EQUIPMENT AND INSTRUMENTATION QUALIFICATION

Val•i•da•tion (văl´ĭ-da´shən) n. Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

– USFDA

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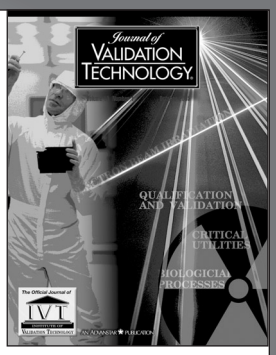

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EQUIPMENT AND INSTRUMENTATION QUALIFICATION

A Practical Guide to Applying Impact and Risk Concepts to Equipment Qualification for Non-Critical Processes for Topical and Oral Product Applications

BY MIGUEL MONTALVO

INTRODUCTION

In recent years, the Food and Drug Administration (FDA)-regulated industry has been listening to agency representatives and consultants talking about the need to implement a risk-based approach to decision-making processes. I totally agree with the need to implement this "common-sense" approach, but my question is this: Is this actually a new approach?

Industry personnel have been considering risk in everyday decisions, but have not realized or documented these decisions properly. I think that the key issue here is formal documentation. In the future, the industry must focus on and devote more time to pursuing and completing risk-related documentation. Firms must develop procedures to adequately document risk-based decisions, estimate their criticality, and evaluate their impact. The FDA is even implementing this approach internally for its inspection plans.

Another statement with which I totally concur reads: "Risk management is nothing more than resource management." Risk management is the process of identifying the critical areas on which each entity within the industry must focus its resources rather than stubbornly applying effort on the less critical aspects of operations. This is especially true for operations such as the typical cosmetic, or Over the Counter (OTC) drug site that manufactures hundreds of different products in fully flexible facility equipment set-ups with minimum resources, which permits them to compete in their selected markets.

SCOPE

In this article, I will describe a practical approach to applying impact and risk concepts to the processes and documentation related to facility systems and processing equipment qualifications within the cosmetic and OTC drug (topical and oral) manufacturing segments. In addition, I will describe the procedural requirements and the documentation needed to use impact and risk concepts during the definition of the systems and equipment qualification requirements. The article is not intended to describe the "Risk Assessment" tools in detail, but to provide a guide for the application of these tools.

Within the article, I will make reference to the International Society for Pharmaceutical Engineering's (ISPE) impact concepts from their "Baseline Engineering Guides" – specifically to Volume #5 on *Commissioning and Qualification* (see Reference 2). There are three different levels of impact: direct, indirect, and no-impact. Following are their basic definitions:

- Direct Impact System – equipment or system that will have focused and immediate impact on product quality
- Indirect Impact System – equipment or system expected to have incidental or secondary impact on product quality
- No-Impact – no impact, direct or indirect, on product quality

For the purpose of this article, I will focus on the first two categories having direct and indirect impact on product quality. In addition, the article will focus on the Installation Qualification (IQ) and Operational Qualification (OQ) sections of the qualification process. Performance Qualification (PQ) should be conducted exclusively on critical, direct impact systems. Test requirements should be specific to the system and its application.

Typical examples of critical direct impact systems would include a purified water system that produces processed water for formulations and a product-filler being tested for different volumes, weights, and counts.

As discussed in the introduction, manufacturers of oral and topical products should focus their qualification efforts on critical, direct impact systems. There is no requirement to conduct a PQ for every system or piece of equipment in the facility. Specific process or product steps, functions, and parameters will be tested during the process validation for each individual process being challenged.

POLICY AND PROCEDURE

The first thing that a facility requires is a policy and procedure document that defines the implementation of the chosen approach. The policy will include the scope and objective of the program, the personnel responsible for its implementation, the steps in determining test requirements based on impact or risk, and the documentation to be generated as a result of the analysis (including the protocol testing requirements). The procedure will establish the steps to determine an adequate level of testing using the impact assessment concepts and a risk criteria developed by the management team. Some of the decisions that can be based on impact or risk include:

Which Sections of a System Need to be Qualified?

- Throughout my years of experience, I have often heard industry experts discussing the need to qualify individual components of a system versus qualifying only the critical components, for example, a pump within a water system. In a critical operation, such as an aseptic manufacturing area whose water source is a Water for Injection (WFI) system, qualifying every component may make sense. However, a topical product manufacturer that does not have the resources to qualify every pump, assuming a direct impact system, must focus on the critical components.

Which Pieces of Equipment within a Processing or Compounding Area or on a Packaging Line Require Qualification?

- Does an OTC drug or cosmetic facility need to qualify storage tanks (no mixing capability) or just the mixing tanks and kettles? Do they need to qualify every component of a packaging line? I have seen industry consultants require an OTC manufacturer qualify the line conveyors. This is neither practical nor effective, especially for the typical cosmetic or OTC drug manufacturer making topical products with no dosage limits.

Typically, I will recommend that these manufacturers focus their efforts on those pieces of equipment that might have an effect on product quality such as the filler, capper, labeler, or any heating or shrink-wrapping equipment that could cause heat shock to the product.

Which Parameters Should be Tested and at What Level?

- Does an OTC drug or cosmetic facility need to test all systems at "worst-case" or the extreme parameter limits? How many runs or tests should be completed? A manufacturer can select those parameters that are critical to the operation of the equipment or system rather than testing all parameters without determining their impact levels.
- Manufacturers will also be expected to test more for critical parameters and for critical operations. There is no need to test at "worst-case" conditions for every parameter. If the system is a direct impact system, the manufacturer should test at worst-case or extreme conditions only those parameters that are most critical for the operation or that have a critical impact on the process results.

Decisions on Criteria and Equipment Specifications versus Process Needs

- The user must decide whether the qualification will be tested against process-specific needs or equipment design specifications. There are advantages and disadvantages with each option. If focused on process needs, the qualification will be simpler, but the risk is that the equipment may be needed later for a different process and would require qualification for the new set of parameters.

I suggest the implementation of different levels of qualification based on categories (see Recommended Strategies below). The selection criteria I recommend for the different categories are a combination of the ISPE impact assessment and risk concepts. The specific requirements for each level of qualification must be determined and included in the procedure, which should include the steps required to categorize the different systems and equipment and the documentation requirements needed to justify the selection and present the rationale.

Included as attachments, the procedure contains suggested protocol templates that take into consideration the qualification levels previously described in the procedure. You may wish to maintain a template for each level. This will simplify the process of developing these protocols for the document's author or owner.

The documentation of any specific decision based on impact and risk concepts for a particular system or equipment must be included in the applicable protocol with its rationale. The document must use the data and evaluations completed during design and process development such as study reports, specifications, and drawings.

The policy or procedure must also describe the specific approach for equipment that is controlled through Programmable Logic Controllers (PLC), higher level or distributed control systems, and those requirements applicable to electronic signatures and records according to the Code of Federal Regulations (CFR) 21, Part11.

RECOMMENDED STRATEGIES

There are specific qualification protocol requirements for different impact and risk-level equipment or systems. Following are the suggested strategies for applying impact and risk concepts during the development of qualification protocols:

Impact Levels

Direct Impact System
Product Failure, Risk, or Hazard Level

Level I – Oral or Topical Product with Dosage Limits

- ➢ Installation
  - ✓ Include more detail as defined in the internal policy and procedure requirements.
  - ✓ Refer to specific recommendations for IQ protocols below.
- ➢ Operational Qualification
  - ✓ Consider operational functions, sequences, controls, or alarms.
- ➢ Challenge Parameter Ranges, Worst-Cases, or Extremes
  - ✓ Use with critical parameters only.

Level II – Oral or Topical Products with No Dosage Indications

- ➢ Installation
  - ✓ Include less detail as defined in the internal policy and procedure requirements.
  - ✓ Refer to specific recommendations for IQ protocols below.
- ➢ Operational Qualification
  - ✓ Consider all operational functions or sequences.
  - ✓ Controls exist on critical parameters.

Indirect Impact System

Installation

- ➢ Include minimum detail as defined in the internal policy and procedure requirements.
- ➢ Refer to specific recommendations for IQ protocols below.

Operational Qualification

- ➢ Test only those operational functions that could impact product quality.

Specific Test Requirements

Included here are some specific areas within the protocols on which to use different levels of test requirements:

Installation Qualification (IQ)

- ➢ Main Component Verification
  - ✓ Use only critical components for indirect impact systems.
  - ✓ Include only critical controls and instrumentation or components for direct impact systems.

- ➢ Calibration
  - ✓ Reduced list of critical instruments for indirect impact systems and risk level II direct impact systems.
  - ✓ Most instruments in direct-impact systems are at risk level I.

- ➢ Input and Output Verification
  - ✓ Critical parameters for indirect impact systems only.
  - ✓ Expanded list for direct impact systems.

Operational Qualification (OQ)

- ➢ Select the Critical Parameters
  - ✓ May use risk assessment or analysis
  - ✓ Select number of tests for each

- ➢ Select the Responses or Resulting Characteristics to be Verified Based on Risk
  - ✓ May use a formal risk assessment or analysis

Specific Operational Qualification Requirements by Impact Level

Indirect Impact System

Verify the basic operational functions - only those that could impact the product quality.

- ➢ Functional Testing
  - ✓ Include critical parameters at nominal set-point values
  - ✓ Verify only critical responses or characteristics

- ➢ Normal Variation of the Parameter Value around the Nominal Set-Point
  - ✓ Controls verification
  - ✓ Motor verification
  - ✓ Sequence verification (if applicable)

Direct Impact Systems – Risk Level II

Verify the basic operational functions including critical alarms.

- ➢ Functional Testing
  - ✓ Test parameters at operational limits or specifications (not necessarily extremes, but reasonable operational limits)
  - ✓ Verify critical responses or characteristics

- ➢ Use lower and upper set-point values while trying to meet the overall operational limit range considering the normal variation.
  - ✓ Controls verification
  - ✓ Motor verification
  - ✓ Sequence verification (if applicable)
  - ✓ Critical alarms verification and reporting.

Note: Define the list of critical alarms to be challenged during the development of the specific protocol. Not all alarms need to be challenged because the system is not a Risk Level I (critical) direct impact system. Only include the "out of limits/specifications" alarms in the critical operational parameters.

Direct Impact Systems – Risk Level I

Verify the basic operational functions including the alarms that could impact product quality. Challenge parameter ranges and worst-cases or extremes only for critical parameters.

➢ Functional Tests
- ✓ Test parameters at operational extreme limits
- ✓ Verify critical responses or characteristics
- ✓ Test minimum and maximum parameter set-point levels without using the actual operational limits as the set points.

Note: If the normal or expected parameter variation is considered, this will create a different process and the parameters values will be out of limits most of the time.

- Controls verification – more detailed
- Motor verification
- Sequence verification (if applicable)
- Most system alarms verification and reporting.

Test all alarms on the parameters and conditions that could have an impact on product quality, not necessarily all of them. Need to define the list of alarms to be challenged during the development of the specific protocol.

No Impact Systems

Systems, components, or equipment that do not fall within any of the categories above will be described as having "no-impact" or limited risk.

Legacy Systems and Equipment

IQ documentation requirements for legacy systems and equipment will be established using the same analysis as noted above. Special considerations may be required with legacy systems. For example:

- Some documents may not be available. The need for these documents must be evaluated in terms of impact on equipment operation and maintenance.
- Documents, such as drawings and specifications, may have to be developed "as is" or "as built."
- Data required for risk assessment may be taken from historical data, such as product failures or complaints, instead of from designs.

Operational requirements must be similar to new systems or equipment.

Change Control

The approach to change control is similar to that already discussed, for example:

- Apply the same approach used for qualifying equipment to determine requirements after change implementation.
- Utilize direct and indirect impact concepts to determine the need for qualification testing and the required level for that testing.
- Make the evaluation part of the change control procedure and documentation. Include the rationale for the decision in the procedure.
- Ensure that the evaluation includes a determination that the changes implemented did not create new hazards or risks.

CONCLUSION

Using a practical approach to determine qualification requirements is essential for manufacturers in the cosmetic or OTC drug market. Resource management is their basic mode of operation. To remain competitive, these manufacturers must be selective in terms of the level of qualification testing and the equipment to be qualified. This article has offered a guide to making those decisions in a procedural, documented process to provide manufacturers with a means of remaining in compliance while using their resources in an effective manner. ❑

ABOUT THE AUTHOR

Mr. Miguel Montalvo is a Director of Validation Compliance for AAC Consulting Group, Inc., providing specialized compliance-focused consulting and management of validation projects for customers around the world.

Before joining AAC in 1999, Mr. Montalvo held positions of increasing responsibility in the areas of validation, technical services and quality operations over a period of 19 years in companies such as Millipore Corporation, Raytheon Engineers and Constructors, Mova Pharmaceutical Corp., Bristol-Myers Squibb, and Baxter Healthcare Corporation.

He has managed validation efforts for several facilities under start-up conditions and major renovations with processes including bulk API's, solid-dosage, parenterals, topicals, liquids and medical devices for customers in the pharmaceutical and biotechnology segments.

Miguel holds an MBA and a BS in Chemical Engineering from Rensselaer Polytechnic Institute. His expertise includes areas such as process and cleaning validation, use of statistics in different applications, facility and equipment qualification with focus on sterile operations and validation of sterilization and depyrogenation processes. He has been a speaker at validation-related conferences around the world for such groups as IIR, IVT, and Barnett International. His articles and papers have appeared in the American Pharmaceutical Review and the Journal of Validation Technology publications. He is a member of the Editorial Advisory board for the Journal of Validation Technology.

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Article Acronym Listing

CFR	Code of Federal Regulations
FDA	Food and Drug Administration
IQ	Installation Qualification
ISPE	International Society for Pharmaceutical Engineering
OQ	Operational Qualification
OTC	Over the Counter
PLC	Programmable Logic Controller
PQ	Performance Qualification
WFI	Water For Injection

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2. ISPE Baseline Engineering Guides – Volume #5, "Commissioning and Qualification," 2001.
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Design, Qualification, and Validation of Water Systems

BY VINEET SHARMA

Introduction

Water is the most widely used raw material in the manufacture of Active Pharmaceutical Ingredients (API), intermediates, and finished dosage forms. As a raw material, high purity water is unique in that it is the only component that must be produced by the manufacturer, because it is not available from a vendor in a ready-to-use form.

Water is utilized in the production of every type of pharmaceutical; in some products, such as parenterals, it is a critical component. It is, perhaps, the most important of all pharmaceutical utilities. In many pharmaceutical formulations, it is used as an excipient cleaning agent. Many API manufacturing and formulation facilities have United States Pharmacopoeia (USP) Purified Water (PW) systems while sterile manufacturing facilities have USP Water-for-Injection (WFI) systems.

The USP includes description and guidance for all types of water used in the processing of pharmaceuticals. Specific monographs in the USP include: PW, WFI, sterile water-for-injection, and bacteriostatic water-for-injection. Water used in the production of API, in many instances, may be potable water obtained from wells or other surface sources. These sources are considered acceptable provided water quality standards are established that are consistent with the compendial national primary drinking water standard of the U.S. Environmental Protection Agency (EPA), or with other regulatory requirements for drinking water. The API manufacturer should verify that the water is tested routinely to assure compliance with chemical and microbiological standards. In many cases, sufficient data may be available from the municipal water authority to support the use of the water, and only periodic monitoring may be necessary by the API manufacturer. This is applicable when the API manufactured is non sterile and its formulated product is in oral dosage form. In cases such as these, the municipally supplied water must be equivalent to potable grade water.

Description

Purified water is water for the preparation of medicinal products other than those that require the use of water that is sterile or apyrogenic. Control of water quality, in particular, the microbiological quality, ionic impurities, and Total Organic Carbon (TOC) are the major reasons the pharmaceutical industry devotes considerable resources to the development and maintenance of water purifying systems.

One must have a clear understanding of all aspects of the contemporary technology involved in a pharmaceutical PW system, as well as the rationale behind Food and Drug Administration (FDA) requirements for the preparation and storage of PW. The factors that influence water system design are based on: 1) different water sources and the impurities they contain; 2) differences and similarities among the various types of water used in pharma plants; 3) how the different types of impurities, including, ionic, organic, microorganism chloramines, etc., can be removed; 4) proper sizing; and 5) the varied equipment used to achieve a reliable, cost-effective system.

Water Purification Techniques

- ***Reverse Osmosis (RO)***

  USP has proposed specifications for purified water. More selective testing for conductivity and TOC have given these specifications more importance, which reflects in the quality of water produced. A two-pass RO system, which has the ability to remove bacteria, is the heart of a treatment system.

There are several variables to consider when designing an RO system. Membrane type and flow rate recovery are the key factors. Pressure vessels holding these membranes play an important part in controlling bacterial growth. The typical function of a two-pass RO would be to reduce the ionic impurities to prescribed levels, TOC, and microbiological substances. Since membranes reject ions having molecular weights greater than 150 dalton, a membrane typically rejects 99.9 percent of organics present.

- ***Electrodeionization (EDI) system***

  The USP purified water monograph calls for the online conductivity of water. Conductivity of below 1.3 microsiemens/cm, at a temperature of 25°C is required at stage I testing. An EDI system is used to get water exceeding this quality, having resistivity in the range of 12-15 Mohm.

- ***Ultrafiltration***

  To ensure the product water quality at POU (Point Of Use) complies with highly purified water specifications, the water is passed through ultrafiltration membranes to remove bacteria and endotoxins from the purified water on a continuous basis. Polyethersulfone hollow fiber membranes are used because of their hygienic design and the thermal tolerance of the membrane, which allows hot water sanitization.

System Designing

The major factors for designing a purified water system include:

- Capacity of purified water required
- Water quality attributes
- Selection of membrane

System design must meet the requirements for total water output and for quality level. This is done prior to the design qualification of the system. This checks the quality of feedwater, which enters the purified water system.

The concentration factor of a cross-flow membrane filtration system is determined by system recovery, which is the ratio of permeate to feed volume. For example, a system providing 15 gpm (56.8 Lpm) of permeate from a 20 gpm (75.7 Lpm) feed stream would be operating at 75 percent recovery and would increase the concentration of unwanted substances in the reject stream by a factor of four.

For most water purification systems, recovery rates are well defined and predictable. If a system approaches or exceeds the designed recovery, concentrated salts may form a scale on the membrane surface. Solubility limits aren't generally a concern with systems such as Ultra Filtration (UF) that pass dissolved salts through the membrane.

The solubility levels of dissolved mineral salts, $C0_2$, and silica, are greatly affected by pH. Membrane systems rejecting substantial quantities of dissolved constituents must operate at concentration factors safely below any solubility limits.

The use of membrane technology to produce water of greater and greater purity is rapidly evolving under the pressure of new product quality specifications. Membrane technology is well suited to achieving multi-component water specifications, given the fundamental nature of the separation process. Meeting a resistivity or conductivity specification as the sole gauge of water quality, however, can be more challenging.

Membrane technology is capable of producing water with resistivity greater than 1 megohm when applied in a two-pass RO system that is properly designed and operated. A series of controlled experiments has shown that membrane rejection will fluctuate in response to the feed's Total Dissolved Solids (TDS), pH values, cross flow rates, and element recovery levels. The performance of elements in the second pass of an RO system can be most dramatically affected.

These variations, while not significant in the majority of applications, become crucial to the success of high-purity water processing. In addition, the presence of minor feedwater constituents, such as alkalinity and ammonia, is seen to play a dominant role in achieving high-purity permeate. Polyamide (PA) thin-film composite membranes have charge characteristics that influence their separation capabilities, and the nature of these characteristics can be altered by the feedwater pH. The majority of PA RO membranes are negatively charged when operated on the pH levels most commonly encountered in water applications.

pH

When the pH drops below a membrane's isoelectric point (generally between pH 4 and pH 5), these membranes become positively charged. The isoelectric point is that pH point at which the membrane has no net charge. This substantially decreases their performance when the permeate quality is being measured by conductivity. Acid transport through the membrane accounts for much of this apparent

fall-off in performance. The effect is completely reversible when the pH is returned to near-neutral levels. The acid transport is facilitated by the presence of unreacted "end" groups in the PA barrier layer. Depending on the amount of unreacted groups present in a particular membrane, different responses to pH changes may be seen.

High pH levels can also reduce the rejection of PA membranes as measured by conductivity. As with the low pH phenomenon, the threshold value at which this decline occurs is unique to each membrane type. In general, pH values above 8.5 can be problematic. An acid addition to lower the pH will correct this condition. The reason(s) for this membrane performance change at high pH is not well understood. At a higher pH the concentration of hydroxide ion becomes significant, and PA membranes do not exhibit high rejection of hydroxide. To maintain charge neutrality, a cationic counter-ion "leaks" through the membrane with each hydroxide ion passed.

Feedwater

PA membrane performance is also a function of the relative conductivity of the feed-water. When the feedwater has a minimal TDS (Total Dissolved Solid), which has very low conductivity, the membrane capability to reject ions is reduced. Therefore, the ion rejection rate observed on the second pass is usually lower than that measured on the first pass. This reduced rejection must be taken into account when estimating the final permeate quality of a two-pass system.

Also basic to membrane separation is the effect of feedwater chemistry. Chemistry takes center stage when the desired product is high-purity water and the benchmark is conductivity. Dissolved gases such as carbon dioxide (CO_2) and ammonia (NH_3) can dramatically affect permeate conductivity. Since gases readily pass directly through the RO membranes, these uncharged, gaseous constituents cannot be effectively dealt with in their original state by membrane technology alone. In the case of CO_2, however, it is possible to force a conversion to bicarbonate (HCO_3-) and carbonate (CO_3^{2-}) ions by raising the feedwater pH. These ions are both rejected by PA RO membranes. By increasing the pH of the feed solution, a portion of the CO_2 present is shifted to HCO_3- and/or CO_3^{2-} depending on the pH level reached. With proper pH control, greater than 98 per cent of bicarbonate and carbonate can be removed in the first pass of a two-pass system. This method of control is generally most effectively implemented when used prior to the first-pass RO. It is much more difficult to control caustic injection of the second-pass RO feed due to the difficulties encountered when measuring and adjusting the pH of low TDS water.

