FACILITY VALIDATION

Theory, Practice, and Tools

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Preface

Pharmaceutical companies typically require considerable resources in terms of time, money, and specialized personnel to validate a manufacturing facility, and this can be overwhelming to a small company or plant with limited resources. The cost of validating a plant has increased over the years, reflecting higher standards required by the regulatory authorities or by companies adopting inefficient and ineffective validation practices. Because of the latter problem, the word "validation" still has a negative connotation in the pharmaceutical industry and is still understood by some as unrestrained bureaucracy, paperwork, and procedures whose roots and logic are obscure and which serve only to slow progress. In short, validation provides no beneficial contribution to a project — it only adds cost.

To analyze and investigate this problem in more depth, this book focuses on validation aspects pertaining to the startup of a new or upgraded manufacturing facility. The "theory, practice, and tools of facility validation" are defined.

A scenario is sketched of facility construction costs continuing to escalate with ever-decreasing resources and time allocated to many projects; tied in with this are many far-reaching changes taking place in the application of the current good manufacturing practice (cGMP) regulations relating to the pharmaceutical industry. Regulatory authorities are expecting the rigor of control of pharmaceutical manufacturing to continuously improve over time. This is forcing companies to evaluate their validation programs to investigate ways of streamlining the process of validation. Methods that satisfy quality needs, business needs, and regulatory requirements are used to ensure that the industry remains competitive and compliant in an effective and efficient manner.

Various policies, guidelines, and regulations relating to GMP in the pharmaceutical industry worldwide, particularly those regulations affecting the various aspects of facility validation, are defined and described. The relationship between validation and GMP is then further expanded on to define the scope and extent of regulatory requirements for validation.

Validation concepts, definitions, and terminology associated with GMP and validation is discussed in an effort to provide some consistency to avoid confusion and misinterpretation of regulatory expectations within the industry. The philosophy and key principles of validation (life-cycle approach to validation and qualification practices) are detailed. What it takes to set up an infrastructure for implementing a validation program to address all of the essential validation disciplines is also presented.

The life-cycle approach is presented for the qualification and validation of a pharmaceutical manufacturing facility explaining the sequence of relevant engineering and validation activities typically followed in a project. Common pitfalls and problems associated with facility validation projects are presented to highlight the various difficulties and constraints that a validation team has to manage.

Twenty steps and good validation practices are advocated to reduce project resource requirements, project costs, and time schedules, improve commissioning and validation efficiencies, with efficient start-up of the plant.

The various benefits of implementing the good validation practices to address the most common problems associated with facility validation projects are expounded. The book warns of dire consequences if companies do not adopt and follow these best practices.

This book makes a solid case for the benefits of companies following a simple, practical, scientific validation program that is based on common sense. It demonstrates that design, engineering, commissioning, and validation activities can be integrated and streamlined to accelerate the start-up effort, reduce the validation effort and costs, produce superior documentation, and ensure that product is produced in a cGMP-compliant facility. It proves that even though the original focus of validation was to satisfy regulatory expectations, facility validation has in fact become a good business and engineering practice that enhances reliability, cost, and quality. Properly executed validation pays for itself, often in nonfinancial ways.

Validation professionals are challenged to never allow themselves to become complacent about investigating and employing new approaches and technologies and must continue to develop standards and guidelines for increasing the quality, effectiveness, and value of validation activities and to make these available to help companies to keep their good validation practices current in order to control the cost of validation. In this way validation will take the lead, refocus, and begin to dispel the negative perceptions and reverse this disturbing trend toward unnecessary or inefficient facility validation activities to provide positive impact to the corporate bottom line.

Author

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Introduction

In the past decade, many far-reaching changes have taken place in the application of the current good manufacturing practice (cGMP) regulations relating to the pharmaceutical industry. The words "current" and "good" in cGMP create the expectation for the rigor of control of pharmaceutical manufacturing to continuously improve over time, and convey the notion that as soon as a practice becomes recognized as valuable in assuring the quality of drug products, that practice becomes the standard for the industry. Thus, continuous quality improvement is ingrained in the cGMP concept.

