads and Calculations

The ventilation requirements for a laboratory design should account for the actual loads using a room-by-room analysis, as many laboratory spaces are heat load driven. Generic heat loads per square foot should not be used for design values for lighting and equipment.

8.3.1.2 Ambient Outdoor Design Conditions

Generally, quality laboratories will use a significant amount of outside air due to make up air requirements (e.g., fume hoods, biosafety cabinets, and local exhaust ventilation points). Selection of appropriate outside air design conditions is important, as this will drive the capacity of utility systems.

Outdoor design conditions should be based on historical local weather data records; i.e., ASHRAE or local weather data. It is considered good engineering practice to select ambient outdoor design conditions that are likely to occur over most of the cooling and heating periods. Generally, ambient outdoor design conditions are not selected for recorded extremes, i.e., highest or lowest temperature ever recorded. The design should incorporate some level of risk analysis, as defined in Chapter 6 of this Guide, to evaluate the cost, probability of occurrence, and impact on the process within the laboratory.

8.3.1.3 Indoor Temperature and Humidity Conditions

Temperature and humidity conditions are defined as those that, under normal circumstances, provide a comfortable working environment.

There can be instances where temperature and humidity conditions are determined by product or processes.

Where laboratory areas have different temperature and humidity conditions (zones), dedicated HVAC systems should be considered for each zone of temperature and humidity control. Consolidation of HVAC systems to reduce initial cost should be evaluated against installed cost and operating cost.

Individual areas may need separate thermostatic control (e.g., local terminal reheaters) due to variation in cooling loads from area to area and potential impact on the testing performed. Areas of similar use and internal heat gain can be combined in a single zone.

Humidification should be controlled to maintain a stable environment. Where room loads are similar and stable, this can be accomplished centrally through an air handling unit-mounted humidifier. For systems where centrally located humidifiers cannot maintain design humidity levels, use of terminal humidifiers should be considered.

Where steam humidification is used to maintain winter humidity conditions, the quality of the steam should be considered. Impact on product quality and testing also should be considered. Plant steam may contain chemical additives that inhibit corrosion, but may affect process test results. These conditions may require the use of additive free steam, which is normally generated from Reverse Osmosis (RO) systems.

8.3.1.4 *Pressurization*

Quality laboratories may be designed with negative pressure relative to adjacent corridors and offices, so that contaminants, fumes, or smells do not migrate into these areas. The generally preferred method of achieving space relative pressurization is by maintaining a fixed differential between supply and exhaust air flows. Room pressurization monitoring is not usually required in this situation.

Specific areas within a laboratory may be required to be positive pressure relative to surrounding areas. Intermediate air locks may be used where pressurization is required to manage airflow direction for an area. If room differential pressure is considered a critical parameter for in product testing, monitoring and control may be needed.

8.3.1.5 *Ventilation*

Ventilation design should determine the minimum requirement for supply air based on the dissipation of the heat loads by laboratory equipment, environmental requirements, building envelope, and personnel.

Note: these requirements usually exceed the minimum ventilation requirements for the space.

Laboratory equipment, which includes ventilated enclosures (e.g., biosafety cabinets, fume hoods) should be identified in the HVAC design. This type of equipment should be integrated into the ventilation and control systems, particularly in two speed or variable air volume systems.

Fire and explosive conditions should be considered in the design of quality laboratory ventilation systems.

It may be appropriate to incur the costs of providing controls to the laboratory equipment to minimize the ventilation requirements, e.g., extract air volume control on a fume hood. Minimization of ventilation rates should maintain a safe environment for personnel.

8.3.1.6 *Design Air Change Rates*

Air change rates should be based on make-up air requirements or heat load.

The proper air flow rates and air management strategy (air lock configuration) should be established for areas that are designed to maintain a cleanliness classification. (Most areas of a quality laboratory are not required to achieve a cleanliness classification, e.g., Grade D.)

Air change rates also may be driven by internal heat load from personnel, lights, and equipment. For further information on equipment heat load, see Section 8.3.1.8 of this Guide.

8.3.1.7 *Filtration*

Generally, quality laboratory areas do not have to achieve a particulate classification. The accepted industry practice for filtration levels is typically, a pre filter and final filter (i.e., ASHRAE MERV 8 and final filter ASHRAE MERV 13 or 14). Local conditions may require alternative strategies to manage the quality of the supply air.

Specific user requirements may state that a particulate classification is designated for a specific area or type of space. In these instances, the use of terminal HEPA filters may be warranted along with the associated gowning and airlock strategies.

8.3.1.8 Acoustic Considerations

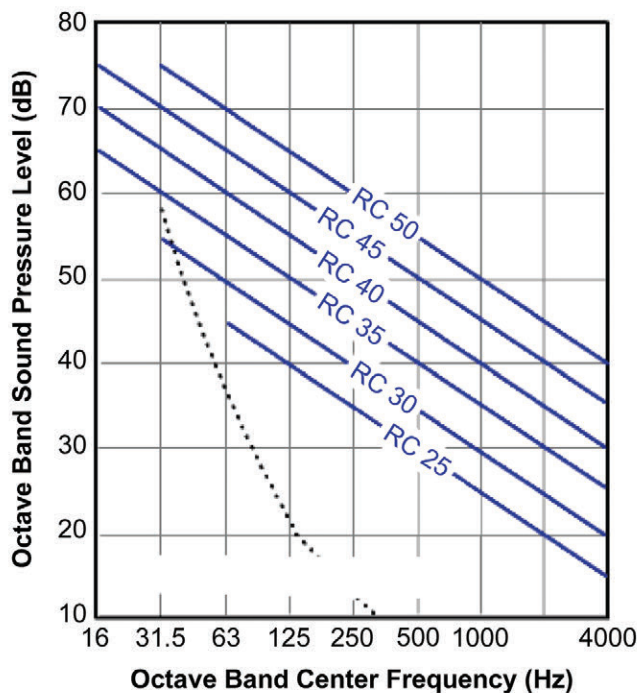
There are various rating systems used to categorize sound, e.g.:

- Room Criteria (RC)
- Noise Criteria (NC)
- A-weighted Sound Level (dBA)
- Loudness level (Sones)

A-weighted sound level rating is a convenient single number rating system that is easily measured. The various octave band noise levels that are measured are combined to form a single number. Using sound level ratings is not as adequate as other rating systems. Two different sounds or noises that occur across different spectrums will have different effects but can have the same sound level rating.

Rating systems such as NC or RC provides criteria across several octave bands and is the preferred criteria. Sound criteria are specified through a single number rating, e.g., RC 45, see Figure 8.1.

Figure 8.1: Rating System for Sound Criteria



Using a rating system can provide a more accurate and objective method to specify and allow the HVAC design to achieve acceptable noise levels in a quality laboratory.

Although most of the focus of acoustical criteria centers on reducing the noise level inside the laboratory, outdoor HVAC equipment noise should also be reviewed for its impact on neighboring structures and local noise regulations.

8.3.1.9 Specialty or Miscellaneous Considerations

Internal heat load from personnel, lights, and laboratory equipment can be substantial in a quality laboratory and can drive airflow more than make-up air requirements. Calculation of heat load from equipment should include a diversity factor. This should consider that not all equipment will be operating simultaneously and that electrical equipment nameplate data is not necessarily all converted to heat, unless specifically stated by the equipment manufacturer. Consolidating of equipment arrangements to a specific area within the quality laboratory or a separate room can allow a more strategic approach to the HVAC design, see Figure 8.2.

Figure 8.2: Example of the Quantity of Laboratory Equipment Encountered in a Quality Operations Laboratory Supporting Pharmaceutical Manufacturing



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8.3.1.10 HVAC System Diversity

The concept of using airflow diversity should be considered for quality laboratories, when a large part of the make-up airflow is dictated by the amount of make-up air devices that are dependent on end user behaviors, i.e., opening and closing of fume hoods.

For the purposes of this Guide, HVAC system diversity is defined as:

"A system diversity factor represents the maximum number of exhaust devices (i.e., fume hoods, safety cabinets, ventilated enclosures, point exhausts) with sashes open (at the design sash opening) or in use simultaneously. A diversity factor, X (<1), represents the total amount of make-up air required by exhaust devices multiplied by X ."

Example: if a laboratory make-up air requirement from all exhaust devices (i.e., fume hoods) is 10,000 cubic feet of air per minute (CFM) and a diversity factor of 75% is applied, the total amount of make-up air required for fume hoods will be $10,000 (0.75) = 7,500$ CFM.

The diversity factor should be applied carefully in the design process and the following should consider by project teams:

- Size of the facility

- Total number of fume hoods (or similar containment device)
- Number of fume hoods (or similar containment device) per end user
- Agree on what “full open” for a fume hood means. Note: depending on the sash arrangement, this can take on a variety of definitions
- Type of exhaust controls
- Number of devices that need to operate continuously due to chemical storage requirements or contamination prevention
- Pre-investment in future capacity for projected research programs

The list is intended to highlight examples of discussion points to review when considering applying a diversity factor.

An advantage of applying a diversity factor is a lower initial capital cost. Mechanical systems usually account for a large portion of a building's cost and influence the size of a building.

8.3.1.11 Energy Efficiency/Sustainability

HVAC system design should include a thorough review of opportunities to include energy saving features. If there are established organizational utility, energy, or minimum efficiency guides or standards they should be identified and applied in the HVAC design. Evaluation of alternatives should include an energy analysis that compares annual energy costs to initial investments.

In addition, there are established programs, e.g., (Leadership in Energy, Environment, and Design (LEED) that provide a framework for building design, operations, and maintenance that promote efficient and sustainable buildings. The process takes a life cycle approach and encompasses many aspects of a building, i.e., impact to local environment, energy, etc. These programs can provide a lower life cycle cost to operate and maintain a facility, as well as less tangible benefits.

8.3.1.12 HVAC Handling of Biological or Chemical Compounds (Segregation and Containment)

The handling of biological or chemical compounds should undergo a risk assessment to categorize and rank compounds to establish the appropriate level of containment. Engineering controls used for containment are considered in order to have the proper context for HVAC design.

Quantities of biological or chemical compounds handled in quality laboratories are usually smaller than in production facilities; therefore, quality laboratories do not usually have the same approach for engineering controls and HVAC design.

Smaller quantities allow for handling in containment type devices; e.g., glove boxes, biological safety cabinets, and fume hoods, which are the primary method of engineering controls. The type of engineering control used is usually determined by the ranking assigned to the compound in the risk assessment. Factors considered include:

- Exposure limits
- Type of compound, e.g., liquid, solids, aerosols

Engineering controls used in the laboratory may be sufficient to provide a reliable and subsequent low risk of exposure so that additional controls are not needed from the HVAC system that serves the area.

Where the assessment of risk is high, despite the use of engineering controls, additional measures can be taken in the HVAC design to segregate the HVAC system (dedicated system) and provided additional filtration for return/exhaust systems. In addition, the area can be segregated in a separate room which can act as secondary containment.

8.3.2 HVAC Design Considerations

8.3.2.1 Supply Systems

Supply air systems typically include all outside air conditioning, filtering, and supply fans. These systems can be:

- Individual units for each quality laboratory
- Central station units for each zone
- A manifold of central station units for supply to the entire quality laboratory block or building

Advantages for each strategy should be considered and evaluated.

Supply systems also include critical components for air volume control and final trim heating, cooling, and humidification requirements.

8.3.2.2 Exhaust Systems

Exhaust air systems typically include all branch and main ducts, inlet valves or dampers, and individual or central station fans for exhaust from the specific equipment, or entire quality laboratory block or building. Exhaust re-entrainment along with placement and velocity control should be considered for quality laboratory exhaust.

Computational Fluid Dynamic (CFD) studies may be beneficial. These would examine the wind-wake impact of the exhaust systems on fresh air intakes for the facility and surrounding facilities.

Advantages for each design strategy should be considered and evaluated.

Depending on the specific hazards, manifold exhaust system designs, especially risers and headers, can affect the control zone philosophy for the facility and such aspects should be coordinated.

8.3.2.3 Return Systems

Return systems typically include air from non-contaminated spaces for re-conditioning at supply air systems. These systems typically include terminal devices and return fans with relief air paths in temperate climates to achieve more economic operation.

8.3.2.4 Duct Work

Duct work can consist of:

- Sheet metal
- Composite
- Fiberglass Reinforced Plastic (FRP)

The selection of materials should be based on local codes and regulations and consider the type of vapors that the duct work may be required to transport. Access, duct accessories, sealants, insulation, structural and connecting elements, and construction and installation methods are considered critical to HVAC system design.

The available or built in allowance for future increases to air volume requirements in the facility, distribution mains, and risers should be identified for sheet metal designs.

8.3.3 HVAC Control Systems

HVAC control systems should:

- Satisfy the requirements for commissioning and qualification for the Quality Laboratory
- Have the capacity to monitor and control all devices in the scope
- Have the speed and flexibility to produce all aspects of facility control in an acceptable manner
- Be secure
- Have configuration management

Quality laboratories may have internal organizational requirements for GxP equipment monitoring. Environmental monitoring in critical areas may include differential pressure, particle monitoring, or temperature and humidity monitoring.

Control systems consist of basic analog and digital inputs, and digital and analog outputs. These points monitor and control the specific variables judged necessary to control the HVAC system. The control system typically has a centralized or distributed capacity for math functions for simple and complex sequence of operations process logic. The continuing development of control system functionality is making advanced systems strategies affordable at the commercial level. PID control loop strategies can be complemented by completely adaptive loop stabilization strategies. These should be challenged during commissioning to ensure that they perform to meet the user requirements.

Control systems may have proprietary internal communication architectures. In architectural designs, system speed and robust communication stability for all control areas should be established.

When deciding which manufacturer to use for a building control system, input from the proposed manufacturer's engineering support should be obtained early in a facility design. This input can help in the decision process to eliminate or accept systems based on the ability to handle the scope.

Control systems may have the capacity to monitor and control equipment over commercial protocol gateways, such as BACnet, LonWorks, and Modbus or industrial protocols such as Hart/Fieldbus. These make integration of PLC controlled terminal equipment (such as variable frequency drives) possible, and can help provide an integrated expandable solution. Communication protocols for the exportation of monitoring data (SCADA side) also can include protocols, such as OPC to connect internal short term data history with external long term data storage systems.

Controls systems also should have or provide security and security levels for protection of controlled parameters and control code. There also should be integrated systems for revision control, backing up, and restoring control code, I/O point configurations, controller configurations in DCS, and communication configurations.

The HVAC control system is necessary for the operation and monitoring of the facility devices for HVAC operation. A complete working system can have the ability to manage the facility in the most efficient manner if planned, installed, and commissioned to do so.

8.3.3.1 Constant Air Volume (CAV) System "Monitoring Only"

The Constant Air Volume (CAV) system, with monitoring only, is the simplest system from a design, installation, and maintenance viewpoint. A CAV system provides a relatively constant amount of ventilation airflow or Cubic Feet of air per Minute (CFM). It is the highest operating cost alternative as the volume of air is a constant volume which is the most costly to heat, cool, and move. It is normally referred to as the uncontrolled system. Issues can cause a change in volume which only system monitoring can detect. Issues such as fan slippage, bearing failure, damper failure, or something as simple as a rag being sucked into the system can cause a change in air volume creating a failure condition.

The CAV system should provide a constant volume of ventilation air flow throughout the laboratory and through the fume hoods and other exhaust devices during the occupied and unoccupied periods, 24 hours a day, 7 days a week. It is the simplest system to design. The amount of airflow is selected during the system design and is based upon the room's ventilation requirements to handle the worst case room comfort conditioning and any other special requirements. The CAV system requires the least amount of sensing devices and a minimum amount of knowledge and support personnel, due to its simplicity.

Laboratories can experience changes with the addition of testing of new products, the addition of fume hoods or other protective devices, and the blocking of supply and exhaust vents because of nuisance noise levels or annoying flow patterns. It is considered good practice to measure air flow periodically making necessary adjustments to fixed position dampers to make up any air flow differences created by periodic system planned, or unplanned, modifications.

The CAV ventilation has one major aspect for consideration. This system is the simplest and most cost effective at installation but it is the highest energy consumption system. The CAV system has no provisions for reduced ventilation during unoccupied times. In specific applications, because of its simplicity and first time cost, the CAV system can be the optimum system of choice.

Figure 8.3: Typical CAV Ventilation System

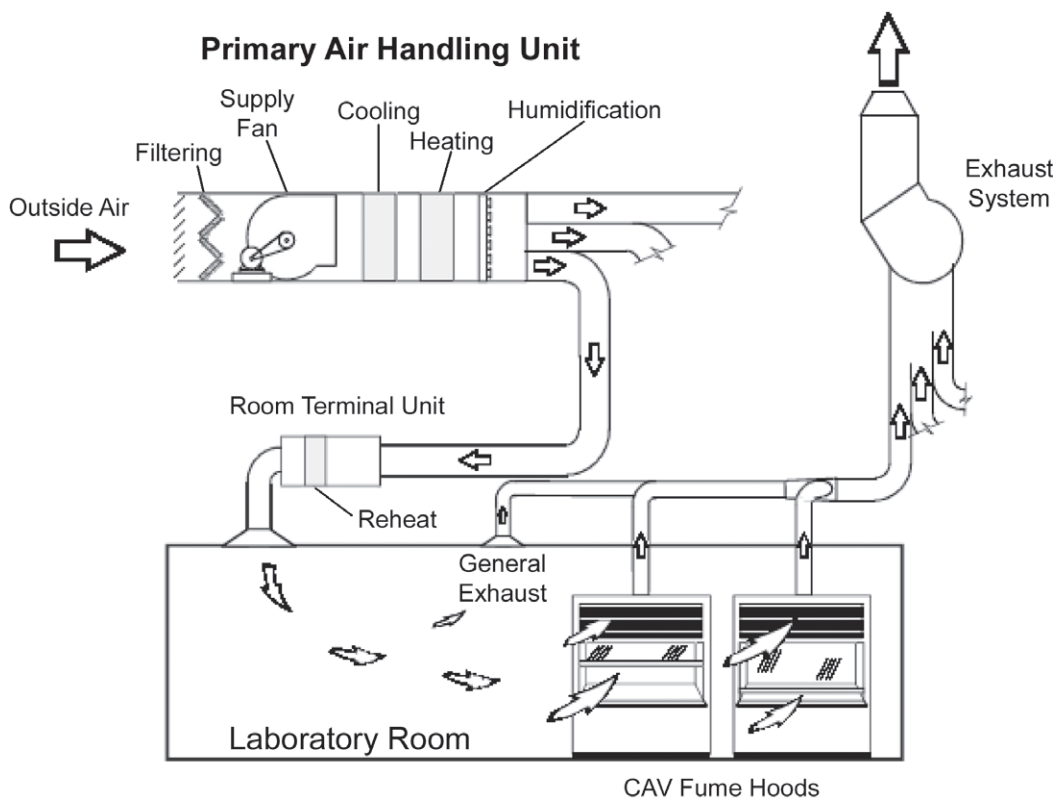


Figure 8.3 illustrates a typical CAV ventilation system applied to a laboratory room having fume hoods. The CAV system draws a constant volume of outside air into the air handling unit (AHU) where it is filtered and conditioned (cooled or heated and humidified) to meet the needs of the space. A constant volume of conditioned air (normally at a cooler temperature than the room air) is supplied throughout the entire area served by this AHU. The temperature of the air that is supplied to the individual laboratory room is raised by a room terminal unit reheat coil, to meet occupant comfort or other needs of the specific room.

