



Good Practice Guide

Quality Laboratory Facilities

Facility and Personnel

Process and Equipment

Design and Organization

Utility and Support Space

Connecting a World of
Pharmaceutical Knowledge



Document Sharing Hub

Simplified On-line TOC Measurement

Ideal for PAT, QbD, and Other Quality Optimization Initiatives

With the widest range of pharmaceutical Total Organic Carbon (TOC) analyzers and sensors, ready-to-use Sievers Standards, validation documentation, Quality System Optimization (QSO) services, technical support, and more than 20 years' leadership in measurement technologies for pharmaceutical water, GE Analytical Instruments offers a complete solution for:

- Compliance with US, European, Chinese, Indian, and the Japanese (JP 16) Pharmacopeia TOC monitoring requirements
- Continuous on-line quality assurance
- Real-time pharmaceutical water testing and release
- On-line cleaning validation and verification
- Optimizing and rationalizing cost-effective sampling plans with lower risk

The featured Sievers 500 RL TOC Analyzer offers:

- Unsurpassed accuracy and precision
- Broad range of detection (0.03 ppb to 2,500 ppb as C)
- Four-port Super **iOS** that automates all validation protocols
- Easy operation, no reagents, and low maintenance
- The most reliable TOC system suitability measurement available

Learn more. Contact us at +800 255 6964,
geai@ge.com, or visit www.geinstruments.com.



Sievers 500 RL On-Line
0.03 ppb to 2,500 ppb



CheckPoint Pharma On-Line/Portable TOC Sensor
0.21 ppb to 1,000 ppb



Sievers 900 Laboratory and GE Autosampler
0.03 ppb to 50 ppm



Sievers 900 On-Line
0.03 ppb to 50 ppm



Sievers 900 Portable
0.03 ppb to 50 ppm



GE imagination at work



Documents

Document Sharing Hub



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.

Limitation of Liability

In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, or the authors, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2012. All rights reserved.

No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-936379-43-9

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.



Acknowledgements

Chapter Writers and Reviewers

The following individuals took lead roles in the preparation of this document. The company affiliations are as of the final draft of the Guide.

James M. O'Brien (Chair)	NAMA Industries, Inc.	USA
Euan D. Smith (Co-Chair)	MSD	United Kingdom
Mark A. Butler	IPS	USA
Mary Ellen Craft	Fluor	USA
Thomas J. Creaven	Schering-Plough Corp.	USA
Cesar B. Daou, PE	Daou Engineers Inc.	USA
Donna A. DeFreitas	Vanderweil Engineers	USA
James J. Dolceamore	AstraZeneca Pharmaceuticals LP	USA
Dr. William E. Ferguson	Ferguson Consulting LLC	USA
Frederick L. Fricke, PhD	FDA	USA
Peter B. Gardner	Torcon Inc.	USA
Michelle M. Gonzalez	BioPharm Engineering Consultant	USA
Gerard J. Guillorn	M+W Shanghai Co., Ltd.	USA
Terry A. Jacobs, AIA	Jacobs/Wyper Architects, LLP	USA
Kaushik S. Master	Amgen Inc.	USA
Catherine E. Middelberg	Pfizer	USA
Kimberly D. Snyder	Proteus	USA
Dr. Gregory L. Tewalt	Samsung Biologics	South Korea

Many other individuals provided topics and comments prior to, and during, the writing of this Guide; although they are too numerous to list here, their input is greatly appreciated.

Cover photo: courtesy of Chiesi Farmaceutici S.p.A., www.chiesigroup.com.