Figure 1

Common water chemistry reactions

$CO_2 + H_2OH_2CO_3$ (carbonic acid)
$H_2CO_3H{+}{+}HCO_3$ (bicarbonate ion); pKa = 6.38
HCO_3-H++ CO_3 (carbonate ion); pKa = 10.37
NH_4+H++ NH_3 (ammonia); pKa = 9.25

If elevating the pH of the feedwater is not practical, CO_2 and a portion of the feedwater alkalinity can be removed through the use of a degassifier. Acid injection ahead of such a unit will make this technique most efficient, because this will convert the majority of the alkalinity present to CO_2. The degassifier can be located either ahead of the first RO machine or between the two passes.

Ammonia

Another water chemistry variable that can play a large role in successfully achieving high-purity water is the presence of ammonia. Ammonia can be present due to chloramination or organic contamination of the feedwater. The use of chloramine treatment by municipalities is becoming more common, particularly for surface water sources. There may be an ammonia residual present in the water from the initial chloramine generation or from the subsequent liberation of ammonia during its treatment by activated carbon or ion exchange.

At neutral and acidic pH conditions, the ammonia is ionized and present as ammonium ions (NH_4+). The addition of a strong alkali to raise the pH will produce ammonia. Like carbon dioxide, the uncharged ammonia will pass through the membrane and contaminate the permeate. When a system feedwater contains ammonium ions, the need to add a caustic for CO_2 removal must be carefully balanced with the need to prevent passing ammonia into the permeate.

System Design

A system designer must take great care when fine-tuning the operating parameters and the water chemistry involved in the application of two-pass RO for generating high purity water.

Component design is an important consideration. While component design has become more sophisticated in recent years, each of the following system elements can benefit from further thought:

Carbon beds

Carbon beds remove organic compounds from the feedwater. One of the most common organic compounds removed is chlorine, which municipalities use to control bacterial growth in drinking water. Since carbon beds filter the organic material needed for bacterial growth, this material becomes concentrated in the carbon beds. If the beds are not properly maintained, they can harbor bacteria and endotoxins. Hot water or steam should be used periodically to purge the system of such contaminants. It is important that the Standard Operating Procedures (SOPs) include these maintenance procedures.

Holding tanks

The design element that causes the most concern vis-à-vis the holding tank is the vent filter. Most new tanks utilize jacketed vent filters to prevent condensate or water from blocking the hydrophobic filter. It is important that maintenance SOPs include procedures for regular checking of the vent filter integrity. For this reason, the filter should be located in a position that provides easy access for testing. The SOPs should also include complete flushing or draining of the holding tanks on a regular basis.

Heat exchangers

The heat exchanger should be designed to prevent distillate contamination from feedwater. Double tubesheet design and positive pressure are the two most common methods used; if positive pressure is utilized in the design, monitoring systems should ensure that higher pressure is constantly maintained on the distillate side.

Condensers

It is important that the condenser be designed with double tubesheet to ensure that the distillate will not come in contact with the coolant, thus preventing recontamination. Another consideration for distillation stills is the quality of the steam supplied to the process; the quality of the steam must be controlled to prevent recontamination.

Pumps

All pumps experience wear and some burn out; it is, therefore, important that the maintenance SOPs include a program for the upkeep of all pumps in the system. If a pump is not in continuous operation, the reservoir is a potential source of contamination. When the pump is not in use, water may collect in the low point of the pump housing, potentially harboring microorganisms. It may be advisable to install a drain in the low point of the pump housing.

Piping

High purity water systems utilize stainless steel (SS) piping in their construction. Where low-level metal contamination is a concern, polyvinylidene fluoride (PVDF) piping has been used in place of the SS piping. Systems utilizing PVDF piping, however, require additional support in the piping layout. While the system is in use, the circulation of hot water may reduce the rigidity of the piping, causing it to sag. In cases where the piping sags or bends, stress can create fissures in joints, which may result in leakage and contamination. Other considerations for the piping include the elimination of "dead legs" and the use of welding or sanitary fittings for all joints and connections in the system design. Internal surfaces of the piping should be electro polished with 20 Ra.

Installation Requirements

Qualifying an installation helps in ensuring that the validation is not put at risk and is successfully completed. Once the installation is finalized, a complete and up-to-date description and design drawing of the system should be added to the file and included in the final report. It is important that the design drawing include all components of the system and clearly identify all sample points and their designations. If the design drawing does not include these elements, the water system is considered to be in an "objectionable condition" and the validation is at risk.

The following factors should be critically evaluated during installation:

Dead Legs

One common problem with piping layouts in either hot or cold circulating high quality water systems is that of "dead legs." A dead leg is a length of piping, more than six pipe diameters (6d) in length, that drops from the circulation loop and is, therefore, not subject to the positive effects of continuous water circulation. Water can collect in dead legs, providing an opportunity for the formation of bio film and the growth of microorganisms. Dead legs should be eliminated from circulating water systems, and there should be routine sanitation procedures in place to assure adequate cleaning and maintenance of the system.

Slope Verification

This is checked to verify the slope in piping at the time of installation. The ratio of the slope to the length of pipe should not be more than 1:100. Pipe slopes are maintained such that water from the system is drainable to a low point drain.

Welding Inspection

All weld joints in the system should be thoroughly checked for the following parameters:

1. Pinholes must be absent.
2. Weld bead appearance must be regular and uniform.
3. Thermal cracking must be absent.
4. Weld seam color must be absent.
5. Weld thickness must not be more than 20% of the tube thickness.
6. Stainless steel oxidation products must be absent.
7. Welded tubing sections must be aligned properly.
8. Weld shape must be noticeably convex.

Pressure Test

This test is conducted to ascertain that the system is integral. Perform hydraulic tests at pressures of at least two-times the anticipated maximum operating pressure or 150 psig, whichever is more.

Passivation Test

This test is performed to remove all oxidizable matters from the system.

Operational Requirements

After successful installation qualification, a report is prepared. The second step is operational qualification, which is carried out to ensure that the system meets the requirements as specified in system designing. Important activities that must be carried out include:

Water Velocity Test

This test is conducted to check the quantity of water at the point with all other outlets in usage at rated flow. The flow velocity should not be less than 1.5 m/sec.

Reynolds Number Determination

The Reynolds number measures the turbulence of water flowing in the distribution pipelines. If the Reynolds number is above 2000, the water has turbulent flow. If the Reynolds number is below 2000, the water may have laminar flow, which may lead to biofilm development.

Pre Validation Requisites

The suitability of the system to consistently produce water of acceptable quality should be validated prior to production, and appropriate operating and testing controls should be in place before the water is used for routine manufacturing. Once a water system is validated, criteria for controlling the microbial quality of purified water should be established. These criteria may vary from process to process or from manufacturer to manufacturer.

Documented written procedures should be established for the operation and control of critical water systems. These procedures should include a description of the system including: schematics: the identification of all outlets; usage points and sampling ports; the requirements for routine maintenance of the system; the procedures for testing, including the method of analysis and the frequency; and microbial action levels for each water type.

Specification for microbiological quality, including action and alert levels, should be established, and periodic testing should be conducted according to a consistent sampling schedule and standard methods of analysis. The particulars of the sampling frequency and the stringency of the test specifications will vary depending on the stated quality of the water and the point in the process at which the water is being used. If the water is used in the final wash of the cake in a centrifuge for a non sterile manufacturing facility

that may ultimately be used in the formulation of a sterile drug product, the water quality standards should be higher than those normally specified for purified water.

In addition to total microbial count, the presence of objectionable microorganisms in water systems is another concern for the API manufacturer. The presence of a specific contaminant could be more significant to an API manufacturer than the total number of microorganisms. It is up to the manufacturer to establish a microbiological profile of their water systems against a set of established standards, to examine the ways in which both the water and the product are manufactured, and to establish acceptable action levels based on the highest risk product manufactured with the water. The presence of these contaminants should be evaluated in terms of the source water, the ultimate use of the product, the nature of the product, and the potential harm to the user.

SOP development and confirmation

Once the system design and installation has been finalized, the next step is to develop the operational parameters along with cleaning and sanitizing protocols. Once developed, these procedures become the SOPs for the system's normal operation. During this step, data are collected over a period of two to four weeks. Samples should be collected daily after each purification step and from all points of use. At the end of the period, if the system has successfully generated water of the appropriate quality, these procedures are established as the water system's SOPs.

Demonstration of effectiveness

During this phase of the validation, the objective is to demonstrate that the water system consistently produces water of the desired quality when operated within the parameters outlined in the SOPs over a long period of time. It is important that the data is collected in accordance with the SOPs. At a minimum, WFI system samples are taken daily from one POU and weekly from all POU. This type of operation should identify any inconsistencies in the feedwater quality due to seasonal variations or other changes in the quality of the source water. A water system cannot be considered validated until the manufacturer has a year's worth of operational data.

Data compilation and sign-off

The final step in validating a high purity water system is assembling the data into a validation report. The final report should include all the data collected in Phases I, II, and III, along with any conclusions derived from the data. Once the final report is complete, it is important to ensure that the appropriate personnel review and sign-off on it.

Any validation strategy should include the elements outlined above: development of the SOPs through data collection, a demonstration that the SOPs are effective, and assurance that the system is capable of consistently producing, over a long period, water that meets the quality specifications.

Commonly Overlooked Items

While including the above elements in the validation strategy increases the odds of successfully validating the water system, even a well-thought out strategy is susceptible to failure because of often-overlooked details. The validation process is long and complex and small details can be overlooked. Following are some of the more commonly overlooked considerations:

1. Feedwater

During a water system validation, consideration must be given to the quality and seasonal variation of the feedwater. In some instances, it is also beneficial to consider the quality of water in surrounding municipalities in the event that water must be diverted from an alternate, neighboring source. (Feedwater may be diverted as a result of such events as construction or an emergency such as a major fire. In such cases, the feedwater entering the facility may be contaminated with elevated levels or different types of flora.)

A schedule of routine monitoring is the best way to ensure a membrane system is operating under optimal conditions. For small, POU systems it may be more cost-effective to replace membrane elements rather than to institute a monitoring program. However, it's important to monitor process variables such as inlet pH, hardness levels, turbidity, temperature, iron, chlorine, conductivity, flow rates, and operating pressures for larger systems.

Operational data should be recorded frequently, ideally, every day or once per shift. This data may be used to spot trends in operating conditions and alert the user of pertinent maintenance issues, such as membrane replacement or cleaning. Feedwater data can also be used to assess the effectiveness of the pre-filtration system.

Crossflow membrane filtration, whether combined with an existing treatment system or used alone as the primary treatment method, offers benefits not attainable with con-

ventional filtration. If a process requires ultrapure water, RO systems have a proven track record. Even if a process doesn't require water with the highest degree of purity, membrane technology can offer many advantages. When designed with careful attention to system chemistry, cross-flow requirements and proper pretreatment, a membrane system should provide trouble-free performance for many different applications, with little required maintenance.

2. Air Contamination

A common omission from SOPs is a list of the correct procedures to preclude contamination from non-sterile air after a water system is drained. POU piping extensions, particularly those that utilize tubing or hoses for application, can allow non-sterile air to come in contact with the system when the valves are not opened in the proper sequence. The SOPs should be reviewed to ensure that proper valve sequencing prevents contamination from non-sterile air.

3. Microbial Limits

When establishing the microbial specifications for a high purity water system, the most commonly used reference is the USP 24. It is important to understand that the limits set forth by USP 24 are not absolute, and as such, the FDA does not view them as pass or fail limits. Instead, they are viewed as action limits and in some cases may not be stringent enough. It is important that users take into account not only the USP guidelines but also their understanding of the dosage form in which the high purity water will be used when setting alert or action limits. For example, in situations in which the final dosage form does not have a preservative system, more stringent action limits may be required to produce safe and effective products. Conversely, some dosage forms that have low moisture content may tolerate higher microbial levels, and as such, the action limits may be established at higher values.

When alert and action limits have been established, it is imperative that the user has an SOP for investigating deviations. Once a deviation is detected, the user must investigate the cause, determine a corrective action, and assess the impact of the contamination on the adulterated product. Throughout this process, the findings and conclusions should be documented and assembled in a corrective action report. Finally, there should be a process in place to confirm any changes to the system or to the SOPs as a result of the corrective action.

4. Cost of Operation

Although not factors in validation, cost considerations are important. High purity water systems, which operate between 65˚ and 80˚ C, are generally recognized as self-sanitizing. While these systems cost more initially than "cold" systems, the savings realized through reduced operations, maintenance, and testing—and the prevention of potential problems—may make the investment worthwhile.

Purified Water System Validation

Validation and qualification of water purification, storage, and distribution are fundamental parts of Good Manufacturing Practice (GMP) and form an integral part of a GMP inspection. The qualification of a purified water system is unique in that performance must be proven over an extended period of time and is subject to variation in use rate and initial feedwater quality.

The emphasis placed on water quality within the pharmaceutical industry is considerable. Therefore, it is vital to ensure that a water system has been designed, installed, tested, and commissioned correctly and that it performs exactly to its original specification to the end user and to regulatory requirements.

System Validation, Preparation

When validating a high purity water system, there are several aspects that should be considered. Documentation should include a description of the system along with a drawing. The print should show all equipment in the system from the water feed to POU. It should also show all sampling points and their designations. When a system has no print, the situation is usually considered an objectionable condition. The thinking is that without a print, a system cannot be validated. How can the chemist or microbiologist know where to sample if there is no drawing? In those facilities observed without updated prints, serious problems were identified in their systems. The print should be compared annually to the actual system to insure its accuracy, to detect unreported changes, and to confirm reported changes to the system.

System Validation, First Phase

After all the equipment and piping has been verified as installed correctly and working as specified, the initial phase of water system validation can begin. During this phase, the operational parameters and the cleaning and sanitation procedures and frequencies will be developed. Sam-

pling should be done daily after each step in the purification process and at each POU for two to four weeks. The sampling procedure for POU sampling should reflect how the water is to be drawn, for example, if a hose is usually attached, the sample should be taken at the end of the hose. If the SOP calls for the line to be flushed before use of the water from that point, the sample is taken after the flush. At the end of the two to four week time period, the firm should have developed its SOP's for operation of the water system.

System Validation, Second Phase

The second phase of the system validation is to demonstrate that the system will consistently produce the desired water quality when operated in accordance with the SOPs. The sampling is performed as in the initial phase and for the same time period. At the end of this phase, the data should demonstrate that the system will consistently produce the desired quality of water.

System Validation, Third Phase

The third phase of validation is designed to demonstrate that when the water system is operated in accordance with the SOPs over a long period of time it will consistently produce water of the desired quality. Any variations in the quality of the feedwater will be picked up during this phase of validation. Sampling is performed according to routine procedures and frequencies. For WIF systems, samples should be taken daily from a minimum of one POU. All POUs should be tested weekly. The validation of the water system is completed when the firm has a full year of data.

Validation Method Recap

While the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system. First, there must be data to support the SOPs. Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications. Finally, there must be data to demonstrate that seasonal variations in the feedwater do not adversely affect the operation of the system or the water quality.

Validation Documentation

The last part of the validation is the compilation of the data, with any conclusions, into the final report. The final validation report must be signed by the appropriate people responsible for the operation and the quality assurance of the water system.

When the validation documentation does not include operating procedures to preclude contamination of the system with non-sterile air remaining in a pipe after drainage, it typically causes contamination of the system. This is an issue to be avoided. It was noted above in the section on "Commonly Overlooked Areas."

Ideal Purified Water System

In this section, we will deal with how an ideal purified water system meets the requirements of purified water as prescribed by the USP monograph.

Evaluate Water

Potable water from the municipal supply source is first tested for the amount of chlorine present in the water. This free chlorine is added at the supply source i.e., the municipal source. The hardness, pH, and conductivity of the water are checked to evaluate the quality of water. The amount of microbial contamination present in the water is also checked. Microbial quality is checked by adding sodium thio-sulphate to remove chlorine completely from the water to obtain actual representative microbial counts.

Filtration

The first processing step is usually filtration with a multi-media filter containing gravel, manganese greensand, and anthracite. The primary purpose of the manganese greensand is to remove iron, but it also serves as a very good particle filter. The anthracite provides a "light" layer that is easily backwashed, alleviating much of the load from the greensand, and allowing the sand to perform more effectively. These two media types together are effective at removing suspended solids at sizes as small as five to ten micron (μm).

Softening

The second processing step is typically water softening, using ion exchange softening. The water softener is used to remove hardness (calcium and magnesium) from the water, replacing these with sodium ions. Removing hardness protects the RO system by keeping hardness scale from forming on the membrane surface. It is best to avoid using an acid addition to control scale. This method has the disadvantage of increasing the free carbon dioxide (CO_2) by shifting the bicarbonate to carbonic acid that, in turn, dissociates into CO_2 and water. The resulting carbon dioxide will pass through the membrane, producing a high-conduc-

tivity product water as the CO_2 re-associates with the water to reform ionic bicarbonate. Acid addition creates a problem in meeting the proposed pH specifications (five to seven) for *USP 23* Purified Water, since an RO system will inherently reduce the pH because of the shift in the alkalinity or carbon dioxide ratio.

After de-chlorination and pH adjustment, the water is filtered through a two-pass RO system to remove dissolved solids. It is important to note that the RO system must contain high-rejection thin-film type membrane elements. Preferred are sanitary-design PA membranes that reject more than 99.0% sodium chloride and have stainless steel permeate tubes.

A two-pass RO provides "double barrier" removal of microbes because the product water, or permeate, from the first pass is used as feed for the second pass. However, an RO system does not offer complete assurance that the product water will be totally free of bacteria.

As soon as the water is fed into the primary feed or softening unit, chlorine is added into the water stream. Water is then passed through pressure sand filters connected with kinetico valves. Here, the heavier particles in the water are retained; this water is then passed through a softening unit containing cations, connected with a kinetic valve. Water hardness is removed by the addition of a brine solution in the cation-softening unit. De-chlorination of free chlorine present in the water is done by the addition of sodium meta bisulphate (SMBS), the quantity of SMBS required is three-times the addition of chlorine in water. An antiscalent agent is added so that the scale formation salts precipitate. At this stage, the water's pH is maintained slightly on the alkaline side. All scaling salts, which are in precipitated form, are filtered out through the membrane cartridge filter. The permeate water is then fed into RO module one. The total length of the RO module one is 6 meters. Here the de-salination of water takes place by RO process. Permeate water is then passed into RO module two; the length of this module is 6 meters. Again de-salination of the remaining water takes place. The permeate water is then passed through an ultra filtration membrane having molecular weight cut off at 18,000 dalton.

Sanitization

To control microbial growth, RO systems must be chemically sanitized on a regular basis. Prior to sanitization, it is important to chemically clean the first-pass RO system. This helps to disrupt any biofilm that protects viable bacteria from contact with the sanitant. It also removes foulants that will react with and chemically deplete the sanitizing agent. Typically, this is done in a two-step process. The first step commonly involves the use of an acid cleaner such as citric acid to remove the inorganic foulants. Next, a high-pH cleaner such as sodium hydroxide is used in order to remove organic foulants. Then the system is sanitized with one of the following agents: formaldehyde, hydrogen peroxide, or peracetic acid/hydrogen peroxide. It is important to consult the manufacturer of the RO system to determine the correct concentrations of the chemicals that are compatible with the membranes in the system, and to always rinse with purified water before changing chemicals.

Both cleaning and sanitization processes consist of four steps. First, the cleaning chemical is mixed with permeate water in a clean-in-place (CIP) tank. Second, the chemical solution is re-circulated through the RO system for 15 to 30 minutes. Then, the system is left to soak for 20 to 30 minutes. The system should be started once every five to ten minutes for a short time to allow fresh solution to contact the membrane. Finally, the system should be rinsed with permeate water until the residual cleaning or sanitization chemicals have been removed

Testing

The water is tested for residual chlorine and free chlorine. The feedwater is tested for the absence of hardness to the RO membrane by the titration method. The water's pH should be slightly alkaline i.e., between 7.5 – 8.5 pH. The absence of anti scaling agents is tested in permeate water after passing through the RO membrane. Then, water emitting from the ultra filtration membrane is tested for microbiological contamination. The water is distributed to different plant sources through a storage tank in a closed loop system. This system must be sanitized at intervals of seven days, because the water is circulating at ambient temperature.

Water at all POU, as well as in the after-storage tank, should be tested for the presence of chemicals and microbiological agents. The Total Organic Carbon (TOC) analysis of the water should also be carried out.

Chlorine Treatment

Chlorine readily combines with chemicals dissolved in water, microorganisms, small animals, plant material, tastes, odors, and colors. These components "use up" chlorine and comprise the "chlorine demand" of the treatment system. It is important to add sufficient chlorine to the

water to meet the chlorine demand and provide residual disinfection.

The chlorine that does not combine with other components in the water is "free" (residual) chlorine, and the "breakpoint" is the point at which free chlorine is available for continuous disinfection. An ideal system supplies free chlorine at a concentration of 0.3-0.5 mg/l. Simple test kits, most commonly the DPD (diethyl phenylene diamine) calorimetric test kit (so called because diethyl phenylene diamine produces the color reaction), are available for testing breakpoint and chlorine residuals in private systems. The kit must test free chlorine, not total chlorine.