8.3.3.2 *Constant Air Volume (CAV) System "Monitoring and Controlled"*

This system is essentially the same as the CAV system described in Section 8.3.3.1 of this Guide, although its cost is slightly higher because it uses both monitoring and control. The monitoring aspect may be the same as used in the CAV system described, but the system can be adjusted only by a mechanic adjusting the fixed position damper until the desired adjusted flow is reached.

The controlled system has an added dynamic of controlled sensing and repositioning, typically done through a Building Automation System (BAS). This system has an equivalent operating cost to that of the CAV system (monitored only). If the monitored only system is not well maintained, it can potentially have a higher operating cost.

The dynamics of controlled are achieved by use of volume dampers equipped with either electronic or pneumatic damper actuators and with feedback of position or airflow. The control system should maintain the required air flow at its respective set point in response to actual airflow measurement, to ensure full pressure independent closed loop control.

This system does not offer any savings in energy consumption because the outcome remains a constant volume system running 7 days a week, 24 hours a day. This system is considered easy to operate and is considered self balancing.

8.3.3.3 *Constant Air Volume (CAV) System "Two Position Control"*

The third level of automation to consider in laboratories is two position control achieved through volume dampers. These dampers may be the type described in Sections 8.3.3.1 or 8.3.3.2 of this Guide, equipped to operate in two fixed positions. The difference is that the two position system has a means to provide two levels of ventilation airflow. Standards and codes typically allow the provision of a lesser ventilation rate when a laboratory is unoccupied. The setback position, or unoccupied mode, is an agreed upon setback that maintains the laboratory in a safe mode when it is unoccupied. It is a system that will save cost during the unoccupied mode; the air flow is reduced, as well as the heating and air movement requirements.

Two separate levels of airflow in a two-position CAV system is usually achieved by adding a control device, typically a variable speed device, on the fan motor power circuit. This enables the fan to be run at a lower speed and deliver less air through the primary AHU and exhaust system when less ventilation air is required. The actual amount by which the supply can be reduced during the unoccupied time is mostly dependent upon the extent that the exhaust air can be reduced.

There are two methods of control which are most often executed as a part of the building automation system.

1. The use of a timer control with the possibility of overriding the setback with a phone call to the building control center.
2. Utilizing motion and/or the laboratory light switch along with a timer allowing the sensing of off hour occupancy through the motion detector or the light switch being on.

This system of operation offers a savings in energy consumption because the air exchange rate can be appreciably reduced during unoccupied mode, which can be as many as two shifts per day during the week and all weekend.

8.3.3.4 *Low Air Volume System – Supports Low Volume Fume Hoods and Can Be a One or Two Position Type of System*

This system is the same as those described in Sections 8.3.3.1, 8.3.3.2, or 8.3.3.3 of this Guide with the difference being that the fume hood chosen is of the low volume design. In this case the end user is already reaping the benefit of the low volume fume hood design. The Variable Air Volume (VAV) system has the ability to vary the amount of supply and exhaust air to closely match the facility and individual laboratory needs at any given time.

8.3.3.5 *Variable Air Volume (VAV) System – the Right Amount of Airflow*

This system offers the combination of air volume control throughout via improved safety and economy of operation. This is the most costly system and it is installed and operated in conjunction with a building automation system. This system operates in conjunction with fume hoods varying the flow of air to meet the required velocity to maintain capture as the sash is positioned. With the fume hood sash fully opened the volume of air required is equal to the width and height of the opening multiplied by the capture velocity. As the sash is lowered the volume of air required is lessened by the width times the reduced height times the capture velocity. With a laboratory that is fume hood intensive the savings in operating cost can be substantial. Closing of the fume hood can support gaining these savings.

In a VAV type of ventilation system, the individual laboratory room air needs will vary, mainly in accordance with the extent that the VAV fume hood sashes are open. If fume hood users open their sashes only when access is actually needed to the inside of the hoods, the amount of air that needs to be supplied to the laboratory rooms can be minimized. Additionally, first time cost savings of reduced sized HVAC equipment that includes air distribution ductwork, primary mechanical systems (boilers, chillers, pumps, etc.), and primary AHUs, can be achieved by performing a diversity calculation. The diversity is calculated based on reasonable and agreed upon assumptions that at any given time some of the many fume hoods will be in the closed position. An example of this is an eight hood laboratory and the diversity being six hoods in the open position and two hoods in the closed position at all times. The diversity calculation would be 75%. This calculation will reduce the size of the fans, as well as the heating and cooling coils, and the ductwork and associated components of the system for the diversified reduced volume.

Communications to the building automation system is the most important aspect of achieving full VAV control. Volumes of air to the room vary with heating, cooling, and pressurization needs. The volumes vary further depending on number of fume hoods and sash position. In addition, the room is affected by areas of containment for solvent mixing and dispensing, as well as ventilation for special equipment needs. The devices typically used on these systems are variable volume dampers which are positioned in response to sensors within the supply and exhaust ductwork of the room. Variable volume dampers housed within the fume hoods are positioned by face velocity sensors or sash position sensors. Setback during unoccupied hours is achieved by timing circuits, as well as occupancy sensors. The system gets more sophisticated as the need to save money over the long term becomes a consideration.

Figure 8.4: VAV Ventilation System Applied To a Laboratory Room

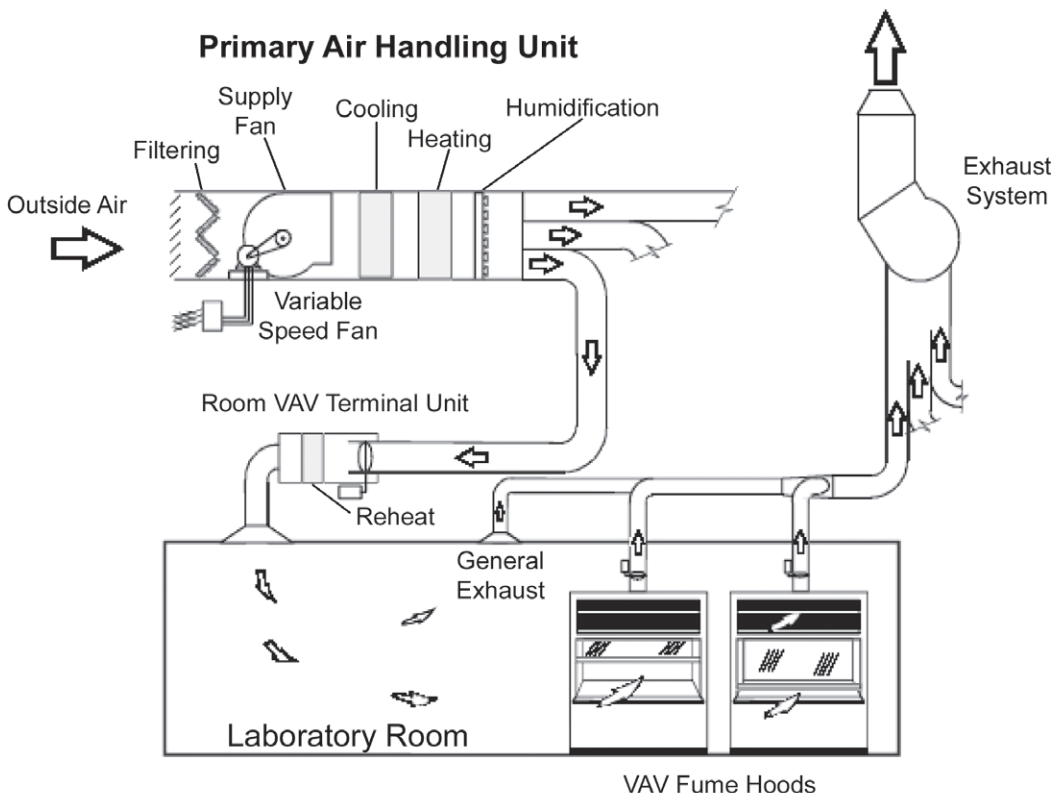
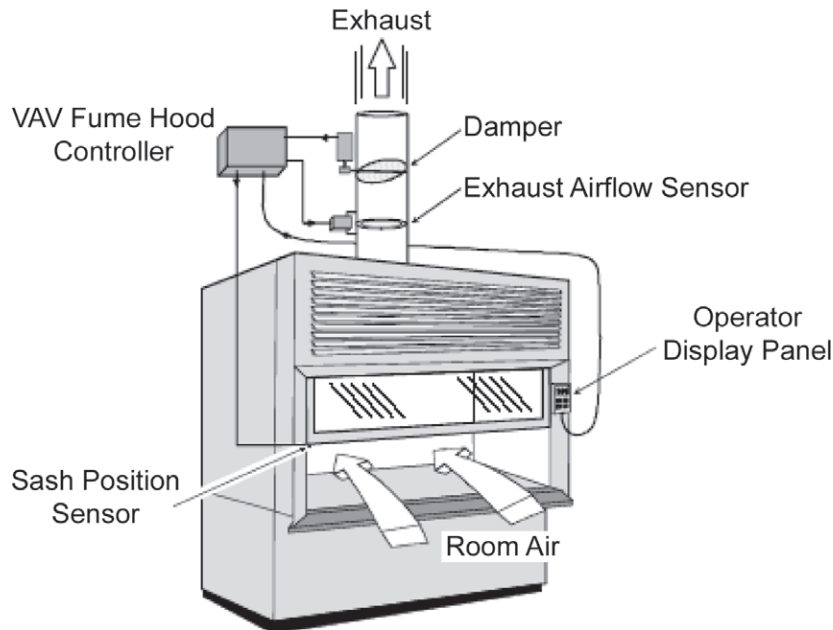


Figure 8.4 illustrates a typical VAV ventilation system applied to a laboratory room having fume hoods. With this system, a sufficient volume of outside air is drawn into the primary AHU where it is filtered and conditioned (cooled or heated and humidified) to meet the needs of the space. Conditioned air (normally at a cooler temperature than the room air) is supplied throughout the entire area served by this AHU. As the air is supplied to the individual laboratory room, it passes through the room's VAV terminal unit, which contains a means to modulate the airflow supplied to the room to meet the actual needs. In addition, the temperature of the supply air can be raised by a room terminal unit reheat coil to meet occupant comfort or other needs of the specific room.

After passing through the room, the air is exhausted out of the laboratory facility by the exhaust system at the required room ventilation rate. In addition, the individual fume hoods have a VAV terminal unit that is varied in proportion to the size of the fume hood sash opening. See Figure 8.5 for the control arrangement, which provides an operator display panel that shows the status and performance of the fume hood. Aside from the basic indication of safe or unsafe operation, there is the option of a digital display of average face velocity, colored indicator lights to call attention to marginal and unsafe conditions, and an audible warning so that laboratory room occupants are alerted of an unsafe fume hood condition. Additional display panel features can include an emergency purge provision to increase the fume hood airflow in case of a spill, fire, or violent reaction.

A variation on the VAV control strategy is demand control. This approach uses a wall mounted sensor to detect chemical (usually Volatile Organic Compounds (VOCs)) levels in the room, adjusting the air volumes to ensure that the chemical levels in the room air remain within specified limits. The company's Environmental, Health, and Safety (EHS) department should be consulted to ensure that the system will be effective for all materials that will be used within the laboratory.

Figure 8.5: VAV Fume Hood and Controls

For further information see the ISPE Good Practice Guide: HVAC [30].

8.3.4 Design Review

Quality laboratory HVAC systems provide comfort and safety for personnel when handling hazardous, potent, or sensitive compounds and reagents, as well as providing protection to the sample under test and conditions necessary for reliability and repeatability of the test. Proper ventilation maintains the health, safety, and well being of personnel and minimizes product contamination risks.

The HVAC system design should be subject to review during design development. This review should consider HVAC equipment failure modes and their potential impact on the quality laboratory operations.

Using an airflow diagram the following should be considered:

- Start-up and shutdown modes
- Setback and unoccupied modes
- Leakage and contamination paths
- Mechanical failure of a fan
- Special sequences of operation for smoke, spill, or other emergency conditions
- Failure of all fans due to electrical interruption, restart under generator conditions, etc.
- Failure of HVAC controls
- Room/zone fail safe modes
- Door interlocks

- Equipment interlocks
- Drainage of condensate from cooling coils and humidifiers
- User action in event of failure (especially if power fails and critical parameters cannot be monitored)
- Additional air flow resistance because of in-line bag filters, ceiling HEPA filters

9 Electrical

9.1 Introduction

This Chapter addresses requirements for electrical systems within quality laboratories. This Chapter covers the concept of critical parameters for the various types of laboratory environments. Specifically, it concentrates on the control of high risk critical parameters as well as design requirements that relate to power distribution, area classification, lighting, grounding, communication, and wiring methods. Consideration is also made of other strong economic and operating factors influencing system design. For further information on Risk Assessment, see Chapter 5 of this Guide.

Detailed design guidance and recommendations are evaluated based on the functionality of the laboratory and its various subsets. Factors such as schedule, budget, reliability, economic analysis criteria, and future growth and flexibility are considered to determine electrical system recommendations for any specific situation.

The costs of electrical requirements may be reduced based on reduced motor power consumption by use of alternative technologies, such as isolation and barrier or closed processing systems.

9.2 General Requirements

The systems discussed in this Chapter are not systems which could potentially impact or invalidate test results, as they do not directly influence the finished product specification. Designs should follow Good Engineering Practice (GEP).

9.3 Power Distribution

Although the power system does not potentially impact or invalidate test results, reliability is important. The effects of loss of power or poor power quality (voltage: interference voltage; frequency, e.g., caused by VFDs) on a critical piece of equipment or instrument should be considered and the resulting failure conditions examined.

It is recommended that for emergency conditions the power availability includes Uninterruptible Power Supply (UPS) and appropriate line conditioning for critical processes. Consideration for UPS systems and line conditioners should be made for laboratory equipment such as HPLCs and their associated computer support equipment so that a controlled shut down can be accomplished and stored data and programs can be saved.

Redundant fan systems may be employed in support of fume hoods to assure constant performance should one fail avoiding any contamination of the environment while protecting the scientist. These fans may be large and not easily backed up. In case of power failure, the laboratory may need to be evacuated.

Note: Consideration should be given to a three-phase/three-wire system as it is cost effective during construction as well as during operation.

9.4 Area Classification

Installation of electrical equipment should comply with the requirements of the NFPA 70 [34] or other local country codes (or regional equivalents), such as the NFPA 45 [6]. The installation of electrical equipment should be rated appropriately regarding explosion hazard and in accordance to NEMA specifications.

While electrical area classification is not a GMP issue, it may affect location and type of equipment. It should be considered in conjunction with level of protection requirements.

In regard to both cost and cleanability, considerations should be made to locate light switches in corridors outside of process rooms or in other electrically non-classified rooms. This would allow for the use of switches rated for general-purpose use, which are much less expensive and easier to keep clean, or which have been moved to an area where cleanability is less of a concern.

These advantages should be weighed against convenience to the operator, especially if it involves leaving a controlled area.

Laboratories requiring solvents for the HPLC process should be evaluated. Typically, an area is designated for solvent blending as well as solvent dispensing. This area should be hazard rated requiring ventilation and specific power requirements. Consideration should be given to providing backup power to the facility especially where air movement is used to maintain the hazard rating of a given area. Additionally, electrical exclusion zones may be appropriate in hazardous working areas.

9.5 Lighting

Recommended lighting and lighting fixtures for GEP include:

1. Lighting level is recommended to be at least 70 ft. candles (750 lux) in the laboratory work areas. Common travel areas should be in compliance with local energy standards. For US installations, one may want to follow the recommendations of the Illumination Engineering Society of North America.
2. All lighting fixtures should be accessible to allow proper maintenance, including the changing of lamps and the repair or replacement of the ballast. This may require the remote placement of the ballast.
3. All lighting fixtures should be properly rated for the area in which they are used, including electrical classification and surface temperature.
4. All lighting fixtures used in laboratory areas should allow for cleaning. Where needed, the fixture should be able to withstand the pressure and temperature of any water streams used for wash down. It may be necessary to use a glass shield instead of plastic.
5. The lighting plan should provide adequate lighting and ease of maintenance.
6. The color rendition and intensity of lighting equipment used for inspection, cleaning, or viewing of colorimetric titrations may be considered critical. If so, they should be considered in conjunction with the inspection or cleaning of equipment.
7. Emergency lighting should be included as needed by the NFPA 101: Life Safety Code [35]. Emergency lighting is expensive and difficult to keep clean; therefore, light fixtures with battery pack should be considered as it is cost effective and, easy to clean and maintain. This battery pack will allow the fixture to provide emergency illumination. Consideration should be given to make provision for an un-switched source for the emergency lighting ballast.

9.6 Grounding

Grounding methods used in a laboratory should be arranged and designed to prevent accumulation of dust or foreign materials or be accessible for cleaning. For example, a static ground connection may be designed using an insulated wire instead of a bare wire. The insulated wire would be less likely to accumulate dusts and would be easier to clean.

In a case with portable equipment, a static grounding reelite should be located in the process room. Wherever flammable liquids are dispensed or transferred grounding cable reelites should be considered. Since grounding reelites are difficult to keep clean, it may be necessary to locate them behind a recessed access panel.

The effect of improper grounding upon electronic equipment may be considered a critical issue in isolated cases; if so, it should be considered in conjunction with the electronic equipment. Isolated ground receptacles should be considered. In areas for analytical balances and where organic solvents or other explosives are handled grounding is necessary.

9.7 Telephones, Paging, and Radio Systems

All communication equipment used in a GMP area should be designed to allow for cleaning. This may require the equipment to be rated for wet locations. Communication equipment used in certain GMP areas should be arranged and designed to prevent any accumulation of dust or foreign materials. For example, paging speakers might be recessed into the wall or ceiling in such areas.

The effect of communication system Radio Frequency Interference (RFI) upon some electronic equipment may be considered critical in isolated cases; if so, the selection of the communication system should be considered in conjunction with the electronic equipment.

9.8 Laboratory Information Management System

The Laboratory Information Management System (LIMS) is in use in quality laboratories for managing the acquisition, reporting, and storage of data. In many laboratories, the LIMS is a manual system using quality control records, hard copied protocols, and operational documents along with the scientist's notebook. If there is a paper based system with stand alone computerized instruments, such as HPLCs, it is important to incorporate the printouts into the process giving the scientist an audit trail and allowing checks to be made on the data in the logbook against electronic data.

