**PDHonline Course K108 (2 PDH)**

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# An Introduction to Pharmaceutical Validation

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# An Introduction to Pharmaceutical Validation

## Course Content

### INTRODUCTION

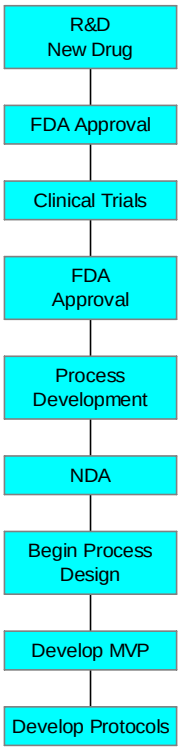
The pharmaceutical industry is perhaps the fastest growing industry in the United States and will provide engineers with employment for many years to come. Facilities are being constructed to manufacture ever more complex compounds. The traditional organic reaction compounds are being replaced with products from the fermentation of bacteria, algae, viruses and mammalian cells.

Whether the product comes from reactors, extractors or fermenters the process falls under the scrutiny of the Food and Drug Administration (FDA). A primary rule of the FDA is that you must prove that the process you are using is under control. We satisfy that FDA requirement by validating the process.

Several States have now determined that pharmaceutical validation is an engineering activity and as such must be under the control of a professional engineer if performed by other than employees of the facility. This decision is critical and opens up new employment opportunities to the engineer. To take advantage of this opportunity you must understand the validation process.

The intent of this first course is to provide an introduction to the validation process and give the engineer enough information to aid in various validation decisions.

A SIMPLFIED DRUG / VALIDATION PATH



## AN ABREVIATED HISTORY OF A DRUG

The process from drug discovery / development to the pharmacy shelf is considerably longer than the preceding chart; the content is reduced but the path is visible.

- XYZ Corporation develops a new drug product in its R&D labs.
- Following lab tests on animals with similar body chemistry the product is submitted to the FDA with a listing of potential benefits for humans or animals (the FDA controls drugs for humans and for animals).
- A series of controlled and carefully monitored clinical trials is established and run.
- The FDA reviews the results of the clinical trials and approves the drug for use.
- XYZ begins the development of the Process by which it will manufacture the new product.
- An NDA (New Drug Application) is submitted to the FDA for the Process.
- Engineering design is begun. The validation process can now begin with the development of the Master Validation Plan (MVP).
- The FDA audits the new facility, reviews the validation effort and approves the new process and facility
- Production begins

## THE VALIDATION PROCESS

Validation of pharmaceutical operations is a requirement of the FDA under 21CFR (Congressional Federal Register). Facilities requiring FDA Validation include all active drug compounds whether bulk, intermediate or finished goods. Additionally items labeled as medical devices [heart valves, sutures, medical tools and items such as blood bags and tubing, etc.] fall under this requirement.

There are three accepted Validation Processes:

| | | |
|---|---|---|
| 1. | Retrospective Validation | Performed on a process which has been in operation for some time and for which there is considerable production data available for analysis. |
| 2. | Concurrent Validation | Performed on a process which has or is just being brought on line. |
| 3. | Prospective Validation | Performed before the process is brought on line. This is considered the normal approach. |

In this course material we will only consider the Prospective Validation approach since this is the most commonly encountered process.

Validation is essentially proof that what the drug manufacturer lists as its process for manufacturing the product is followed. The process of validation includes a series of tests for each piece of equipment impacting drug efficacy, purity and quality. The testing under each of these items is assembled into a protocol. Essentially the protocol tells the validation engineer what is to be tested, how it is to be tested and how many times it is to

be tested. The FDA tends to work with the old adage: “Once is an accident, twice is a coincidence and three times is proof.”

## DEFINITIONS

Before we get into the details of validation we need to understand the words in use throughout the industry. The following definitions will help in understanding the process.