**Connecting a World of
Pharmaceutical Knowledge**

ISPE Headquarters

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

ISPE Asia Pacific Office

73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office

Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office

Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

AVA **Documents**
Document Sharing Hub

Table of Contents

1	Background and Purpose	7
1.1	Background	7
1.2	Purpose.....	8
1.3	Objectives	8
1.4	Scope of This Guide	9
1.5	Issues Which Define the Design of Quality Laboratories.....	9
2	Concepts and Regulatory Philosophy	11
2.1	Introduction	11
2.2	Facility, Equipment, and Personnel.....	11
2.3	GMP Requirements	16
2.4	General Laboratory and Support Space Characterizations	17
2.5	Speciality Laboratories.....	23
2.6	Specialty Compound Laboratories.....	27
3	Laboratory Process and Equipment	31
3.1	Introduction	31
3.2	Areas Supporting General Laboratory Processes and Procedures	31
3.3	Functional Area Equipment Allocation	32
4	Hazard and Safety	37
4.1	Introduction	37
4.2	Occupational Exposure Limits	37
5	Risk Assessment	45
5.1	Introduction	45
5.2	Regulatory Review.....	46
5.3	Assessing Risk.....	46
6	The Project Execution	49
6.1	The Laboratory Design Process	49
6.2	The Project Team.....	52
6.3	The Basis of Design.....	54
6.4	Design Development.....	58
6.5	Construction.....	58
6.6	Commissioning and Qualification.....	59
6.7	Budgeting.....	59
6.8	Cost Control During Construction	62
7	Architectural.....	69
7.1	Introduction	69
7.2	Laboratory Design and Organization	70
7.3	Architectural Finishes.....	81
7.4	Laboratory Design Check List.....	82
7.5	Organization of Quality Laboratory Spaces	84

8	HVAC	87
8.1	Introduction	87
8.2	User Requirements	89
8.3	HVAC Design Parameters	93
9	Electrical	107
9.1	Introduction	107
9.2	General Requirements	107
9.3	Power Distribution	107
9.4	Area Classification	107
9.5	Lighting	108
9.6	Grounding	108
9.7	Telephones, Paging, and Radio Systems	109
9.8	Laboratory Information Management System	109
9.9	Wiring Methods	110
10	Laboratory Site Utility and Support Systems	111
10.1	Introduction	111
10.2	Laboratory Water	111
10.3	Additional Programming Considerations	136
10.4	Utility and Support Spaces	139
11	Commissioning and Qualification	141
11.1	Introduction	141
11.2	Scope	142
11.3	Developing a Commissioning and Qualification Strategy	143
11.4	Commissioning as Good Engineering Practice (GEP)	145
11.5	Qualification	147
12	Appendix 1 – European Considerations	149
12.1	Introduction	150
12.2	The Differences	150
12.3	European Association Contact Details	152
13	Appendix 2 – References	155
13.1	Further Reading	158
14	Appendix 3 – Glossary	159
14.1	Acronyms and Abbreviations	160
14.2	Definitions	163