In developing the electrical requirements for the quality laboratory it is important to know the LIMS system in use. Computerized LIMS systems may supplement existing manual systems or replacing manual systems with a fully computerized system. Computers which are stand alone automation and control systems as well as data collection devices associated with testing equipment are not part of the LIMS system. These systems perform only limited functions related to a single activity such as the automation and control dedicated to a single device such as the GC or HPLC. These control type computers typically are integrated into the LIMS computerized system which can be beyond the bounds of the laboratory to quality management and reporting centers.

The LIMS equipment has to be considered when developing the overall laboratory electrical and automation needs. Dedicated circuits are a consideration that will eliminate power fluctuations caused by other laboratory equipment. Uninterruptible power supplies either dedicated at the circuit level or centralized should be considered. Usually the philosophy is protection of the equipment rather than maintaining equipment operation during power failures. UPS systems, sized to allow the controlled shut down of this equipment, usually is the choice for cost considerations as well as operation efficiency and safety.

In support of the LIMS network throughout designers should consider what is provided in the way of communications wiring and point of use jacks. Additionally, specialty lighting needs to be considered to avoid glare and allow for the comfort of the operator during long term use.

9.9 Wiring Methods

Wiring should be designed to allow proper maintenance including the accessibility to junction boxes and outlet boxes.

Conduits and raceways should be labeled for ease of identification.

Wiring methods and materials should be compatible with the process materials. For example, a PVC coated conduit may be needed.

Wiring should meet the requirements of the latest edition of the NEC.

Signal and power wiring should be separated to avoid noise crosstalk.

Wiring in GMP areas should allow for cleaning of exposed surfaces. For example, wiring devices may be designed to withstand washes and to prevent any accumulation of dust or foreign materials. This may require the use of flush mounted boxes, and the placement of conduits in areas outside the operating areas, with minimum penetrations into the operating area. Sealing conduits between areas may be necessary.

10 Laboratory Site Utility and Support Systems

10.1 Introduction

In addition to the utilities normally needed such as domestic water and standard electricity, specialty support systems such as purified water, compressed air, and site support systems infrastructure need to be considered in support of the quality laboratory. The size and extent of a new or expanded laboratory can trigger a power substation expansion or require a new stand alone substation. Centralized boiler, chiller, and emergency generator capacity should be tested to meet the new requirements.

Chilled water requirements, typically provided at a temperature of 43°F (6°C) or cooling to relieve the high heat stress generated by specific devices should be considered. For autoclaves, a sufficient supply of steam and return of condensate will be needed or as an alternative sufficient electricity to generate steam in place with a supplier provided steam generator. A supply of compressed air, usually with a minimum pressure requirement of 6 bar (87 psi) is necessary to operate larger autoclaves.

Varying grades of water are essential to various use points within a laboratory. For use points such as autoclaves and environmental chambers, pretreatment of the water helps to avoid buildup within the steam generator or humidifier systems. For the various quality tests, the necessary level of water purity can be achieved by point of use final filtration systems supplied by the potable water system. Where the laboratory is supplied from the same generation system as the manufacturing area, it may be necessary to separate the systems, using a break tank to remove any risk of cross contamination.

10.2 Laboratory Water

Laboratory water requirements may differ from those for manufacturing. This Chapter provides an overview of the different laboratory water purification and distribution approaches available, as well as a step by step method to help to determine what type of system design will best meet a the user's needs.

10.2.1 System Design Considerations

Water quality requirements for laboratory purposes vary widely depending upon the type of analysis to be performed and the governing organization.

The determination of laboratory water needs may be complex, as pharmaceutical waters are focused on manufacturing applications. Non-pharmacopeial related agencies, which cover water quality for laboratory purposes, such as ISO, ASTM, CLSI, typically are used as a source of information.

The wide range of user needs leads to a variety of possible approaches. Specific laboratory user information is needed to design a cost effective and efficient solution. The design team should provide information including, but not limited to, the issues listed:

Defining User Needs

1. What laboratory tasks will require water?
2. What quality of water is needed for each task?
3. What are the regulations that must be complied with?
4. What is the location of each task?
5. Is there a work pattern for each task?

6. Can these tasks be clustered in various laboratory locations (e.g., by water quality needed, analytes of concern)?
7. Can one group of tasks be served by one POU outlet?
8. How much water is needed at each POU and by task or task group?

Solution Design Based on User Needs

1. What points of use are needed?
2. What water characteristics (quality, etc.) are needed at each point?
3. What purification technologies could be used to produce the water qualities required?
4. What types of distribution system could be suitable?
5. Other parameters to be considered, such as:
 - a. Building characteristics
 - b. Laboratory architecture
 - c. Criticality of water in the process
 - d. Water source options
 - e. Ergonomics of use points and drains
 - f. Economics

10.2.2 Determining User Needs

10.2.2.1 Quality Needs

Laboratories often require a selection of waters with distinct purity specifications, dependent upon analytical applications and regulatory requirements. Compendial procedures will need to use compendial specified waters.

Potential impurities in PW may be grouped into:

- Inorganic ions (typically monitored as conductivity or resistivity, or by specific chemical tests)
- Organic compounds (typically monitored as TOC or by specific tests)
- Bacteria (monitored by cultivative total microbial plate counts or other methods)
- Endotoxins (monitored by LAL test)
- Nucleases (monitored by specific enzyme assays)
- Particulates (typically managed by filtration, but not monitored usually)
- Gases (typically managed by degas/purification equipment and monitored by specific tests, if required)

Within any of these groups, particular substances also may have a specific interference in a particular test, such as components that produce over-lapping peaks in chromatography or contaminants in the water that are identical to the analytes in the test sample.

Table 10.1 provides guidance regarding the types of impurities that may be important for an application when choosing a water system. Quantified impurity levels are not provided because of the wide variations in water purity needed within any one type of application. Table 10.1 is intended primarily for the design engineer who may not have an analytical laboratory background, and could serve as a basis of discussion with laboratory personnel regarding specific water grade/purity needs.

Table 10.1: Importance Level (Widely Observed) for Parameters/Contaminants in Different Techniques*

Technique	Application Sensitivity**	Importance Level of the Water Contaminants					
		Inorganic Ions	Organic Compounds	Particulates	Bacteria	Endotoxin	Nuclease
Bacterial Culture	Low – High	Low	Medium	Medium	Medium	Low	Low
Clinical Biochemistry	High	Medium	Low	High	Medium	Low	Low
Electrochemistry	Low – High	Medium – High	Medium – High	Medium	Low – High	Very Low	Very Low
Electrophoresis (Polyacrylamide Gels)	High	High	High	Medium	High	Low	Low (High for Protease)
Electrophoresis (Agarose Gels)	High	High	Medium	Medium	High	Low	High
Electrophysiology	Low – High	High	High	Medium	High	High	High
ELISA	Low – High	Low	Medium	Medium	High	Low	Low
Endotoxin Determination	Medium – High	Low – High	Medium – High	Medium – High	High	High – Very High	Low
Flame-AAS	Low – High	High	Low	Medium	Medium	Very Low	Very low
GF-AAS	High	Very High	High	High	High	Low	Low
GC	Low – High	Low – High	Medium – High	Medium	Low – High	Very Low	Very Low
GC-MS	High	High	High	Medium	High	Very Low	Very Low
General Wet Chemistry	Low – High	Low	Low	Medium	Low	Very Low	Very Low
Glassware Washing	Low – High	Low – High	Medium – High	Medium	Low – High	Low	Very Low – Low
Histology	Low – High	Low	Medium	Medium	Medium	Medium	Very Low
HPLC	Low – High	Low – High	Medium – High	High	Low – High	Low	Very Low – Low
LC-MS	High	High	High	High	High	Low	Low
Hydroponics	Low – High	Low	Medium	Medium	Low	Very Low	Very Low
ICP-AES	High	High	Medium	Medium	High	Very Low	Very Low
ICP-MS	High	Very High	High	High	High	very Low	Very Low
Immunocytochemistry	High	High	High	High	High	High	Medium
Ion Chromatography	Low – High	Medium – Very High	Medium – High	High	Medium – High	Very Low	Very Low

Table 10.1: Importance Level (Widely Observed) for Parameters/Contaminants in Different Techniques* (continued)

Technique	Application Sensitivity**	Importance Level of the Water Contaminants					
		Inorganic Ions	Organic Compounds	Particulates	Bacteria	Endotoxin	Nuclease
Mammalian Cell and Tissue Culture	High	High	High	High	High	Very High	High
Microbiological Media Preparation	Low – High	Low	Medium	Medium	High	Low	Very Low
Microbiological Analysis	Low – High	Low	Medium	Medium	High	Medium	Low
Molecular Biology	High	High	High	High	High	Low – Medium	Very High
Monoclonal Antibody Research	High	High	High	High	High	Very High	Low
Plant Cell and Tissue Culture	High	High	High	High	High	Medium	Medium
Radioimmunoassay	Low – High	Low	Medium	Medium	High	Very Low	Very Low
Solid Phase Extraction	High	Medium	High	Medium	Medium	Low	Low
Spectrophotometry	Low – High	Low	Medium	High	Low	Very Low	Very Low
Steam Generation	Low – High	Low	Medium	Medium	Low	Low	Very Low
TOC Determination	High	High	High	Medium	High	Medium	Low
Trace Metal Detection	High	Very High	High	Medium	High	Low	Low
Notes: 1. Table 10.1 is provided as an example of the widely observed importance level of a selection of water quality parameters/contaminants in different laboratory techniques. The level of importance depends on the sensitivity expected for the application, the material used, the method applied, and the regulatory constraints. A range of levels is listed for a number of attributes because of a wide variety in water purities needed for the many forms of the technique and types and levels of analytes involved. 2. Application sensitivity refers to the level of analyte detection, quantitation, or contaminant impact expected with that application. Typically: High = ppb or higher sensitivity levels, Medium = ppm to ppb sensitivity levels, and Low = ppm or lower sensitivity levels.							

Table 10.2 lists the purity specifications for commonly used laboratory water grades. These should be considered as minimum specifications. Additional considerations may be listed in source documentation for these water grades. A laboratory's water purity needs for particular applications may exceed minimum requirements for a specific attribute of a given water grade. More stringent requirements and additional purification technologies may be applied to maintain several attributes at lower levels. Conversely, the most suitable water grade for a particular application may exceed the purity needs of specific attributes for the application. Unless otherwise mandated by regulatory requirements, the water purity provided may be optimized with the water purity needed. Maintaining a higher water purity than needed by applications can be costly and usually is unnecessary, unless it is a regulatory requirement or expectation.

Table 10.2: Specification Summary for Various Non-Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories

Organization/ Reference	ISO3696 (1995) Water for Analytical Laboratory Use			ASTM D1193 (2006) ^(Note 1) Standard Specification for Reagent Water				ASTM D5196 (2006)	CLSI 4th Ed (2006)
Water Grade or Type	Grade 1	Grade 2	Grade 3	Type I	Type II	Type III	Type IV	Standard Guide for Bio-App lications Grade Water	CLRW (Specified quantitative attributes only)
Specified Source and Purification Approaches	Grade 2 Source; RO +0.2 µm Filt, or DI +0.2 µm Filt, or Re-Dist (in glass)	Multiple- Dist. or DI or RO +Dist	Single- Dist. or DI or RO	< 20 µS/cm Source (Distillation, Equiv.); MB-DI +0.2 µm Filt	Distillation or Equiv.	Distillation, DI, EDI, and/or RO +0.45 µm Filt	Distillation, DI, EDI, and/or RO	Drinking Water Source; Suitable process (es)	*
pH value at 25°C (Inclusive range)	*	*	5.0 to 7.5	*	*	*	5.0 to 8.0	*	*
Conductivity µS/ cm @ 25°C, max	0.1	1.0	5.0	0.0555	1.0	0.25	5.0	*	*
Resistivity MΩ- cm @ 25°C, min	*	*	*	18	1.0	4.0	0.2	18.2 ±1 ^(Note 2)	10
Temperature Compensated Conductivity Measurement?	YES	YES	YES	YES	YES	YES	YES	YES	YES
TOC (as C), max	*	*	*	50 µg/L (50 ppb)	50 µg/L (50 ppb)	200 µg/L (200 ppb)	*	20 µg/L (20 ppb)	500 ppb
Oxidizable Substances (Permanganate Red. Subst.)	*	*	*	*	*	*	*	*	*
Oxidizable Matter O ₂ Content mg/L, max	*	0.08	0.4	*	*	*	*	*	*
Absorbance at 254 nm and 1 cm Optical Path Length, Absorbance Units, max	0.001	0.01	*	*	*	*	*	*	*
Residue after Evaporation on Heating at 110°C, mg/Kg, max	*	1	2	*	*	*	*	*	*
Residue after evaporation on heating at 105°C, mg/100mL, max	*	*	*	*	*	*	*	*	*
Silica (as SiO ₂) mg/L, max	0.01	0.02	*	*	*	*	*	*	*
Total Silica µg/L, max	*	*	*	3	3	500	*	*	*

Table 10.2: Specification Summary for Various Non-Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories (continued)

Organization/ Reference	ISO3696 (1995) Water for Analytical Laboratory Use			ASTM D1193 (2006) ^(Note 1) Standard Specification for Reagent Water				ASTM D5196 (2006)	CLSI 4th Ed (2006)
Water Grade or Type	Grade 1	Grade 2	Grade 3	Type I	Type II	Type III	Type IV	Standard Guide for Bio-App lications Grade Water	CLRW (Specified quantitative attributes only)
Specified Source and Purification Approaches	Grade 2 Source; RO +0.2 µm Filt, or DI +0.2 µm Filt, or Re-Dist (in glass)	Multiple- Dist. or DI or RO +Dist	Single- Dist. or DI or RO	< 20 µS/cm Source (Distillation, Equiv.); MB-DI +0.2 µm Filt	Distillation or Equiv.	Distillation, DI, EDI, and/or RO +0.45 µm Filt	Distillation, DI, EDI, and/or RO	Drinking Water Source; Suitable process (es)	*
Sodium µg/L, max	*	*	*	1	5	10	50	*	*
Chloride µg/L, max	*	*	*	1	5	10	50	*	*
Heterotrophic Bacteria Count cfu/mL, max	*	*	*	Type A: 0.01 (1 cfu/ 100 mL)	Type A: 0.01 (1 cfu/ 100 mL)	Type A: 0.01 (1 cfu/ 100 mL)	Type A: 0.01 (1 cfu/ 100 mL)	1 (100 cfu/ 100 mL)	10
	*	*	*	Type B: 0.1 (10 cfu/ 100 mL)	Type B: 0.1 (10 cfu/ 100 mL)	Type B: 0.1 (10 cfu/ 100 mL)	Type B: 0.1 (10 cfu/ 100 mL)		
	*	*	*	Type C: 10 (1000 cfu/ 100 mL)	Type C: 10 (1000 cfu/ 100 mL)	Type C: 10 (1000 cfu/ 100 mL)	Type C: 10 (1000 cfu/ 100 mL)		
Bacterial Endotoxins EU/mL or IU/mL	*	*	*	Type A: 0.03	Type A: 0.03	Type A: 0.03	Type A: 0.03	0.01	*
	*	*	*	Type B: 0.25	Type B: 0.25	Type B: 0.25	Type B: 0.25		
	*	*	*	Type C: *	Type C: *	Type C: *	Type C: *		
Nitrates ppm, max	*	*	*	*	*	*	*	*	*
Aluminium ppb, max	*	*	*	*	*	*	*	*	*
Heavy Metals ppm, max	*	*	*	*	*	*	*	*	*
Other Inorganic Attributes	*	*	*	*	*	*	*	*	*
Particulate and Colloids	Implied limitation by 0.2 µm filter	*	*	Implied limitation by 0.2 µm filter	*	Implied limitation by 0.45 µm filter	*	*	Implied limitation by 0.22 µm filter

Table 10.2: Specification Summary for Various Non-Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories (continued)

Organization/ Reference	ISO3696 (1995) Water for Analytical Laboratory Use			ASTM D1193 (2006) ^(Note 1) Standard Specification for Reagent Water				ASTM D5196 (2006)	CLSI 4th Ed (2006)
Water Grade or Type	Grade 1	Grade 2	Grade 3	Type I	Type II	Type III	Type IV	Standard Guide for Bio-Applications Grade Water	CLRW (Specified quantitative attributes only)
Specified Source and Purification Approaches	Grade 2 Source; RO +0.2 µm Filt, or DI +0.2 µm Filt, or Re-Dist (in glass)	Multiple-Dist. or DI or RO +Dist	Single-Dist. or DI or RO	< 20 µS/cm Source (Distillation, Equiv.); MB-DI +0.2 µm Filt	Distillation or Equiv.	Distillation, DI, EDI, and/or RO +0.45 µm Filt	Distillation, DI, EDI, and/or RO	Drinking Water Source; Suitable process (es)	*
Nucleases, Proteases	*	*	*	*	*	*	*	Limited as needed for certain applications	*

Notes:

- * Not Specified, Not Required, Not Applicable, or No Limit
- 1. Water may be produced with alternate technologies if specifications are met and water is appropriate for the application.
- 2. If in-line resistivity testing is not possible, then the total concentration of inorganic ions must not exceed 1 µg/L for cations such as Aluminum, Ammonium, Arsenic, Cadmium, Chromium, Cobalt, Copper, Iron, Lead, Magnesium, Nickel, Potassium, Sodium, Titanium, Zinc, and anions such as Chloride, Nitrate, Phosphate, Sulfate, and Fluoride.