Contact Time with Microorganisms

The "contact (retention) time" in chlorination is that period between introduction of the disinfectant and when the water is used. A long interaction between chlorine and the microorganisms results in an effective disinfection process. Contact time varies with chlorine concentration, the type of pathogens present, pH, and the temperature of the water. The calculation procedure is given below:

Conditions

Contact time must increase under conditions of low water temperature or high pH (alkalinity). Complete mixing of chlorine and water is necessary, and often a holding tank is needed to achieve appropriate contact time. In a private well system, the minimum-size holding tank is determined by multiplying the capacity of the pump by 10. For example, a 5-gallons-per-minute (gpm) pump requires a 50-gallon holding tank. Pressure tanks are not recommended for this purpose since they usually have a combined inlet/outlet and all the water does not pass through the tank.

An alternative to the holding tank is a long length of coiled pipe to increase contact between water and chlorine. Scaling and sediment build-up inside the pipe make this method inferior to the holding tank.

Calculating Contact Time

To calculate contact time, one should use the highest pH and the lowest water temperature expected. For example, if the highest pH anticipated is 7.5 and the lowest water temperature is 42 °F, the "K" value (from *Figure 2*) to use in the formula is 15. Therefore, a chlorine residual of 0.5 mg/l necessitates 30 minutes contact time. A residual of 0.3 mg/l requires 50 minutes contact time for adequate disinfection.

Figure 2

Minutes required = K/Chlorine residual (mg/l)

K Values to Determine Chlorine Contact Time			
Highest pH	Lowest Water Temperature (degrees F)		
	>50	45	<40
6.5	4	5	6
7.0	8	10	12
7.5	12	15	18
8.0	16	20	24
8.5	20	25	30
9.0	24	30	36

CONDUCTIVITY

The proposed USP PW monograph will call for on-line (or immediate off-line) conductivity at or below 1.3 µS/cm [when the temperature is at or above 25°C (77°F)] at stage 1 testing. The second stage testing calls for off-line analysis showing a conductivity of 2.4 m S/cm (at 25° ± 1°C). This off-line conductivity requirement is higher than the on-line requirement allowing for the increase in conductivity due to the contribution of dissolved CO_2 gas present in the water. A key to producing water that meets the on-line requirement is the removal of CO_2 from the water.

When CO_2 gas is dissolved in water, a portion reacts with the H_2O molecules to form carbonic acid. Being a dissolved gas, the CO_2 passes completely through an RO membrane, and once the CO_2 re-associates with water molecules to form bicarbonate in the RO product water, it contributes to the conductivity of the permeate water.

There are three reactions (equations) that govern the chemistry of CO_2 in water:

1. $CO_2 + H_2O <\!\!\longrightarrow H_2CO_3$
   (carbonic acid)

2. $H_2CO_3 <\!\!\longrightarrow H^+ + HCO_3^-$
   (bicarbonate ion);
   $pK_a = 6.38$

3. $HCO_3^- <\!\!\longrightarrow H^+ + CO_3^{2-}$
   (carbonate ion);
   $pK_a = 10.37$

When gaseous CO_2 is dissolved in water, a portion is hydrated to form carbonic acid (equation 1). This carbonic acid dissociates into bicarbonate and hydrogen ions. At a pH of 4.3, very little of the carbonic acid is dissociated. At a pH of 6.38, the molar concentration of carbonic acid equals that of the bicarbonate and hydrogen ions. At a pH of 8.3, there is no longer an appreciable amount of CO_2 or H_2CO_3 present in the water. Above this pH, the bicarbonate ion is converted to carbonate and H^{+} $^{-}$ as shown in equation 3.

As the pH increases, all three equations are driven to the right and there is less CO_2 available in the gaseous form. Since RO membranes cannot reject gaseous CO_2, the permeate conductivity is lowest when the feed pH is near or above 8.3. When the pH is above 8.3, the CO_2 is found in the form of the carbonate and bicarbonate ions, which are easily rejected by RO membranes.

Maintenance

The integrated system includes continuous on-line monitoring at appropriate locations throughout the system. To minimize microbiological contamination, water systems for pharmaceuticals manufacturing should have corrective facilities. This means access to the system for sanitization or introduction of steam, chlorination, storage at elevated temperatures, etc. Any cleaning chemicals used should not affect the equipment, the membranes, or resins in the system. Proper rinsing should be ensured.

Preventive maintenance of water systems is an important issue because it has direct impact over the quality attributes of purified water. Good preventive maintenance programs will not only increase the life of the PW system, but will also contribute to consistently keeping the water quality below the specified limit over a period of time.

The need for preventive maintenance is based on various factors such as increase in the pressure differential across the membranes, or slow but steady deviation of quality attributes from its baseline value.

Routine preventive maintenance for membranes can be achieved by chemical treatment or by hot water treatment. Whole water systems, from distribution storage tanks to user points, can be sanitized with a hot water treatment in a loop by maintaining the temperature between 80°C to 85°C.

CGMP (current Good Manufacturing Practice) Compliance Issues

Satisfying regulatory concerns is primarily a matter of establishing proper specifications and of using effective and appropriate methods to verify and record that those specifications have been satisfied.

Fundamental conditions expected to aggravate a microbial problem typically include system design conditions such as: stagnant conditions, areas of low flow rate, poor quality feedwater, etc.

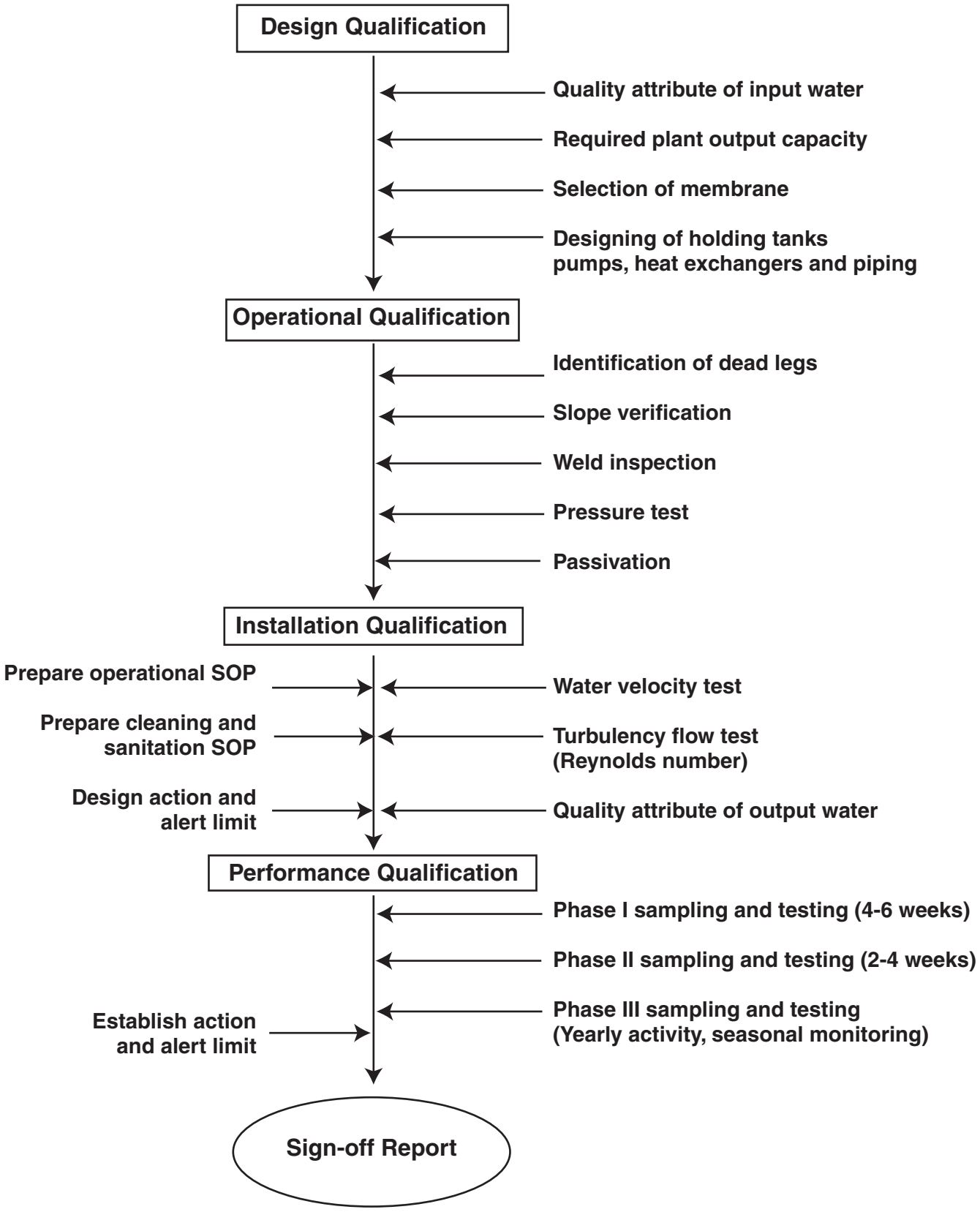
Measures to alleviate such problems include:

- Continuous, turbulent flow
  Water from storage tanks should be distributed to the sampling points in a turbulent flow. This flow is recommended so that the biofilm does not have time to settle on the surfaces. Reynold's number measures turbulent flow. If the Reynolds number is above 2000, the system has a turbulent flow. If the Reynolds number is below 2000, the system may have laminar flow.
- Elevated or reduced temperatures
  Water is distributed at ambient temperature, since final water quality is measured after the water moves through the ultra filtration membrane when it need not be distributed at an elevated temperature. Only at the time of sanitization is the temperature increased to 80°C - 85°C.
- Smooth, clean surfaces that minimize nutrient accumulation
  Electro polishing of the inner surfaces should be around 280 grit; this minimizes the development of biofilm.
- Frequent draining, flushing ,or sanitizing
  After sanitization, water should be drained from the draining point as well as from all user points.
  - Flooded distribution loop (maintenance of positive distribution loop pressures)
  - Properly designed, installed, and maintained system
  - Identification and removal of dead legs
  - Slope verification test of piping
  - Vent filter integrity test

While the control of chemical quality is important, the primary challenge in a pharmaceutical water system is maintaining the microbial quality. The industry and the regulatory community have recognized the effectiveness of

Figure 3

Stages of Water System Qualification



maintaining a continuously re-circulated system at high temperatures (65°C-80°C) in preventing microbial growth. Distillation has a long and well-documented history of success, but need not be the only technology considered for producing water with endotoxin limits. RO is the only other technology accepted by the USP for WFI. Ultrafiltration has been successfully used to produce water with strict endotoxin limits that meets WFI attributes, but it cannot, by regulation, be used to produce compendial grade WFI.

Each pharmaceutical steam and water treatment system must be viewed in its entirety, because design and operational factors affecting any unit operation within the system can affect the whole system. It is useful to identify both the quality parameters of water entering the system and the quality parameters of the water or steam to be produced. Water quality should be enhanced with each successive step. It does not necessarily follow that measures enhancing one quality attribute (such as conductivity, particulate level, or color) will always enhance another (such as microbial population).

Conclusion

This article has discussed various issues related to water purification techniques. Design requirements for a new purified water system have been discussed at length. Various activities, which must be carried out to satisfy installation and operational requirements, were considered with emphasis on certain critical parameters.

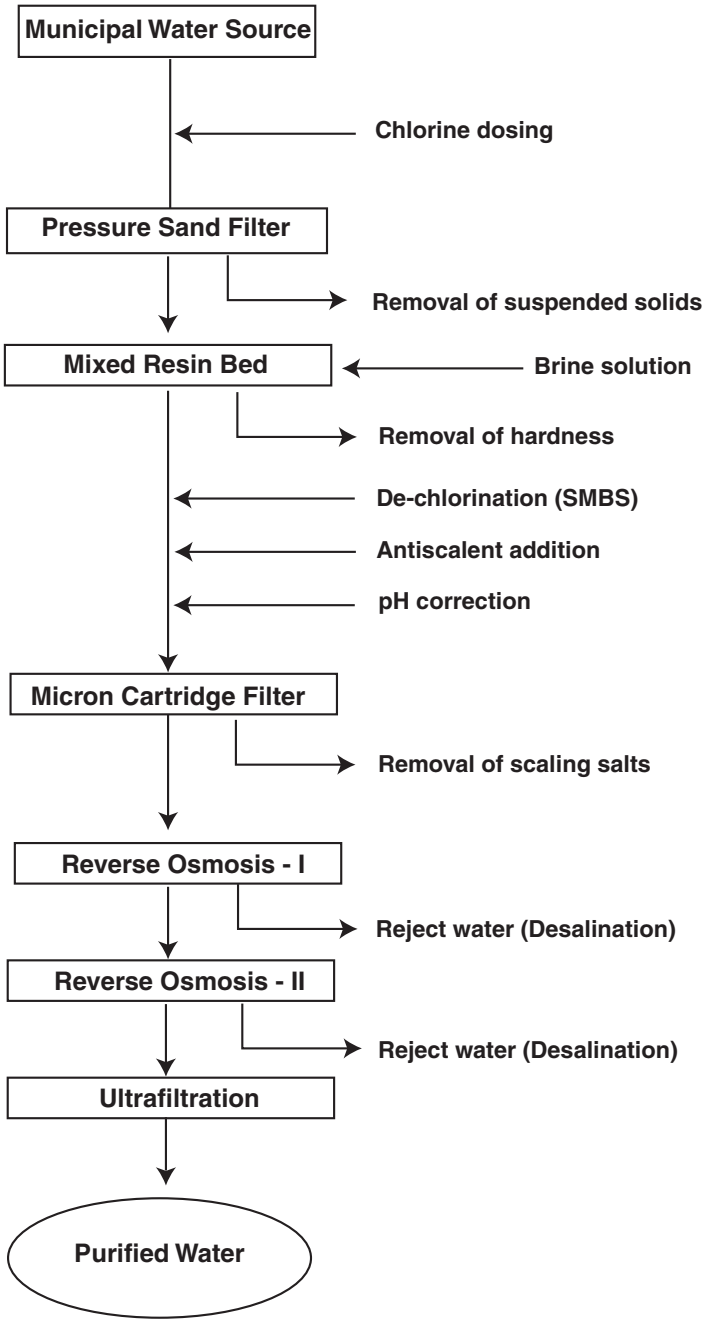
We reviewed activities necessary before starting validation activities that help to carry out validation activity smoothly. Validation of water systems, a must to meeting regulatory requirements, is carried out after the successful completion of installation and operational requirements was reviewed and defined in detail.

Ideal purified water was reviewed in terms of design, installation, and operational parameters along with GMP requirements. Preventive maintenance, an area that gets little attention, but has great impact on the quality attributes was also considered. Finally, we looked at cGMP compliance issues in brief.

The raw water quality that one must start with can have a major influence on the type of system employed in filtration. An early determination of the different water qualities available and the quantities of water that must be produced in future, have a significant impact on the final design output. Relevant factors for consideration include the methods of pretreatment given the feedwater quality and the ratios of various water qualities to be produced. Capital and operational expenditures, system validation, and documentation have been described. ❑

Figure 4

Flow Chart of Purified Water System



Article Acronym Listing

API	Active Pharmaceutical Ingredient
cGMP	Current Good Manufacturing Practice
CIP	Clean-in-Place
DPD	Diethyl Phenylene Diamine
EDI	Electrodeionization
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
PA	Polyamide
POU	Point of Use
PVDF	Polyvinylidene Fluoride
PW	Purified Water
RO	Reverse Osmosis
SMBS	Sodium Meta Bisulphate
SOP	Standard Operating Procedure
SS	Stainless Steel
TDS	Total Dissolved Solids
TOC	Total Organic Carbon
UF	Ultra Filtration
USP	United States Pharmacopoeia
WFI	Water-For-Injection

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Suggested Reading

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Recent FDA and International Regulatory Efforts Affecting Facility and Utility Systems Design and Qualification

BY MIGUEL MONTALVO

Introduction

It is clearly recognized that the use of adequate facilities and utility systems has a critical effect on our capacity to produce products, that consistently meet pre-defined specifications. The adequate design of such facilities and ancillary systems is vital to the overall success of any manufacturing process/operation.

The harmonization of the compliance requirements established by regulatory agencies around our global industry is an ongoing reality. It will be a continuous process, and may take a few more years to represent a tangible difference, but the changes can be perceived, and are being documented at this time. These harmonization processes are already having an effect on how we plan for and document the qualification of facilities and utility systems.

This harmonization is gaining strength with recent efforts primarily conducted by two main bodies:

- The International Standards Organization (ISO)
- The International Conference on Harmonization (ICH)

The FDA is a member of the ICH and participates in meetings and decisions by this group of regulatory bodies representing the countries that have major pharmaceutical presence in the world markets. As part of the FDA's "Initiative on cGMP's for the 21st Century: A Risk Based Approach," the agency has committed to support the harmonization process.

In this article, we will present:

- Status and recent developments from ISO and ICH
- How the FDA 21st Century initiative addresses the overall harmonization process
- How these activities affect our facility/utilities qualification plans

ISO and their Standards

In terms of ISO, there are recent standards, which are being developed or have been published. These standards are in a "review" period, which will last several years. Some of the ISO standards, which are already being referenced in our documentation and qualification protocols, are the ISO-14644 and ISO-14698 standards. These sets of standards are focused on the developing Classified Environments (ISO-14644) and Bio-Contamination Control (ISO-14698 standards). The standard ISO-14644-1 is replacing the Federal Standard 209-E, which was made obsolete in 2002. The FDA recognized this change in their latest Draft Guidance for Aseptic Processing by including the ISO Classifications in their document. The ISO-14644 series of standards also include other documents for Design, Operation, and Monitoring of the classifications, which can be used as reference for pharmaceutical facilities design and qualification.

Other documents from ISO include:

- **ISO-9000, 9001:2000** – these standards provide the basis for the FDA 21 CFR Section 820, which addresses the Quality System Regulation for Devices, and which will be used as the guide during quality systems audits by the FDA at pharmaceutical facilities. Many vendors/suppliers are conforming to these ISO standards, and the future clearly dictates that the pharmaceutical industry will move in that same direction as the FDA enforces the quality systems approach in their inspections and become more harmonized with other global regulatory agencies.

- **Risk Assessments Management** – the FDA has not determined the standard to follow to perform the risk assessments/management within the pharmaceutical industry, but it is expected that the ISO-14971 document may be used as a direct reference or as a template for the standard to follow. Everybody is familiar with the new FDA risk-based approach for inspections/observations, but FDA needs to establish some type of guidance document related to addressing the process that, hopefully will result in a standard for industry to follow.

ICH Meetings and Guidance Documents

ICH, meetings are being held at global locations with participation from all major regulatory agencies and FDA representatives. The basic goal of the ICH is to have "…increased international harmonization, aimed at ensuring that good quality and, safe, effective medicines are developed and registered in the most efficient and cost effective manner." (Statement by the ICH Steering Committee, Tokyo, October 1990.)

An ICH meeting was held in Brussels in July, 2003 and the attendees agreed to work on the following aspects.[1]

Common vision and approach to an international plan for a harmonized pharmaceutical quality system

- Integrated approach to risk management and science
- Vision implementation through Expert Working Groups (EWG)

The most recent ICH meeting (ICH6) took place in Osaka, Japan, in November 2003. His Excellency, Dr. Eisuke Mori, Senior Vice-Minister of Health, Labor, and Welfare, opened the plenary session of the ICH6 Conference stressing that "in the rapid progression of global drug development the ICH principal philosophy, "…harmonised technical requirements to facilitate the development of new drug products to benefit patients and public health by ensuring timely access to innovative drugs…" is of ever increasing importance.[2] The ICH has formed different teams (Expert Working Groups) to work on different areas. These groups are working on standard scope documents for their charters and guidance documents which by the end of 2004. One of the focus points during the meetings was the discussion of "opportunities and new challenges for regulatory harmonization…"[2] An example of how the ICH is pursuing this objective is the work being done with relation to the Common Technical document – common format for license application in the three ICH regions. Consistent with the ICH effort, the FDA included in their Initiative on Pharmaceutical cGMP's for the 21st Century: A Risk Based Approach, as one of their primary objectives, to harmonize standards/regulations. Their participation in the ICH conferences and working groups is part of the process for achieving this organizational objective.

Recently, the ICH developed a guidance document for the Active Pharmaceutical Ingredients (API) manufacturers that is considered the "current GMP's for the production of Active Pharmaceutical Ingredients". It is the ICH-Q7A – "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients." This guidance document utilized the FDA Draft guidance for API's (FDA draft guidance on "manufacturing, processing, or holding active pharmaceutical ingredients" from March 1998) that was never finalized. The Q7A document reflects the overall direction taken by the ICH. We will discuss later in the article how this document relates to facilities design and qualification, and the changes that it is proposing to the steps used in implementating a new/modified facility for pharmaceutical production.

FDA Initiative on cGMP's for the 21st Century: A Risk-Based Approach

In discussing the harmonization of the globally regulated pharmaceutical industry and that effort that will affect our pharmaceutical facilities in the future, we need to address the FDA policies and their "Initiative for the Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach." As discussed previously, this initiative is already being implemented, and the FDA involvement with the ICH and their guidance documents is just the beginning of things to come.