| | |
|---|---|
| Validation | The process of proving something works as designed or required. |
| Protocol | A scientific testing plan which will prove that the equipment or process performs exactly as intended in the design documents. |
| Drug | Under FDA jurisdiction drugs consist of the classically defined materials but also include non drug items such as medical devices, medical gases, drug delivery systems, drug containers, surgical tools, medical screws used in bone repair and a variety of items too long to list. |
| Purity | Absence of contaminating materials. Pills contain diluting compounds since most drug doses are too small to be made into pills of the pure compound. As an example synthetic thyroid hormones are given in doses ranging from 20 to 300 micrograms. A pill made of pure hormone would be too small to be seen and thus the compound is diluted with a non drug material to allow for home use. These approved diluents are not considered contaminants. |
| Efficacy | Provides the claimed medical effect. As an example aspirin is claimed to relieve headache pain; clinical testing (controlled testing) proves that aspirin actually relieves headache pain in most people. |
| Quality | This contains some concepts of purity but also may consider such characteristics as: percent of drug compound in the pill, physical condition of the pill, appearance of the pill, etc. |
| Acceptance Criteria | Approved test results indicating that the equipment / process responds in the proper manner. As an example if an oven is supposed to heat the product to 200 ºC for thirty minutes; then acceptance criteria would be a demonstration that the product is actually heated to 200 ºC throughout and the oven is capable of holding the product at this temperature for thirty minutes. |
| Master Validation Plan: | A written description of the process and a delineation of which pieces of equipment will receive which protocols. All equipment affecting quality, purity and efficacy will receive at least an IQ and an OQ but may not have an individual PQ. |

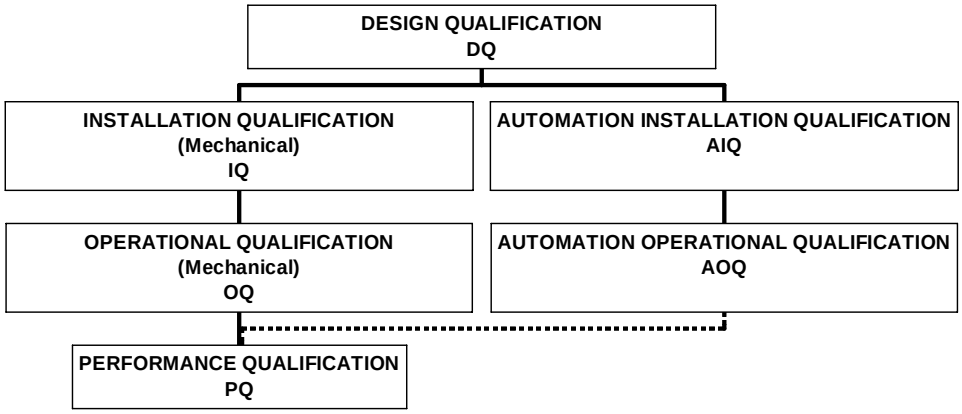
## THE PATH TO A VALIDATED SYSTEM

To understand the validation process we need some indication of the position of the various protocols in the pharmaceutical validation process.

The following is a listing of the most common protocols in use:

| | Validation Protocol | Position in Validation Program |
|---|---|---|
| DQ | Design Qualification | Before Design |
| IQ | Installation Qualification | After Installation |
| OQ | Operational Qualification | After IQ and AIQ if present |
| PQ | Performance Qualification | After OQ and AOQ if present |
| AIQ | Automation Installation Qualification | After Installation |
| AOQ | Automation Operational Qualification | After AIQ |
| PV | Process Validation | After all other protocols |

PROTOCL RELATIONSHIPS




Prior to commencing testing each protocol must be reviewed and approved by a variety of individuals within the facility. This approval generally comes from the following individuals: Regulatory Affairs Manager, Quality Manager, Validation Manager, Engineering Manager, Production Manager and on occasion the Maintenance Manager. This review and approval process was established to insure that the protocol is designed to operate the equipment in compliance with the approved SOP's and that it is testing for critical parameters affecting product quality, purity and efficacy.

## WHAT GETS VALIDATED

Not everything in a new process needs validation.

What gets Validated depends to some extent on the type of process involved: liquid, solid, machining, extrusion, cleaning, etc. Generally plant utilities will not be tested [plant steam, plant air, bulk nitrogen, chemicals storage]; utilities within the manufacturing unit may be tested depending on the question: "Does this affect product quality, efficacy or purity?" For example a plant steam supply would not be tested whereas a pure steam generator driven by the plant steam would be tested. A pump

moving the product might receive Installation and Operational Qualifications and be tested as part of a system in the Performance Qualification.

If the manufacturing process is performed under clean manufacturing conditions the HVAC system may be tested for temperature and humidity control if critical but certainly for control of air borne particulate if the product is exposed to room air. In most cases the clean areas must meet specific FDA and EU requirements for viable and non-viable particulate counts in the conditioned air. A decision as to where and how this testing is to be accomplished must be made taking into account probable air flow patterns and production operations, which may cause surface particulate to become air borne.