Table 10.3: Specification Summary for Various Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories

Organization/ Reference	European Pharmacopoeia 7.0 (2011)			Japanese Pharmacopoeia 16 (2011)		US Pharmacopeia 34 (2011)	
	Purified Water	Water for Injection	Highly Purified Water	Purified Water	Water for Injection	Purified Water	Water for Injection
Specified Source and Purification Approaches	Drinking Water Source; Dist. or DI or RO or other suitable methods	Drinking Water Source; Distillation	Drinking Water Source; e.g., 2-pass RO + suitable techniques such as UF and DI	Water Source; RO, UF, Deionization, Distillation, or a combination thereof	Water or Purified Water Source; Distillation or RO-UF	Drinking Water Source; Suitable Process	Drinking Water Source; Distillation or equiv./superior process
pH value at 25°C (inclusive range)	*	*	*	*	*	*	*
Conductivity µS/cm @ 25°C, max	5.1 ^(Note 1)	1.3 ^(Note 1)	1.3 ^(Note 1)	2.1 ^(Note 2) [1.3 ^(Note 1) in JP Info Ch. 21]	2.1 ^(Note 2) [1.3 ^(Note 1) in JP Info Ch. 21]	1.3 ^(Note 1)	1.3 ^(Note 1)
Resistivity MΩ-cm @ 25°C, min	*	*	*	*	*	*	*
Temperature Compensated Conductivity Measurement?	NO (YES, if validated)	NO (YES, if validated)	NO (YES, if validated)	*	*	NO	NO
TOC (as C), max	0.5 mg/L (500 ppb) ^(Note 3) [Alt to Ox Sub]	0.5 mg/L (500 ppb) ^(Note 3)	0.5 mg/L (500 ppb) ^(Note 3)	0.50 mg/L (500 ppb) ^(Note 3)	0.50 mg/L (500 ppb) ^(Note 3)	Instrument response to 0.50 mg/L standard (500 ppb) ^(Note 3)	Instrument response to 0.50 mg/L standard (500 ppb) ^(Note 3)
Oxidizable Substances (Permanganate Red. Subst.)	Negative to test [Alt to TOC]	*	*	*	*	*	*
Oxidizable Matter O ₂ Content mg/L, max	*	*	*	*	*	*	*
Absorbance at 254 nm and 1 cm Optical Path Length, Absorbance Units, max	*	*	*	*	*	*	*
Residue after Evaporation on Heating at 110°C, mg/Kg, max	*	*	*	*	*	*	*
Residue after evaporation on heating at 105°C, mg/100mL, max	*	*	*	*	*	*	*
Silica (as SiO ₂) mg/L, max	*	*	*	*	*	*	*
Total Silica µg/L, max	*	*	*	*	*	*	*

Table 10.3: Specification Summary for Various Pharmacopeial Water Grades that may be used in Pharmaceutical Laboratories (continued)

Organization/ Reference	European Pharmacopoeia 7.0 (2011)			Japanese Pharmacopoeia 16 (2011)		US Pharmacopoeia 34 (2011)	
Water Grade or Type	Purified Water	Water for Injection	Highly Purified Water	Purified Water	Water for Injection	Purified Water	Water for Injection
Specified Source and Purification Approaches	Drinking Water Source; Dist. or DI or RO or other suitable methods	Drinking Water Source; Distillation	Drinking Water Source; e.g., 2-pass RO + suitable techniques such as UF and DI	Water Source; RO, UF, Deionization, Distillation, or a combination thereof	Water or Purified Water Source; Distillation or RO-UF	Drinking Water Source; Suitable Process	Drinking Water Source; Distillation or equiv./superior process
Sodium µg/L, max	*	*	*	*	*	*	*
Chloride µg/L, max	*	*	*	*	*	*	*
Heterotrophic Bacteria Count cfu/mL, max	Action Level 100 [in monograph, mandatory]	Action Level 0.1 (10 cfu/ 100 mL) [in monograph, mandatory]	Action Level 0.1 (10 cfu/ 100 mL) [in monograph, mandatory]	Action Level 100 [in Info Ch. 21, non-mandatory]	Action Level 0.1 (10 cfu/ 100 mL) [in Info Ch. 21, non-mandatory]	Max. Action Level 100 [in Info Ch. 1231, non-mandatory]	Max. Action Level 0.1 (10 cfu/ 100 mL) [in Info Ch. 1231, non-mandatory]
Bacterial Endotoxins EU/mL or IU/mL	< 0.25 (dialysis solutions only)	<0.25	< 0.25	*	< 0.25	*	< 0.25
Nitrates ppm, max	0.2	0.2	0.2	*	*	*	*
Aluminium ppb, max	10 (dialysis solutions only)	10 (dialysis solutions only)	10 (dialysis solutions only)	*	*	*	*
Heavy Metals ppm, max	0.1 ^(Note 4)	*	*	*	*	*	*
Other Inorganic Attributes	*	*	*	*	*	*	*
Particulate and Colloids	*	*	*	*	*	*	*
Nucleases, Proteases	*	*	*	*	*	*	*

Notes:

- * Not Specified, Not Required, Not Applicable, or No Limit
- 1. In-line/Stage 1 Conductivity specification at 25°C with other values at other temperatures. EP's WFI and HPW and USP's PW and WFI additionally have off-line Stage 2 and 3 specifications which may alternatively be met.
- 2. Performed as an atmosphere and temperature equilibrated test. Alternatively, per JP Chapter 21, the test may be performed in-line with the specified limit at 25°C and other values at other temperatures. There is no USP <645> Stage 3 option in JP.
- 3. Due to significant figures, EP's TOC specification is not greater than 549 ppb, whereas JP's and USP's is not greater than 504 ppb.
- 4. Not required if Conductivity meets WFI specifications.

The water grades denoted in Tables 10.2 and Table 10.3 frequently do not specify limits for all the groups of impurities. This is particularly marked for the USP [36], EP [37], and JP [38] specifications for grades of pharmaceutical water; such grades may not be appropriate for all laboratory related uses. For water to conform to a particular application, its suitability for the intended use should be verified and the continuation of purity should be ensured.

In addition to their purity specifications, waters which need to meet regulatory requirements may have additional requirements, including:

- Which feed water is to be used
- Limitations on how the water is to be purified
- How and where the purity attributes are to be monitored
- How the monitoring equipment is to be calibrated
- How the purification system performance is to be trended and maintained

Where a particular type of water is specified, e.g., when using an ASTM method, these requirements must be met by the purification system selected.

Where laboratory water quality needs differ from those in manufacturing (e.g., microbiological limits), it may be necessary to establish laboratory water specifications to be met to avoid requiring the laboratory to use water attributes and limits to manufacturing water standards that are not required.

10.2.2.2 *Quantity Needs*

The water demand profile is needed to size the water generation system(s) and determine if any distribution loops are needed. The water demand/diversity information should include volume delivery information, including maximum demand, batch or continuous delivery needs as well as maximum and average flow rates, the time required to deliver the specified quantity of water, frequency of use or operation, pressure, and temperature. These values should be obtained or estimated in real time, as well as over an operating shift or day.

Normal and worst case water usage profiles should be prepared for 24-hour and 7 day periods. This information, along with diversity of use, dictates the design specification for the system(s).

10.2.2.3 *Data Collection*

Table 10.4 provides an example table for data collection.

Table 10.4: Example User and Water Data Collection Worksheet

User		Water Quality Need		Water Quantity Need							
Location (Note 1)	Lab Analysis or Equipment	Regulatory Requirement if Applicable (E.G., GMP, GLP, ISO, CLSI)	Purity of Water Needed as Required by Equipment or Procedure	Use Rate of Equip. or Task ^(Note 2)	Duration	Estimated Volume per Use	Number of Uses per Day ^(Note 3)	Volume Used per Day	Water Temp. Needed	Water Pressure Needed	Comments (Note 3)

Notes:

- 1. Floor, room, and area (e.g., tech support or QA).
- 2. For example: glassware washer, pipette washer, autoclave, or task/analysis.
- 3. Often several uses may be always sequenced together. For example, glass washer and autoclave. This must be noted in the comment section to ensure that Step 1 (glass wash cycle) is not considered without Step 2 (autoclave wash cycle) in a demand profile.

Water use information should be compiled and grouped according to the layout and common test requirements. For example, one POU may be used to supply water for several laboratory analyses.

10.2.2.4 Monitoring Needs

Monitoring requirements for water purification systems should be assessed. It should be established that a water purification system produces water of suitable purity, which is fit for purpose. Testing should be performed to ensure good component operation and to minimize operational cost and quality risks; however, it may not be practical or cost-effective to monitor all, or even many, potential impurities after each stage of purification in laboratory equipment. Tests to ensure that the water purification and distribution systems are working adequately usually are performed in addition to the measurement of specific control checks (e.g., baseline blanks) as part of test procedures. A general approach is shown in Table 10.5.

Table 10.5: Monitoring Requirements for Types of Impurities

Impurity Type	Monitoring	Type	Location	Frequency
Ions	Conductivity or Resistivity	In-line	Pre/Post RO, post IX, post EDI, product	During operation
Organics	TOC	On-line or off-line	Product	During operation or occasionally
Particles	Particle count*	On-line	Product	Very rarely used
Bacteria	TVC, epifluorescence	Off-line	Product	Typically weekly (use dependent)
Endotoxins	LAL	Off-line	Product	Occasionally (use dependent)
Large Bio-active Molecules	Specific tests	Off-line	Product	Occasionally (use dependent)
Gases	Specific tests	On-line	Product	As required
*Normally managed by filtration.				

Key parameters that should be measured or used include:

- Resistivity for ionic contamination
- TOC for organic impurities
- Total viable counts as a measure of bio-burden

Where biological contamination is critical, measurements of endotoxin and nuclease levels also can be valuable. Concentrations of weakly-ionized silicon and boron species may be controlled by suitable system design, and if required, specific monitoring.

Generally, parameters are measured in the product water or as close to the dispense point as practical. This gives values for the water actually used and also avoids breaking into the water purification circuit. The exception is resistivity which is measured in-line at several points. It provides an indication of RO, EDI, and ion exchange performance and can be measured after, and on occasion, before (calculation of % ionic rejection) these technologies.

The frequency of off-line measurements varies considerably. It should be based on an assessment of the effects of loss of water purity and the likelihood of a problem. Confidence, obtained by regular, relatively frequent logging initially, enables the period between analyses to be decreased with time. Particular care should be taken after activities that may introduce impurities, such as changing components and sanitization.

Based on system design, scale differences, or regulatory requirements, the same design concepts normally are not applied for similar functionality exactly or systematically to both large (production) systems and small (laboratory) water systems. Parameters monitored in large water systems may not be systematically measured in small systems. Comparing the rationale of monitoring to the constraints involved, e.g., the importance of making a microbiological measurement between two purification stages that are located close to one another, compared to the risks/constraints of installing a sampling port between the two purification elements, may be used as justification for the difference in approach. This difference in approach also could be linked to the water system design selected. A laboratory water system should not be considered as a “black box.” The control of intermediate water purification operations in the

system allows the anticipation of problems, and subsequently improves compliance with good practices; therefore, based on the regulatory requirements, an analysis of the equipment design/content may be required to ensure compliance.

The extent of monitoring required depends on the size and complexity of the system(s).

10.2.2.5 Compliance

Laboratory equipment installed in pharmaceutical laboratories or used for laboratory applications may require compliance with specific regulations including:

- Quality management systems (e.g., Good Laboratory Practices, GMPs)
- Pharmacopeia (e.g., USP [36], EP [37], and JP [38])
- CFRs or local regulations
- Other water standards

Additional regulations also may be requested (e.g., CE, UL marks) as a general organizational policy requirement or for local legal compliance; therefore, it is important to define the list of compliances required to select the final laboratory water solution.

10.2.2.6 Laboratory Environmental Needs

A comprehensive review of all the laboratory work spaces requiring access to laboratory water should be performed to select suitable systems, which meet user requirements, including:

- Quantity of points of use needed
- Location of the different areas needing water and the possibility to group them ,
- Location of the POU (e.g., rooms, elevation, at sinks)
- Use constraints defined by some procedures including:
 - Maximum distance to the use location
 - Filling large containers
 - Large flow rates
- Site-location constraints including:
 - Limited access (e.g., cleanroom, off hours use)
 - Contaminating atmospheric conditions (e.g., volatile organics, corrosive vapors)
 - Noise considerations
 - Utilities available (e.g., electricity, source water, drain)
 - Space available

10.2.2.7 Costs

A comprehensive cost analysis that includes the direct and indirect life cycle costs of the proposed laboratory water choice(s) should be developed by the laboratory water owner.

Direct life cycle costs for the system include, e.g.:

- Capital costs including:
 - Engineering
 - Equipment and material procurement
 - Construction/installation
 - Commissioning/qualification
- Operating costs including:
 - Consumable (e.g., filters)
 - Utilities (e.g., water , energy)
 - Calibration
 - Maintenance
 - Training

Note: more automated systems may be more expensive to purchase and less expensive to operate.

Indirect costs are an estimate of the potential costs in case of problems. Such an analysis should cover, as a minimum, the costs associated with water quality or quantity problems (e.g., when facing a lack of suitable water during several hours or days).

10.2.3 Water Purification Technologies

There are various combinations of purification technologies with which it is possible to produce the waters that may be required in laboratories. The technologies are similar in type to those used for production purposes, usually on a smaller scale and different in detail. For further information, see the ISPE Water and Steam Systems Baseline® Guide (Second Edition) [39].

10.2.4 Laboratory Water Supply Options

There are a range of means of providing pure water for laboratory applications. For applications of low volume or which are localized to one area, the choice usually is between a single dedicated water purification system, typically fed from municipal water, and the use of packaged water.

For larger scale installations, a water purification solution can be based on the combination of one or more approach, including:

- A purification system with permanent extensive distribution system to the entire building
- One or more local purification systems with local distribution loop to a floor or laboratory

- Small purification system with local storage and loop
- Individual point-of-use units supplied with city water
- An extension of a distribution system used for production of pharmaceuticals
- Water polishers or dispensers fed from any of these distribution systems

10.2.4.1 Water Generation System and Distribution Options

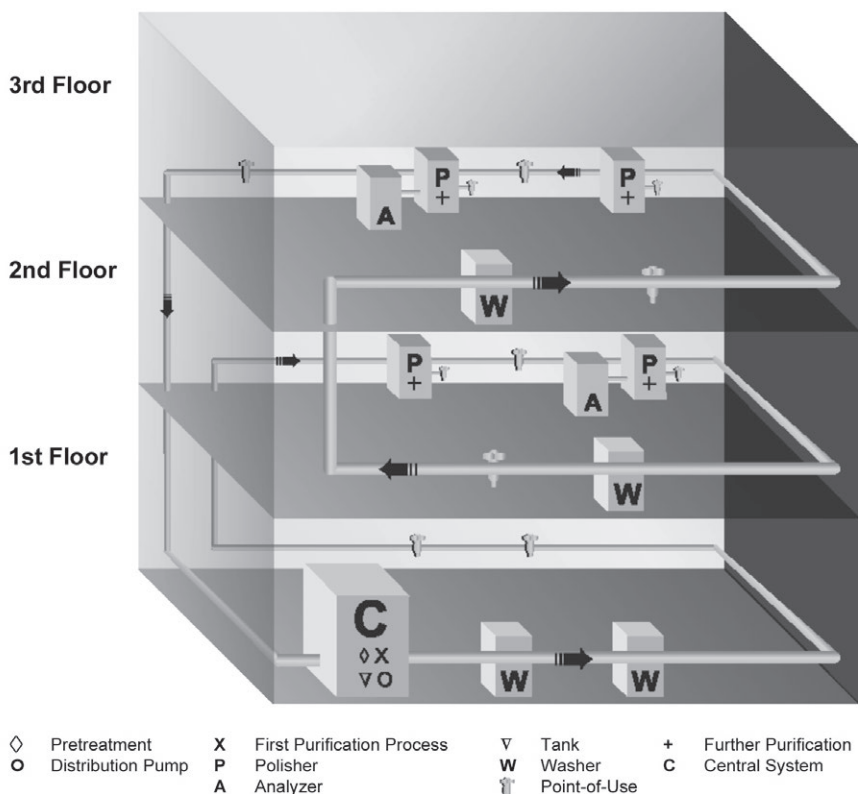
When water is required at multiple locations or when large volumes of water are necessary, several different design possibilities exist:

Large – Central System for Entire Building

A large make-up system for which the storage is in one location, with PW distributed throughout several laboratories or floors, can provide water throughout an entire building. These systems typically are custom designed. POUs can be connected directly from the distribution loop or the loop water can be treated by local polishers (units designed to further purify pre-PW) to give enhanced purity to meet special applications. This approach also enables the distributed water in the loop to be of lower purity.

Use of multiple make-up water purification systems providing PW to the same storage reservoir and distribution loop and located in the same location provides some redundancy at the primary make-up level, reducing the risk of completely shutting down a facility. When one system is down for routine maintenance or service, the other system should continue to provide PW.

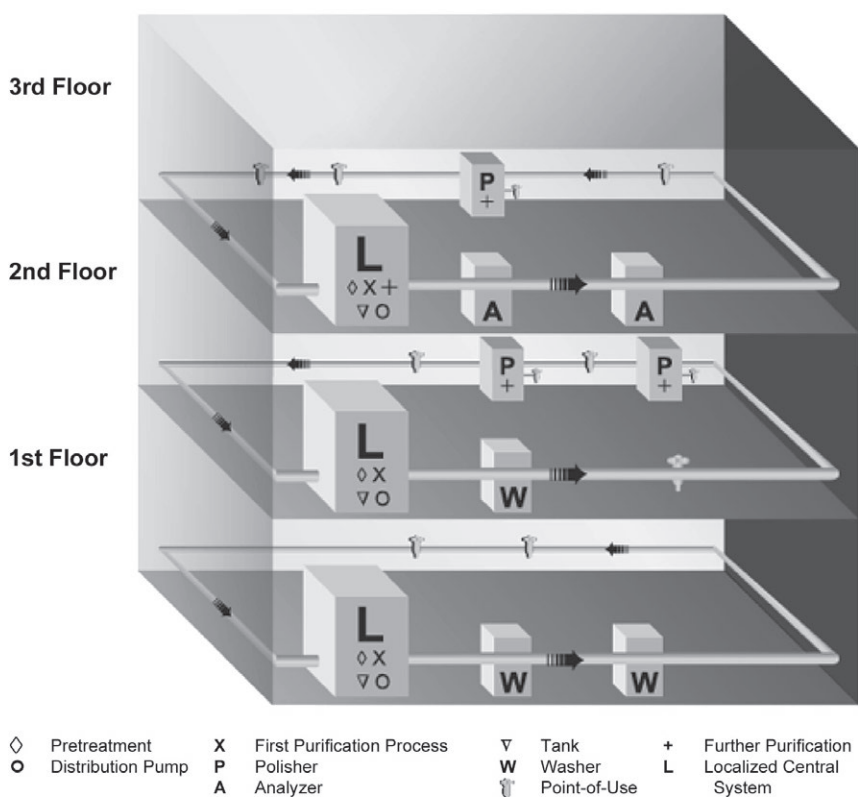
Figure 10.1: Example of Central System



Localized – Central System for a Floor/Laboratory

Several local loops (with each loop providing water floor by floor or department by department) enable each smaller system to be designed to meet specific local requirements. For example, when a high volume of water is required at a specific location (e.g., dishwashers and washing) and demand is much less in other locations, a better approach may be to dedicate a system to this high demand location rather than trying to provide for this in the complete distribution network. Medium sized generation systems typically are standard pre-packaged units with a custom designed distribution system.