The FDA initiative was launched in August 2002 to:

- Encourage new technology advances and ensure policies are based on state-of-the-art pharmaceutical science
- Facilitate industrial application of modern quality management techniques and base reviews and inspections on these requisites
- Institute a quality systems approach
- Encourage implementation of the risk-based approach

These objectives are directly related to ICH efforts and FDA involvement with that organization. The overall objective of the FDA, as a result of their role in ICH, is to develop an international plan for a harmonized pharmaceutical quality system. This will affect how we design and qualify facilities in our industry if we consider the effects of implementing the "quality systems" approach to inspections. The FDA has established a working group within the agency called the "CGMP Harmonization Analysis WG" to work in conjunction with the ICH, and provide a status report of the harmonization process by May 2004.

As part of its ICH participation, the FDA was involved in the development of the "Q7A – Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients." This guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000.

Effects on Facility and Utility Qualifications – Quality Systems Approach and ICH Q7A

The FDA's efforts to establish a quality systems approach for their inspections will have a major impact, resulting in increased focus on specific areas affecting our validation processes. *With relation to facility and utilities design and qualification, the following points must be noted:*

- **Design Qualification/Review** – is a basic component of the quality system regulation, and will be applied to pharmaceutical facilities in the future. It is not a "new" concept. Actually, it is a common sense thing to do. We need to ensure our design meets the requirements defined in our user/functional specifications. By design, we include documents such as design specifications, design detailed specifications, design drawings and all other documents related to the design of facility/utility systems.
- **Purchasing Controls** – Vendor/Contractor selection is "key" to an effective qualification/project implementation. Again, a common sense issue. The proper vendor selection can result in adequate design, construction, testing, and documentation of these steps, which will facilitate the implementation/qualification phase.
- **Monitoring and Control** – is the responsibility of the designer, construction manager, and plant engineer in charge of the project that all "agreed upon" design requirements are met during construction, start-up and commissioning.
- **Routine Monitoring after qualification** – is also critical to maintain the "validated status" of the system/facility.

Both the FDA implementation of the quality system approach and the new ICH Q7A guidance document for APIs indicate that the design process will have to be formalized. It also mandates that the review of the design meet the predefined specifications and be properly documented. This is directly stated in the ICH Q7A document when it refers to qualification of equipment and ancillary systems (facilities and utilities) as a four-step process: Design Qualification, Installation Qualification, Operational Qualification, and Performance Qualification.[3]

Typical Qualification Steps (3)	ICH Q7A Requirements (4)
Installation Qualification	Design Qualification or Review
Operational Qualification	Installation Qualification
Performance Qualification	Operational Qualification
	Performance Qualification

Design Qualification Review

We are familiar with the last three steps noted in the chart, however, design qualification is not a typical step in the pharmaceutical facilities/utilities arena. I use the term 'Design Review' more than 'Design Qualification,' since I feel that is a better description of the process – a review of design to meet the pre-established system/facility requirements. This process must be properly planned, executed,

and documented, and the quality organization must be involved in the review/approval of design documents. It is recommended for a new project/modified facility to develop a project plan to include the design review process and documentation. If there is a need for a reference, the industry can use 21 CFR 820 as a guide.

Going back to the FDA and their initiative, the recently revised draft guidance for aseptic processing includes some statements in the introduction that compares favorably with the overall effort to increase focus on design activities and documentation. *For example:*

- Goal – "…build quality into products using science-based facility, equipment, and systems design."
- "Ensure reliable and robust product protection through adequate design and control." (Refer to suggested reading: "*Guideline on Sterile Drug Products Produced by Aseptic Processing,*" FDA Draft Guidance Doc. from 8/22/03.)

The message is again clear with respect to the importance of the design phase during a project. Validation personnel have known this fact for a long time, but the rest of the operational departments in a pharmaceutical facility must now understand this concept and apply it, since it is becoming a requisite and is no longer just a "nice" idea.

Plan for Compliance

In order to organize our efforts to comply with current and upcoming regulatory requirements, the idea of preparing a master project plan (not to be confused with a Validation Master Plan) takes on more importance in the overall success of our projects.

- Audits of vendors and suppliers
  - Proactive review of turn-over packages/forms
- Develop Factory Acceptance Testing (FAT) protocol in agreement with supplier – if applicable.
- Master Project Plan to include (required by ISO-14644)
  - Basis of design – process/product
  - User/functional specifications
  - Definition of responsibilities
  - Scope of installation
  - Cost/time considerations
  - Quality plan to Include: (ISO-9000/9001)
    - Design review with pre-determined acceptance criteria
    - FAT/Site Acceptance Testing (SAT) Requirements
    - Start-Up and Commissioning
    - Qualification Requirements

Design Review and Qualification

The elements of a design review process include:

- Documented review and approval of drawings to meet specifications. For example, keep adequate meeting minutes – document agreements.
- Review performed at defined/periodic stages and at completion. The requirements will be pre-defined in the master project plan above.
- Design conforms to an agreed list of requirements – refer to ISO-14001/14004.
- User functional areas must be represented including the quality group.

Harmonization Challenges – Effects on Facilities with Classified Environments

One of the areas that is experiencing major changes with the new FDA Aseptic Draft Guidance and the EU Revision to their Annex I for Sterile Medicinal Products is the area of manufacturing of sterile/aseptically produced products and their environmental classifications for rooms/facilities in which these operations occur. There are still major inconsistencies between both agencies in their requirements, and our hope is that the harmonization effort will provide the method and forum to standardize these requirements, and make it easier for industry to comply.

ISPE Efforts

The International Society of Pharmaceutical Engineers (ISPE) is a separate institution that is also trying to develop global standards for the design and engineering of the facilities within the pharmaceutical industry. This organization is definitely becoming a globally-recognized leader in developing documents, references, and positions within our industry. Their Baseline Pharmaceutical Engineering Guides provide a good reference on how to design/construct/test/qualify new or modified facilities and utility systems for the pharmaceutical industry. These baseline guides are being referenced in global meetings and discussions, and they will also support the industry/regulatory agencies harmonization process.

Conclusion

In conclusion, the harmonization process is a fact! It is already having an effect on how we conduct facility and utility systems qualifications, and the process will continue. The qualification process for a facility/utility system will become a four-step process, including the Design Qualification/Review, IQ, OQ, and PQ. The industry must be aware of the existence of the ICH and ISO standards, and be up-to-date with their plans, meetings, and new/revised guides. The FDA is an integral part of the ICH group and the harmonization of standards is one of the major objectives of their 21st Century cGMP Initiative. ❑

About the Author

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Suggested Reading:

• "*Guideline on Sterile Drug Products Produced by Aseptic Processing*", FDA Draft Guidance Doc. from 8/22/03

• European Commission Annex 1, Manufacture of Sterile Medicinal Products – Revised on May 2003, effective Sept. 2003

• ISPE Baseline Pharmaceutical Engineering Guides

• FDA Second Progress Report and Implementation Plan issued on September 3, 2003 – Pharmaceutical cGMP's for the 21st Century: A Risk Based Approach

Article Acronym Listing

API:	Active Pharmaceutical Ingredients
CFR:	Code of Federal Regulations
cGMP:	current Good Manufacturing Practice
EWG:	Expert Working Groups
FAT:	Factory Acceptance Testing
FDA:	Food and Drug Administration
ICH:	International Conference on Harmonization
ISO:	The International Organization of Standardization
ISPE:	International Society of Pharmaceutical Engineers
OQ:	Operation Qualification
PQ:	Performance Qualification
SAT:	Site Acceptance Testing

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A Practical Approach to Validation of HPLC Methods Under Current Good Manufacturing Practices

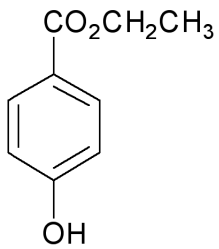
GHULAM A. SHABIR

Introduction

Analytical methods validation is an important regulatory requirement in pharmaceutical analysis. High-Performance Liquid Chromatography (HPLC) is commonly used as an analytical technique in developing and validating assay methods for drug products and drug substances. Method validation provides documented evidence, and a high degree of assurance, that an analytical method employed for a specific test, is suitable for its intended use. Over recent years, regulatory authorities have become increasingly aware of the necessity of ensuring that the data submitted to them in applications for marketing authorizations have been acquired using validated analytical methodology. The International Conference on Harmonization (ICH) has introduced guidelines for analytical methods validation.[1,2] The U.S. Food and Drug Administration (FDA) methods validation draft guidance document,[3-5] as well as United States Pharmacopoeia (USP)[6] both refer to ICH guidelines. These draft guidances define regulatory and alternative analytical procedures and stability-indicating assays. The FDA has proposed adding section CFR 211.222 on analytical methods validation to the current Good Manufacturing Practice (cGMP) regulations.[7] This would require pharmaceutical manufacturers to establish and document the accuracy, sensitivity, specificity, reproducibility, and any other attribute (e.g., system suitability, stability of solutions) necessary to validate test methods.

Figure 1

The chemical structure of ethyl 4-hydroxybenzoate.



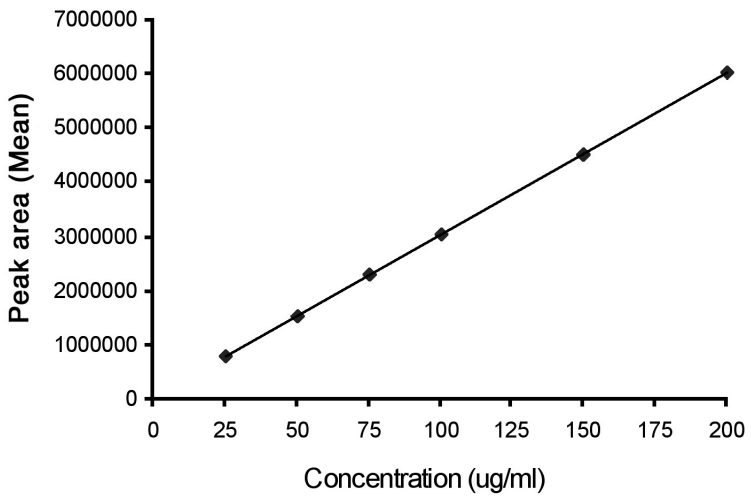
Regulatory analytical procedures are of two types: compendial and noncompendial. The noncompendial analytical procedures in the USP are those legally recognized as regulatory procedures under section 501(b) of the Federal Food, Drug and Cosmetic Act. When using USP analytical methods, the guidance recommends that information be provided for the following characteristics: specificity of the method, stability of the analytical sample solution, and intermediate precision. Compendial analytical methods may not be stability indicating, and this concern must be addressed when developing a drug product specification, because formulation based interference may not be considered in the monograph specifications. Additional analytical tests for impurities may be necessary to support the quality of the drug substance or drug product. Noncompendial analytical methods must be fully validated. The most widely applied validation characteristics are accuracy, precision (repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity, range, and stability of analytical solutions.

The parameters that require validation and the approach adopted for each particular case are dependent on the type and applications of the method. Before undertaking the task of method validation, it is necessary that the analytical system itself is adequately designed, maintained, calibrated, and validated.[8] The first step in method validation is to prepare a protocol, preferably written with the instructions in a clear step-by-step format. This

approach has been reported previously.[8] In this paper, it is intended to review and demonstrate practical approaches to analytical method validation in detail with reference to an HPLC assay of ethyl 4-hydroxybenzoate *(Figure 1)*. Ethyl 4-hydroxybenzoate alone or in combination with other esters of p-hydroxybenzoic acid, or with other antimicrobial agents, is used as a preservative in pharmaceutical formulations.

Figure 2

Graph measured peak area versus ethyl 4-hydroxybenzoate concentration demonstrating linearity.



Experimental

✔ Chemicals and reagents.

All chemicals and reagents were of the highest purity. HPLC-grade acetonitrile was obtained from Merck (Darmstadt, Germany). Water was purified with a Millipore Milli-Q system (Watford, UK). Ethyl 4-hydroxybenzoate (Batch #1005425) was supplied by Lancaster Synthesis (Morecambe, England).

✔ HPLC instrumentation.

The HPLC system used for the validation studies consisted of a Waters Alliance 2690 Separations Module to a 996 photodiode-array (PDA) detector. The control of the HPLC system and data collection was by a Compaq computer equipped with Waters® Millennium32 software (version 3.20). The second HPLC system used for intermediate precision studies consisted of Perkin Elmer: model series 200 UV visible detector, series 200 LC pump, series 200 autosampler, and a series 200 peltier LC column oven were used to chromatograph the solutions. The data was acquired via PE TotalChrom Workstation data acquisition software, (Version 6.2.0) using PE Nelson series 600 LINK interfaces. Both HPLC systems including software (Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11) were validated prior to use for the test method validation.

All chromatographic experiments were performed in the isocratic mode. A C^{18} symmetry analytical column from Waters (located in Milford, MA, United States) 3.9 x 150 mm, 5 mm particle size was used. The mobile phase consisted of a mixture of acetonitrile, water solution (65:35, v/v). The flow rate was set to 1.0 ml/min, and the oven temperature to 25˚C. The injection volume was 20 µl, and the detection wavelength was set at 254nm.

✔ Preparation of mobile phase.

The mobile phase was prepared by adding 650 ml of HPLC-grade acetonitrile in 1000 ml of water (65:35, v/v). The mobile phase was filtered under a vacuum through 0.45 mm nylon filters and degassed before use. Also, the mobile phase continuously was degassed with an on-line degasser.

✔ Preparation of standard and sample solutions.

Ethyl 4-hydroxybenzoate (100 mg) was weighed accurately and added to a 100 ml volumetric flask before being dissolved in acetonitrile. A 2.0 ml aliquot of stock solution was diluted to 100 ml in the mobile phase, yielding a final concentration of 20 µg/ml. Standard solutions for the evaluation of ethyl 4-hydroxybenzoate linearity were prepared over a concentration range of 5.0-40 µg/ml, to 25, 50, 75, 100, 150, and 200% in the mobile phase.

Results and Discussion

✔ Validation of the chromatographic method: Linearity and range

The linearity of the method should be tested in order to demonstrate a proportional relationship of response versus analyte concentration over the working range. The linearity range for evaluation depends on the purpose of the analytical test method. The ICH guidelines specified a minimum of five concentration levels, along with certain minimum spec-

Figure 3

Results of assessment of the linearity of the HPLC method for the assay of ethyl 4-hydroxybenzoate employing the analytical working standard dissolved in mobile phase

Concentration (µg/ml)	Concentration as percent of 20 µg/ml	EP peak area as mean of 3 injections	Peak area RSD (%)
5	25	792862	0.13
10	50	1535889	0.16
15	75	2308902	0.21
20	100	3057149	0.13
30	150	4546415	0.10
40	200	6027790	0.25
Correlation coefficient: r^2 = 1.000; Equation for regression line: y = 29935x + 51338 (n = 3)			

Figure 4

Accuracy/recovery of ethyl 4-hydroxybenzoate from samples with known concentration

Sample number	Percent of nominal	Recovery (%) (n = 3)	RSD (%) of area response factor
1	50	99.67	0.16
2	75	99.78	0.21
3	100	99.85	0.13
4	150	99.87	0.10
Mean recovery: 99.8%; RSD 0.09%			

ified ranges. For assay, the minimum specified range is from 80-120% of the target concentration. For an impurity test, the minimum range is from the reporting level of each impurity to 120% of the specification. Acceptability of linearity data is often judged by examining the correlation coefficient and y-intercept of the linear regression line for the response versus concentration plot. The regression coefficient (r^2) is > 0.998 is generally considered as evidence of acceptable fit of the data to the regression line. The y-intercept should be less than a few percent of the response obtained for the analyte at the target level. The Percent Relative Standard Deviation (RSD), intercept, and slope should be calculated. In the present study, linearity was studied in the concentration range 5.0-40 µg/ml (25-200% of nominal concentration, n = 3) and the following regression equation was found by plotting the peak area (y) versus the ethyl 4-hydroxybenzoate concentration (x) expressed in µg/ml: y = 29935x + 51338 (r^2 = 1.000). The demonstration coefficient (r^2) obtained for the regression line demonstrates the excellent relationship between peak area and concentration of ethyl 4-hydroxybenzoate *(Figure 2)*. The data obtained from linearity experiments are presented in *Figure 3*. The range is derived from linearity studies, and depends on the intended application of the test method. It is established by confirming that the assay procedure provides an acceptable degree of linearity, accuracy, and precision when applied to samples containing amounts of analyte within, or at the extremes of the specified range, of the test method. The range is normally expressed in the same units as the test results obtained by the method. In this study, the data obtained during the linearity and accuracy studies was used to assess the range of the assay method. The precision data for this assessment was the precision of the three replicate samples analyzed at each level in the accuracy studies. The valid analytical range of the method is that range of concentrations, which pass the linearity and accuracy criteria, and yields an RSD of < 2%. The linearity data described earlier demonstrates acceptable linearity for ethyl 4-hydroxybenzoate over the range of 80 to 120% of the target concentration. The RSD values obtained for the recovery of ethyl 4-hydroxybenzoate at 50, 75, 100, and 150% of target are 0.16, 0.21, 0.13, and 0.10%, respectively. Each value was the result of three individual sample preparations and analysis. These data support a method range of 80 to 120% of the target concentration.

Accuracy/recovery studies

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value.[6] Accuracy is usually determined in one of four ways. First, accuracy can be assessed by analyzing a sample of known concentration (reference materials), and comparing the measured value to the true value. The second approach is to compare test results from the new method with results from an

Method validation provides documented evidence, and a high degree of assurance, that an analytical method employed for a specific test, is suitable for its intended use.

existing alternate well-characterized procedure that is known to be accurate. The third approach is based on the recovery of known amounts of analyte. This is performed by spiking analyte in blank matrices. For assay methods, spiked samples are prepared in triplicate at three levels over a range of 50-150% of the target concentration. The percent recovery should then be calculated. The fourth approach is the technique of standard additions, which can also be used to determine recovery of spiked analyte. This approach is used if it is not possible to prepare a blank sample matrix without the presence of the analyte. Accuracy criteria for an assay method (FDA) is that the mean recovery will be 100 ± 2% at each concentration over the range of 80-120% of the target concentration. The ICH[2] recommends collecting data from a minimum of nine determinations over a minimum of three concentration levels covering the specified range (e.g., three concentrations, three replicates each).

In the present study, a number of different solutions were prepared with known added amounts of ethyl 4-hydroxybenzoate and injected in triplicate. Percent recoveries of response factor (area/concentration) were calculated. The results of accuracy studies are shown in *Figure 4*, and it is evident that the method is accurate within the desired recovery range.

Specificity of the Assay and Degradation of Active Constituent

In order to design a chromatographic system for the analysis of an active component of a pharmaceutical product, it is essential to have a good knowledge of; (1) susceptibility of the drug to degradation and its degradation pathway; (2) assay interference by possible degradants or synthesis precursors; and (3) assay interference by chemicals employed in sample preparation and excipients in the formulation.

Degradation products may be formed by acid/base hydrolysis, oxidation, Ultraviolet (UV) irradiation, heat, light, etc., however, it is not within the scope of this paper to discuss in detail the elucidation of degradation pathways.

In the present study, initially, a reference standard of

Figure 5

HPLC chromatogram of ethyl 4-hydroxybenzoate.

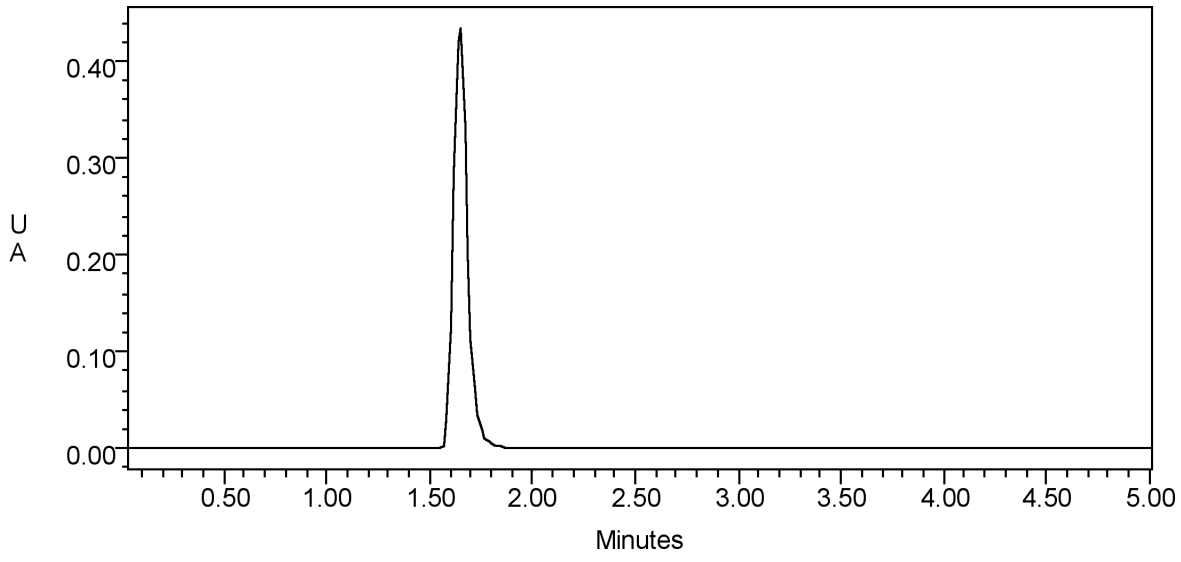
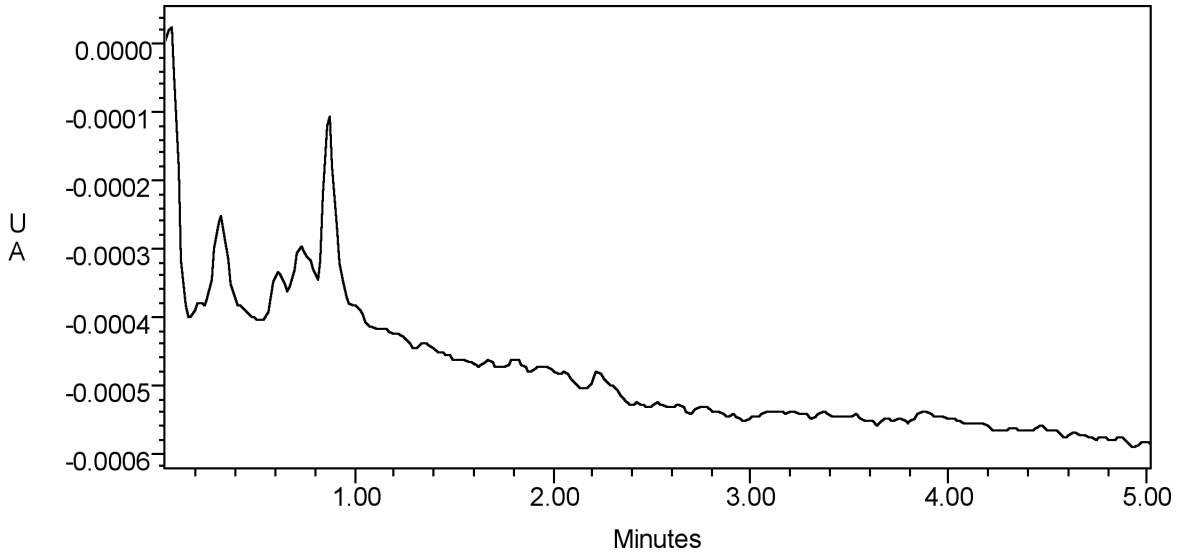


Figure 6

HPLC chromatogram for placebo. The analyte peak was eluted at 1.58 minutes.



ethyl 4-hydroxybenzoate was chromatographed. *Figure 5* clearly demonstrates that ethyl 4-hydroxybenzoate is well separated from any potential interference. Assay interference was investigated by injecting placebo. No interfering peaks *(Figure 6)* were observed. Therefore, this method was specific for ethyl 4-hydroxybenzoate.