**THE PROTOCOLS**

An **Installation Qualification** [IQ] is intended to prove that the equipment is installed according to the manufacturer's requirements and the design documents. The initial portion of the IQ is verification that the equipment installed matches the design requirement and specification; is what was ordered and received. The IQ proof includes verification of proper utility supply and connection, proper mounting of equipment, and proper connection to up and downstream equipment. A review of connections to controls and all instrumentation is required which must include an analysis of critical verses non-critical instrumentation. This analysis of critical instrumentation is based on a determination of which instruments provide the operator with information which impacts quality, efficacy and purity [examples being pH, TOC, conductivity and temperature]. A verification of materials of construction and that the equipment is included in lubrication, maintenance and calibration systems is included to ensure non-contamination and that proper operation will be ongoing.

An **Automation Installation Qualification** is executed if the system contains computer, DCS or PLC controllers. Because of the critical nature of these controls and the frequency of this type of controller on even simple equipment we see more and more of these protocols. Generally installation testing consists of verification of proper wiring (I/O's), software backup and utility connections.

Frequently the IQ (mechanical) and the AIQ (controls) are combined into one protocol, still called an AIQ.

An **Operational Qualification** [OQ] is prepared to test aspects of the operation of the equipment when operated according to facility SOP's. Depending on the equipment, this protocol will test various aspects of equipment's operations: flow for pumps, rpm's for agitators, temperature distribution for heating and cooling equipment, purity for pure steam generators and Water for Injection systems, proper cycles for autoclaves to ensure sterility, etc. An analysis of the results of testing may include graphical and statistical techniques.

Thermal testing for heating and cooling systems will include the use of multiple calibrated thermocouples recording data over an extended time period with an accuracy of ±1/2 degree C. The purpose of this testing is to ensure that the entire interior of the equipment [where product will be exposed] is at temperature uniformity as described in the process documents. This requirement for uniformity requires an analysis of the

equipment to locate probable hot or cold spots since not every point within the equipment can be tested. This data will be analyzed statistically for variations outside specific ranges allowed for the process. In the case of sterility testing in addition to thermal mapping of the inside of the heating device [autoclaves, pasteurizers, vessels, piping and filters, etc.] bacterial strips are generally included to allow for assurance of kill of heat resistant bacteria. This is one of the testing plans where the "three is proof" rule applies; each heat study is run three times and to succeed there must be three consecutive good tests.

Control systems are generally tested through an **Automation Operational Qualification** (AOQ) in this phase to ensure transmitted data is not altered by outside forces such as radios and lighting systems, induced voltages from power surges and similar events. Control equipment is also tested to ensure that the equipment operates as intended by the design documents through all automatic, semi-automatic and manual operations and that the operator can perform any required function. Testing is performed to ensure that data can be transferred both up and down the control hierarchy: for example recipes controlling the process can be transferred into the control system and production data can be transferred out of the system to a supervisory or data archiving system. All such transfers must occur without loss or alteration to the data.

Frequently the preceding four protocols (IQ, OQ, AIQ, AOQ) are combined into one document which is called an AIOQ or Automation Installation and Operational Qualification.

A **Performance [Process] Qualification** will test the equipment or entire process streams for compliance with the process parameters when operated in accordance with approved SOP's. This may include the use of placebo compounds similar to the drug compound to control expense, some decisions will be required to ensure that the placebo indeed reflects the physical properties of the product in each case. These tests will be similar to those used in the OQ but generally will test for results of the operations. For example whereas the OQ tested for temperature in a dryer the PQ will test for product dryness or other factors affecting product efficacy, quality, purity or contamination from the process operations. Depending on the process and chemistry we may test for bacterial contamination, any degradation of the product by contact with the materials of construction of the process or contact utilities, degradation caused by hot spots within the process and conformance of the product produced with the original product specifications. A **PV (Process Validation)** may be substituted for the PQ depending on the process.

The intent here is to gain proof that the equipment performs specified actions on 100% of the pharmaceutical product as required by the process steps provided in the process description.

Since the PQ tests the entire process there is no PQ for automation.

## PROTOCOL EXECUTION

This is the fun part. Having written protocols ranging from twenty to one-hundred and fifty pages now is the time to enjoy the fruits of all that labor.

No protocol execution can occur until the protocol is approved. In most companies the execution is squeezed into spaces in the start up activity and indeed may be performed in conjunction with commissioning testing.

Execution of the IQ requires no particular assistance from the facility personnel unless equipment must be disassembled. The engineer performing the execution will gather all field information and record that data in an approved copy of the protocol in blue or black ink. Wrinkles and stains on the executed document provide the FDA with some indication that the protocol was actually executed in the field, not sitting at a desk.

Execution of the OQ requires that the equipment be operating. This in turn requires that the facility provide operating personnel who at a minimum have been trained on a draft SOP for the equipment. It is generally beneficial if the validation engineer is also trained in the SOP.