Figure 10.2: Example of Localized Systems



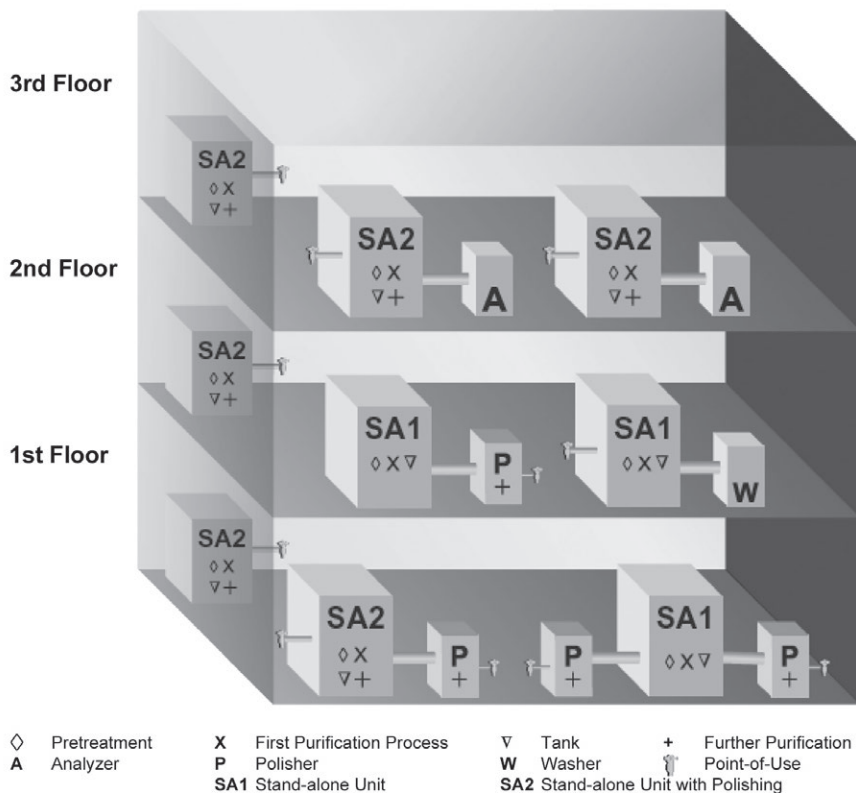
Small – One or More “Individual” Units per Building, Floor, or Laboratory

POU systems (often referred to as bench top units), can provide a variety of different water qualities and quantities at a much smaller scale than the large production or centralized systems. In practice, they can be located in a range of locations, e.g., on the wall or under bench, and can include storage and local distribution. They also can include various monitoring and dispense options. They typically are pre-designed, pre-packaged, and compact units.

The use of distribution loops may be avoided, while meeting multiple applications, with multiple individual POU units, which include the make-up purification system, storage, and additional polishing, as required.

When compared with packaged waters, the advantages of POU systems include purification and monitoring of water on an on-going basis and that it is available on demand. For instruments or analyzers used for manufacturing purposes, calibration and maintenance are vital to increase the probability of ongoing good operating and performance conditions. System designs which facilitate such operations can be advantageous.

Figure 10.3: Example of Small Stand alone Units



Note: in addition to approaches shown in Figures 10.1, 10.2, and 10.3, another approach is to use large or medium loop systems for most applications and address specific needs using individual POU systems or local loops, which include the make-up purification system, storage, and additional polishing at a much smaller scale and as required. This approach should avoid the need to extend piping to all departments, potentially simplifying the design of the main water purification system.

Supply from a Manufacturing Plant

When PW is available from an adjacent production area, this could be distributed through a loop to the laboratory block or locally as an extension of the loop. The water could be treated to meet specific local requirements. Note that the distribution piping, if extended to the laboratory, may have more design, quality, and maintenance requirements (e.g., microbiological) to maintain, than a dedicated laboratory system. Contamination risks from a multipurpose system (e.g., manufacturing and laboratory) should be considered.

10.2.4.2 Packaged Water

Packaged water is a possible alternative source of laboratory grade water. There are two general applications and associated purity levels typically used:

1. Very high purity waters for specific analytical purposes where small volumes are needed.
2. Less pure waters considered to be equivalent to compendial PW for general laboratory use where larger volumes typically are used. The latter types of packaged waters may be used in small scale manufacturing and process development applications that may be considered as “laboratories.”

Simplicity and Cost Advantages of Packaged Laboratory Waters

The potential simplicity of using a packaged form of water may seem a more cost effective and suitable option to satisfy a relatively small volume and perhaps a high purity requirement, when considering the capital and operating costs, as well as complexity of designing, installing, qualifying, maintaining, and monitoring a water purification system, regardless of size.

Packaged waters may be purchased in containers of manageable size and packaging configurations that allow their integration into laboratory operations in a similar way to other laboratory reagents, complete with expiration dating, lot numbers, and documentation certifying purity or compliance with standards. Allowed contaminants leaching from the packaging into the water may not be consistent with the implications of the name of the water and this should be considered. A risk assessment may be performed to determine the potential impact of the contaminants on the uses of these waters; therefore, the potential cost and complexity of such risk-based assessments may need to be included in the decision process to assure that the packaged water approach will be acceptable.

Purity

Compendial monographed sterile packaged water purity requirements are defined in the USP with less stringent inorganic specifications and less sensitive organic contaminant tests. The EP and JP also use less sensitive wet chemical tests for these packaged waters. These less stringent specifications allow the presence of organic or inorganic packaging leachables that could exceed the specifications for bulk PW, the minimal purity required by most compendia for pharmacopeial testing. A review and investigation of the purity documentation (Certificate of Analysis or Certificate of Compliance) should be performed to determine if the stated purity (or compliance with compendial specifications) relates to the source water placed into the container, or whether it relates to the guaranteed purity of the water within the container throughout its shelf life.

PW packaging often is plastic or may have elastomeric closures or container entry ports, all of which may leach organic plasticizers, molding releasing agents, or glues and associated solvents and monomers into the water. The organic extractables may become evident with escalating TOC levels over the water's shelf life. Some elastomers, as well as glass packaging materials, may be prone to leach inorganic ions into the water, degrading its conductivity and pH. Inert packaging materials which usually are used only for special purposes or more costly waters intended for specific analyses such as HPLC, may be an exception.

Packaging leachables are partially controlled by the specifications for the waters (because of selective and broad inorganic limits and a selective organics test insensitive to many extractables). There is potential for variability in the levels of packaging leachables:

- Over the shelf life of different container types
- From supplier to supplier
- Potentially from batch to batch of a given supplier

This potential variability in purity may require risk-based assessments for containers to assure suitability.

If the water's microbial content is a concern for laboratory applications, any claimed bioburden level by the packaged water's quality documentation is likely to be a transient attribute, and compromised as soon as the package is opened.

Verification of Suitability of Packaged Waters

If a packaged form of PW is being considered for use in place of bulk PW produced by an on-site water purification system and the purity specifications are not identical, the laboratory should verify fitness for use in each of its applications (e.g., as per USP Chapter <1231> [36]). In-house specifications (e.g., TOC and conductivity) should be

established for these packaged waters, tested on samples taken from representative containers, rather than basing acceptance upon the Certificate of Analysis, to help ensure that unsuitable packaged waters will not be used in susceptible applications.

Suitability verification may not be required if the packaged water is being used for an analysis for which the water was specifically labeled and intended, such as water for HPLC analyses; despite this, such waters may not be suitable for all HPLC analyses. A risk-based approach to assessing overall application suitability is considered appropriate.

As soon as the package is opened and air is allowed to enter the container, the purity starts to degrade. For packaged waters, it is recommended that water from these containers is used for only a short period of time after opening unless, the purity degradation the water will experience has been shown to be inconsequential to its laboratory applications.

If the water required for a given laboratory's operations is not a compendial grade, but rather a grade specified, e.g., by ASTM, ISO, Clinical and Laboratory Standards Institute (CLSI), or similar organizations, the suitability of packaged forms of these waters for the user application should be verified, unless certified for a specific purpose by the manufacturer of the packaged water. In addition, because some of these water grades have microbial and endotoxin specifications in addition to their chemical specifications, consideration should be given to the potential negative impact on these attributes from how water is removed from the package and by how long the opened package is kept in use.

Balance of Cost and Suitability

Packaged waters may be appropriate in laboratories, particularly where there is a need for a minimal amount for specific compatible applications. Where water is more generally needed for analytical applications, the risks and cost of assuring suitability for each application, potentially for each new batch or shipment received, should be balanced against the cost of installing and maintaining a purification system to produce bulk water, the application suitability for which may be related directly to ongoing quality monitoring.

10.2.4.3 Related Considerations

Quantity Needs

Large distribution configurations usually are considered when PW is required at different locations or in large volumes. It may be practical to meet high local flow or pressure requirements by additional local pumps and reservoirs, even with a large distribution system.

The distribution design should maintain water quality provided by a centralized system. The general advantages and limitations, described in the ISPE Baseline® Guide Water and Steam Systems (Second Edition) [39], for the different distribution configurations (loop, etc.) could be directly applied for the selection of the distribution configuration used in a laboratory.

Quality Needs

In general, a large system should be considered when an equivalent water quality is required in a variety of locations. Specific higher water purity requirements can be accounted for by individual polishing equipment. As the number of different water qualities required in an area increases, so does the importance of individual POU systems to account for specific needs. Several local distribution systems may be more effective in meeting diverse water purity requirements, if they can be localized.

Designing a large system that will produce water based on the most stringent water purity application requirements, may be an alternative approach; however, this solution is considered unlikely to balance the advantages and limitations (costs, complexity of maintaining high water quality in a distribution system). As the length of the distribution increases, the greater the difficulty in maintaining the equivalent levels of quality at all points, and the greater the risk of contamination (particularly bacteriological). The distribution design, materials in contact with the water and components installed, etc., can affect differences in quality significantly.

Monitoring and Compliance Needs

The greater the degree of equipment centralization, the more monitoring controls are localized. Time spent on checking/controlling satisfactory equipment operation (when compared with individual POU systems); may be optimized by localization; however, providing monitoring information to users (quality parameters, etc.) may be important. In a centralized configuration, the installation and associated costs of remote control/alert or individual monitoring equipment at the points where such information may be important should be considered.

A system that will distribute water to different locations with different regulatory requirements should align the main part of the installation requirements (design, equipment selection, maintenance program, etc.) to the most stringent regulatory requirements.

Environmental Constraints

The overall laboratory architecture and that of the various departments and floors in a building should be analyzed. If a single large system is chosen, its distribution should comply with typical design practices (see the Water and Steam Systems Baseline® Guide (Second Edition) [39]) and it should be verified that successful installation is possible (wall supports, etc.). The total length and height between the lower and upper distribution points will have a significant impact on the final distribution design, and on whether the water quantity and quality can be delivered consistently as requested. If large-scale storage and distribution are considered for an existing building, the available architecture (door openings) should be able to accommodate integration of the solution (storage, etc.). Exposed distribution system pipework can provide needed flexibility for distribution system modifications. The noise level should be taken into consideration when choosing the location where a water system will be installed, as equipment delivering large volumes of PW is in general noisier than standard laboratory equipment. These factors should be studied when a new construction is planned.

Space available within the laboratory may be restricted. Distribution equipment and local units will use bench/wall space, or storage space if located under-bench. Placement of these alternatives should be considered.

Maintenance Needs

In a single main installation, the advantage of having less systems to maintain may be offset by the complexity of the installation and the distribution system. A trained technician may need to be available to deal with issues in a timely fashion. The risks of problems usually increase with the complexity and length of the distribution; therefore, more frequent maintenance may be required, and depending on the configuration selected, this may affect laboratory operations.

Risk Management

The consequences of a lack of water caused by preventive or corrective maintenance should be analyzed and compared to the user requirements at the laboratory, departmental, and floor levels. A sanitization or a repair of the distribution system will not have the same consequences if the installation is a centralized system and distribution is for the entire building, rather than for a department or a laboratory. A duplex (multiple) approach minimizes the risk of interruption of water supply; however, it adds additional costs and is limited to cover the problems linked to the make-up system. Distribution complexity, length, operating conditions (pressure, temperature, equipment, etc.) will be directly related to risk management and should be considered before making the final configuration decision. For example, horizontal distribution (one floor) compared to vertical distribution (over several floors) will minimize pressure-drop related issues and optimize the linear velocity of water in the pipes.

Users' Convenience

The location and quantity of the PW POUs may depend upon user requirements such as:

- The time spent to get water

- Frequency at which water is required
- The risks associated with a decrease in water quality during transportation

The final solution proposed should take into consideration the potential water purities required and provide an optimized way of providing users with water of the appropriate quality.

Future Laboratory Expansion or Modifications

Information on future modifications of the installation should be considered when making final design/configuration selections. As distribution complexity increases, so does the level of risk, difficulty, and expense associated with changes to the laboratory's distribution to serve future needs. The possible need to perform a revalidation could add complexity and cost. Smaller size production units also allow an easier renewal program, as the investment can be planned over several years, renewing one smaller installation at a time.

Costs

The total costs equal the combination of the capital investment, operating, and risk management costs.

In addition to these total costs, the financial investment strategy of the organization (high capital – low operating costs) will have an impact on the final decision.

Initial investment will depend on site specific factors; in general, local systems are likely to be less expensive if there are few users who are widely distributed and with disparate water requirements. A large or medium distributed system is likely to be more cost-effective for large volume usage of a similar water quality within one building.

Comparison

The final choice should be the result of an analysis based on the advantages and disadvantages of the various configurations in regard to the quantities and qualities of water required, geographic distribution of these requirements, budget, etc.

Establishing these needs is critical. The strengths and weaknesses of the various configurations are summarized in Table 10.6. These comments are for guidance only as other factors may drive the final choice.

Table 10.6 provides a comparison of the advantages and limitations of various system design options, which provides an overview of which factors should be considered when going through the selection process.

Table 10.6: Comparison of Laboratory Water Delivery Schemes

Scheme Design Attribute	Large – Central System for Entire Building	Localized – Central System for a Floor or Laboratory	Small – One or More “Individual” Units Per Floor or Laboratory	Supply From Manufacturing Plant	Packaged Water
Availability	Custom designed purification and distribution system	Prefabricated purification unit plus custom distribution system	Prefabricated purification unit with local POU(s) or very limited distribution	Distribution system connected to or part of manufacturing system	Commercially available from scientific supply houses/catalogs
Capital Cost Per System	Large	Moderate	Low	Low – High (loop design dependant)	N/A
Capital Cost Per Unit Volume	Low – Moderate	Low – Moderate	Moderate – High	Low – Moderate	N/A
System Owner/Financial Responsibility	Site Dependant	Department	Department/Project	Manufacturing	Department/Project
Operating Costs • consumables • calibration requirements • monitoring • utilities • maintenance • revalidation	Site Dependant	Site Dependant	Moderate per unit volume	Site Dependant	High per unit volume
Failure Impact (quality or supply)	System Dependant – typically large to moderate	System Dependant – typically moderate	System Dependant – typically limited	System Dependant – potentially large	Typically Limited
Maintenance	Specialized Maintenance Personnel	Experienced/ Trained Personnel	Trained Users	Manufacturing Responsibility	None
Design and Construction	Complex	Moderate	Low	Complex	None
Location					
a. Space	Large, but only 1 area	Medium in support area	Small, but could be multiple	Distribution piping only	Transfer/storage area and quantity dependant
b. Noise	Very noisy, but only 1 area	Medium in support area	Low	Low	None
Water wastage	Technology Dependant	Technology Dependant	Technology Dependant	Low	None
Poor feed water quality management	Treatment at central unit (single point)	Treatment at each unit	Treatment at each unit	Manufacturing Responsibility	N/A
Upgradability (e.g., changed usage or quality requirement)	Replace/upgrade or add – significant engineering needed	Replace/upgrade/ add – some engineering needed	Replace/upgrade or add unit	Supply Dependant	Buy more
Relocation	Difficult	Medium	Easy	N/A	N/A
Revalidation	Complex	Moderate	Easy – Moderate	Easy – Moderate	N/A
Importance of Supplier Certification Program	Variable	Variable	Variable	Manufacturing Responsibility	Critical
Quality Variability at different use points on a loop	Design dependant	Design dependant	N/A	Low	N/A

Table 10.6: Comparison of Laboratory Water Delivery Schemes (continued)

Scheme Design Attribute	Large – Central System for Entire Building	Localized – Central System for a Floor or Laboratory	Small – One or More “Individual” Units Per Floor or Laboratory	Supply From Manufacturing Plant	Packaged Water
Management of Water System by User	Access Limited/ Remote	Generally Accessible	Local	Access Limited/ Remote	N/A
Need for Water Usage Suitability Verification	Low – during qualification then by meeting specs in routine sampling	Low – during qualification then by meeting specs in routine sampling	Low – during qualification then by meeting specs in routine sampling	Low – during qualification then by meeting specs in routine sampling	High (potentially with every batch or shipment or even every container)
Assurance of Quality at time of Use	Validation, periodic sampling, and centralized monitoring	Validation, periodic sampling, and centralized monitoring	Localized monitoring and sampling	Manufacturing group responsible for validation, periodic sampling, and centralized monitoring	Refer to in-house testing and quality control process
Sanitization	Whole system shut-down	Local system shut-down	Individual unit	Whole system shut-down	N/A
Regulatory Requirements for System Management	Defined by the most stringent requirement in the whole system	Defined by the most stringent requirement in the localized system	Defined by specific local requirements	Defined by the most stringent requirement in the whole system	Defined by specific local requirements
Meeting Users Water Quality Needs	Distributed water quality established for the building, polish at POU as necessary	Distributed water quality established for the local needs, polish at POU as necessary	Water quality established for each POU	Water quality established by manufacturing, polish at POU as necessary	Water quality established by suitability verification
N/A = not applicable					

10.2.5 Maintenance

Preventive maintenance on a laboratory water purification system usually helps to anticipate problems and ensure the long-term performance and reliability of the water purification system.

A maintenance program should be defined and its definition should be based on the manufacturer’s maintenance recommendations and on a risk impact analysis.

A maintenance program may include the replacement schedules for consumables and spare parts caused by wear and tear, preventive verification/tests on critical components, and the definition of the monitoring program. Definition of the monitoring program could reiterate the operating ranges, the alert, and actions levels that were defined for the different parameters, as well as maintenance actions to be conducted when values are out of range.

When equipment is not used in a regulated environment, the actions performed on water systems used in a pharmaceutical laboratory should be documented. This traceability allows greater efficiency during any future troubleshooting actions. When the equipment is used in a regulated environment, or depending on its classification in terms of criticality, the level of regulatory practices and the preventive maintenance frequency will be different.

10.2.6 Instruments and Calibration

Calibration is required by quality management systems (pharmaceutical GMPs, ISO 9001 [40], etc.) on equipment used to measure, control, or monitor. The reliability and confidence obtained from a value provided is linked to the calibration method, calibration frequency, and results obtained.

The measurement of quality parameters, e.g., conductivity, TOC, and bacteria, after each purification step, may not be relevant in a laboratory water system when the distances between two purification stages are minimized and the risks of contamination through insertion of “sanitary” sampling instruments may be higher than the anticipated benefits. The measurement of water quality and operating parameters after major water purification steps in a laboratory water system may help to anticipate operating and performance problems.