Precision

Precision is the measure of the degree of repeatability of an analytical method under normal operation, and is normally expressed as the percent relative standard deviation for a statistically significant number of samples. Precision may be performed at three different levels: repeatability, intermediate precision, and reproducibility.

Figure 7

Demonstration of the repeatability of the HPLC assay for ethyl 4-hydroxybenzoate as shown by the results of 10 replicate injections of one solution at 100 percent of the test (20 mg/ml) concentration

Injection number	RT (min)	Peak height (µV)	Peak area (µV s)
1	1.57	855847	3109735
2	1.58	858249	3100787
3	1.58	854532	3099540
4	1.58	856705	3103544
5	1.57	857058	3101464
6	1.57	854755	3099731
7	1.57	855098	3102575
8	1.58	854078	3103159
9	1.58	856416	3104217
10	1.58	849916	3091891
Mean	1.58	855265	3101665
RSD (%)	0.18	0.25	0.14

Repeatability

Repeatability (intra-day assay precision) is the results of the method operating over a short time interval under the same conditions (intra-assay precision). It should be determined from a minimum of nine determinations covering the specified range of the procedure (for example, three levels, three repetitions each), or from a minimum of six determinations at 100% of the test or target concentration. A precision criterion for an assay method is that the instrument precision (RSD) will be ≤1%, and for the impurity assay, at the limit of quantitation, the instrument precision (repeatability) will be ≤ 5%. Documentation in support of precision studies should include the standard deviation, relative standard devi-

Figure 8

Demonstration of the intermediate precision of the HPLC assay for ethyl 4-hydroxybenzoate results in relative percent purity area

	HPLC system 1			HPLC system 2		
Sample	S1 (50%)	S2 (100%)	S3 (150%)	S1 (50%)	S2 (100%)	S3 (150%)
Operator 1, day 1	99.83	99.79	99.76	99.76	99.83	99.83
Operator 1, day 2	99.76	99.74	99.74	99.82	99.80	99.78
Operator 2, day 1	99.71	99.76	99.77	99.75	99.76	99.69
Operator 2, day 2	99.53	99.62	99.57	99.79	99.81	99.82
Mean (HPLC systems)	99.71	99.73	99.71	99.78	99.80	99.78
Mean (Operators)	99.79	99.79	99.78	99.70	99.74	99.71
RSD (criteria ≤ 2%)	S1+S1	S2+S2	S3+S3			
HPLC systems	0.05	0.05	0.05			
Operators	0.06	0.04	0.05			

ation, coefficient of variation, and confidence interval. In this study, precision of the method was evaluated through the repeatability of the method (intra-assay precision) by assaying ten replicate injections of ethyl 4-hydroxybenzoate at the same concentration (20 μg/ml), during the same day, under the same experimental conditions. The RSD values of the retention time, area, and height of ethyl 4-hydroxybenzoate peak were found to be < 0.3%, as presented in *Figure 7*.

Intermediate Precision

Intermediate precision (inter-day variation) is the results from within lab variations, due to random events, such as different days, analysts, equipment, etc. In determining intermediate precision, experimental design should be employed, so that the effects (if any) of the individual variables can be monitored. Precision criteria for an assay method is that the intra-assay precision will be ≤ 2%, and for impurity assay, at the limit of quantitation, the instrument precision will be ≤ 5%, and the intra-assay precision will be ≤10%. In this study, intermediate precision (within-laboratory variation) was demonstrated by two operators, using two HPLC systems, and evaluating the relative percent purity data across the two HPLC systems at three concentration levels (50%, 100%, 150%) that cover the ethyl 4-hydroxybenzoate assay method range (5.0-40 μg/ml). The mean and RSD across the systems and analysts were calculated from the individual relative percent purity mean values at 50, 100, and 150% of the test concentration. The RSD values presented in *Figure 8* were less than 1% for both systems and operators, and illustrated the good precision of the analytical method.

Reproducibility

Reproducibility[1] is determined by testing homogeneous samples in multiple laboratories, often as part of inter-laboratory crossover studies. An example of reproducibility criteria for an assay method could be that the assay results obtained in multiple laboratories will be statistically equivalent, or the mean results will be within 2% of the value obtained by the primary testing lab. For an impurity method, results obtained in multiple laboratories will be statistically equivalent, or the mean results will be within 10% (relative) of the value obtained by the primary testing lab for impurities. Reproducibility is not normally expected if intermediate precision is performed.

Limit of Detection and Quantitation

The Limit of Detection (LOD) and Limit of Quantitation (LOQ) tests for the procedure are performed on samples containing very low concentrations of analyte. LOD is defined as the lowest amount of analyte that can be detected above baseline noise; typically, three times the noise level.

Figure 9

HPLC chromatogram for limit of detection (2 ng/ml)

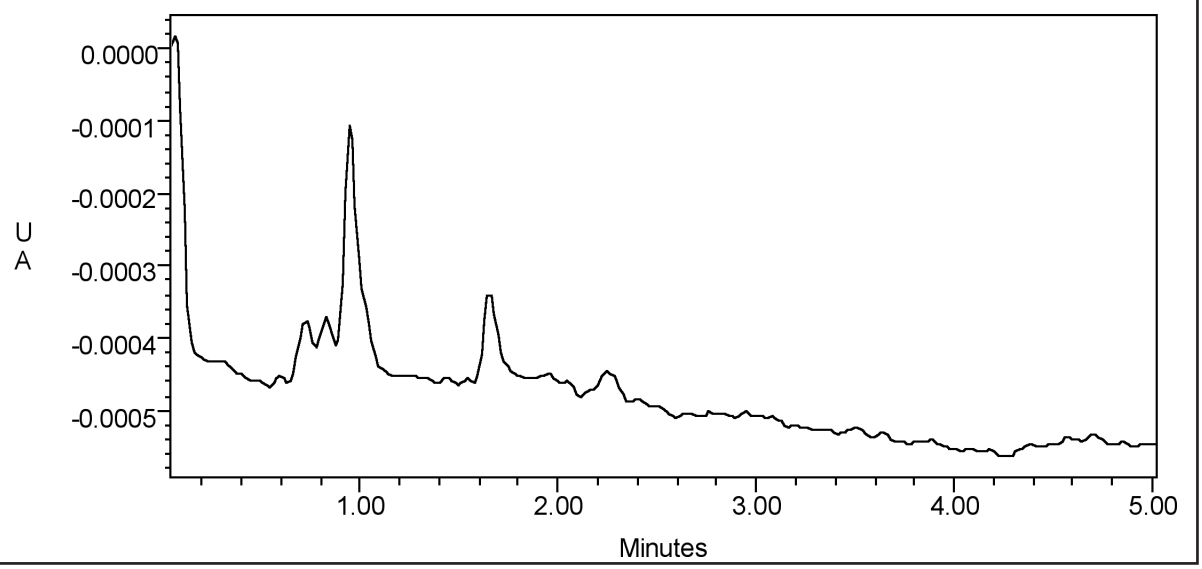


Figure 10

HPLC chromatogram for limit of quantitation (5 ng/ml).

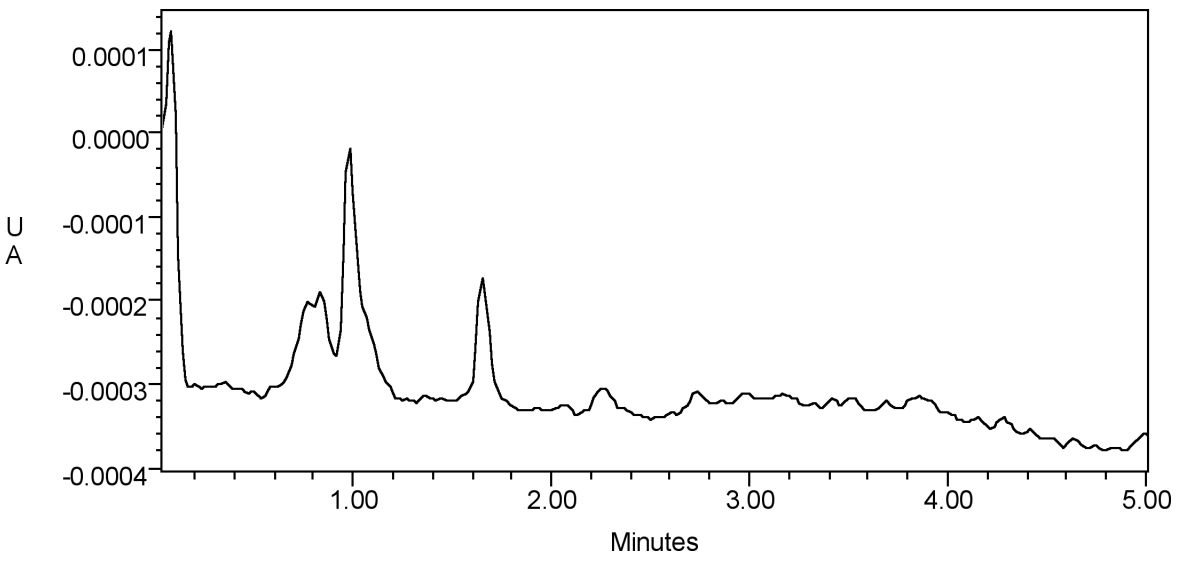


Figure 11

Stability of ethyl 4-hydroxybenzoate in solution (n = 6)

Time (hour)	RT (min)	Peak area RSD (%)	Peak Height RSD (%)	Percent recovery	Percent of initial
0	0.14	0.70	0.80	99.88	
24	0.18	0.15	0.27	99.82	
48	0.29	0.30	0.51	99.78	99.35

Figure 12

Demonstration of the system suitability of the HPLC assay for ethyl 4-hydroxybenzoate

System Suitability Parameter	Acceptance Criteria	Results	
		HPLC system 1	**HPLC system 2**
Injection precision for area (n = 10)	RSD ≤ 1%	0.15	0.11
Injection precision for retention time (min)	RSD ≤ 1%	0.18	0.11
USP tailing (T) for ethyl 4-hydroxybenzoate peak	T ≤ 2	1.05	1.03
Theoretical plates (N) for ethyl 4-hydroxybenzoate peak	N = > 2000	5276	6628

LOQ is defined as the lowest amount of analyte which can be reproducibly quantitated above the baseline noise, that gives S/N = 10.

In this study, LOD for a 20 µl injection of ethyl 4-hydroxybenzoate standard (signal to noise = 3) was 2.0 ηg/ml *(Figure 9),* and the LOQ (signal to noise = 10) was 5 ηg/ml *(Figure 10)* and RSD < 2% (n = 6).

Stability of Analytical Solutions

Samples and standards should be tested over at least a 48 hour period (depends on intended use), and quantitation of components should be determined by comparison to freshly prepared standards. A stability criterion for assay methods is that sample and standard solutions and the mobile phase will be stable for 48 hours under defined storage conditions. Stability is considered to be acceptable when the change in the standard or sample response is within 2% relative to freshly prepared standards. In this study, the stability of ethyl 4-hydroxybenzoate solutions was investigated. Therefore, test solutions of ethyl 4-hydroxybenzoate were prepared using the conditions cited in Section 2.4. They were chromatographed at the beginning, and after 24 and 48 hours. The stability of ethyl 4-hydroxybenzoate and the mobile phase were calculated by comparing area response and area percent of two standards at 20 µg/ml over time. Standard solutions stored in a capped volumetric flask on a laboratory bench under normal lighting conditions for 48 hours, and were shown to be stable with no significant change in ethyl 4-hydroxybenzoate concentrations over this period *(Figure 11)*. This is indicated by <1% changes in area between T = 0 hours and T = 48 hours. Based on these data that show quantitative recovery through 48 hours, ethyl 4-hydroxybenzoate solutions can be assayed within 48 hours of preparation.

System Suitability

System suitability tests are an integral part of HPLC methods, and are used to verify that the accuracy and precision of the system are adequate for the analysis to be performed.

Parameters, such as plate count, tailing factor, resolution, and repeatability (RSD of retention time and area for six repetitions) are determined and compared against the specifications set for the method. The parameter to be measured and their recommended limits[4,9] obtained from the analysis of the system suitability sample are shown in *Figure 8*. In the present study, the system suitability test was performed on both HPLC systems to determine the accuracy and precision of the system, by injecting ten injections of a solution containing 20 µg/ml of ethyl 4-hydroxybenzoate. RSD for peak area and retention time < 1%, tailing factor (T) < 2 and theoretical plate (N) were > 5000 for both HPLC systems, as can be seen in *Figure 12*.

Conclusion

It is clear from the various guidelines issued by regulatory authorities that analytical methodology should be thoroughly validated under Current Good Manufacturing Practice (cGMP). HPLC assay of active ingredients in pharmaceutical products, and subsequent method validation, can be complex and time-consuming. However, a well-defined protocol and documented validation plan simplifies and shortens the process, while also providing regulatory agencies with evidence that the analytical system and method is suitable for its intended use. This paper is intended to provide guidance on how to perform method validation for HPLC that generates both useful and meaningful data that meets all FDA, USP, and ICH validation requirements for pharmaceutical analysis. ❑

Article Acronym Listing

CFR:	Code of Federal Regulations
cGMP:	current Good Manufacturing Practice
FDA:	Food and Drug Administration
HPLC:	High Performance Liquid Chromatography
ICH:	International Conference on Harmonization
LOD:	Limit of Detection
LOQ:	Limit of Quantitation
PDA:	Photodiode Array
RSD:	Relative Standard Deviation
USP:	United States Pharmacopoeia
UV:	Ultra Violet

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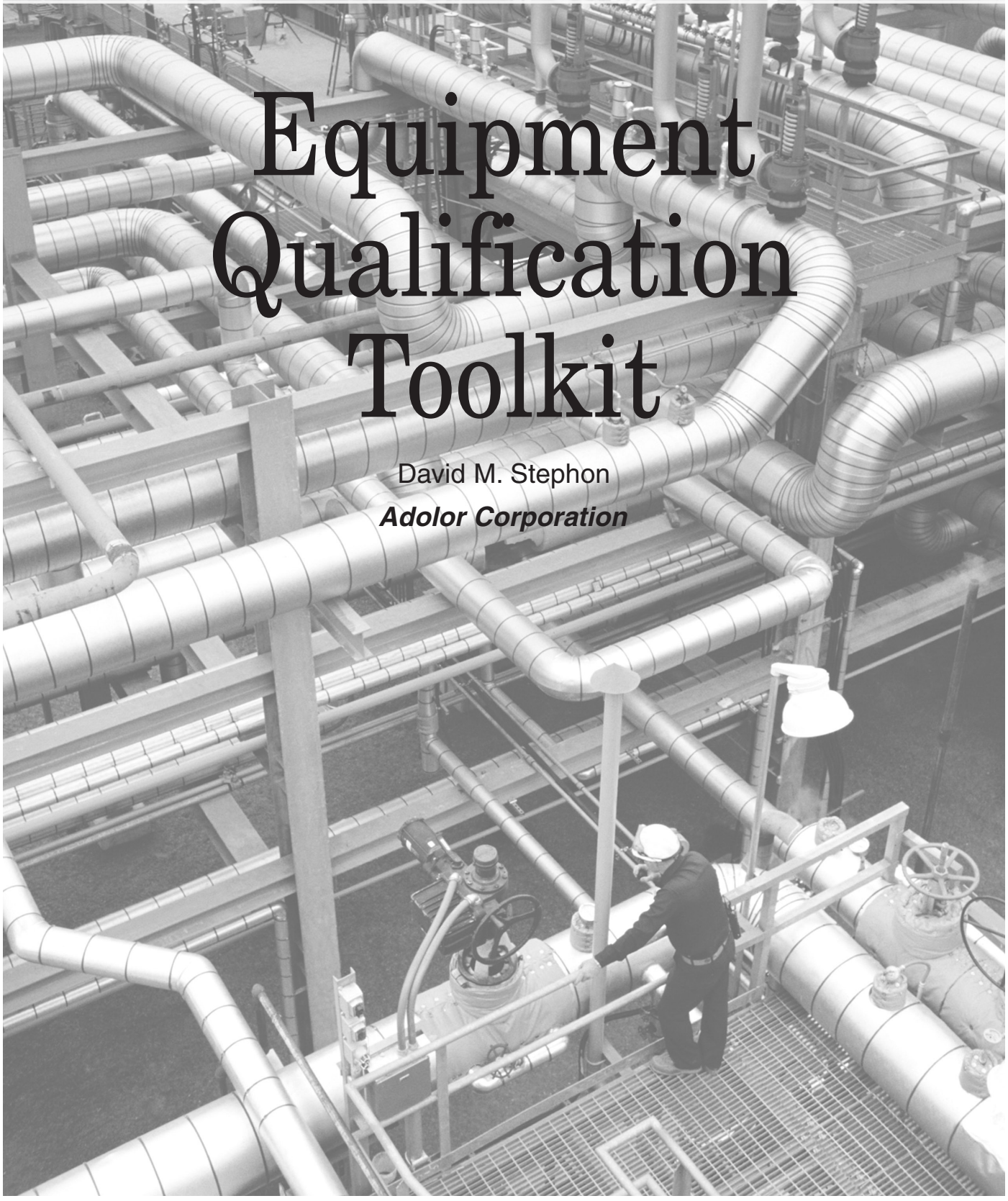

Equipment Qualification Toolkit

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In recent years, the pharmaceutical industry has come under an increasing amount of scrutiny by the Food and Drug Administration (FDA) for a variety of regulatory compliance issues. Daily headlines in the healthcare industry trade press have repetitively discussed compliance issues with regularity. The pharmaceutical industry's response to these challenges has been to take a positive approach in order to provide education, information, and communication on these issues, rather than counterattacks towards the regulatory agencies, including the FDA, that have cited these deficiencies. This educational approach probably can be attributed to lessons learned within the industry regarding regulatory compliance.

"Throughout the regulated pharmaceutical industry, it has been recognized that equipment qualification is a prerequisite to any validation activity."

The manufacture of pharmaceutical products, biologics and medical devices are regulated by Good Manufacturing Practice (GMP) regulations. GMP ensures that consumer products are both safe and effective, and includes many requirements for the drug or medical device manufacturer to follow, including testing of raw materials, manufacturing controls, documentation requirements, handling of deviations, laboratory controls, and personnel training.

Another aspect of GMP regulations is the requirement to use equipment that has been demonstrated to be suitable for its intended function. The suitability of the equipment used to manufacture, package, label, and test drugs and medical devices has a direct effect on the quality of the product. Compliance with FDA requirements related to equipment suitability or "qualification" can result in greater control and assurance that products are both safe and effective.

For years, equipment qualification and validation were areas that were addressed, if at all, only after equipment was designed, purchased, and installed. Manufacturers viewed the generation, execution, and detail of this documentation as an afterthought. In recent years, FDA and other regulatory agencies have focused on compliance data and documentation. This, in turn, resulted in a movement in the pharmaceutical industry to start conducting self-assessments and internal audits in order to evaluate firsthand the firm's compliance status on an ongoing basis. The results of these self assessments allowed pharmaceutical manufacturers to develop proficient skills in the areas of qualification and validation. This increased knowledge in the rationale behind compliance emerged as a conduit for the integration of validation and equipment qualification requirements into the total project process. This integration of the compliance and business requirements has served to provide manufacturing, processing, and laboratory equipment better suited for its intended use.