In this environment, the pharmaceutical industry also constantly seeks improved manufacturing efficiencies to attain marketplace strategic advantage with "cost of goods" and "speed to market" imperatives and increasingly more costly capital expenditures are devoted to achieving this competitive advantage. These strategies often include building new or modernizing existing manufacturing facilities. The design, construction, commissioning, and validation of these pharmaceutical facilities are significant challenges for project managers, as well as engineering and quality professionals. Constantly caught in a dilemma of budget and schedule constraints, companies have to deliver a quality end product that complies with all building, environmental, health and safety codes, laws, and regulations and in addition they must also comply with one very important legal criterion: They must be validated to meet the cGMP regulations.

Historically, the legal requirement for validation in the pharmaceutical industry originated in 1978 in the U.S. with the Food and Drug Administration (FDA) issuing amendments to the Code of Federal Regulations (CFR) that set forth current cGMP regulations (FDA CFR Title 21)[1] for the manufacturing, processing, packaging, or holding of human and veterinary drugs. This precipitated a widespread rush by pharmaceutical manufacturers to institute formalized validation programs suited to their individual needs, financial capabilities, and company philosophies.

These regulations have been written in such a way as to leave the interpretation to the user, and confusion and misinterpretation by the industry on the scope and extent of this validation requirement has led to ever-increasing costs of bringing pharmaceutical facilities in compliance with these cGMPs.

The cost of validating a facility is determined by the time spent on documentation, the development of protocols and SOPs, and the time spent on actual fieldwork, data collection, and analysis.[2] These costs have increased over the years, reflecting higher standards required by the regulatory authorities, because industry has adopted inefficient and costly blanket validation compliance strategies. As a result, there is a continuing struggle and challenge to meet regulatory requirements, keep overhead costs down, and run a profitable business. For interest, a good rule of thumb is that,

for typical pharmaceutical plant expansion projects, total "validation costs may run from 4 to 8% of the total project cost."[3]

For a new or upgraded facility, commissioning and facility validation is the foundation for assuring success in future manufacturing process validation. Before you begin validating a manufacturing process, an acceptable facility and the utilities and equipment to support manufacturing operations must be in place.

Facility qualification and validation activities will establish and provide documentary evidence that:

- The premises, facilities, and equipment have been designed in accordance with the requirements of cGMP. This constitutes design qualification (DQ).
- The facilities and equipment have been built and installed in compliance with their design specifications. This constitutes installation qualification (IQ).
- The facilities, utilities, and equipment operate in accordance with their design specifications. This constitutes operational qualification (OQ).
- The facilities, utilities, or equipment that can affect product quality performs as intended, meeting predetermined acceptance criteria. This constitutes performance qualification (PQ).[4]

Process validation can commence once the facility has been validated (IQ + OQ + PQ). A specific process will consistently produce a product meeting predetermined specifications and quality attributes. This constitutes process validation (PV).[4]

These qualification and validation activities play a crucial role in delivering operationally effective, safe, and efficient facilities, manufacturing process utilities, and equipment, and also provide the medium by which compliance is achieved, demonstrated, and retained.

Facility validation represents the last phase of the design and construction of a pharmaceutical facility and is beset by the following major problems:

- Validation activities form a significant percentage of time and money in most pharmaceutical capital projects, and the cost of validating and maintaining facilities designed to meet cGMP requirements is spiraling out of control. These costs have increased over the years, reflecting higher standards required by the regulatory authorities as interpreted, and also because industry has adopted inefficient and costly blanket validation compliance strategies. This is because most organizations lack a clear understanding of the reason for validation, fail to develop procedures to allow them to conduct efficient validation, and rarely allow sufficient time and resources to plan for validation activities.
- Compared to disciplines like chemistry and engineering, validation is a relatively new technology, and many of the people in key senior management positions today do not fully appreciate the extent and scope of validation, the resources required, and its beneficial contribution to a project. This means that validation project teams are often under resourced for the scope and duration of projects.

- Advancing manufacturing technology makes new facilities increasingly more complex and brings higher expectations for output, quality, and efficiency. Fears of plant shut-downs and possible financial losses are forcing validation teams to qualify or validate noncritical cGMP systems that really only require commissioning.
- Plant commissioning is a vital element in the process of delivering new facilities and represents the last phase of the design and construction of a pharmaceutical facility before validation. Project system and equipment commissioning activities are often not planned sufficiently well and timelines allocated for execution are underestimated. This, together with varying commissioning practices and methodologies, results in costly delays and stressful implementation when project teams undermanage the tasks of starting up and turning over facilities. This lack of effective commissioning and the consequent slippage in the project time line can restrict the amount of time left to do the validation.