Frequency of calibration should be based on the type of measurement performed (e.g., temperature, conductivity, TOC, pressure), the type of instruments used (method, model, etc.), and the importance of the measurement for the application, in addition to the importance of the application in the entire process. The frequency should be defined following a risk impact analysis approach.

10.2.7 Commissioning and Qualification

Commissioning and qualification of water systems are discussed in Chapter 11 of this Guide. The same qualification approach should be followed for laboratory water systems should be qualified using equivalent approaches to those for the manufacturing systems.

If the laboratory water system is an extension of a manufacturing distribution loop into the laboratory area, the issues and testing that apply to the validation of the water system for manufacturing also apply to the POUs in the laboratory area.

Where the water system is exclusively for laboratory use, the specific purity attributes required in the laboratory may differ from those required for water used for manufacturing. These laboratory purity differences (or impurity allowances) may be reflected in the use of different or considerably scaled down purification unit operations, and different system materials, distribution system designs, and POU valve types than are typically present in manufacturing water systems.

Small, tightly packaged bench-top or wall-mounted water purification units may be designed to operate to the point of reduced quality (e.g., exhaustion) from one or more purification modules; the point of reduced quality usually is signaled by a built-in sensor. There is a risk of producing and using unacceptable water associated with these types of laboratory water system designs; maintenance approaches should be evaluated prior to system selection and purchase, and challenged or verified during qualification. The high number of purity attribute, operational, maintenance, and design differences between manufacturing and laboratory water systems usually requires the strategy for the qualification process for laboratory water systems to differ from that typically used for manufacturing water systems.

10.2.7.1 Importance of Internal Laboratory Water Specification Standards

The minimum chemical purity of water normally required for analytical purposes is compendial PW. A pharmaceutical laboratory PW system may not require a microbial specification, because only the water's chemical purity is of consequence to a number of laboratory uses.

Where the water purity attributes required from a laboratory water system differ from the purity attributes needed by and described by an organization's raw material standards or monographs for manufacturing PW or water for injection(s) systems, separate specifications to define laboratory water quality should be developed. These specifications may be the basis for the acceptance criteria for water system qualification processes; documented standards for the quality of waters needed in the laboratory should be defined. Where these standards are not defined, the laboratory may be required to apply water attributes and limits from manufacturing water standards. The manufacturing water attributes and limits may be unnecessary or not sufficiently stringent and for which the laboratory water systems may not have been designed to control these appropriately.

10.2.7.2 Tailoring Laboratory Water System Qualification to Intended System Capability

Large laboratory water systems may be entirely custom designed and built. These systems can be designed to include special monitoring and sampling capability between unit operations.

For medium to smaller sized laboratory water systems, smaller purification units with preconfigured unit operations usually are obtained as a single unit. These preconfigured units may provide less opportunity for sampling between modules for monitoring individual unit operations.

Requirements to verify the performance of individual unit operations should be determined based on the overall system design and quality needs. Retrofitting sampling capabilities for qualification purposes to prefabricated systems may not be feasible, as they often are compact, “well-tuned” systems.

Smaller bench-top or wall-mounted single POU systems also may have limited user access to on-board gauges and instruments for calibration and standardization purposes.

Where gauges and instruments are for informational purposes only (e.g., to signal performance changes in the system), and definitive QC testing is performed either off-line (with occasional grab samples) or by portable in/at/on-line instruments that can be calibrated/standardized, then lack of access may not be a problem. Where the on-board gauges and instruments are intended for QC purposes, then user accessibility, the ability to calibrate, and pharmacopeial compliance of instrument features are considered more significant. Therefore, such capability should be investigated during the water system selection process in order to ensure compliance with user and regulatory needs.

A systematic duplication of the qualification approach used for manufacturing water system designs may not be appropriate for laboratory water systems. The duration of the qualification process, which includes the PQ, should be customized for the evaluation of the laboratory water quality attributes and the nature of the water system's operation. For example, if there are no microbial attributes of concern for the laboratory water, the only impact of biofilm development would be to reduce the longevity or efficiency of chemical purification unit operations. This would be apparent in the chemical quality of the effluent water. Without microbial attributes of concern in the final water, the period of qualification and frequency of sampling may be tailored to evaluate the consistency of the chemical purification processes. However, if the unit operations are not intended to be periodically replaced because of exhaustion, such as RO modules, periodic microbial monitoring may be of operational value, rather than being a quality requirement *per se*.

The qualification of a laboratory water system may be more limited (or more stringent) than that for a manufacturing water system, and the protocols should be developed to accommodate those differences, as long as the total qualification process reveals the operational consistency of the water system for controlling the quality attributes of concern. If a specific water system monitoring feature or a particular quality attribute is an absolute requirement for an organization's water system validation program, a laboratory water system that contains those features and is able to control the mandated purity attributes should be purchased and installed.

10.2.7.3 Special Validation Considerations for Small Laboratory Systems

Conductivity Compliance and Consistency

Most small water purification units, especially the compact, prefabricated, single POU systems, contain an on-board conductivity/resistivity instrument with its sensor positioned within the finished water stream. If the purification unit has been in a “stand-by” mode, system manuals often instruct the user to initially recirculate the water through the unit or flush water to drain until the conductivity/resistivity reading gives acceptable values. If that instrument can be calibrated and complies with the compendial requirements, the readings can be evaluated against those compendial specifications. If, however, the instrument cannot be calibrated or otherwise does not meet compendial requirements, it can still be used as an informational instrument whose performance should be periodically compared or correlated to an instrument that does meet compendial requirements through the in-line testing of the same water. The

relationship of those data correlations can then impart a level of confidence to the informational instrument readings for day-to-day operations. Since the on-board instrument is only an informational instrument, periodic testing on water from the system using a compliant instrument is needed to assure ongoing compendial compliance. Whenever, the product water does not meet those conductivity specifications after appropriate recirculation or flushing to drain, it is usually a sign that a purification module within the unit should be replaced. After such a replacement has been executed, the water generally resumes conformance with the conductivity specifications. Having procedures in place to assure proper use of the water system with appropriate precautions to preclude using unacceptable water is very important. Verifying that this exhaustion/module replacement/use resumption phenomenon reproducibly occurs also can be an element of the system's qualification.

TOC Compliance and Consistency

It is not universal for such compact, prefabricated purification units to contain on/at-line TOC monitoring. For those that do not have built in TOC monitoring capability, the TOC test for such systems should be performed either on grab samples from the system or by connection, often at a use point, to a TOC instrument. The TOC purification capability of such a system is an attribute that could, like conductivity, change dramatically in a short period of time because of the way this purification equipment may be operated with ionic exhaustion usually signaling a need for reactive maintenance. Without on/at-line TOC monitoring it is impractical to determine TOC with every use, unlike what is usually possible with in-line conductivity. The consistency of TOC concentrations is important to validate, not only during routine use up to the point of potential TOC removal exhaustion, but also immediately after any purification module replacement when TOC spikes are not uncommon. Therefore, the duration of frequent grab sample or on/at-line TOC monitoring during qualification needs to at least encompass a period long enough to verify the predictability of TOC removal exhaustion, which may occur either before or after ionic exhaustion. In addition, after a specified long idle period between system uses, the point in time after pre-use flushing or polishing recirculation when the monitored conductivity signals that the water is ionically acceptable for use, also should be verified as attaining acceptable TOC quality.

Consistency of Other Attributes

This same approach as used for TOC should be applied to any quality attribute defined as important and not routinely monitored with every use. This attribute performance characterization could then be incorporated into usage and maintenance SOPs for the system (which may be different from those recommended by the purification unit manufacturer) that would preclude unwittingly making and using unacceptable quality laboratory water. The qualification process could then verify that these other attributes, though infrequently routinely tested, are consistently met when the system is operated appropriately.

10.3 Additional Programming Considerations

Road and Parking Modifications:

- Parking lot expansion/parking spaces needed
- Contractor's gated opening, roadway and parking area
- Logistics plan for contractor lay down and temporary site offices/trailers
- Facility ring road consideration
- Security buffer from either known or unknown risks
- Cafeteria access for deliveries and waste removal
- Lighting and storm drainage

Security Requirements:

- Guard house, site security
- Access control card key/other.
- Fencing
- Access pedestrian, employee, services.
- Lighting/power
- Phone/data

Site Modifications for Expansion:

- Grading and tree removal
- Storm water and site drainage
- Landscaping consistent with the existing plant design
- Temporary trailers equipped with appropriate field office cubicles

Fire Protection:

- Water tank
- Loop extension, permitted pressure drop

Power:

- Existing substation
- New substation
- Emergency (existing capacity or new capability)

Chilled Water:

- Existing capacity or new

Steam:

- Existing capacity or new
- Pure Steam (Clean Steam), e.g., for autoclaves

Compressed Air:

- Existing capacity or new

Gases:

The list of gases in the requisite purity used by a quality laboratory usually depends on the range of instruments used. Examples include:

- Hydrogen
- Helium
- Nitrogen (Note: mass spectrometer min. 6 bar, (87 psi) high requirement for purity (vaporizer))
- Argon
- Oxygen
- Carbon dioxide
- Synthetic air

A central carbon dioxide supply (incubation cabinets) should be considered. For gases supplied from a central system consideration should be given to:

- Existing or new capacity
- Truck access
- Distribution upgrade to meet the laboratory needs

For further information, see the ISPE Good Practice Guide: Process Gases [31].

Sewer:

- Existing capacity or new

Building Automation System:

- New or existing BAS and utility monitoring system
- Networking needs for new laboratory facility

Cafeteria:

- Expansion to accommodate new head count

Waste Room:

- Dumpster requirements
- Permitting
- Hazardous waste storage facility for flammable materials built in accordance with the National Electric Code governing the storage of flammable hazardous waste or other appropriate local codes

Information Systems:

- Computer room space to meet expansion needs
- Expand/replace computer hardware to meet planned increase in transactions
- Modify computer software to handle planned increase in transactions
- Modify existing computer software to meet changes to business procedures
- Obtain software licenses to handle increased number of users
- Hardware/software to meet workstation needs of additional head count
- Expand/replace network infrastructure to handle expansion needs
- Document all changes and provide space for related documentation
- Validate changes according to system life cycle
- Provide necessary resources to complete expansion tasks related to information systems

10.4 Utility and Support Spaces

The quality laboratory is programmed with its associated support spaces such as a solvent storage room, stockroom, glass wash room, scientific write up spaces, and laboratory management offices. Additionally, consideration should be given to janitor's closets, closets for analyst's smocks, general storage, and a room for effluent transfer and disposal.

Spaces associated with telephone, data, and specialty services requiring closet support space should be programmed into the design. The specialty requirement for power, emergency power, and cooling should be considered.

Consideration should be given to spaces allowing laboratory adaptability to accommodate change. Support spaces need to be generous enough so that physical and infrastructure changes can be accomplished. These spaces should not be customized to meet an immediate need. Services distributed to the laboratory should be run overhead or in an interstitial space. Adequate space should be provided allowing maintenance and repair without interruption of laboratory operations.

11 Commissioning and Qualification

11.1 Introduction

It is the intent of all regulatory agencies to verify that manufacturers' reduce and control risk to product quality and patient safety. To meet these expectations, industry has developed a methodology to produce documented evidence that facilities are built to design specifications and that equipment and systems are installed correctly and operate in accordance with the specifications.

Commissioning should be performed by appropriate experts who will safely set configure equipment and systems to ensure that:

- Start-up and shutdown occur in the proper sequence
- Alarms are generated in accordance with the specifications
- Generated data is accurate
- The equipment or system operates as specified

Qualification leverages commissioning to provide documented evidence that equipment and systems meet acceptance criteria for critical aspects identified by risk assessment or regulatory requirements.

In August of 2007, the American Society for Testing and Materials (ASTM) published a new standard titled "*A Standard Guide for Specification, Design and Verification of Biopharmaceutical Manufacturing Systems and Equipment*," designated E2500-07 [24]. This Guide is based on a risk management and process knowledge approach to the specification, design, and verification of equipment and systems that could affect product quality and patient safety. Under section 1.3 of this Guide, it clearly states it may be applied to laboratories and associated equipment and information systems. In the standard, commissioning and qualification are an approach to verifying systems are "fit for intended use, have been properly installed, and are operating correctly." ISPE's Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment [29] reflects the principles and practices outlined in this standard. Similarly, this Chapter of the Quality Laboratory Guide promotes the use of ASTM standard E2500 [24] to verify that a laboratory facility is "fit for use."

Additional guidance documents that are relevant to commissioning and qualification of laboratory facilities that should be referenced include:

- ICH Q8 Pharmaceutical Development [41]
- ICH Q9 Quality Risk Management [27]

Other ISPE Guides relevant to commissioning and qualification of laboratory facilities should be referenced as necessary and include:

- ISPE Baseline® Guide: Water and Steam Systems (Second Edition) [39]
- ISPE Good Practice Guide: Maintenance [32]
- ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems [42]
- ISPE GAMP Good Practice Guide: A Risk-Based Approach to Calibration Management (Second Edition) [43]

11.2 Scope

Laboratory utilities, electrical and information systems, and laboratory equipment within the scope of the Guide are listed in the Table 11.1. Other laboratory equipment and systems that are beyond the scope of this Guide because of the diversity of their function in a laboratory environment include:

- Bench-top analytical, assay or microbiological identification equipment
- Portable equipment (particle counters, filter integrity testers, etc.)
- Autoclaves (decontamination, component and media preparation)
- Glass washers, cage and cabinet washers, ultrasonic sinks, etc.
- Refrigerators and freezers
- Incubators
- Centrifuges
- Shakers
- Robotics (automated sampling)
- Laboratory Information Management Systems (LIMS)
- Building Automation Systems (BAS), Building Management Systems (BMS)
- Chromatography Data Systems (CDS)

Table 11.1: Typical Laboratory Systems and Equipment

Electrical Systems	Piping and Drainage Systems	HVAC Systems	Building, Equipment and High Purity Utilities
Main and Secondary Distribution	Domestic Hot and Cold Water	Supply and Exhaust Air Handling	RO, DI, USP and WFI Distribution and Generation
Clean Power (Electromagnetic Fields and Harmonic Interference Shields)	Central Compressed Air	Smoke Detectors and Dampers	Clean In Place Distribution
Emergency Power	Fuel Oil or Natural Gas	Heating Hot Water	Clean Steam Generation, Distribution and Condensate
Uninterruptible and Emergency Power Supplies	Specialty Gases	Plant Steam and Condensate Return	Environmental and Stability Chambers
Fire Alarm	Vacuum	Cooling and Chilled Water	Fixtures, Casework and Architectural Finishes
Security and Surveillance	Sprinkler/Fire Protection	HEPA Filters	Vibration control and floor loading
Lighting levels and control (including dark rooms, ultraviolet, etc.), Receptacles	Laboratory Drainage	Humidity and Temperature Control	Eyewash and Safety Showers
Telecommunications/LAN	Sanitary Storm, and Sewer	Fume Hoods and Glove Boxes	Hazardous Materials and Waste Storage and Disposal
Motor Starters, Motor Control Centers, Variable Frequency Drives	Radioactive and Biological Waste Storage	Automated Environmental Monitoring	Document Retention
Audio/Visual	Decontamination and Cleaning Distribution Systems	Biosafety and Containment Cabinets and Laminar Air Flow Hoods	Sample and Reagent Management and Storage

11.3 Developing a Commissioning and Qualification Strategy

The risk assessment document (see Chapter 5 of this Guide) should be utilized to develop a verification plan that defines the commissioning and qualification strategy. This verification plan should specify what is to be commissioned and what is to be qualified, based on a pre-determined acceptable quality risk level. This document also should define what tests and inspections will be performed, by whom and when, what documentation is necessary, what the acceptance criteria or standard for the system will be, and the necessary approvals. This may take the form of a "Master Plan" that encompasses the entire facility, or it may be confined to an individual system or piece of equipment. A Validation (or Verification) Master Plan (VMP) should be generated to describe all commissioning, qualification, and validation efforts that are planned for the project. These activities should be based on science, and

product and process knowledge, as well as regulatory requirements, industry standards, and owner's expectations. This document also should address change management as a result of commissioning or qualification activities. As a "living document," this plan is subject to revisions that reflect changes in scope or design of the facility.

With regard to the content of a verification plan, ASTM E2500-07 states under section 7.0 [24]:

7.4.2 Verification Strategy:

- *The acceptance criteria and verification strategy should be documented in appropriate verification plans.*
- *The verification plan should define what constitutes acceptable documentation of subsequent verification activities.*
- *The verification plan should be developed and approved by subject matter experts. Verification plans for systems containing critical aspects should be approved by the quality unit.*

It is a recommended GEP to commission all facility equipment and systems to ensure that they are installed in accordance with the specifications, and operate to meet the specifications. This effort becomes the basis of an equipment history file or system reference, aiding maintenance and engineering personnel in repair or replacement assessments, and cost and capability analyses. Documented commissioning of these systems by subject matter experts should assure that the design criteria and specified operating requirements will be met and failure potential minimized.

For example, in a new manufacturing facility project, there will be a validated process, operating on qualified equipment and control systems, with data and information management systems recording critical process parameters, events, and alarms. Utilities may directly affect product quality, while others indirectly support the process. There are also those systems that support operation of the facility, but do not have any effect on the quality of the manufactured process.

A quality laboratory facility can be defined in a similar way. There will be validated methods and operations performed on qualified equipment and control systems, with data and information management systems recording test results used for in-process testing or product release. Utilities may directly affecting the result of the testing, while others support the operation of the facility, but have no affect on test results.

The risk management program should dictate any decision on system or equipment qualification requirements. Qualification should be focused on critical aspects addressed in the process (sample handling, analytical method) related to risk assessment. The determination to qualify should be based on the compliance drivers: product quality impact and patient safety. The risk assessment, having defined risk, would allow the verification plan to define the necessary testing aspects in place to mitigate impact to product quality and patient safety. For example, temperature control within a specified range in a microbiological laboratory or incubation area may provide a better survival condition for damaged or slow-growing cells than typical storage conditions would provide. A qualification of temperature maintenance and system control functions (alarms, trends, etc.) could be needed, in order to provide a high degree of assurance that growth is promoted and a microbial contaminant could be isolated. Conversely, those failures that would result in a loss (reject) of product due to a test failure would be considered quality non-impacting since an Out of Specification (OOS) product would not be released. These types of failure would have a negative affect for a manufacturer both financially and on market supply (patient care), and generally would not be considered acceptable practice.

Just as the requirements of the validated manufacturing process are critical to the assessment of systems in a manufacturing environment, the requirements of the validated test methods can play a major role in the assessment of systems in a laboratory environment. For example, the USP defines two grades of water:

1. Water for Injection
2. Purified Water

These are considered to be pharmaceutical products. If a validated method specifically calls for either of these two quality grades of water, the system delivering the water should be qualified and maintained in that state. This ensures that the type of water needed for analytical testing used in the test meets the requirements of the validated method. The quality of the water used in testing may be important and how that water is labeled and tested can mean the difference between commissioning only and the need for qualification.