Execution of the PQ requires full scale operations of all of the equipment in a process stream and thus full support for the validation engineer. At this stage of the validation process the process SOP's must be in final form and all instruments calibrated.

## THE FINAL REPORT

The Final Reports for all protocols [IQ, OQ, AIQ, AOQ and PQ] will be prepared following an analysis of the data accumulated during testing.

For an IQ this may be a simple statement that the equipment is properly installed and ready for testing under the OQ. The OQ testing (execution) may not begin until the IQ Final Report has been approved by the same management positions, which approved it for execution (Engineering Manager, QC Manager, etc.).

For an OQ the Final Report will include the types of data accumulated and the analysis of that data. A conclusion will be drawn from that data indicating whether or not the equipment performs as designed and as required by the design documents. The PQ testing (execution) may not begin until the OQ Final Report has been approved by the same management positions, which approved it for execution (Engineering Manager, QC Manager, etc.).

The Final Report for the PQ will consist of an analysis of the data gathered during testing with a conclusion as to the effectiveness of the equipment to provide proper treatment of the drug substance. This document also requires approval.

## RE-VALIDATION

On occasion a "re-validation" activity is required. This activity is essential under the following conditions These conditions are not all inclusive.

A major piece of equipment effecting Quality, Efficacy or Purity has been rebuilt or extensively repaired by other than direct replacement of *essentially identical parts*. Replacing a 5 Hp 1725 rpm, Frame 46 motor from GE with the same motor (Hp, rpm and

frame) from Westinghouse is essentially identical parts replacement, replacing the same motor with a 7.5 Hp unit is not *essentially identical parts*.

Sterile piping systems have been altered by additions or deletions involving opening up the pipe, welding on the pipe, significantly changing the pipe routing or installing new components.

A change in the process where the temperatures, pressures and other process parameters affecting Quality, Efficacy or Purity have been changed and now lie outside the original validation testing.

Each potential for re-validation requires evaluation. That evaluation is best accomplished by looking at the testing that would be used for a new system built like the "changed" system and comparing it to what was actually done originally. Any marked difference most likely means a re-validation is needed. Actually this is a point where asking the local FDA field agent is probably a good procedure both politically and technically.

## OTHER DOCUMENTS

Additional documents are frequently required by the company or are considered beneficial before or during the validation process:

Design Qualification: This document is a testing / review of the design before construction has advanced too far. The intent is to review the Process Design with an eye to probable conformance with the desired result.

User Requirements: This is a developmental process in which utility needs are established; generally completed prior to the start of design. Here the chemists / pharmacists and engineers come together to determine what temperature, pressure, humidity and physical conditions will be required to make the process function. An example would be: What temperature is to be required in the interior of a reactor. This sets the minimum steam pressure requirement for the facility.

Factory Acceptance Tests: These FAT's are designed to ensure that the purchased equipment meets the specification requirements in the design documents prior to being shipped to the end user. Tests will include controls, speeds or throughput, conformance to dimensions, adequacy of documentation and the meeting of FDA cGMP [current Good Manufacturing Practices] guidelines.

Site Acceptance Tests: These SAT's are essentially the same as the FAT's above but are performed at the facility of the end user although not necessarily in the final position in the manufacturing facility.

Cycle Development Tests: These CD's are tests to determine the optimum set points for equipment controls to provide the best match to the requirements of the process design. As an example, an autoclave cycle might be adjusted to ensure maximum bacterial kill based on the various configurations of materials to be placed in the autoclave for sterilization. An evaluation of the various configurations must be

made to minimize the amount of testing and yet maximize the potential for successful sterilization. This evaluation must take into account the properties of saturated steam and the physical limitations of the equipment to be sterilized with thought to total steam penetration to all parts of the equipment [ie. inside of tubing, bottles, syringes, etc.].

Construction Turnover Packages: This document should contain all the data relative to installed equipment including such non process and diverse items as HVAC systems, building drainage and perhaps most importantly red-lined P&ID's for the process. Here we will find welding records for process piping and records of all contractor purchased materials which were used in the construction activity.

Commissioning Documents: These testing document are relatively new to the pharmaceutical industry and contain portions of the IQ and OQ and may be used as data sources for both documents. However, these are not an FDA requirement as are the IQ, OQ and PQ.

The History File: This is not a document but a file containing all of the information on a particular piece of equipment. For example a Sterilizer History File would contain the original purchase specification and order, the operating, maintenance and calibration manuals, the P&ID, materials of construction certifications, the U-1 report, and all applicable protocols (IQ, OQ, AIQ, AOQ, and PQ) in the original and executed form plus all Final Reports. A single stop by the FDA inspector at this file tells him everything about this equipment and its validation.