Pharmaceutical industries, regulatory authorities, institutions, and corporations in places such as the U.S., Europe, and Japan are harmonizing their regulations and practices relating to cGMP, and nations worldwide are gradually adopting these rules, regulations, and practices.

As GMPs must remain current, so too must there be continuous quality improvement over time in what could be termed good validation practice (GVP). Ways of streamlining the process of validation, with methods that satisfy quality needs, business needs, and regulatory requirements must be investigated to ensure that the industry remains competitive and compliant in an effective and efficient manner.

This book presents the author's experience in validating upgraded manufacturing facilities and proposes methodologies to improve, integrate, and streamline the facility validation approaches to control the cost and time of validation, with the resultant efficient start-up of pharmaceutical manufacturing facilities.

This book presents, reviews, analyzes, and discusses the following:

- Chapter 1: The Regulatory Requirements for Validation in the Pharmaceutical Industry
  - The regulatory requirements of good manufacturing practice (GMP)
  - The relationship between validation and GMP
  - The impact of changing regulations on the scope and extent of validation
  - The future of GMP
- Chapter 2: The Fundamentals and Essentials of Validation
  - Validation concepts, definitions, and terminology
  - The philosophy and key principles of validation
  - Organizing and planning for validation
  - The essential validation disciplines
- Chapter 3: The Practice of Facility Validation
  - A typical life-cycle approach for the qualification and validation of a pharmaceutical manufacturing facility

- Chapter 4: Twenty Tools Recommended for Facility Validation
  - Common problems associated with facility validation
  - Good validation practice
- Chapter 5: Good Validation Practice
  - Benefits of following good validation practice
  - Consequences of not following good validation practice
- Chapter 6: Conclusions and Future Directions

This book offers the industry an opportunity to rethink current practices regarding this powerful and valuable quality system, viz. validation, so that we can address problems and shortcomings, identify inefficient validation activities, and implement new approaches to reduce costs and improve efficiency. The book identifies opportunities for improving the following critical areas in a facility validation project: project organizational structure, project team responsibilities, project scope definition, project planning and scheduling, commissioning program, construction turn-over and plant startup, documentation management, and maintenance of validation status.

Validation is a function of risk aversion and the cost of validation is related to the amount of (quality) risk that we wish to avert.[5] This book demonstrates that design, engineering, commissioning, and validation activities can be integrated and streamlined to accelerate the startup effort, reduce the validation effort and costs, produce superior documentation, and ensure that product is produced in a cGMP-compliant facility. It also proves that even though the original focus of validation was to satisfy regulatory expectations, facility validation has in fact become a good business and engineering practice that enhances reliability, cost, and quality.

The information presented in this book will provide:

- Practical approaches that may be used for integrating the commissioning and validation of GMP facilities for companies new to validation or companies with limited validation resources.
- Guidelines to pharmaceutical manufacturers, engineering, quality, and validation professionals for assessing the detail, efficiency, quality, and cost of their programs and will describe some of the practical approaches that may be used to facilitate new facility startup and operation.
- A positive contribution to the future cGMP standards to be set by the regulators of the pharmaceutical industry.

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Contents

1 The Regulatory Requirements for Validation in the Pharmaceutical Industry

1.1 THE REGULATORY REQUIREMENTS OF GOOD MANUFACTURING PRACTICE (GMP)

Most countries have laws and regulations that cover the manufacture, sale, and distribution of drug or medicinal products. These laws and regulations are normally governed by some form of health regulatory authority whose duty it is to promote health and to protect the public from health hazards. These regulatory authorities will want to be sure that the pharmaceutical products used in their country are safe to use, efficacious, properly made, and of the right quality.