There may be instances where the application of risk assessment determines that qualification is not needed, but is mandated (or interpreted to be) by specific regulation. An example of this is contained in the USP requirement to conduct sterility testing under the same conditions as product manufacturing. It is the responsibility and prerogative of an operating organization to interpret regulation and apply science-based judgment to their qualification decisions.

11.4 Commissioning as Good Engineering Practice (GEP)

The ISPE Baseline® Guide, Commissioning and Qualification [25], defines commissioning as “A well planned, documented, and managed engineering approach to the start-up and turn-over of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations.” The components of a commissioning effort for a new or renovated laboratory will be similar to those outlined for manufacturing facilities. It is important to utilize the risk assessment results to identify those variables that directly affect system operation that could result in adverse business or regulatory exposure, potentially resulting in additional testing in commissioning in support of qualification.

User requirements, functional and design specifications, recognized industry standards from established organizations, or qualified personnel, should be used and referenced to define checks, tests, adjustments, inspections, and performance requirements in the commissioning test document. Established organizations include:

- International Society of Automation (ISA)
- American Society for Testing and Materials (ASTM)
- International Organization for Standardization (ISO)
- International Electrotechnical Commission (IEC)
- National Institute of Standards and Technology (NIST)
- Association for the Advancement of Medical Instrumentation (AAMI)
- American National Standards Institute (ANSI)
- American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE)
- Institute of Electrical and Electronic Engineers (IEEE)
- American Society of Mechanical Engineers (ASME)

Local building codes and all health and safety regulations should be addressed during the design phase of the laboratory, and also should be checked in design review, then verified in commissioning, as needed.

The commissioning test document should identify necessary documentation, such as drawings, manuals and procedures necessary to evaluate, operate, and maintain the system. From a business and quality perspective, a piece of equipment or a laboratory system should be physically maintained and periodically evaluated for optimum operation and efficiency by procedure or policy. Qualification or re-qualification should not be needed to enforce maintenance or performance.

Prior to system acceptance and turnover, as a minimum, commissioning should be conducted or witnessed by a designated owner representative and the results evaluated and approved by the system responsible. Commissioning can include receipt verification and installation verification as defined by the ISPE Baseline® Guide on Commissioning and Qualification [25], or it may begin with factory acceptance testing, site start up, shakedown, and functional testing. The process should be defined by the verification plan. The commissioning process should include requirements to document discrepancies found and changes made during the commissioning effort. A checklist or summary report detailing commissioning results can help to track problem resolutions or “punch list” items, design or system changes, requests for information, and system documentation assembled during the commissioning effort. Once commissioned and placed in service, access to equipment and systems should be placed under facility management to prevent unauthorized or undocumented changes, replacements, or adjustments. A properly planned and executed program and verification plan should minimize qualification discrepancies and deliver the data necessary to properly maintain and operate the system or equipment.

All commissioning results and documentation should be captured in an assembled Engineering Turn Over Package (ETOP). For general reference only, Table 11.2 presents a list of documents, drawings, certificates, and vendor data that are typically included in an ETOP for systems and equipment, as they apply. Review and approval of a commissioning ETOP is based on organization policy and should be defined and approved in the MVP.

Table 11.2: Items Typically included in an ETOP (general reference)

Documents	Drawings	Certifications	Vendor Data
Specifications, Standards and Procedures	Equipment Fabrication and Assembly	Materials Certifications	Recommended Operating and Maintenance Manuals and Procedures
Equipment, Instrument, Valve Lists	Isometrics and Slope Verification	Weld Documentation	Recommended Spare Parts List
Piping and Insulation Line Lists	Piping and Instrumentation	Relief Valve Certification	Vendor specifications
Factory or Site Acceptance Test Plan and Results	Mechanical and Piping Details	Cleaning and Passivation Records	Design Drawings
Alarm Test Records	Field Routing Ductwork, Piping and Conduit	Test and Air Balance Report	Purchase Orders
Grounding Test Records		HEPA Certification	Start-Up Reports
Pneumatic Testing		Utility Balance Reports	Audit and Qualification Reports
Pressure/Hydrostatic/Leak Testing		Calibration	Performance Data
Emergency Power System Testing		Building Permit and Certificate of Occupancy	
Building Inspection Records			
Loop Checks			
Field Verification Reports			
Motor Start-Up and Rotation Checks			

11.5 Qualification

For a laboratory, the impact a facility, system, or piece of equipment may have on patient safety is based on a potential release of an OOS product to market, a test failure affecting market supply, or an impact on the ability to conduct a test as validated. The risk management program and verification plan should identify the critical process and product parameters that are routinely verified by the laboratory, and what areas of the laboratory facility, critical systems, and equipment contribute to the verification of these parameters. Those systems that determine or contribute to critical quality attribute verification should be qualified (or verified) under the auspices of the quality unit. Commissioning documentation and supplier test documentation may be leveraged for qualification purposes according to pre requisites determined in the verification plan. After qualification or verification, a review or summary report should confirm that a facility, system, or piece of equipment is “fit for use.” This statement should be approved by the quality unit (at a minimum).

An owner organization should assess a supplier’s quality systems prior to incorporating vendor documentation or vendor testing of critical parameters in the qualification package. The decision to utilize vendor documentation or supplier testing in the qualification of laboratory systems or equipment needs the concurrence of the quality unit. If issues in supplier practices are identified, it is the owner’s responsibility to identify any necessary remediation, utilizing Subject Matter Experts (SMEs) or qualified personnel.

Appendix 1

European Considerations

12 Appendix 1 – European Considerations

12.1 Introduction

This Chapter reviews the contents of the HVAC information provided in the Chapter 8 of this Guide and identifies the key differences between practices and standard as used in the US and practices in the UK EU.

The majority of the guidance and practices are common, but there are some differences which are highlighted in this Chapter.

A list of relevant learned bodies in European countries has been developed with contact details, see Section 12.3 of this Guide. It is recommended that these associations are contacted in the respective country where the laboratory is to reside.

It should be noted that many global organizations have their own standards and that these are frequently identified as being the 'organization' standard; therefore, local considerations should be respected and the contact list has been included.

"Organization" standards, US, or UK standards usually are the benchmark for the criteria used for laboratory design in many areas around the world.

12.2 The Differences

One of the most fundamental differences that exists between the US and Europe are the units of measurement. The US uses the 'imperial' form of measurement including temperature in degrees Fahrenheit (°F) and pressure in inches water gauge ("w.g.). In Europe and the UK, the metric system is adopted using SI units, e.g., degrees centigrade (°C) for temperature and Pascals (Pa) for pressure. Sometimes millibar (mbar) is also used for pressure.

12.2.1 *Cleanliness Classification*

EN ISO 14644-1 [44] is currently being adopted throughout the USA and Europe. This standard gives ISO classification numbers; ISO Class 1 to ISO Class 9 and gives maximum concentration limits for a range of particles. The ISO classes are determined either at rest or in operation. This is not regulated by EN ISO 14644-1. For further information, see the ISPE Good Practice Guide: HVAC [30].

12.2.2 *Air Filtration Standards*

The filtration classifications referred to in Chapter 8 are taken from the ASHRAE Standard 52.2-2007 [45]. The Minimum Efficiency Reporting Value (MERV) is not generally used in Europe. The standards generally used are BS EN 779:2012 [46] and BS EN 1822-1:2009 [47]. These standards classify filters into four general standards, these being General, Fine, HEPA, and ULPA with an overall range from G1 through F9, H10 to H14, and H15 to U17. For further information, see the ISPE Good Practice Guide: HVAC [30].

12.2.3 *Temperature, Humidity, and Human Comfort*

The environment criteria used for design can be found in the Chartered Institute of Building Services Engineering (CIBSE) guides section A.

The criteria reviews both the requirements of temperature and humidity and overall thermal comfort, the effect of air movement on comfort plus the implications of lighting, sound, and vibration.

CIBSE also have a useful publication on ventilation and Indoor Air Quality (IAQ).

12.2.4 Ductwork

Ductwork construction standards vary in the UK, and the SMACNA standard referred to in Chapter 8 is not commonly used. The construction standards used are those produced by the Heating and Ventilation Contractors Association (HVCA) and vary depending on the materials being used; they are:

- HVCA specification DW/144 for sheet metal ductwork
- HVCA specification DW/154 for plastic ductwork
- HVCA specification DW/191 resin bonded glass fibre ductwork
- There is a range of DW standards available which cover a variety of subjects including ductwork leakage testing, internal cleanliness, etc.

Where room pressure is critical, high quality Class 1 construction including air leakage testing of the ductwork may be justifiable.

12.2.5 Commissioning

The settling to work, balancing of the air systems, and the balancing of any water systems, that may be serving heating and cooling batteries, should be performed in accordance with the Chartered Institute of Building Services (CIBSE) Commissioning codes. These codes cover all air and water systems and automatic controls, refrigeration systems, boilers, and lighting.

Another source of industry standards are the range of commissioning codes produced by the Building Services Research Information Association (BSRIA).

12.2.6 Fume Cupboards (Hoods)

The word fume hood (as opposed to exhaust hood) is a frequently used term. In the UK, this type of enclosure is referred to as a fume cupboard. The design, selection, specification, and installation of fume cupboard are covered by BS EN 14175-6:2006 [48].

Where a biological hazard exists, materials are normally handled in a Microbiological Safety Cabinet (MBSC), which are available in three classifications depending on the type of hazardous material being handled. Such cabinets are covered by BS EN 12469:2000 [49].

12.2.7 HVAC Design Parameters

A risk assessment should be performed for all laboratory and cleaning operations. This risk assessment will assist in determining if any of the HVAC design parameters are critical to a GMP issue or to a life safety issue. For further information on risk assessment, see Chapter 5 of this Guide.

Typical temperature criteria for laboratories are the comfort conditions, unless temperature is critical for any tests to be conducted, e.g., 69.8°F (21°C) with a nominal range of $\pm 35.6^\circ\text{F}$ (2°C). HVAC control parameters may be relaxed to conserve energy, but other factors such as condensation and heat stress should be taken into consideration.

As stated in Chapter 8, where additional clothing is worn for higher cleanliness, as in an aseptic laboratory, then the temperature may be lowered to 68°F (20°C).

Humidity ranges between those identified in Chapter 6 of this Guide, but frequently a range of 40% to 60% reduction humidity is targeted with specific control being used where needed by the material being handled.

Air pressure regimes are based on either containment or protection, either of personnel or the product, sometimes both. Air pressure differentials are normally based on the unit Pascal (Pa).

The American Conference of Government Industrial Hygienists (ACGIH) Manual of Recommended Practice for industrial ventilation is used throughout the UK, as well as the USA, mainly for extract ventilation systems.

For the classification of microbiological hazards, the Advisory Committee for Dangerous Pathogens (ACDP) is used for guidance and is related to the materials being handled in the laboratory.

12.3 European Association Contact Details

Country	Associations	Initials	Address	Telephone	Fax	Email	Website
Belgium	The Belgium Royal Association of the Heating, Ventilation and Air-Conditioning	ATIC BELGIUM	Leuvensesteenweg 613, B-1930 Zaventem	0032 2 511 74 69	0032 2 511 75 97	info@atic.be	www.atic.be
Bosnia	Society of Heating, Ventilating Refrigeration, Air-Conditioning and Renewable Energies	HVRAC & RE	Vilsonovo šetalište 9, 71000 Sarajevo	+387 33 656 562/219 or Secretariat tel: +656 562/230	+387 33 653 055		
Croatia		CAHVAE	Berislaviceva 6, 10000 Zagreb	+385 1 422 938	+385 1 422 938	energmag@zg.tel.hr	
Czech Republic	Společnost pro techniku prostředí (Society of Environmental Engineering)	STP	Novotného lávka 5, CZ-116 68 Praha 1	+420 221 082 353	+420 221 082 201	stp_set@mbox.vo.cz	http://www.csvts.cz/stp/
Denmark	Danish Society of Heating, Ventilating and Air-Conditioning Engineers	DANVAK	Højnasvej 83, 1. sal, 2610 Rødovre	+45 3636 9060	+45 4587 7677	info@danvak.dk	
Estonia		EKVU	Rävala pst. 6, EE-0105 Tallinn	+372 671 1350	+372 671 1350		www.hot.ee/ekvy
Finland		FINVAC	Sitratori 5, FIN-00420 Helsinki	358 9 566 0090	358 9 566 00 956		
France	Association des Ingénieurs en Climatique, Ventilation et Froid	AICVF	Ad66 Rue de Rome	33 1 53 04 36 10	33 1 42 94 04 54		
Germany	Verein Deutscher Ingenieure (Association of German Engineers)	VDI	Postach 10 11 39, D-40002 Düsseldorf	(02 11) 62 14-2 51	(02 11) 62 14-1 77	tga@vdi.de	www.vdi.de/vdi/organisation/schnellauswahl/fgkf/tga/index.php
Hungary	Čpétčstudomfnyi Egyesület ČTE, Scientific Society for Building		Fő utca 68, H-1027 Budapest	36 1 201 84 16	36 1 156 12 15	info@eptud.hu, epgep.epte@mtesz.hu	www.eptud.hu www.epgeplap.hu

Country	Associations	Initials	Address	Telephone	Fax	Email	Website
Italy	Associazione Italiana Condizionamento dell'aria, Riscaldamento Refrigerazione	AICARR	Via Melchiorre Gioia 168, 20125 Milano	02 67 47 92 70	02 67 47 92 62	aicarr@aicarr.it	www.aicarr.it
Latvia		AHGWTEL	Vagonu iela 20, LV-1009 Riga	371 7 320727	371 7 615191		
Lithuania	Lithuanian Thermotechnical Engineers Society	LITES	Saulčtekio al. 11, 2040 Vilnius	370 2 76 03 28	370 2 70 04 97	lites@mf.ktu.it	
Netherlands	Nederlandse Technische Vereniging voor Installaties in Gebouwen (Dutch Society for Building Services)	TVVL	De Mulderij 12, Postbus 311, NL-3830 AJ Leusden	+31 33 434 57 50	+31 33 432 15 81	info@tvvl.nl	www.tvvl.nl
Norway	Norwegian Society of HEVAC Engineers, NORVAC	NORVAC	PO.Box 2843 Tøyen, N-0608 Oslo	+47 22 70 83 00	+47 22 69 36 50	norvac@skarland.no	
Poland	Polskie Zrzeszenie Inżynierów i Techników Sanitarnych	PZITS	Ul. Czackiego 3/5, 00-043 Warszawa	+48 22 826 28 94	+48 22 826 28 94	bogdan.mizielinski@is.pw.edu.pl	
Portugal	Ordem Dos Engenheiros		Av, Antonio Augusto Aguiar 3 D, 1069-030 Lisboa	+351 2 313 26 00	+351 2 352 46 32	ordeng@mail.telepac.pt	
Romania	Romanian General Association for Heating, Refrigeration, Air-conditioning, Sanitary and Electrical Engineers	AGFR-AIIR	66 Pache Protopopescu Blvd, 73232 Bucharest 2	40 1 250 65 46; 40 1 642 42 00;	40 1 250 65 46; 40 1 312 68 80; 40 1 210 32 56	agfr@pcnet.pcnet.ro	
Russia	Association of Engineers in Heating, Ventilation, Air-conditioning, Heat Supply and Building Thermal Physics	ABOK	Rohzdestvenka str.11 Russia 103754 Moscow		+7 095 921 8048 (6031, 6946, 7023, 8076, 7286)	support@abok.ru	www.abok.ru
Slovakia	Slovenska spoločnosť pre techniku prostredia – SSTP Slovak Society for Environmental Technology	SSTP	Kocelova 15, 815 94 Bratislava	421 7 5262 882 (5262 955)	421 7 5262 991	sstp@rainside.sk	

Country	Associations	Initials	Address	Telephone	Fax	Email	Website
Slovenia		SITHOK	Aškerčeva 6, 1000 Ljubljana	+386 1 4771 200	+386 1 2518 567	sithok@fs.uni-lj.si	www.drustvo-sithok.si
Spain	Asociación Española de Climatización y Refrigeración	ATECYR	Instituto Eduardo Torroja, C/ Serrano Galvache s/n, 28033 Madrid	34 91 7671355	34 91 7670638	administracion@atecyr.org	www.atecyr.org
Sweden	Tekniska Föreningen-Riksföreningen för Energi-och Miljöteknik (Swedish HEVAC-Society of Energi and Environmental Technology)	VVS	Parmmätargatan 7, S-112 24 Stockholm	46 8 654 08 30	46 8 654 96 83		
Switzerland	Schweizerischer Verein von Wärme- und Klima-Ingenieuren	SWKI	Solothurnstr. 13, Postfach, 3322 Schönbühl	031 852 13 00	031 852 13 01	info@swki.ch	www.swki.ch
Turkey	Türk Tesisat Mühendisleri Derneği	TTMD	Tunus Caddesi, Güfte Sokak, No:8/7 Kavaklıdere, Ankara, Türkiye	312 419 45 71	312 419 58 51	ttmd@ttmd.org.tr	www.ttmd.org.tr
United Kingdom	Chartered Institution of Building Services Engineers	CIBSE	Delta House 222 Balham High Road, London SW12 9BS	44 1 81 675 52 11	44 1 81 675 54 49	secretary@cibse.org	www.cibse.org
	Building Services Research Information Association	BSRIA	Old Bracknall Lane, West Bracknell, Berkshire RG12 7AH	44 134 465600	44 1344 65626	bsria@bsria.co.uk	www.bsria.co.uk
Yugoslavia	Yugoslav Society for Heating, Refrigeration and Air-conditioning,	YUGO KGH	Kneza Milosa 7, PO Box 648, 11001 Beograd	381 11 323 00 41	381 11 323 13 72	smeits@eunet.yu	

Appendix 2

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13.1 Further Reading

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Appendix 3

Glossary

14 Appendix 3 – Glossary

14.1 Acronyms and Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ACDP	Advisory Committee for Dangerous Pathogens
ACGIH	American Conference of Government Industrial Hygienists
ADA	Americans with Disabilities Act
AHJ	Authority Having Jurisdiction
AHU	Air Handling Unit
ANSI	American National Standards Institute
API	Active Pharmaceutical Ingredient
ASHRAE	American Society of Heating, Refrigeration and Air Conditioning Engineers
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials (International)
BAS	Building Automation Systems
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BMS	Building Management Systems
BOCA	Building Officials Code Administrators (International)
BOD	Basis of Design
BSC	Biosafety Cabinet
BSL	Biological Safety Level
BSRIA	Building Services Research Information Association
CAPA	Corrective and Preventative Action
CAV	Constant Air Volume
CDC	Centers for Disease Control and Prevention (US)
CDS	Chromatography Data System
CE	Conformité Européenne
CFD	Computational Fluid Dynamic
CFM	Cubic Feet of air per Minute
CIBSE	Chartered Institute of Building Services Engineering
CLSI	Clinical and Laboratory Standards Institute
CSI	Construction Specification Institute
DCS	Distributed Control System
DEA	Drug Enforcement Administration (US)
DI	Deionized
DNA	Deoxyribonucleic Acid

