# Validation of Pharmaceutical Processes: Sterile Products

# VALIDATION of PHARMACEUTICAL PROCESSES

## Sterile Products

Second Edition, Revised and Expanded


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# VALIDATION of PHARMACEUTICAL PROCESSES

The complexities of developing this second volume on validation involved a dependence on many sources. We were helped and encouraged by a great many people who listened to our ideas and gave us the benefit of their thoughts. Foremost among these were our wives, Helen Carleton and Linda Agalloco, as well as our children, Brant and Penny Carleton, and Stephen, Andrea, and Adam Agalloco, who, throughout these many years of preparation, encouraged us, propelled us to think more aggressively, played devil's advocate, and considered ideas and topics with us. Most of all, we are grateful for their love and understanding.

# Preface

Given the increased demands and opportunities for innovation in pharmaceutical operations, the exchange and sharing of information must be more available today than it has been in the past. Somerset Maugham once wrote that "perfection is nothing more than a complete adaptation to the environment; but the environment is constantly changing, so perfection can never be more than transitory." *Validation of Pharmaceutical Processes: Sterile Products* provides the contemporary information needed to understand and develop pharmaceutical manufacturing and control technology. We have revisited the subject of validation for sterile products with the objective of updating the subject matter consistent with the changing environment in which we all work and live. The first edition, *Validation of Aseptic Pharmaceutical Processes,* was developed to fill what, at that time, was a substantial void in the information available on the validation of sterile production systems, equipment, and processes. In the intervening years, we have received considerable praise from individuals in the industry who found this text useful in the performance of their duties. As the years passed, it became obvious to both of us that a new edition of our text was warranted. The goal of this latest edition is to encompass the changes that have taken place throughout our industry. Given the increasing rate of change with which we all must deal, this new edition will some day provide a less-than-contemporary view of validation practices; however, in the interim, it should serve as a useful guide to validation methodologies for the preparation of sterile products.

*Validation of Pharmaceutical Processes: Sterile Products* is a reference book for managers, supervisors, and scientists in the pharmaceutical industry. It is intended for pharmacists, engineers, chemists, microbiologists, and individuals in other disciplines who require detailed insight into the practice of validation in support of sterile products. The book focuses on pharmaceuticals; however, judging by comments we have heard about the first edition, we are certain it will find application in biotechnology, medical devices, and diagnostics. Although the title of the book has changed, the coverage of sterile products is every bit as complete. In preparing this volume, we critically reviewed all of the material that had been included in the first edition. A limited number of chapters are unchanged, primarily because the original effort was found to still be technically correct and useful. The remaining chapters have been either revised by the original authors or by a new author to

provide new insight to the subject matter. We have also added several new chapters to expand the coverage of validation as it is currently practiced.

*Validation of Pharmaceutical Processes: Sterile Products* is a compilation of compliance and regulatory principles, documentation practices, scientific approaches, and engineering concepts that can be used independently or in combination to validate products, processes, and equipment. The methods presented are guides and are not intended to establish definitive standards that must be followed.

A subject as broad and complex as validation in the pharmaceutical industry has widespread applications, affecting regulation, compliance, product and facility registration, current Good Manufacturing Practices, research and development, quality assurance, manufacturing, and facility design. The idea of validation was originally conceived as a means for independent confirmation of drug product quality. In the years since its introduction to the industry, validation has changed the industry more than perhaps any single influence in the last 20 years. This change has brought about both positive and negative effects that reach to the very core of our institutions and livelihood. Validation has had so significant an impact on the global health care business that expanded coverage and reevaluation of its precepts is certainly necessary. To that end, *Validation of Pharmaceutical Processes: Sterile Products* is an attempt to fulfill the information void relative to validation that continues to exist in our industry.

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## STERILE PRODUCT MANUFACTURING

# 1

# Why Validation?

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## I. OVERVIEW

The prime objective of anyone working in a pharmaceutical plant, whether in production or quality control, is to manufacture consistently products of the requisite quality at the lowest possible cost. Quality requirements are defined by the user's need for product safety, efficacy, and ease of use. In this chapter it will be shown that validation is essential for the achievement of this objective.

The United States Food and Drug Administration (FDA), defines *process validation* as follows:

> Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes [1].

Although this official regulatory definition is relatively new (1987), the concept of validation is not new to the pharmaceutical industry. It has been performing validation for years because:

> It would not be economically feasible to use equipment not knowing if it will produce the product we want, not to employ people with no assurance that they can do the job, nor fail to implement in-process checks or examinations to assure that products meet specifications [2].

Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an everincreasing interest in validation owing to the industry's greater emphasis in recent years on quality assurance and productivity improvement. Validation is a necessary part of a quality assurance program and is fundamental to an efficient production operation.

Furthermore, the limitations of end product testing to assure quality have become more clearly understood. The performance of sterility testing, 100% inspection for particulates, an assay for the active ingredient, or other such, cannot guarantee that each unit of the product meets specifications. Thus, the heavy emphasis on quality assurance, Good

Manufacturing Practices (GMPs), "building quality in," and in-process control, all of which imply and require validation.