As a consequence, government regulatory authorities usually have a system of registration or licensing for drug products, and will not allow a medicine to be sold or supplied for use unless it has been properly registered or licensed. Compliance with a specified GMP requirement is used by most countries as the basis for licensing manufacturers of pharmaceutical products. The authorities also want to know that in day-to-day production the product is made properly and to the right quality standards. That is, they will want to be sure that the manufacturer is working in accordance with the principles of good manufacturing practice (GMP).

GMP is the acronym used internationally to describe a set of principles and procedures, which, when followed by manufacturers of pharmaceutical or therapeutic goods, helps ensure that the products manufactured will have the required quality. The GMPs describe the methods, equipment, facilities, and controls required for producing pharmaceutical products. GMP rules are directed primarily to diminishing the risks inherent in any pharmaceutical production, which cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination and mix-ups. The federal regulations are called "current" good manufacturing practice (cGMP) regulations, to emphasize that the expectations for compliance are dynamic.

Official government publications on GMP may be called regulations, codes, guides, or directives. At the present time, different countries and trade blocs throughout the world have adopted rules and regulations relating to GMP that, at a high level, are similar in scope and effect. Countries such as Canada, Japan, and the United States have their own specific GMP regulations, but many others have adopted

and adapted policies, guidelines, and regulations. The following publications are some examples of GMP regulations, guides, or directives:

- The World Health Organization (WHO) Essential Drugs and Medicine Policy on Good Manufacturing Practice in Pharmaceutical Production (WHO 2000).[1]
- The Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products (PIC/S August 2001).[2]
- The European Community (EC) Guide to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use (EC November 2001).[3]
- The FDA Current Good Manufacturing Practice Regulations in Manufacturing, Processing, Packing, or Holding of Drugs (21 CFR Part 210) (FDA April 2001, originally published in 1978).[4]
- The FDA Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals (21 CFR Part 211) (FDA April 2001, originally published in 1978).[5]
- The FDA Guidance Document for Industry: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (FDA August 2001).[6]
- The International Conference on Harmonisation (ICH), Harmonised Tripartite Guideline: Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients [ICH (Step 4), November 2000].[7]

According to the World Health Organization,

> GMP is that part of quality assurance (QA) which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.[1]

They go further and say that GMP is concerned with both production and quality control (QC). Table 1.1 summarizes the WHO basic requirements of GMP.

The Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products (August 2001), the European Community (EC) Guide to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use (2001), and the draft Canadian Health Products and Food Branch Inspectorate Good Manufacturing Practice Guidelines (June 2001)[8] all subscribe to the same quality management philosophy and require the same essential GMP elements as described in Table 1.1. This harmonization initiative facilitates the removal of barriers to trade in pharmaceutical products, promotes uniformity in licensing decisions, and ensures the maintenance of high standards of quality assurance in the development, manufacture, and control of pharmaceutical products throughout various countries.

The FDA Current Good Manufacturing Practice Regulations are referenced in Chapter V, Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (1999), which states:

> A drug or device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packaging, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.[9]

These cGMPs were set forth by law in the Code of Federal Regulations (CFR), namely, Title 21 (Food and Drugs) CFR Parts 210 and 211 in 1978. The U.S. was the first country where noncompliance with regulatory requirements became prosecutable with the Code of Federal Regulations.

21 CFR Parts 210 and 211 regulations contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to

TABLE 1.1
WHO GMP Requirements for Pharmaceutical Products

1. All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications
2. Critical steps of manufacturing processes and significant changes to the process are validated
3. All necessary facilities for GMP are provided, including:
   - Appropriately qualified and trained personnel
   - Adequate premises and space
   - Suitable equipment and services
   - Correct materials, containers, and labels
   - Approved procedures and instructions
   - Suitable storage and transport
   - Adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management
4. Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided
5. Operators are trained to carry out procedures correctly
6. Records are made, manually and/or by recording instruments, during manufacture to show that all steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated
7. Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form
8. The proper storage and distribution of the products minimizes any risk to their quality
9. A system is available to recall any batch of a product, from sale or supply
10. Complaints about marketed products are examined, the cause of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent reoccurrence

Source: World Health Organization (WHO), Essential Drugs and Medicine Policy on Good Manufacturing Practice in Pharmaceutical Production, 2000. Available: http://www.who.int/medicines/organization/qsm/activities/qualityassuran…/orggmp.htm.