Throughout the regulated pharmaceutical industry, it has been recognized that equipment qualification is a prerequisite to any validation activity. While the terms "qualification" and "validation" have been used interchangeably to have the same meaning, it is read-

ily recognized under current compliance trends that the term "validation" refers to activities that are consistent with the FDA's definition of "establishing, through 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." This definition of validation has been appropriately applied to other activities, such as analytical control methods, process, cleaning, and software systems.

Qualification is the action of proving that any equipment works correctly and leads to expected results. The term "validation" is sometimes broadened to incorporate the concept of qualification. The term "qualification" is also applied to other GMP-related activities, such as utility qualification, water, and Heating Ventilation and Air Conditioning (HVAC) systems, as well as facility and employee qualification. When the concept of validation is extended to equipment used for manufacturing, packaging, labeling, or control testing, validation means qualifying (or verifying) that the equipment consistently functions within a specified range of operations.

Equipment used in the pharmaceutical, biological, or medical device industries, whether it be for manufacturing, processing, labeling, packaging, or laboratory control testing, is required to be qualified for use. The same principles and definition of validation, as stated above, apply to equipment qualification. Only now we are demonstrating the suitability of a "component or validation," in the same way, for example, as we use "qualified" or trained personnel as a prerequisite to perform any validation or other GMP-related activity. Properly installing equipment and verifying its performance for its intended use is a pre-validation activity in demonstrating that a manufacturing process, packaging operation, or quality control test method performs reliably and consistently. Equipment qualification incorporates extensive testing, verification, and documentation to establish that equipment meets minimum requirements and functions as desired. Qualification is required to not only provide assurance of the current state of control, but must also substantiate the existence of procedures and practice that maintain the equipment in continuous working order. ❑

EQUIPMENT QUALIFICATION TOOLKIT

Terminology

Audit: *Systematic and independent examination to determine whether quality activities and related results comply with planned arrangements, and whether these arrangements are implemented effectively, and are suitable to achieve objectives.*

Calibration: *The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, and the corresponding known values of the measurand.*

Corrective Action: *Short-term action taken to eliminate the causes of an existing nonconformity, defect, or other undesirable situation in order to prevent recurrence.*

Defect: *Non-fulfillment of an intended usage requirement or reasonable expectation, including one concerned with safety.*

Design Review: *Documented, comprehensive, and systematic examination of a design to evaluate its capability to fulfill the requirements for quality, identify problems, and propose the development of solutions.*

Equipment Design Qualification: *The initial phase of qualification in which specifications and requirements are developed and established.*

Equipment Installation Qualification: *Documented verification that determines whether all necessary equipment components were delivered and correctly*

connected, and installed in an environment suitable for required operation based on the manufacturer's requirements (e.g., voltage, frequency, temperature, humidity, space, etc.)

Equipment Operational Qualification: *Documented verification which determines that equipment performs as expected throughout its entire operating range.*

Equipment Performance Qualification: *Documented verification that determines that the equipment performs as expected during routine use, under both routine and unusual conditions.*

Equipment Qualification: *The practice of establishing that equipment operates as it was designed for its intended use in a reproducible manner.*

Factory Acceptance Testing (FAT): *Pre-delivery equipment testing designed to establish confidence that the equipment and ancillary systems will meet functional requirements, and is capable of consistent operation. FAT is performed at the supplier site, and the results are used to release the equipment for shipment.*

Good Manufacturing Practice (GMP): *Regulations that must be followed for the manufacture, processing, packing, or holding of a drug product. GMP practice include Title 21 Code of Federal Regulations (CFR), Parts 210-211, and European Community (EC) Directive 91/356/EEC for products destined for the U.S. or EC, respectively.*

Grade: *Category or rank given to entities having the same functional use, but different requirements for quality.*

Inspection: *Activity, such as measuring, examining, testing, or gauging one or more characteristics of an entity, and comparing the results with specified requirements in order to establish whether conformity is achieved for each characteristic.*

Preventative Action: *Long-term action taken to eliminate the cause(s) of a potential nonconformity, defect, or other undesirable situation in order to prevent recurrence.*

Preventative Maintenance: *A maintenance system designed to detect and prevent problems before they occur.*

Qualification Protocol: *A written procedure that states how qualification testing will be conducted, including test parameters and acceptance criteria.*

Quality: *The total characteristics of an entity that bear on its ability to satisfy stated and implied needs.*

Safety: *State in which the risk of harm or damage is limited to an acceptable level.*

Standard Operating Procedure (SOP): *A document that describes how to perform an operation or task. SOPs contain step-by-step instructions of how an operation or task is carried out in order to complete the operation or task reliably and consistently.*

Supplier*: Organization that provides a product or service to the customer. Also referred to as a vendor.*

Validation*: Established 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.*

Verification: *The process of evaluating the products of a given phase to ensure correctness and consistency with respect to products and standards provided as input to that phase.* ❑

Regulatory Interpretation

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The regulatory compliance expectation for equipment qualification has its origins in the Good Manufacturing Practice (GMP) regulations under several sections of the Current Good Manufacturing Practice (cGMP) for the Manufacture, Processing, Packing or Holding of Drugs. Most notably under subparts D for Equipment, but also under Section 21 Code of Federal Regulations (CFR) 211.160(b)(4) under Subpart I, Laboratory Controls. While the word "qualification" is not specifically mentioned in 21 CFR 211, the interpretation of these regulations through the years by both industry and regulatory agencies, such as the Food and Drug Administration (FDA), has allowed terms like Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) to evolve. Consequently, other terms were added to this growing list of terms and nomenclature, most notably acronyms, such as Factory Acceptance Criteria (FAT), Site Acceptance Criteria (SAT) and Design Qualification (DQ).

"FDA field investigators are trained to ask questions on the suitability of equipment used to manufacture and test pharmaceuticals."

As with any compliance topic, regulatory agency interpretation of current expectations also plays a role in the development of knowledge for the pharmaceutical industry, which is geared to be proactive in minimizing compliance issues. For example, a typical FDA inspectional observation FD-483 reads:

"…Failure to assure automatic, mechanical, electronic, or other equipment used in the manufacture, processing, packing and holding of a drug product, performs or functions satisfactorily. Specifically, your firm failed to perform Installation Qualification, Operational Qualification or Performance Qualification studies on any equipment used in the manufacture of your drug products…" (FDA Warning Letter [WL-5-8], Nov 18, 1997).

This FDA-483 refers to a specific 21 CFR 211 GMP requirement; in this case 21 CFR 211.68(a) under Subpart D, Equipment. Here, the FDA investigator has provided a prime example of the Agency's current expectation for a manufacturer to have IQ, OQ and PQ for manufacturing equipment.

While the two terms are related, and often used interchangeably, it is readily recognized by today's performance standards, that the terms "validation" and "qualification" have different meanings. The term "validation" has the distinct advantage of being around much longer in the pharmaceutical industry than qualification. Historically, validation was defined in the now infamous May, 1987 FDA Guideline *General Principles of Process Validation*.[1] This document defines validation as it is still applied to as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." Qualification is often referred to as a condition or state of control that must be met in order to assure the validity and reliability of test results. Therefore, it is best to refer to qualification as a precursor to validation in the broadest of terminology. Thus, processes and systems are validated using qualified personnel and qualified equipment.

Manufacturing and processing equipment is likely

to have a vital and critical impact on the quality of the product, and even small differences between equipment operational capability can potentially have a large effect upon a process. Often, the nature of such an effect will not be noticed until well into the process, where it could conceivably be difficult to detect. Proper qualification of manufacturing equipment establishes the reliability of the operation, and the output of the equipment. Analytical equipment, on the other hand, while being very important to establishing the quality of the product, has a defined and measurable output that can be readily evaluated.

The regulatory expectation for equipment qualification is further exemplified in the *Current Good Manufacturing Practice for Finished Pharmaceuticals* under Subpart D, Equipment. Under 21 CFR 211.65(a) it states:

> *Equipment shall be constructed so that surfaces that contact products shall not be reactive, additive or absorptive so as to affect the safety or quality profiles of drug products.*

The intent of this section is to promote the use of inert materials during equipment fabrication that is intended for pharmaceutical manufacturing. To accomplish this, product contact surfaces for equipment are usually fabricated from high grades of stainless steel, such as 316L and 304. In addition, equipment fabricators would want to incorporate certain tests at their site, for example, that would allow determination of surface finish, and quantitation of residual iron contaminants on the surface, in addition to other process quality control tests. These test results are later challenged under the pharmaceutical manufacturer's FAT at the equipment fabricator, prior to shipping the equipment to the manufacturing site.

In addition to the current cGMP requirements for Finished Drug Products, the May 1996 *Current Good Manufacturing Practices; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals*, also state the requirement for equipment qualification:

> *"A written plan describing the process to be validated, including production equipment, and how validation will be conducted, including objective test parameters, product and/or process characteristics, predetermined specifications, and factors which will determine acceptable results."*
>
> *"The manufacturer's determination of equipment suitability shall include testing to verify that the equipment is capable of operating satisfactorily within operating limits required by the process."*

If your company has experienced an FDA inspection, the FDA field investigator probably asked questions about your company's equipment procedures. FDA field investigators are trained to ask questions on the suitability of equipment used to manufacture and test pharmaceuticals. For example, the *FDA Compliance Program/Pre-Approval Inspections Compliance Policy Guide* (CPG) 7346.832 states:[2]

> *"The field investigator will be responsible for determining the adequacy of the facility, personnel and equipment qualification information as part of the cGMP inspection of the particular facility."*

These GMP regulations and regulatory interpretations form the basis for FDA expectations that manufacturing, packaging, and labeling equipment be qualified and demonstrated suitable for their intended use. In addition, laboratory equipment must also be demonstrated as being suitably qualified for use. In response to this, laboratory, as well as manufacturing equipment vendors in the last ten to fifteen years, have responded to FDA and other regulatory agencies for industry requirements and regulatory expectations for equipment qualification, by providing qualification services and/or executable qualification protocols as part of their equipment sales and installation package. ❑

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Equipment Qualification: *Getting Started*

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There are three (3) primary levels of qualification which apply to equipment qualification. These include Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). These equipment qualification "steps" are commonly referred to as their respective acronyms IQ, OQ, and PQ. There are other qualification steps that are also used, for example, Design Qualification (DQ) and Maintenance Qualification (MQ). These latter qualification definitions, DQ and MQ, while used in industry, really are backwards and forward extensions, respectively, of the common three (3) qualification category types. There is also a category collectively referred to as "legacy qualification," used to qualify existing equipment that was previously in your facility prior to your firm's equipment qualification initiative.

"It is important to understand compliance requirements when sourcing equipment."

Typically, the first step in developing a procurement methodology for the acquisition of equipment and qualification, especially custom equipment, is the development of user requirements. The user requirements allow creation of a Request For Proposal (RFP) to prospective equipment vendors. As part of the selection process, an assessment of the equipment vendor may be performed. Assessments of the vendor by the pharmaceutical manufacturer usually include teams of engineers, manufacturing, and quality staff. Such assessments often allow the pharmaceutical manufacturer to determine if the equipment fabricator has a suitable quality system in place, has experience in providing equipment to the pharmaceutical industry, and understands documentation requirements. In sequence, the equipment is selected, specified, and designed as appropriate for the intended application, then the equipment is bid, purchased, and fabricated, followed by delivery and installation.

It is important to understand compliance requirements when sourcing equipment. Equipment specification and design can vary greatly between cGMP and non-cGMP equipment. Equipment used in pharmaceutical manufacturing must meet all GMP requirements as specified under 21 CFR 211, current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals. The specific section is listed under SubPart D, Equipment, under Section 21 Code of Federal Regulations (CFR) 211.63, 211.65, and 211.67. These regulations detail equipment requirements. The pharmaceutical industry has interpreted these regulations so that performance standards can be defined for equipment fabrication methods, materials of construction, surface finishes, and controls. However, documentation requirements often cause confusion between the pharmaceutical manufacturer and the equipment fabricator.

While equipment fabricators will supply a general set of documents, such as fabrication drawings, material lists, parts lists, and Standard Operating Procedures (SOPs), normally more detailed procedures are required by the pharmaceutical manufacturer's engineering department. This includes more detailed documentation, such as instrumentation loop drawings, software coding, logic diagrams, calculations, and welding cer-

tifications. In some cases, the equipment is shipped and installed at the pharmaceutical manufacturer without requesting the required documentation upfront. This can interfere with the proper execution of the equipment qualification by the pharmaceutical manufacturer after delivery and installation. This is where a well-designed RFP or equivalent document can often help. Rather than request the equipment vendor to provide the required documentation after the placement of an order, or after delivery of the equipment, exact documentation requirements are determined prior to placing the order and incorporated into the specifications. While this is time consuming, equipment requirements become part of the bid package and specifications, and can later be used during the equipment qualification execution.

The equipment should only be bid to equipment vendors who have met the minimum standards for fabrication quality and compliance uniformity. This is often determined by conducting a vendor assessment that can involve an inspection of the vendor's facilities, and review of their internal procedures, production capabilities, previous work, and financial stability. In some cases, a quality questionnaire completed by the prospective vendor can also provide assistance in the evaluation process. Purchase orders should include provisions for pre-shipment factory testing and training. Factory testing of the equipment and staff training on the equipment is a valuable prequalification exercise that should be used. Indeed, the design and execution of the Factory Acceptance Test (FAT) by the equipment vendor, and review and critique by pharmaceutical manufacturer, serves as the precursor to the actual performance of the equipment qualification.

The most opportune time to identify problems, correct problems, incorporate changes or upgrades, and conduct testing is prior to the equipment leaving the factory, rather than have these problems later arise during the formal equipment qualification by the pharmaceutical manufacturer. This also serves as a good opportunity to train personnel who will later be responsible for the operation, cleaning, and maintenance of the equipment. Typically during the FAT period, maintenance personnel can use this time to understand from the equipment vendor's expert staff how to maintain and troubleshoot the equipment. Users can work on the equipment for a short time to understand its capabilities, as well as recommended modifications, some of which may be considered for implementation prior to shipment. Overall, the integration of the qualification needs to be incorporated into the FAT process and orientation exercises.

Maintenance Triggers for Qualified Equipment

- Replacement of key components in the system
- Loss of product quality
- Upgrades to equipment
- Change in location
- Change in personnel

When the equipment is finally delivered and installed, this regulatory compliance integrated thinking must be continued. The installation exercise should be conducive to working with the equipment for its intended use. Another general consideration is the development of a master plan. Project execution plans are often one of the first documents generated for a project. Each section of a master plan should include scope, development, design, execution methodology, required resources, safety, construction, and environmental considerations. The mechanism for communicating the overall methodology, resources, and time for qualification is referred to as the Master Plan. The Master Plan is a high-level document that highlights the requirements for equipment qualification, lists equipment that will require qualification, and specifies the format to be used for all documentation. While Master Plans are typically used for facility qualifications, they incorporate the details necessary to plan for equipment qualification, and should be used for manufacturing, as well as laboratory equipment. Maintaining the qualified status of the equipment should be outlined in the master validation plan. Continued qualification includes managing and evaluating changes to the equipment, periodic checks (e.g., performance verification), calibration, and performing preventative maintenance, and for cause maintenance, as required. All for cause (non-scheduled) maintenance operations should be documented using a change control system in order to substantiate that the equipment is still performing within requirements and specifications as outlined in the Functional Requirements Specifications (FRS). ❑

Equipment Qualification: *Design Qualification*

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Design Qualification (DQ) is used as a start-up activity before the equipment is purchased and installed. DQ defines the functional and operational specifications of the equipment, and provides guidance in the selection of the equipment vendor. DQ ensures that equipment will have all the necessary functions and performance criteria that will allow the equipment to be successfully implemented for the required application. DQ is mainly used for the design and fabrication of equipment that will be specially designed for the customer. DQ ensures that the equipment will have all the necessary functions and performance criteria that will enable the equipment to be successfully qualified for its intended application. The proper implementation of DQ requires that planning for location and required utilities be considered before the equipment is delivered to the site. In addition, the specifications, as well as the equipment's impact on the overall performance of the site's utilities, such as water, gases, electrical, steam, Heating Ventilation and Air Conditioning (HVAC), exhaust, plumbing, and cooling water are evaluated. Miscalculations in the DQ can potentially have a significant impact later on. For example, determining the incorrect specifications during the DQ phase that will later be used during the Operational Qualification (OQ) of the equipment, can cause substantial delays and consume time and resources. Furthermore, the equipment vendor evaluation, which is often concurrently conducted during the DQ phase, allows the equipment's capability to be determined. DQ should be performed when new equipment is being purchased, or when existing equipment is being used for a new application.

"...change control, in terms of revision control of functional specifications, is advantageous during the execution of the DQ phase."

DQ serves as the precursor to defining the equipment Installation Qualification (IQ) and OQ protocols. Typically, when purchasing new equipment, the Quality Assurance (QA) department will be involved in the selection of a suitable equipment fabricator. The equipment is first selected, specified, and designed as appropriate for the intended use. Next, the equipment is identified from a suitable vendor, purchased and (if required) fabricated. Finally, the equipment is delivered and installed. However, current Good Manufacturing Practice (cGMP) requirements require that certain regulatory requirements be satisfied during this process. Under the cGMP for Finished Pharmaceuticals, 21 Code of Federal Regulations (CFR) 211.62, 211.65 and 211.67 state the general requirements for equipment design qualification. Industry has interpreted these regulations, from an engineering standpoint, as the requirement to have fabrication methods, materials certification, and specifications for surface finishes and controls. The level of detail that one company may require when purchasing equipment may vary greatly in some cases. Reputable equipment fabricators will normally supply a general set of documen-

tation, such as fabrication drawings, material lists, parts list, and equipment operational procedures. In addition, the equipment vendor should supply, or have available, more detailed documentation, including loop diagrams, software coding procedures, ladder logic diagrams, calculations, construction logs, and welding certifications.

Factory Acceptance Testing (FAT) is performed to have assurance that the equipment and components arrive at the drug manufacturer's site, and meet all specifications for construction and operation. Typically, the drug manufacturer's QA, engineering, and manufacturing representatives inspect, test, and document the equipment before it leaves the vendor's facility, insuring that the equipment will meet qualification criteria. Vendor factory release testing is conducted to demonstrate equipment suitability and performance before it is shipped to the manufacturer.

DQ is required to be completed prior to the equipment delivery and execution of Site Acceptance Testing (SAT) and IQ. Even at this early stage, change control, in terms of revision control of functional specifications, is advantageous during the execution of the DQ phase. When installing multiple equipment types, often a Validation Master Plan (VMP) or qualification plan is helpful in identifying start and end activities, precursor events, project team members, resource requirements, and associated costs. A Request for Proposal (RFP) is required to be developed from the User Requirement Specifications (URS), and submitted to prospective equipment vendors that have the operating and design principles of the equipment class that is being considered for purchase. Typically, a technical assessment conducted by the engineering and manufacturing department, and a vendor assessment are conducted during this part of the DQ phase. Ideally, an audit team with process engineers, quality professionals, and manufacturing personnel are assembled to conduct a quality, as well as a technical assessment of the equipment vendor. As part of the DQ phase, the vendor should be qualified for use. The returned and completed RFP from the vendor becomes a useful performance audit standard in which to evaluate the vendor's capabilities. In addition, a pre-audit quality questionnaire, if designed and used properly, can often pay dividends during the actual vendor audit by confirming commitments and verifying claims made on the returned quality questionnaire.

The RFP should also include a request for a list of references from customers that have acquired similar equipment. These references should be checked from a qualified member of the project team. When one than more vendor is being evaluated, a comparability matrix can be developed using weighted scores for evaluation and listing critical attributes, specifications and requirements that the firm is requiring the equipment to be capable of performing. This is especially critical when purchasing customized equipment. In some cases, the equipment may be used for different applications with associated different functional and performance requirements. Under these circumstances, it is recommended that a description be developed for the most critical applications, and to specify the functional and performance specifications that will meet the criteria for all applications.

Design Qualification Protocol Elements

- Description
- Selection of the Specific Equipment Application
- Description of the Intended Operating Environment
- Definition of URS
- Preliminary Selection of Functional and Performance Specifications
- Preliminary Selection and Assessment of Suitable Vendors
- Demonstration of the Vendor's Ability to meet FAT Requirements
- Final Selection of the Vendor
- Documenting the Final Equipment Functional and Operational Specifications

Your firm's QA department will also want to perform an assessment of the potential equipment vendor(s) to ensure that all equipment that will be purchased will be able to undergo successful qualification after the equipment is purchased and delivered. The QA department's responsibility is to verify the product lifecycle of the equipment vendor, and the vendor's ability to support the equipment and purchase. Sometimes, a vendor quality questionnaire is helpful in collecting this information, which can also be supplemented by an onsite physical audit. ❑

A sample equipment vendor quality questionnaire is included on the following pages.

Equipment Vendor Quality Questionnaire – Sample (Full Assessment)

	Distributor/Broker Information
Primary Contact	
Full Street Address	
Telephone Number	
Fax Number	
Web Site/ E-Mail Address	
	Fabrication Site
Primary Contact	
Full Street Address	
Telephone Number	
Fax Number	
Web Site/ E-Mail Address	
Equipment	1.
	2.
	3.