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

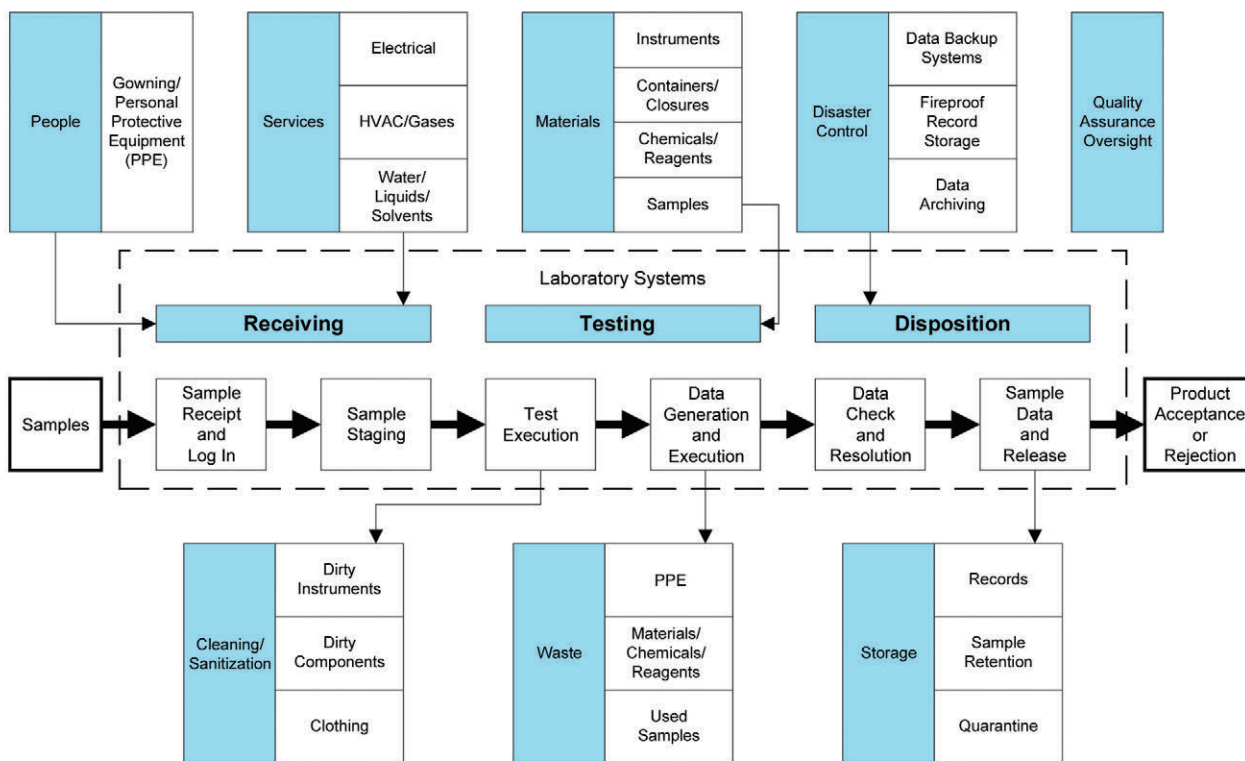
2.2.1 Facilities

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 biohazard 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									
<i>*Note: UPS requirement for instrumentation is dependent on laboratory program.</i> 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.

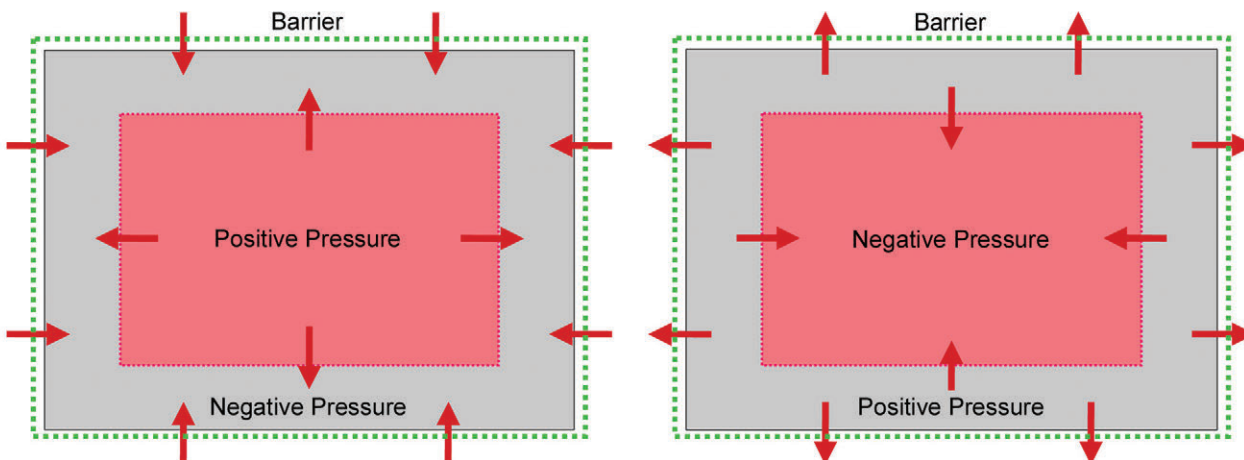
The design should consider the primary objective and design the area pressurization accordingly, see Chapter 8 of this Guide on HVAC.

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.