TABLE 1.2
FDA Requirements for GMP

1. Subpart A: General provisions
2. Subpart B: Organization and personnel
3. Subpart C: Buildings and facilities
   - Design and construction features
   - Lighting
   - Ventilation, air filtration, heating, and cooling
   - Plumbing
   - Sewage and refuse
   - Washing and toilet facilities
   - Sanitation
   - Maintenance
4. Subpart D: Equipment
   - Equipment design, size, and location
   - Equipment construction
   - Equipment cleaning and maintenance
   - Automatic, mechanical, and electronic equipment
   - Filters
5. Subpart E: Control of components and drug product containers and closures
6. Subpart F: Production and process controls
7. Subpart G: Packaging and labeling control
8. Subpart H: Holding and distribution
9. Subpart I: Laboratory controls
10. Subpart J: Records and reports
11. Subpart K: Returned and salvaged drug products

Source: Food and Drug Administration (FDA), Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals (21 CFR Part 211), Rockville, MD, 2001. Available: http://www.cfsan.fda.gov.

be used for, the manufacture, processing, packaging, or holding of a drug to assure that such drug meets the requirements of the Act as to safety, identity, strength, and quality and purity characteristics.

For the purposes of this book, the focus is only on those particular Part 211 regulations affecting facility, utility, and equipment validation, namely, subparts C and D are referenced in full. Table 1.2 summarizes the various subpart headings for CFR Part 211 regulations.

In the following sections, the GMP regulations from various organizations and countries affecting facility, utility, and equipment are evaluated and expanded on to elucidate their impact on facility validation.

1.1.1 Buildings and Facilities

Element 11 (Premises) of the WHO GMP; Part Four, Chapter 3 (Premises and Equipment) of the EC Guidance document; and Subpart C of the federal CFR sections 211.42 to 211.58 deal with cGMP requirements associated with buildings and facilities.

These regulations are of prime concern when a new facility is being designed and built, or when significant changes are being made to existing systems. The pharmaceutical facility should be designed and constructed in a manner that permits cleanliness and orderliness, and prevents contamination. Regular maintenance is required to prevent deterioration of the premises. The ultimate objective of all these endeavors is product quality.

Facility problems are quite commonly listed in observations (483s) made by FDA investigators when conducting GMP compliance audits of pharmaceutical manufacturers. To quote some common observation examples:[10]

- The room was not designed and constructed to facilitate cleaning and disinfections.
- The HVAC and dust collection systems are not validated.
- There are no approved procedures for maintaining the HVAC and dust control systems throughout the plant.
- There are no temperature or humidity specifications for the area.
- Sensors for monitoring warehouse temperature have not been calibrated since their installation three years ago.
- Air recirculated in the compressing area has never been tested for particulate matter. Validation of the air handling system is inadequate.
- There is inadequate segregation of manufacturing or testing areas for high-risk products from other manufacturing areas.[11]
- There is malfunctioning of the ventilation system, resulting in possible migration of materials between manufacturing areas.[11]
- Temperature and humidity not controlled or monitored where required.[11]

> Many companies focus on the facility and equipment problems only when they receive an FDA-483 warning letter and are prepared to make capital expenditures promptly. It is important that such companies do not lose sight of the real problems; most often, the control systems that should have prevented the problems in the first place failed.[12]

1.1.1.1 GMP Principles

The following GMP principles apply to design and construction features, lighting, utilities, ventilation, air filtration, heating and cooling, plumbing, sewage and refuse, washing and toilet facilities, sanitation, and maintenance.

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.[13] Buildings shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations [21 CFR §211.42(a)].[5] Operations can often be so crowded that proper cleaning is not possible, or products are so close together that mix-up possibilities are increased.

Buildings shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination [21 CFR §211.42(b)].[5] Crowded conditions and inadequate space have contributed to product mix-ups.

The flow of materials shall be designed to prevent contamination [21 CFR §211.42(b)(cont.)].[5] The key here is to prevent contamination. Generally, items should not move back and forth from less clean areas to more clean areas.