General Information

1. Please state your firm's Corporate Headquarters information, including name of primary site contact, full street address, telephone number, fax number, and web site/e-mail address.	
2. Will your firm permit an on-site visit? If no, please explain.	❑ Yes ❑ No _____
3. In what year was the company established?	
4. Attach an organizational chart showing reporting structure of company.	
5. Total number of employees.	
6. Number of employees within the quality unit?	
7. How many shifts operate at the fabrication site?	
8. What percent of staff is temporary/contractual?	
9. Do you provide new employee training (e.g., covers skills, GMP/International Organization for Standardization (ISO)/Quality concepts? If no, explain.	❑ Yes ❑ No _____
10. Is there current employee training (e.g., covers skills, GMP/ISO/Quality concepts)? If no, explain.	❑ Yes ❑ No _____

Equipment Vendor Quality Questionnaire – Sample (Full Assessment)

11. Are written training records maintained for all employees? If no, explain.	❑ Yes	❑ No _____
12. Does the quality unit have sign-off on SOPs? If no, then who does?	❑ Yes	❑ No _____
13. Which departments review and approve master production documents?		
14. Is there an SOP system for making changes to engineering drawings, Process and Instrumentation Diagrams (P&ID) and other control documents? If no, please describe system used.	❑ Yes	❑ No
15. Will you agree to provide notification of significant changes made to the equipment fabrication/ software development process being used?	❑ Yes	❑ No
16. If yes to #14, please list contact person and contact information.		
17. Which department approves equipment specifications?		
18. Is a confidentiality agreement required to audit your facility? If yes, attach a copy of agreement.	❑ Yes	❑ No
19. Is your firm ISO 9000 certified? If yes, please provide a copy of the most recent registrar accreditation.	❑ Yes	❑ No
20. If your firm is ISO 9000 certified, will you furnish an index of the quality manual? If yes, please attach.	❑ Yes	❑ No
21. Do you understand and experience Good Manufacturing Practice (GMP)?	❑ Yes	❑ No
22. If your firm is not ISO9000 certified or does not practice GMP, what other regulatory or quality program is being utilized?		
23. Has your firm addressed requirements of 21 CFR Part 11, Electronic Records; Electronic Signatures. If yes, describe your program. If no, indicate your firm's understanding of the regulation.	❑ Yes	❑ No
24. Do you employ an SOP or other type of documentation system to describe activities? If no, explain.	❑ Yes	❑ No _____
25. Will your firm furnish an SOP index of procedures? If yes, please attach index.	❑ Yes	❑ No
26. Will your firm provide a certificate of materials? If yes, will a Certificate of Acceptance (COA) be based on your testing, an outside laboratory, or both (please identify).	❑ Yes	❑ No

Equipment Vendor Quality Questionnaire – Sample (Full Assessment)

27. Does your firm have an instrument calibration program (e.g., pressure gauge, calipers, profilometer)?	❑ Yes ❑ No
28. Are there calibration records for each instrument requiring calibration? If no, explain	❑ Yes ❑ No _____
29. Is there a list of approved suppliers for raw materials you purchase (e.g., 316L and 304 steel? If no, describe how suppliers are selected at the time of purchase.	❑ Yes ❑ No
30. Is there a First In First Out (FIFO) system for stock rotation? If no, describe system in use.	❑ Yes ❑ No
31. Are there separate labeled areas for untested, released, and rejected materials? If no, describe the method assuring separation of materials.	❑ Yes ❑ No
32. Is there a written sampling plan for incoming raw materials?	❑ Yes ❑ No
33. Are any of the raw materials accepted only on the basis of the manufacturer's COA without any additional testing? If yes, please explain why identification testing is not performed. If no, how frequently are these materials tested?	❑ Yes ❑ No _____

Equipment (Software)

1. Does your firm have written software design, development, and test procedures?	❑ Yes ❑ No
2. How does formal review of system specifications and integration test plans occur?	
3. What process is used to develop software code by your firm (e.g., Software Development Life Cycle [SDLC])?	
4. What type of software testing is conducted by your firm (e.g., structural, functional)?	
5. Are third-party tools incorporated into the software product? If yes, please explain	❑ Yes ❑ No Explain:
6. Are there formal procedures for deviation, exception, or problem reports?	❑ Yes ❑ No
7. Is the software code maintained in escrow?	❑ Yes ❑ No
8. Does formal separation of duties between development, testing, and release exist in your firm?	❑ Yes ❑ No
9. Please describe your firm's patch/bug-fix process.	

Equipment Vendor Quality Questionnaire – Sample (Full Assessment)

10. Is your firm aware of any FDA warning letters or FD483s issued in relation to the use of any of your software products?	❑ Yes ❑ No
11. Is software designed to allow restricted access to systems limited to authorized individuals as set by the system administrator?	❑ Yes ❑ No
12. Is software designed to permit access only after inputting a user name and password?	❑ Yes ❑ No
13. Is software designed to allow the system to require frequent changes of each username and password?	❑ Yes ❑ No
14. Is software designed to allow for an audit trail of changes to entered data?	❑ Yes ❑ No Please explain:
15. Is software designed to allow archiving of changes to data information by time/date stamps?	❑ Yes ❑ No
16. Is software designed to allow for system validation by the user that demonstrates compliance with 21 CFR 11; Electronic Records; Electronic Signatures?	❑ Yes ❑ No
Equipment (Hardware)	
1. What quality standard(s) does your firm follow to ensure that quality products are produced (e.g., American Society of Mechanical Engineers (ASME), current Good Manufacturing Practice (cGMP), American Society for Testing and Materials (ASTM), etc.)?	
2. Is there a process flow diagram for the fabrication of the equipment piece(s) being purchased? P&ID, diagrams, blueprints? If yes, please attach to questionnaire.	❑ Yes ❑ No
3. Are subcontractors used for any part, or all, of equipment fabrication, raw material, or product testing? If yes, please explain.	❑ Yes ❑ No Please explain:
4. Please explain your firm's program for warehousing, inspection, and release of equipment components and other materials.	
5. Please explain how user requirements and functional specifications are incorporated into your design process.	

Equipment Vendor Quality Questionnaire – Sample (Full Assessment)

6. During equipment fabrication, how are non-conforming events handled (deviations, bad welds, etc.)	
7. Please describe in general what testing is performed on the equipment fabricated (riboflavin, surface finish, etc.)	
8. Is more than one grade of steel used in the fabrication facility (e.g., carbon steel, 304, 316L, etc.)? If yes, explain how these materials are segregated to minimize contamination.	❑ Yes ❑ No

Name and Title of person who completed this questionnaire *(Signature Required):*	
Date this questionnaire was completed:	

Equipment Qualification: *Installation Qualification*

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Based on the outcome from the DQ and initial equipment evaluation, such as testing of the equipment at the vendor site (e.g., FAT), and/or SAT conducted upon initial receipt of the equipment, a formal Installation Qualification (IQ) protocol can be developed. When the equipment and the vendor certifications are received, IQ can proceed. Based on the Design Qualification (DQ) report or executed Factory Acceptance Test (FAT), or red-lined FAT protocol, with required changes, design of the IQ protocol can proceed.

"The IQ protocol should provide complete instructions for performing the IQ requirements..."

It is important to consider location, utility, and space requirements for the new equipment before it arrives on site. A comprehensive understanding of the requirements for the new equipment must be obtained from the vendor well in advance. Issues, such as humidity and temperature requirements for proper operation, and utility needs, such as volt/amp specifications and compressed gas(es) requirements need to be planned for. Care is also required to ensure all safety concerns, such as electrical grounding, are within specified limits, and that correct cables are used for power connections. This is referred to as the pre-installation phase of equipment qualification.

When the equipment actually arrives, the shipment should be inspected for agreement with the Purchase Order (PO) specifications. A visual inspection of the equipment should also be conducted to identify the existence of any physical damage.

The IQ phase ensures that equipment has been properly installed. The IQ must meet the equipment manufacturer's specified guidelines and requirements. Areas, such as supporting electrical utilities, electrical codes, and environmental condition requirements, are required to be evaluated during the IQ phase of qualification. Typical information required during the IQ includes verification of equipment identification, required documentation, such as "as-built drawings" and purchase orders, equipment utility requirements, major component specifications, list of component materials, lubricants, and equipment safety features. Equipment identification would normally include attributes, such as name of manufacturer, purchase order number, serial number, model number, internally assigned equipment or asset number, and the location where the equipment will be installed. Documentation that should be available during the IQ phase includes the equipment manufacturer's

Factory Acceptance Testing Outline – *Sample*

In order to ensure that the equipment is manufactured and performing to specifications and expectations, company representatives will perform the following:

- Audit equipment fabrication site
- Verify existence of vendor requirements
- Witness, verify, and document equipment operation
- Execute equipment safety inspection
- Execute equipment FAT protocol
- Establish required modifications to FAT
- Approve equipment for shipment delivery

and maintenance manual, equipment drawings, such as P&ID. In addition, SOPs that address the equipment set-up, operation, calibration, maintenance, and cleaning should also be available during the IQ phase, and verified as accurate. Equipment utility requirements are used during the IQ phase to compare the manufacturer's specified volts, amps, and for example, compressed air requirements to the "as found" conditions at the time of the qualification.

The IQ protocol should provide complete instructions for performing the IQ requirements for equipment. In addition, SOPs for operation, calibration, cleaning, maintenance of the equipment, as well as associated logbooks, should be established. The equipment manufacturer's operation and installation manual is typically a good source of information for drafting these SOPs.

Execution of the IQ protocol is performed minimally by two (2) trained operators. As in a batch production record, each step in the qualification protocol is required to be initialed or signed, and dated as the steps are executed. Each operator should have the education, training, and experience that supports their participation in the protocol execution. Evidence of the training should be referenced or appended to the protocol. This is also important when third-party operations are used in the execution of the qualification protocol. Verification that a protocol step has been successfully completed can be accomplished by visual inspection, or by a measuring device. The method of determination should be denoted accordingly in the protocol.

During the execution of the IQ protocol, it is important to ensure that all instruments and components of the equipment are properly calibrated. A section in the protocol should denote calibration of critical and non-critical instruments and gauges. The IQ protocol should reference the calibration procedure used, calibration date, and whether or not the calibration was successful.

In the event that a non-conforming event is encountered during the execution of the IQ or any qualification protocol, it is important that a report be generated that explains the occurrence, references the protocol step number, describes the non-conforming event, provides an investigation, actions taken, and states the corrected and conforming test result. It is important that the investigation into the non-conforming event be initiated prior to retesting of the test parameter.

In some cases, it may be preferably to combine the IQ and Operational Qualification (OQ) together into what is commonly referred to as Installation/Operational Qualification (IOQ) protocol. When using this form of protocol, it is important to ensure and document that the IQ portion of the IOQ protocol has been successfully completed before the OQ section is initiated. In fact, the first executable step in the OQ protocol, regardless if it is combined with the IQ, is the verification that the IQ was successfully completed. ❑

A installation qualification protocol sample form is located on the following page.

Installation Qualification Protocol – Sample

Equipment Identification:

- ❑ Purchase Order Number _____
- ❑ Identification Number _____
- ❑ Model Number _____
- ❑ Serial Number _____

System Utilities	Required (Y/N)	Specifications	Completed (Y/N)
Compressed Gas, Water, Nitrogen Supply			
Electrical			
Lighting			
Steam			
Ventilation Requirements			
HVAC Requirements			
Software Requirements			

- ❑ Acceptance Criteria _____
- ❑ Test Results _____
- ❑ Non-Conforming Test Results _____
- ❑ List of SOPs _____
- ❑ Spare Parts List _____
- ❑ Review and Approvals _____

Key Information for Installation Qualification Protocol Design

1. Scope of protocol
2. Pre-execution acceptance/approval of protocol
3. Description of equipment, including manufacturer names, serial number, model, capacity, and function
4. Equipment asset/tag number, location
5. Verification of purchase order
6. Equipment drawings, including an accurate P&ID. The process engineer should be able to identify the critical parts of the process necessary for proper operation of the system
7. An accurate P&ID tag list, sorted functionally and/or numerically
8. Manufacturer's specifications, installation and operation manual, and any recommendations from the manufacturer regarding installation (e.g., critical environmental and utility requirements)
9. A list of critical components – components without which the equipment would not operate properly. This list should also include special long-lead components that could jeopardize start-up and/or production schedules if they were to fail.
10. A complete list of specifications on critical components. A list of limits that the components will ensure, and are designed and engineered to, should be available. If no, specification is available for a component. Suitable judgement should be used in determining a reasonable evaluation criteria.
11. A list of engineering design data on critical parts. In most cases, this information is available on the specification sheets, or is part of the equipment data. If the part is custom-engineered and affects safety or critical operation, a review of the engineering calculations is advantageous.
12. A listing of product contact areas. The product contact, solution contact, air contact areas, as well as all of the materials in contact with any one of these areas, should be identified, and the components listed by lot number.

Equipment Qualification: *Operational Qualification*

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Operational Qualification (OQ) evaluation should establish that the equipment can operate within specified tolerances and limits as established by the equipment manufacturer. OQ requirements involve demonstrating that all equipment and equipment characteristics meet design standards under operating conditions. OQ usually includes verification of equipment parameters, such as speed, RPM, power consumption, and cycle duration. In addition, OQ involves testing and verifying that all sensors, switches, control devices, logic circuits, gauges, system diagrams, and safety controllers are calibrated and operating correctly. The OQ challenges the mechanical ranges of the equipment as intended by the equipment manufacturer. Information required in the OQ includes verification of calibration of the instruments and devices that will be used to control the equipment, such as switches and push buttons, and equipment operation, such as motor rotation direction, RPM, flow rates, etc. Verification that all critical instruments on the equipment have been logged into the calibration system, Standard Operating Procedures (SOPs) are in place for the instrumentation, and all instrumentation is in calibration at the time of qualification testing are typical requirements during the OQ phase.

"...the equipment qualification report should state that the test results conform with the original acceptance criteria and that the equipment has been successfully qualified."

Operational qualifications typically require that the following general information be generated in the functional requirements:

a. Display specifications – if Cathode Ray Tubes (CRTs) are used, or if discrete instrumentation is used, a description of their purpose, and detail of how the instrumentation relates to the process should be provided.
b. Security specifications – all pharmaceutical processing equipment requires evidence of security systems, passive or active.
c. A fundamental sequence of operations – Exactly how is this equipment or process supposed to function and interface with the real world? What are the inputs and outputs? How does it operate? How is it cleaned? How is the equipment set up for use?

In addition, when designing the OQ protocol, additional information should be acquired, such as:

- Does the equipment have several modes of operation? If so, described each mode in detail.
- Does the system use any diagnostics or interlocks?
- Does the system have alarms?
- Are there any other specifications unique to this equipment? If so, these should be listed.

Operational equipment qualifications should be

conducted in two (2) stages: component operational qualifications (of which calibration can be considered a part), and system OQs (including whether the entire system operates as an integrated whole). During the OQ, input and output are evaluated and checked for proper operation. For other devices that are not calibrated or able to be calibrated (such as CRTs, software, Programmable Logic Controllers [PLCs], etc.), special tests must be designed from the developed functional specifications, such that the range of interlocks, alarms, displays, and functional operations are tested adequately to assure consistent operations.

The use of the Piping and Instrumentation Diagram (P&ID) is instrumental in verifying system operations. If possible, tests for each component of the equipment having Input/Output (I/O) requirements for critical parameters should be conducted that verify that it operates according to the designated function of the P&ID diagram. If loop diagrams are provided, these can provide an accurate way to categorize checklists. References to P&ID loops and/or loop diagrams can effectively be used in the individual designed equipment OQ tests.

Determining which equipment functions are to be evaluated during OQ is an important step. Consideration should be provided as to the function of the system as a whole, followed by which specific equipment attributes control those functions. For example, when designing the OQ protocol for a blender or mixer, the system, as a whole, is intended to blend batches of product. However, the specific elements of the equipment that facilitate this operation could consist of a vessel, a mixing arm, and an automated valve at the bottom of the vessel. The fundamental equipment functions that facilitate blending might include the motor on the stirrer, stirring direction, speed, and the actuator that controls the bottom vessel valve. These basic functional attributes of the blender should be tested under the OQ protocol.

Some equipment manufacturers provide diagnostic programs and systems. PLCs normally have force instructions to manually force I/O on and off. Other equipment manufacturers may provide maintenance items that allow diagnostic exercises to be executed on various substructures of the equipment. Another area to consider in designing the OQ is the interlock and alarm listings that are the most comprehensive and organized functional descriptions of the equipment. Tests should be developed that evaluate this functionality. Used properly, these diagnostic, interlock, and alarm tests are invaluable in making the OQ phase of equipment qualification more efficient.

Finally, after execution of the OQ protocol, as in the case with the equipment Installation Qualification (IQ) or PQ, a qualification summary report should be generated and reviewed by the same responsible personnel that reviewed and approved the pre-executed protocol and executed protocol. The final approval should be performed by the QA department. While sometimes executed qualification protocols are used as documented evidence that qualification was successful, generating a separate equipment qualification report is recommended in that it allows a separate written assessment of the qualification exercise. The qualification report should contain a copy of the approved executed protocol, including any primary data and printouts, discussion of test results, discussion of any non-conforming events, and actions taken to prevent recurrence. Finally, the equipment qualification report should state that the test results conform with the original acceptance criteria, and that the equipment has been successfully qualified.

The maintenance of the qualified state for equipment is another important consideration. Under some circumstances, the qualification for processing or laboratory equipment may be needed to be repeated on a periodic basis. This schedule may be determined by the vendor, for example, in the case of some laboratory equipment, which is often referred to as a performance verification. In other cases, abbreviated or full qualification of the equipment may be required if it is determined that the equipment undergoes significant change. Under these cases, an approved change control or change notice form is used to determine and document the level of change, and evaluation of the impact on the equipment's operation and functional capabilities. It is important that a written operating procedure for change control management be employed to evaluate and document all proposed changes to determine the impact on the equipment after the equipment has been deemed to be operating in a state of control after the qualification process has been successfully completed. ❑

An equipment change control sample form is located on the following page.

Equipment Change Control Form – Sample

Equipment/System Description: _____

Description of Change: _____

Requalification Test Requirements:

- ❑ Not Required
- ❑ Full Qualification Required
- ❑ Abbreviated Qualification Required

Qualification Plan to be used: _____

Results of Test Requirements: _____

- ❑ Attached

Qualification Documents Impacted:

- ❑ Installation Qualification
- ❑ Operational Qualification
- ❑ Performance Qualification
- ❑ Calibration
- ❑ Preventative Maintenance

Approved By: _____

Quality Assurance

Equipment Qualification: *Performance Qualification*

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After it has been established that equipment is properly installed and functioning within specified operating parameters, the PQ is performed. The purpose of the PQ is to demonstrate that the equipment can operate reliably under routine, minimum, and maximum operating conditions. The PQ evaluates the equipment's performance under actual use conditions. It is advantageous during the PQ phase of this test phase qualification to have knowledgeable and trained personnel that are familiar with the equipment, involved in creating and approving the PQ equipment protocol.

PQ typically involves:

- Evaluating equipment operation under normal (nominal) processing conditions.
- Evaluating equipment operation at several boundary conditions that would be normally be encountered under routine use. For example, capability that the equipment can operate within a proven acceptable range, intended use of range, worst-case conditions, or edge of failure.
- Evaluation of equipment operation under less-than-optimal conditions to verify boundary criteria
- Retesting within selected boundary criteria to verify that the proper boundary criteria are acceptable to use during routine use.
- Testing of alarm and interlock setpoints resulting from the operational boundary testing. The equipment should be demonstrated to "protect" itself (within reason) from abnormal operating conditions, and alarm, modify, or discontinue the operation accordingly.

"The PQ protocol should challenge the temperature and exposure time that is required to sterilize the components to the required sterility assurance level."

A good example of the design of a PQ protocol is to consider the PQ requirements for a moist heat sterilizer or autoclave. The PQ for an autoclave should include minimum and maximum loads of the components to be sterilized that will represent actual intended use conditions. The minimum and maximum load should represent "worst-case conditions" for positions of the components in the sterilizer. The components should be placed in locations in the autoclave that have the potential to not receive the same heat penetration as other more optimal locations. Resistance Temperature Detector (RTD) and spore strip readings will allow these worst-case conditions to be evaluated. The PQ protocol should challenge the temperature and exposure time that is required to sterilize the components to the required sterility assurance level.

The use of PQ to laboratory instrumentation, such as an High Performance Liquid Chromatography (HPLC), also presents a good example of this qualification phase's application. After completion of the IQ and

OQ phase, PQ can be considered a combination of both routine method specific system suitability requirements and also planned, routine examination of instrument performance, such as calibration checks, and where appropriate, recalibration. In addition to concentration standards, method specific system suitability criteria allows monitoring of the critical components of the equipment. System suitability criteria can include the detector's baseline noise, precision of quantity of analyte injected, peak resolution, peak tailing, and column efficiency. PQ usually consists of a combination of such method specific concentration standards and system suitability criteria applied for each analytical run, together with a regular, planned set of non-method specific calibration checks carried out at appropriate intervals. ❑

Legacy Equipment Qualification

The concept of Legacy Equipment Qualification (LEQ) is used under those circumstances where manufacturing, packaging, labeling, and quality control testing equipment was already in place prior to implementation of the equipment qualification initiative. LEQ addresses the requirements of the three (3) qualification phases, IQ, OQ, and PQ, in a retrospective manner. Under LEQ, a historical review of the equipment's service repair history and frequency, calibration, and maintenance records is conducted to confirm that the equipment operates historically in a consistent and reliable manner. To confirm the reliability of existing equipment, it must also be demonstrated that the equipment can operate satisfactorily within required limits and ranges. It is also important to indicate the period of time that the equipment's history of operation was evaluated, as supported by documentation, such as equipment use, preventative maintenance, and service logbooks. Instances of any for cause maintenance performed on the equipment should be documented, and the impact on the equipment's operational status evaluated. An LEQ summary report is then prepared. A schedule of completion for all existing equipment required to undergo LEQ should be maintained in the Validation Master Plan (VMP).