DX	Direct Expansion
ECL	Exposure Control Limits
EHS	Environmental, Health, and Safety
EP	European Pharmacopoeia
EMA	European Medicines Agency
ETOP	Engineering Turnover Package
EU	European Union
FAT	Factory Acceptance Testing
FF&E	Furniture, Fixtures, and Equipment
FMEA	Failure Mode Effects Analysis
FRP	Fiberglass Reinforced Plastic
GC	Gas Chromatography
GEP	Good Engineering Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GxP	Good “x” Practice (see Section 14.2 for definition)
HACCP	Hazard Analysis Critical Control Point
HAZCON	Hazards of Construction Risk Assessment
HEPA	High Efficiency Particulate Air
HPLC	High Pressure Liquid Chromatography
HPW	Highly Purified Water
HVAC	Heating Ventilation and Air Conditioning
HVCA	Contractors Association
I/O	Input/Output
IAQ	Indoor Air Quality
IBC	International Building Code
IC	Ion Chromatograph
ICH	International Conference on Harmonisation
IEC	International Electrotechnical Commission – Note for Jim: is this correct?
IEEE	Institute of Electrical and Electronic Engineers
IPA	Isopropyl Alcohol
ISA	International Society of Automation
ISO	International Organization for Standardization
IT	Information Technology
JP	Japanese Pharmacopoeia
KF	Karl Fisher
LAL	Limulus Amebocyte Lysate

LEED	Leadership in Energy, Environment, and Design
LIMS	Laboratory Information Management Systems
LOD	Loss on Drying
MBSC	Microbiological Safety Cabinet
MD/V	Methods Development/Validation
MEP	Mechanical, Electrical, and Plumbing
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MSDS	Material Safety Data Sheet
MVP	Master Validation/Verification Plan
NC	Noise Criteria
NFPA	National Fire Protection Association (US)
NIH	National Institutes of Health (US)
NIST	National Institute of Standards and Technology (US)
NMR	Nuclear Magnetic Resonance
NRC	Nuclear Regulatory Commission (US)
NSF	National Science Foundation
OEB	Occupational Exposure Band
OEL	Occupational Exposure Limit
OOS	Out Of Specification
OPC	Open Connectivity
OSHA	Occupational Safety and Health Administration
OTC	Over-the-Counter
POU	Point Of Use
PPE	Personal Protective Equipment
PVC	Poly Vinyl Chloride
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
RC	Room Criteria
RCRA	Resource Conservation and Recovery Act
RFI	Radio Frequency Interference
RH	Relative Humidity
RO	Reverse Osmosis
ROI	Return on Investment
RPN	Risk Priority Number
SAT	Site Acceptance Testing

SCADA	Supervisory Control and Data Acquisition
SMACNA	Sheet Metal and Air Conditioning National Association
SOP	Standard Operating Procedure
TLC	Thin-layer Chromatography
TLV	Threshold Limit Value
TOC	Total Organic Carbon
UPS	Uninterruptible Power Supply
USDA	United States Department of Agriculture
USP	United States Pharmacopeia
VAV	Variable Air Volume
VFD	Variable Frequency Drive
VM	Value Management
VMP	Validation/Verification Master Plan
VOC	Volatile Organic Compound
WFI	Water for Injection
WHO	World Health Organization

14.2 Definitions

Acid

A compound of an electronegative element or radical with hydrogen; it forms salts by replacing all or part of the hydrogen with an electropositive element or radical. Or, a hydrogen-containing substance that when dissolved in water dissociates to produce one or more hydrogen ions (H⁺). Acids cause irritation, burns, or more serious damage to tissue, depending on the strength of the acid, which is measured by its pH.

Airlock

An enclosed space with two or more doors and which is interposed between two or more rooms, e.g., of differing class of cleanliness, for the purpose of controlling the air flow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.

Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body.

Acute Exposure

A single exposure to a toxic substance that results in severe biological harm or death. Acute exposures are usually characterized as lasting up to 14 days.

Aseptic

Not sterile, but contaminants controlled within established acceptable limits.

Autoclave

An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g., filter assemblies, glassware, etc.). Steam pressure is maintained for pre-specified times and then allowed to exhaust. There are two types of autoclaves:

- Gravity displacement autoclave: this type of autoclave operates at 249.8°F (121°C). Steam enters at the top of the loaded inner chamber, displacing the air below through a discharge outlet.
- Vacuum autoclave: this type of autoclave can operate with a reduced sterilization cycle time. The air is pumped out of the loaded chamber before it is filled with steam.

Barrier System

An open system that can exchange contaminants with the surrounding area, and cannot be decontaminated to the extent possible in an isolator system.

Base

Substance whose chemical reaction characteristic is to establish new bonds by the donation of electron pairs.

Basis of Design (BOD)

A “dynamic” design document that describes the purpose of a given system and/or facility and how they will accomplish their required tasks. This document is created and approved before the issuance of bid specifications and may be used to develop them. Until the system is developed this is a conceptual document.

Biohazard

An infectious agent(s), or part thereof, presenting a real or potential risk to human, other animals, or plants, directly through infection or indirectly through disruption of the environment.

Biologic

Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

Calibration

A comparison of a measurement standard or instrument of unknown accuracy to detect, correlate, report, or eliminate by adjustment any variation in the accuracy of the unknown standard or instrument.

Corrective and Preventive Action (CAPA)

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

Current Good Manufacturing Practice (CGMP)

Current accepted standards of design, operation, practice, and sanitization. The FDA is empowered to inspect drug-manufacturing plants in which drugs are processed, manufactured, packaged, and stored for compliance with these standards.

Chromatography

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

Chronic Exposure

Contact with a substance that occurs over a long time (more than one year).

Classified Space

An area with airborne viable and non-viable particle contamination controlled within preset limits. A cleanroom designated by ISO Standard 14644-1 classification units ("In Operation") or European Community (EC) Grades A, B, C, D ("At Rest" and "In Operation"). For pharmaceutical manufacture, a classified space implies ongoing environmental monitoring.

Closed System

System sterilized-in-place or sterilized while closed prior to use, is pressure or vacuum tight to some predefined leak rate, can be utilized for its intended purpose without breach to the integrity of the system, can be adapted for fluid transfers in or out while maintaining asepsis, and is connectable to other closed systems while maintaining integrity of all closed systems.

Commissioning

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

Conceptual Design

Design stage, to generate various alternatives for evaluation. The project team then selects the concepts to be taken forward into the functional design stage.

Containment

Physical means to prevent the entry of hazardous material into the workplace to protect the worker and the work environment from materials that are highly active biologically or pharmacologically, toxic, or biohazardous, usually in addition to protecting the product from contamination.

- Primary Containment: the protection of workers and the product from exposure to potentially hazardous agents, via the use of closed systems and physical segregation.
- Secondary Containment: the control of contaminants, through system and equipment design, to prevent the release of potentially hazardous agents to the outside environment, via spatial layouts and adjacencies, flow patterns and directional airflow and pressure boundaries.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Controlled Drugs

Narcotic drugs and psychotropic substances regulated by provisions of national drug laws.

Cross Contamination

The measurable and detrimental contamination of a drug substance or product by another.

Deflagration

An exothermic reaction, such as the extremely rapid oxidation of a combustible dust or flammable vapor in air, in which the reaction progresses through the unburned material at a rate less than the velocity of sound. A deflagration can have an explosive effect.

Depyrogenation

The removal or destruction of endotoxins.

Design Qualification (DQ)

Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

Detailed Design

Design stage when the documents required for construction bidding and contracting, as well as system and equipment purchase, fabrication, installation and testing are produced.

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 in addition, are subject to Qualification Practices that incorporate the enhanced review, control, and testing against specifications or other requirements necessary for cGMP compliance.

Drug Substance

Any component intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of humans. The term includes those components that may undergo chemical change in the manufacture of the drug product, and be present in the drug product in a modified form intended to furnish the specified activity or effect. A drug substance is an API.

Excipients (USP)

Components of a finished medicinal drug product other than the Active Pharmaceutical Ingredient (API). They are included in the formulation to facilitate manufacture, enhance stability, control release of API from the product, assist in product identification, or enhance other product characteristics.

Expiration Date

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Explosion

A release of energy sufficient to cause a pressure wave; a rapid or sudden release of energy that causes a pressure discontinuity or blast wave.

Explosive Limits

The range of concentrations (% by volume in air) of a flammable gas or vapor that can result in an explosion from ignition in a confined space. Usually given as Upper (UEL) and Lower Explosive Limits (LEL).

Factory Acceptance Test (FAT)

The partial commissioning and qualification of equipment and/or systems prior to their shipment from the fabricator's site.

Finished Product

A medicinal product that has undergone all stages of production, including packaging in its final container.

Fume Hoods

Units that collect fumes from chemicals, solvents, acids, and other hazardous materials. Hoods may include HEPA filters if powders are present, or carbon filters to filter fumes from the work surface and return cleaned air to the room. Most fume hoods are 100% exhausted to outdoors. A glass, Plexiglas™, or acrylic front panel may be included for worker safety.

Functional Design Specification (FDS)

Provides the functional design requirements. The FDS says how the direct impact water or steam system will perform its function. Typically, the FDS is tested or verified during commissioning or qualification.

General Arrangement

A specific version of a general plant layout that includes the system interface points, space requirements, ergonomics, construction issues, manufacturing flow of equipment, materials, and personnel, maintenance requirements and future expansion or alterations.

Glove Port

Attachment site for gloves, sleeves, and gauntlets.

Good Engineering Practice (GEP)

Established engineering methods and standards that are applied throughout a project's life cycle to deliver appropriate, cost-effective solutions.

Good Laboratory Practice (GLP) (MHRA)

GLP embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, veterinary medicines, industrial chemicals, cosmetics, food and feed additives and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

GxP

One or a combination of GCP, GMP, GLP, GDP – usually used for everything of interest for the Regulatory Bodies. One or more of the following would be represented by “x”: Clinical, Manufacturing, Laboratory, Distribution.

Hazard and Operability Review (HAZOP)

The process of systematically reviewing a facility/system/process to determine potential safety concerns.

Hazardous (Classified) Materials

Gases, vapors, combustible dusts, fibers, or flyings that are explosive under certain conditions.

Hazardous Substance

A substance which by reason of being explosive, flammable, toxic, poisonous, corrosive, oxidizing, irritant or otherwise harmful, is likely to cause injury.

High Efficiency Particulate Air (HEPA) Filter

A filter with an efficiency in excess of 99.97% for 0.3 µm particles.

High Pressure Liquid Chromatography (HPLC)

Sometimes called high-performance liquid chromatography, is a separation technique based on a solid stationary phase and a liquid mobile phase. Separations (into distinct bands) are achieved by partition, adsorption, or ion-exchange processes, depending upon the type of stationary phase used. Each band is then profiled as the solvent flows through a UV detector, or by fluorescence, or refractive index detectors.

Indirect Impact System

System that is not expected to have a direct impact on product quality, but typically will support a Direct Impact System. These systems are designed and commissioned following Good Engineering Practice only.

Installation Qualification (IQ)

For “Direct Impact” systems, the documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and is correctly installed.

Isolator

Leaktight enclosure designed to protect operators from hazardous/potent processes or protect processes from people or detrimental external environments or both. A basic enclosure consists of a shell, viewing window, glove/sleeve assemblies, supply and exhaust filters, light (s), gauge (s), Input and Output openings (equipment door airlocks, Rapid Transfer Ports (RTPs), etc.), and various other penetrations. There are two types of isolators:

- Closed Isolators: Isolators operated as closed systems do not exchange unfiltered air or contaminants with adjacent environments. Their ability to operate without personnel access to the critical zone makes isolators capable of levels of separation between the internal and external environment unattainable with other technologies. Because the effectiveness of this separation, closed isolators are ideally suited for application in the preparation of sterile and/or toxic material. Aseptic and Containment isolators are two types of closed isolators.
- Open Isolators: Open isolators differ from closed isolators in that they are designed to allow for the continuous or semi-continuous egress of materials during operation, while maintaining a level of protection over the internal environment. Open isolators are decontaminated while closed, and then opened during manufacturing. Open isolators typically are used for the aseptic filling of finished pharmaceuticals.

Note: Containment, barrier isolation and isolation all refer to the same technology, which is enclosing an environment. In the interest of clarifying the existing confusion between the terms “isolators” and “barriers”, and providing authoritative implementation and validation of isolation technology, the Parenteral Drug Association (PDA) published in October 2000 the Draft for Technical Report No. 34 “Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products”.

Laminar Airflow – Clean Work Station

A workstation in which the unidirectional airflow characteristics predominate throughout the entire airspace with a minimum of eddies (turbulence) to jeopardize critical surfaces.

Microbiology

The study of microscopic life such as bacteria and viruses.

Microorganism

A microbe – A microscopic plant or animal, such as a bacterium, protozoan, yeast, virus, or algae.

Mini-Environment

The actual localized control space limited by a defined enclosure that separates or isolates the inside from the outside environment, such that the transfer of potential contamination from one side to the other is minimized or completely eliminated, depending on the design. Minienvironments are not always isolators.

Material Safety Data Sheet (MSDS)

Document describing the chemical and physical properties of a substance as related to its safe handling and storage. The substance manufacturer originates it.

No Impact System

System that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned following Good Engineering Practice only.

Non-Unidirectional Airflow

Airflow that does not meet the definition of unidirectional airflow; previously referred to as “turbulent” or “non-laminar” airflow.

Occupational Exposure Limit (OEL)

An OEL is a health-based airborne concentration limit to which worker exposure levels should be controlled. Limits are usually expressed as eight-hour time weighted averages for exposures for 40 hours a week over a working lifetime.

Operational Qualification (OQ)

For “Direct Impact” systems, the documented verification that all aspects of a facility, utility, or equipment that can affect product quality, perform as intended throughout all anticipated operating ranges.

Out of Specification

An examination, measurement, or test result that does not comply with pre-established criteria.

Oxidizer

A chemical, which readily oxidizes more reduced substances. Examples of strong oxidizers are ozone, hydrogen peroxide, chloride, persulfates, and oxygen itself.

Packaging

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

Performance Qualification (PQ)

For “Direct Impact” systems, the documented verification that all aspects of a facility, utility or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria.

Pharmaceutical Product

Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

Potent Compound

- A pharmacologically active ingredient or intermediate with biological activity of approximately 15 micrograms per kilogram of body weight or below in humans (therapeutic dose at or below 1 milligram).

- An Active Pharmaceutical Ingredient (API) or intermediate with an OEL at or below 10 micrograms per cubic meter of air as an eight-hour time weighted average (TWA).
- A pharmacologically active ingredient or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses.
- A novel compound of unknown potency and toxicity.

Preliminary Design (IEEE)

The process of analyzing design alternatives and defining the architecture, components, interfaces, and timing and sizing estimates for a system or component.

Product Contact Surface

A surface that contacts raw materials, process materials, and/or product.

Project Execution Plan

A written plan for the project manager to communicate to the user and other stakeholders the approach to be taken for project execution.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Radiopharmaceuticals

Drugs (compounds or materials) that may be labeled or tagged with a radioisotope. These materials are largely physiological or subpharmacological in action, and, in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are injected into the body.

Raw Material

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reactivity

The ability of a substance to undergo a chemical reaction (such as combining with another substance). Substances with high reactivity are usually quite hazardous.

Reagent

A substance used (as in detecting or measuring a component, in preparing a product, or in developing photographs) because of its chemical or biological activity.

Relative Humidity (% RH)

The ratio (measured in percent) of actual water vapor pressure in air to the pressure of saturated water vapor in air at the same temperature and pressure.

Release

The discharge of a microbiological agent or eukaryotic cell from a containment system.

Risk (ICH Q9)

Combination of the probability of occurrence of harm and the severity of that harm.

Risk Control

Process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels.

Risk Management

Systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, and controlling risk.

Sanitization

To make sanitary by cleaning or disinfecting. That part of decontamination that reduces viable microorganisms to a defined acceptance level normally achieved by using a chemical agent, steam or dry heat.

Segregation – Primary

The use of physical facility design elements to define the basic organization of the biopharmaceutical plant design and establish environmentally controlled work areas around specific steps of the process, e.g., the establishment of classified areas. It provides distinct environmental protection for the process/product from contamination, and is traditionally accomplished by the designation of dedicated areas, staff, and supporting mechanical systems. FDA CBER suggests discussion of segregation concepts more specifically, addressing physical segregation or procedural segregation.

Segregation – Secondary

The use of procedural or chronological controls to minimize potential interactions or contamination. It is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary separation mechanisms can vary widely and include storage of raw materials in different stages of quarantine; clean/dirty equipment areas; and general access paths/process areas. Whereas primary segregation controls the immediate quality of the process, secondary segregation measures are traditionally implemented to minimize the potential for human error. FDA CBER suggests discussion of segregation concepts more specifically, addressing physical segregation or procedural segregation.

Site Acceptance Test (SAT)

Inspection and/or dynamic testing of the systems or major system components to support the qualification of an equipment system conducted and documented at the manufacturing site.

Solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Stability

The capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications for a specified anticipated shelf life.

Standard Operating Procedure (SOP)

Written and approved procedures to ensure that activities are performed the same way each time. A comprehensive SOP program must be in place in any regulated organization.

Sterile

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

Sterile Transfer

In biopharmaceuticals, the transfer of material from a vessel to another vessel without contamination from the surrounding environment or from the transfer device.

Sterilization

Refers to the killing of microorganisms in the distribution system. This is normally done periodically by flushing a sterilizing solution, such as hydrogen peroxide or ozone, through the distribution piping system. In some systems, ozone is continuously injected at low levels for continuous sterilization.

Test

An activity in which a system or component is executed under specified conditions, the results are observed or recorded, and an evaluation is made of some aspect of the system or component.

Toxic

Pertaining to a substance that is harmful. The toxicity of a substance is the potential of that substance to cause harmful effects. These effects can strike a single cell, a group of cells, an organ system, or the entire body. A toxic effect may be visible damage, or a decrease in performance or function measurable only by a test. All chemicals can cause harm, but when only a small amount can be harmful, the chemical is considered toxic. Toxic materials may be solid, liquid, gas, vapor, dust, fume, fiber, and mist.

Unidirectional Air Flow

Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel airstreams. **Note:** This type of airflow results in a directed transport of particles from the clean zone.

Uniformity of Airflow

Unidirectional airflow pattern in which the point-to-point readings of velocities are within the defined percentage of the average airflow velocity.

User Requirement Specification (URS)

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

Utility Systems

Facility-wide systems not tailored to a specific process and that do not have contact with the drug substance or potential drug substance.

Validation

Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

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