Operations shall be performed within specifically defined areas of adequate size [21 CFR §211.42(c)].[5] The facility should be designed and constructed in a manner such that it permits cleanliness and orderliness, and prevents contamination. All materials of construction should be low or nonfiber shedding, compatible with cleaning and sanitizing agents, and must be smooth and easy to clean. The facility must have adequate space provided for all operations conducted in the area. Equipment and process flow must be designed to allow a logical flow that will avoid mix-ups of components, drug products, closures, labeling, in-process materials, or cross-contamination. Materials and personnel flow should minimize personnel exposure to critical operations, prevent product mix-ups, maintain microbiological integrity of critical processing zones, and prevent mixing of clean and dirty items. Personnel flow should minimize potential people/product exposure and allow for personnel gowning/de-gowning.

To prevent contamination or mix-ups there shall be separate or defined areas or other control systems for:

1. Receipts, identification, storage, and withholding from use of materials (components, drug product containers, closures, and labeling) pending sampling, testing, or examination before release for manufacturing or packaging.
2. Holding rejected materials before disposition.
3. *Storage of released materials* [21 CFR §211.42(c)(cont.)].[5]
4. *Storage of in-process materials* [21 CFR §211.42(c)(cont.)].[5]
5. Manufacturing and processing operations.
6. *Packaging and labeling operations* [21 CFR §211.42(c)(cont.)].[5]
7. Quarantine storage before release of drug products.
8. *Storage of drug products after release* [21 CFR §211.42(c)(cont.)].[5] Premises should preferably be laid out in a way that allows production to take place in areas connected in a logical order corresponding to the normal sequence of operations. Storage areas should be of sufficient design and capacity to allow for the orderly storage and segregation of the various categories of materials and products: starting and packaging materials; intermediate, bulk, and finished products; products in quarantine, released, rejected, returned, or recalled. Storage areas should be designed and controlled to ensure good storage conditions. Receiving and dispatch bays should protect materials and products from the weather. Weighing of starting materials usually should be carried out in a separate weighing room designed for that use. Premises for the packaging of products should be specifically designed and constructed so as to avoid mix-ups and cross-contamination.
9. *Control and laboratory operations* [21 CFR §211.42(c)(cont.)].[5] Control laboratories should be designed to suit the operations to be carried out in them and are normally separated from production areas. Separate rooms

may be necessary to protect sensitive instruments from vibration, electrical interference, or humidity.

10. *Aseptic processing, which includes appropriate conditions* [21 CFR §211.42(c)(cont.)].[5] The manufacture of sterile products is subject to special building and construction requirements for specialized work areas that will minimize the risks of microbiological contamination, and of particulate and pyrogen contamination.

Operations relating to the manufacture, processing, and packaging of penicillin shall be performed in facilities separate from those used for other drug products for human use [21 CFR §211.42(d)].[5] Dedicated and self-contained facilities must be available for the production of particular products, such as highly sensitizing materials like penicillin and certain hormones, cytotoxics, and biological preparations.

Adequate lighting shall be provided in all areas [21 CFR §211.44].[5] The level of illumination should be appropriate such that it allows work to be accomplished satisfactorily and does not adversely affect, directly or indirectly, the products during their manufacture and storage.

All utilities that could affect product quality (e.g., steam; gas; compressed air; heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action taken when limits are exceeded. Drawings for these utility systems should be available [ICH Q7A GMP Guidance for Active Pharmaceutical Ingredients, Section IV, B].[7]

As a prerequisite for process validation, other aspects of manufacture must be validated, including critical services (water, air, nitrogen, power supply, etc. [WHO GMP in Pharmaceutical Production, Chapter One, sub-section "Validation of Manufacturing Processes," Element 2]).[1] Process utilities coming into direct contact with product should not contaminate or affect the quality of the product. It is interesting to note that this principle is only reflected in GMPs for active pharmaceutical ingredients and is not stipulated in any GMP for finished pharmaceutical products.

Adequate ventilation shall be provided [21 CFR §211.46(a)(cont.)].[5]

Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate [21 CFR §211.46(b)].[5]

Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems to control contaminants [21 CFR §211.46(c)].[5]

Temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, either directly or indirectly, the products during their manufacture and storage [PIC/S. 3.3].[2] Adequate ventilation, air filtration, and exhaust systems should be provided where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms, dust, humidity, and temperature as appropriate to the stage of manufacture.