The pharmaceutical industry uses expensive materials, sophisticated facilities and equipment, and highly qualified personnel. The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures—rejects, reworks, recalls, complaints—is a significant part of the total production costs. Detailed study and control of the manufacturing process—validation—is necessary if failure costs are to be reduced and productivity improved.

The authors' definition of validation and the sense in which it will be used in this chapter is,

*Validation* is the scientific study of a process:

1. To prove that the process is consistently doing what it is supposed to do (i.e., that the process is under control)
2. To determine the process variables and acceptable limits for these variables, and to set up appropriate in-process controls

Process optimization—to optimize the process for maximum efficiency while maintaining quality standards—is a natural consequence of this scientific study of process variables and their control.

Validation lends itself to a variety of approaches. Two commonly used approaches are the retrospective review of historical data and a prospective or concurrent system challenge. Frequently, a combination of these two is used. Also, there are acceptable variations within these two basic approaches. On occasion, there is no appropriate challenge test and, if the process is new, no historical data. In this event, one studies the system design, tests the output of the system, installs appropriate controls, and monitors the system. An example of such a case is a water-for-injection system (WFI) [3].

Validation is a team effort. It will involve people from various functions in the plant. As much as possible, it should involve those who will operate and maintain the equipment or process. Not only is their experience invaluable to the validation work, but the knowledge they attain through extensive validation testing will enable them to continuously maintain, control, and improve the system.

In summary, there are three reasons why the pharmaceutical industry is concerned that their processes perform consistently as expected; that is, they are validated. The principal reason is that validation is essential for *assurance of quality.* Also, it is effective in *reducing costs* and, in most countries, it is a *regulatory requirement.*

1. *Assurance of quality*: Without validation, which implies a process that is well understood and in a state of control, confidence in the quality of products manufactured is impossible. GMPs and validation, two concepts that cannot be separated, are essential to quality assurance. Frequently, the validation of a process will lead to quality improvement, in addition to better quality consistency. This will be discussed at greater length in Section IV of this chapter.
2. *Cost reduction*: Experience and common sense indicate that a validated process is a more efficient process and a process that produces less reworks, rejects, wastage, and so on. Validation is fundamentally good business practice (see Sec. IV).
3. *Government regulation*: Validation is considered to be an integral part of GMPs essentially worldwide [1,4–7]. Compliance with validation requirements is nec-

essary for obtaining approval to manufacture and to introduce new products (see Sec. III).

The benefits of validation will be discussed in more detail later in this chapter. First, the important elements of validation, that define its scope, will be discussed briefly.

## II. ELEMENTS

The validation of a process requires qualification of each important element. The relative importance of an element may vary from process to process. Figure 1 depicts a manufacturing process and lists the related elements and support processes commonly considered for qualification.

### A. MANUFACTURING PROCESS INPUTS

#### 1. Product Design

The product design consists of the formulation, container and closure system, basic manufacturing procedure, and quality control specifications and testing methods. Chronologically, product design is the first element of validation to be studied. Although product design is normally the responsibility of the research and development (R&D) function, it is wise to involve plant personnel, because their experience and knowledge of the plant's capabilities can be very valuable. A poorly designed product can make it impossible to validate and control a process. Consider the consequences of a formulation that is inherently unstable or inadequately preserved, specifications that are too tight, or an analytical method that is not rugged.

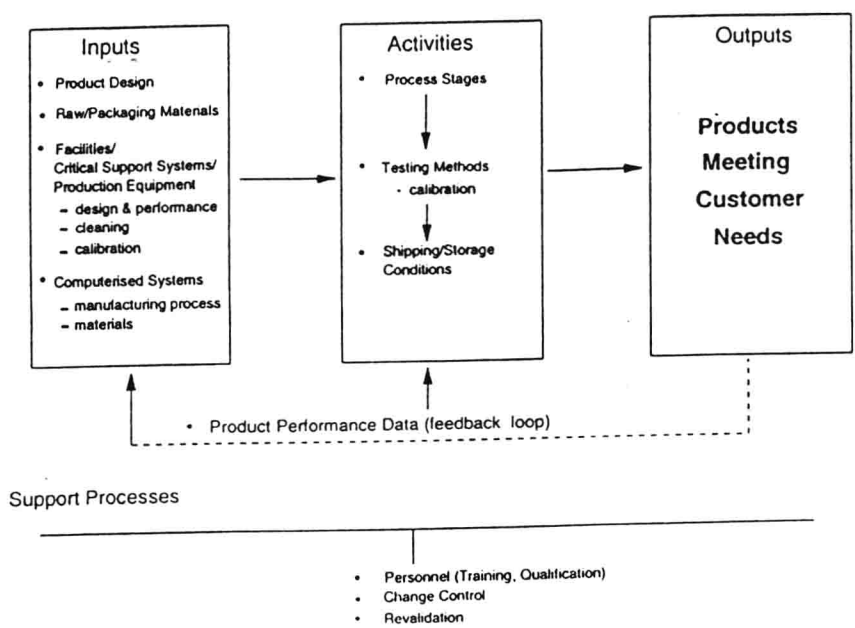


**Figure 1** Manufacturing process model.

The R&D department should provide the plant operations with the following:

1. A robust product design for which the components—formulation, manufacturing procedure, analytical methods, and material and product specifications—have been validated. The manufacturing procedure should be validated by R&D at least on a pilot-batch basis.
2. Identification of the critical variables in the product and process.
3. Tentative limits for these variables. The limits may have to be modified as a result of the process validation studies done by the plant, because many components of the process will be different from those used in R&D studies.
4. Methods to measure, monitor, and control the critical variables.

## 2. Raw and Packaging Materials

Qualification of materials involves the setting of specifications for all critical parameters of these materials. These specifications must be set in light of the purpose and use of the finished product. Frequently the materials will have specifications in addition to those found in an official pharmacopeia, such as a particle size specification for an ingredient in a suspension formulation. Second, *vendors must be qualified.* Vendor qualification usually includes testing of samples and an audit of the vendor's facilities, systems, and process controls.

For a parenteral product, the container and closure system is especially important. Special care needs to be taken to assure the compatibility of the container and closure with the product and that the closure is capable of maintaining the integrity of the product.

Material age and storage are also factors to be considered. In most instances retest dates are established to reevaluate the condition of the material if not used by that date.

## 3. Facilities

The qualification of a facility includes four phases:

Design
Construction
Verification (installation qualification [IQ]; operational qualification [OQ]; performance qualification [PQ])
Ongoing maintenance and monitoring

At the design or planning phase, the purpose of the facility, the product(s) to be manufactured, GMP, and efficiency requirements, as well as cost, must be considered. Flow of material and personnel to avoid crossovers and turnbacks has to be studied. This leads to room and equipment layout. Room surfaces must be designed to be easily cleaned and sanitized. Finally, everything needs to be documented—drawings, written specifications, and all other pertinent material.

The construction phase requires careful supervision to make sure that all the design specifications are being met. The process of verifying that the constructed facility meets all the established requirements starts when construction commences and ends with the installation (IQ) and qualification (OQ, PQ) of the equipment and critical systems. The verification phase should be documented, and design specifications and engineering drawings modified if necessary. The last phase of qualifying a facility consists in establishing appropriate ongoing preventive maintenance, change control, cleaning, sanitization, and environmental-monitoring procedures.

### 4. Critical Support Systems

A support system is any general system that the plant uses in daily operations. These include air systems, the electrical network, water supply, and others. For purposes of validation we are concerned with *critical* support systems. These are systems that must operate at a certain level to maintain the required quality level of the final product. It is evident, for example, that inadequate air filtration could result in a contaminated product, especially when performing an aseptic fill.

Some examples of critical support systems are

Heating, ventilation, and air-conditioning (HVAC)
Water: water-for-injection, purified water, potable water, and steam
Compressed air and gases ($N_2$, $O_2$)
Vacuum and dust collection

The qualification of a critical plant support system consists of four phases:

1. Design
2. Installation (IQ)
3. Challenge and verification (OQ, PQ)
4. Ongoing maintenance and monitoring

Designing the system, or for an existing system defining it, is the first phase. Technical data on system components (filters, deionizers, compressors, valves, and such) must be located, reviewed, and collated. Distribution drawings of the systems must be prepared. While defining an existing system, it is likely that system deficiencies will be identified that must be corrected (plumbing dead legs, incorrect pressure gradients, inadequate filtration, and so on). The second phase involves making sure that the installed system is as designed. The challenge and verification phase makes sure that, for normal and reasonable inputs, the system output is acceptable. Finally, the system must be monitored at regular intervals to make sure that it continues to function properly, and it is maintained according to the manufacturer's recommendations.

### 5. Production Equipment

The qualification of equipment has the same four phases as critical support systems. It starts with the design or selection process, followed by installation (IQ) and verification (OQ, PQ) that the equipment functions as desired. Qualification of equipment also requires the development of written procedures (standard operating procedures; SOPs) that describe the proper operation of the equipment, the development of a preventive maintenance program, the validation of cleaning procedures, and the training of personnel using or supervising the use of the equipment. Cleaning procedures must be shown to adequately remove product or dirt and to leave acceptably low levels of cleaning agents and solvents. If the equipment must be sterile or pyrogen-free, the procedures used to accomplish this must be shown to be effective.

*Calibration* Pharmaceutical processes and support systems use many measuring devices for monitoring and control. This control is accomplished either automatically by an appropriate feedback mechanism or through manual adjustments. In either case, the proper calibration of the measuring device is critical to the process. Some devices that need calibration are thermometers, pressure gauges, relative humidity meters, conductivity meters, timers, and alarms.