Qualification Protocol and Report Design

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It is recommended that a prospective equipment protocol be written and approved for the equipment IQ, OQ, and PQ. In some cases, combining the IQ and OQ to form an Installation-Operational Qualification (IOQ) protocol is acceptable, provided the completion of the IQ is verified and documented prior to execution of the OQ. The qualification protocols are control documents, just like SOPs and batch records, and require final approval before and after execution by the quality unit.

"The final qualification report should summarize the test results and compare these results against the approved acceptance criteria used."

A format is required for stating the equipment qualification requirements, method of verification, and the system for collecting and documenting the information that will be acquired during the execution of the qualification protocol.

The design of the qualification protocol usually involves the following elements:

- **Scope**: *Defines the intended purpose and major functions of the equipment.*
- **Equipment Definition**: *Provides a detailed description of the equipment's hardware/software, utilities, and other components that define the equipment and its functions.*
- **Responsibility**: *Defines the individuals responsible for the preparation and drafting of the qualification protocol, and the individuals expected to execute the testing. As required, define the responsibility of the equipment vendor in the qualification process.*
- **Qualification Procedures**: *Lists the SOPs that define how the qualification will be carried out.*
- **Expected Results/Acceptance Criteria**: *This should list the expected results of each test, with blank fields available to record the actual test results. The protocol should also have prospective fields for documenting any nonconforming events that may be encountered during the execution of the protocol, and remedial/corrective action taken.*
- **Forms, Attachments, Appendixes**: *Any forms, attachments, or appendixes should be listed and attached to the qualification protocol.*
- **Primary Data**: *Primary data generated during the execution of the qualification protocol should be attached or referenced.*
- **Approvals**: *Appropriate review and approval signatures are required for both pre-execution and post-execution.*
- **Change Control/Requalification Criteria**: *In accordance with a lifecycle approach, the VMP that directs equipment qualification requirements should include the criteria for requalification of the equipment when deemed necessary, based on changes. Depending on the extent of the change, abbreviated or full requalification may be required.*
- **Ongoing Monitoring**: *This area should be addressed by ensuring SOPs are in place to address*

[a] equipment security controls to safeguard data integrity [b] data archival and retrieval requirements to ensure that data can be reinstalled, as required (for equipment capability of storing electronic records) [c] system operation (including equipment operator's manuals or a brief listing of operations and parameters) [d] training (to ensure that only qualified operators use the equipment).

- **Maintenance and Calibration**: *Maintenance and calibration schedules should be defined using the equipment vendor's operation manual and/or qualification template as a guide.*

A final equipment qualification report should be written, as opposed to using the approved executed qualification protocol as evidence that the equipment was successfully qualified. The final qualification report should summarize the test results and compare these results against the approved acceptance criteria used.

The author of the qualification report should include a statement that the equipment was successfully qualified. If any non-conforming events were encountered during the execution of the qualification, these should be discussed with an explanation of how they impacted the qualification exercises, investigations, retest results, along with any corrective and preventative action taken. Ideally, a qualification report should be written after each phase of the qualification is completed. However, where the OQ is performed directly after the IQ, or where these two phases are combined, a single qualification report would be considered sufficient. In other cases, a final qualification report can be written after the IQ, OQ, and PQ have been completed.

Furthermore, it is important to ensure that the same individuals from the same functional departments that reviewed and approved the qualification protocols pre-execution, are the same individuals that review and approve the executed qualification protocols and final qualification reports. Exceptions should be documented with appropriate rationale, e.g., training of the replacement personnel, as required. The qualification protocols and reports should be designed to have the QA function always be the last approval signature. It is important not to have another department approve and date the qualification protocol and report after the quality unit has approved it. This could imply that quality has a subordinate role to another functional department, which is contrary to the basic premise of cGMP. ❑

Equipment Qualification Report Contents

- **Equipment Qualification Report Approval***: Upon completion of the equipment qualification report, which includes documentation that the test protocols were successfully followed, executed, and completed, an executive summary should be drafted, and the qualification report circulated for approval by the core project team. Final approval by QA is required.*
- **Executive Summary**: *The executive summary will clearly state that the equipment has been qualified. The summary should include historical information on previous equipment model/type qualifications, as appropriate. This executive summary should also include a list of each of the major tested functions of the components. The executive summary should also note:*
  - **Completed and Approved Equipment Qualification Test Plan:** *A copy of the VMP or equipment qualification master plan should be included.*
  - **Completed and Approved Equipment Installation Qualification Protocol and Attached Test Data (Appendix)**: *This should be appended to the equipment qualification report.*
  - **Completed and Approved Equipment Operational Qualification Protocol and Attached Test Data (Appendix)**: *This should be appended to the equipment qualification report.*
  - **Completed and Approved Equipment Performance Qualification Protocol and Attached Test Data (Appendix)**: *This should be appended to the equipment qualification report.*

About the Author

David M. Stephon has more than 17 years experience in the pharmaceutical industry with in-depth experience in regulatory compliance and quality assurance topics. His experience includes working in quality assurance, compliance, chemistry, manufacturing and control operations for Sterling Drug and Sanofi Research, NanoSystems, and Elan Pharmaceuticals. David is an Editorial Advisory Board member for the Journal of GXP Compliance*, In 2002, David received an Industry Recognition Award from the* **Institute of Validation Technology***. Currently, he holds the position of Senior Director, Quality Assurance, at Adolor Corporation. He can be reached by phone at 484-595-1091, by fax at 484-595-1573, or e-mail at dstephon@adolor.com.*

Article Acronym Listing

ASME:	American Society for Mechanical Engineers	IOQ:	Installation/Operational Qualification
ASTM:	American Society for Testing and Materials	ISO:	International Organization for Standardization
CFR:	Code of Federal Regulations	I/O:	Input/Output
cGMP:	Current Good Manufacturing Practice	LEQ:	Legacy Equipment Qualification
COA:	Certificate of Acceptance	MQ:	Maintenance Qualification
CPG:	Compliance Policy Guide	OQ:	Operational Qualification
CRT:	Cathode Ray Tube	PLC:	Programmable Logic Controller
DQ:	Design Qualification	PO:	Purchase Order
EC:	European Community	PQ:	Performance Qualification
FAT:	Factory Acceptance Test	P&ID:	Process and Instrumentation Diagram
FDA:	Food and Drug Administration	QA:	Quality Assurance
FIFO:	First In First Out	RFP:	Request For Proposal
FRS:	Functional Requirements Specification	RTD:	Resistance Temperature Detector
GMP:	Good Manufacturing Practice	SAT:	Site Acceptance Test
HPLC:	High Performance Liquid Chromatography	SDLC:	Software Development Life Cycle
		SOP:	Standard Operating Procedure
HVAC:	Heating Ventilation and Air Conditioning	URS:	User Requirement Specification
IQ:	Installation Qualification	VMP:	Validation Master Plan

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Basic Operating Principles and Validation of Electron Beam Irradiation Systems

BY JORGE A. SUGRANES, BS, BSIE, MEM, CMFGE

SYNOPSIS

This technical paper summarizes information compiled from a literature review on basic concepts of Electron-Beam technology: the radiation process, operating mechanisms, process control, and validation. The primary intent of this descriptive overview is to present the potential use of ionizing radiation as lethal agent against microorganisms (sterilization method), and provide general guidance for validation.

INTRODUCTION

Electron beam (*E-Beam*) technology (*Ionization ß radiation*) is a process for treating materials with high-energy electrons produced by an accelerator to cause specific effects. In general, radiation may be classified into two groups: electromagnetic and particle radiation. The various types of ionizing radiation in the electromagnetic spectrum produce bactericidal effects by transferring the energy of a photon into characteristic ionization in or near a biologic target.[1]

Electron beam technology is another mode of radiation sterilization that has several advantages over other popular sterilization techniques used by the Pharmaceutical Industry, such as Gamma (γ) radiation (cobalt-60, cesium-136), ETO (ethylene oxide), dry heat, and steam sterilization.

Most relevant advantages that characterize electron beam technology include:

- No load preconditioning needed
- Shorter sterilization exposure time; typically less than 10 minutes
- No chemical residuals
- No degassing or aeration process needed after sterilization
- Environmentally friendly process
- Faster processing
- Lower expenses than with other radiation techniques - in some cases
- Materials or components can be re-sterilized under certain circumstances

As with other technologies, there are some limitations or areas of concern associated with electron beam technology.

Some limitations are noted below:

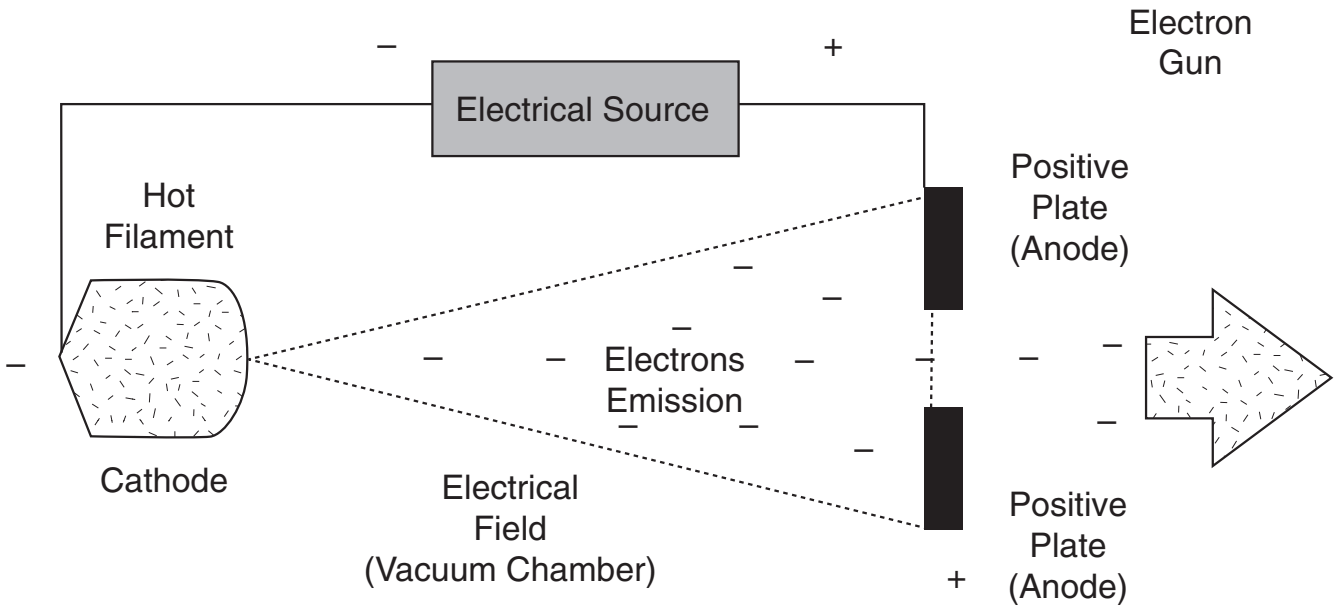
- Short penetration depending on material density
- Dose uniformity; wide dose range may be observed, especially on high density loads
- Orientation of components is important
- Discoloration may occur on some materials

In 1956, the Medical Devices Industry developed the first commercial application of electron beams for sterilization.[2] By the early 1980's the Atomic Energy of Canada Limited (AECL) developed what was then the world's most powerful accelerator, a 10 MeV, (million electron volts) 50kW accelerator capable of meeting needs in most industrial applications.[7] Recent developments have demonstrated the potential of this technology to various industrial applications such as medical devices, cosmetics, and pharmaceuticals.

Industrial electron accelerators can be classified as low-energy, medium-energy, and high-energy machines, based on the energies of the electrons produced. Accelerators producing electrons with energies that are less than 1 MeV are

Figure 1

Electron Accelerator - Free electrons generation



classified as low-energy; medium-energy machines produce electrons with energies in the region 1 to 5 MeV, whereas high-energy accelerators produce electrons with energies that are greater than 5 MeV. Typical industrial applications involve the use of electrons with energies ranging from 3 to 10 MeV.[8]

Accelerators are machines that use electrical energy to generate free electrons (*see Figure 1*), accelerate them to high speeds, and then direct them at materials passing through the accelerator on a conveyor or in another type of flow-through system (*see Figure 2*). The electrons penetrate the material, which can be gaseous, liquid, or solid, and initiate chemical reactions that alter the properties of either the material, or of specific components in or on the material. The types of chemical reactions produced depend upon the nature of the material being treated. The reaction can vary from *polymerization* (plastics and composites) to *degradation* (chemical materials) to *sterilization* by disrupting a microorganism's *DNA* chain.[6] Accelerators are similar to television (TV) sets or x-ray machines in the way they generate electrons. All produce a cloud of *free electrons* by heating a negative *cathode* inside a vacuum chamber.[4, 5]

Once generated, the negatively charged electrons are attracted by a positive electrical potential (≅ 10 kV) applied to an attracting plate (*anode*). The electrons are accelerated by traveling through this electric field, thereby gaining energy. These accelerated electrons are collimated through a window in the anode plate and proceed toward the materials to be treated.

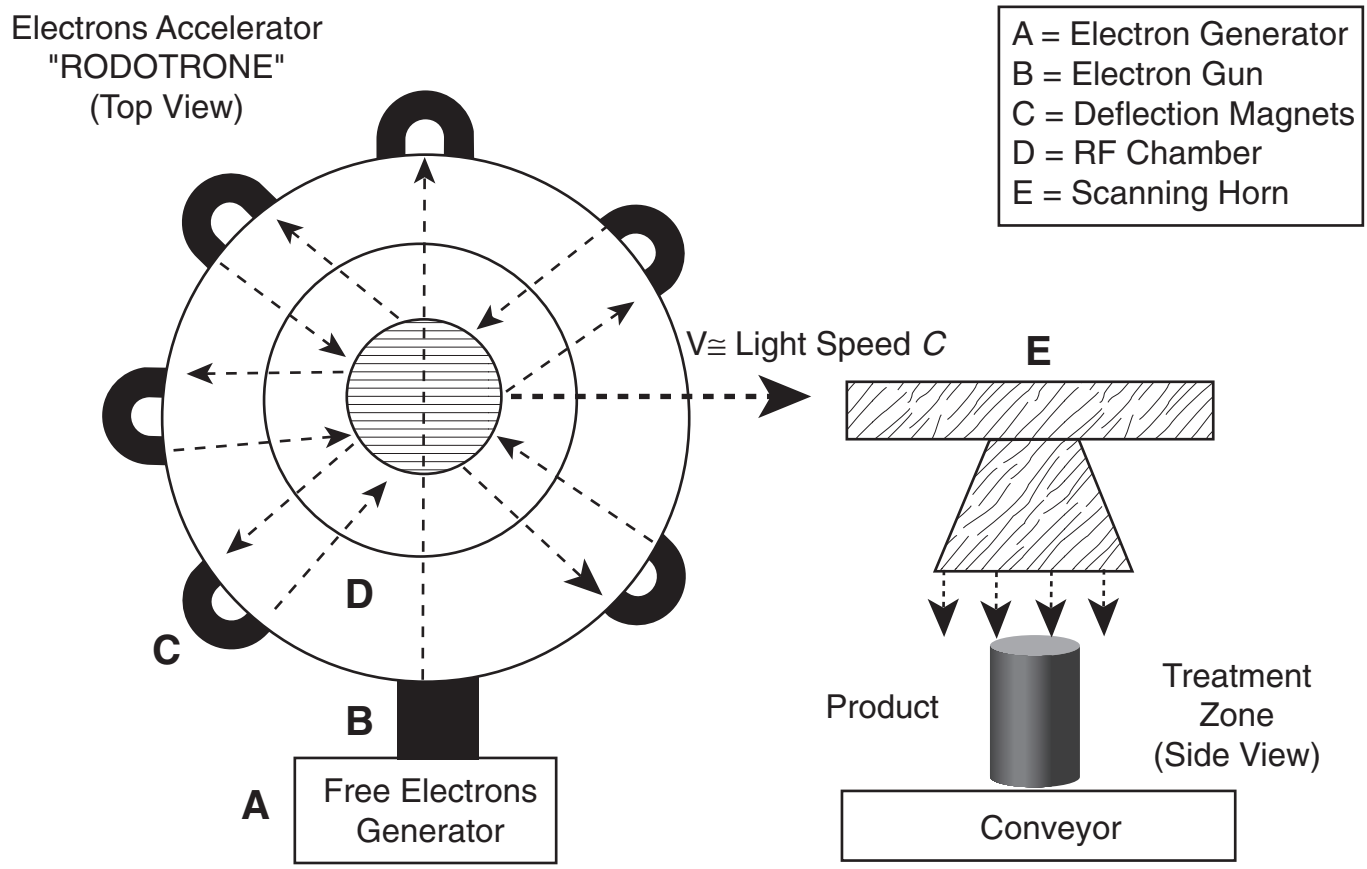
The accelerator, which generates the electrons, operates in both a pulse and continuous beam mode. Considering that high energy levels are required to penetrate the product material, accelerators have been developed that employ multiple stages of acceleration (*see Figure 2)* capable of producing electrons with energies up to 18 MeV. Typically, accelerators producing electrons with energies up to 10 MeV are used in industrial application.

As the beam is scanned through the product, the electrons interact with materials and may create secondary energetic species, such as electrons, *ion pairs*, and free radicals. These secondary energetic species are responsible for the inactivation of the microorganisms as they disrupt the DNA chain of the microorganism thus rendering the product sterile.

Most significant process parameters to be considered for sterilization applications include: energy (volts), power (Watts), exposure time (conveyor speed), dose or energy deposited by the radiation in the unit of mass (Joules/Kg), and penetration (mass density). Compatibility of the material or product to be irradiated is important, too. Selection of materials will depend on the compatibility between product-

Figure 2

Circular Electron Accelerator - Free Electrons Acceleration



container material and container material-irradiation dose. Some questions that must be answered include: Is the product compatible with e-Beam? Is the product compatible with the container material (bottles, bags, caps, closures, etc)? Is the material compatible with e-Beam?

Some common materials compatible with e-beam: [3,4]

- Polyethylene terephthalate (PET)
- Polypropylene (PP)
- Polyethylene (PE)
- High Density Polyethylene (HDPE)
- Vinyl acetate polymer (PVAC)
- Polyvinyl Chloride (PVC)
- Polyvinylidene Fluoride (PVDF)
- Polytetrafluoroethylene (PTFE)
- Other elastomers

Validation Considerations

Validation is the formal process of establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. To consider the validation of sterilization processes, generally, we may make an initial distinction between physical validation and biological validation. The physical validation concept establishes that a product or materials will be subjected throughout a load to the desired and intended treatment by physical methods and controls. On the other hand, the biological validation intends to demonstrate that, with respect to an appropriate test organism, the desired level of sterility assurance will be achieved during routine operation.

With radiation sterilization, the objective of validation is to demonstrate that the required lethal dose is delivered to the entire batch of material or product, taking into consideration the *loading pattern* of product within a package, of packages

on the package carrier in relation to the radiation source, and by using calibrated *dosimeters*. Organisms recommended for biological validation are strains of *B. pumilus, B. cereus,* or *B. sphaericus*, according to dose level.[10] Spores of *Bacillus pumilus* have been used to monitor sterilization processes, however, this is an unusual practice. Radiation dose-setting methods that do not use biological indicators have been widely used to establish radiation processes. Furthermore, certain *bioburden* microorganisms can exhibit greater resistance to radiation than *Bacillus pumilus*.

The validation program of an irradiation sterilization process should include the following elements:

- Audit of irradiator installation for cGXP compliance, regulatory compliance, and safety.

- Installation Qualification of irradiator system (qualification of the electron accelerator unit with emphasis on control systems, automation, software, and hardware).
  - ✓ Equipment documentation
  - ✓ Equipment tests
  - ✓ Equipment calibrations
  - ✓ Irradiator dose mapping

- Process Qualification using a specific product or simulated product:

  - ✓ Product and packaging materials evaluation to determine compatibility with Ionization ß radiation.
  - ✓ Determination of product loading pattern including: a description of the packaged product, orientation of the product with respect to the conveyor flow and electron beam, unit count within the package, package dimensions and mass, the orientation of product within the package, and acceptance variations in these parameters.
  - ✓ Product dose mapping to identify the zones of minimum and maximum dose within the product load with the specific loading pattern and to assess the reproducibility of the process. This information shall then be used in selecting the dose monitoring locations for routine processing. Dose mapping exercises will be carried out at the limits of the density ranges of product categories to be processed irrespective of dose. Product loading patterns and the pathway used for processing will be included in such exercises.

- Product Qualification – Obtaining and documenting evidence that the finished product will be accepted for its intended use after exposure to radiation.

- Product Stability – Demonstrating the ability of the finished product to remain acceptable for intended use throughout its shelf life after exposure to the maximum radiation dose.

- Technical Review - To review, audit, and approve documentation of previous validation elements. Information gathered or produced while conducting validation exercises shall be documented and reviewed for acceptability by a designated individual or group, which obtains the appropriate knowledge and expertise in the validation process.

- Activities performed to support maintenance of irradiator system and validation.

  - ✓ Re-qualification program. Frequency of re-qualification depends on whether there have been any significant process or equipment changes, and any adverse or unusual sterility or functional test results.
  - ✓ Change control program
  - ✓ Calibration program
  - ✓ Preventive and predictive maintenance program
  - ✓ Sterilization dose auditing
  - ✓ Standard Operating Procedure
  - ✓ Training, training, and training

Other important points for consideration during validation are density homogeneity of loading configuration; partial load (maximum and minimum load); single *versus* double pass (to reduce maximum to minimum dose ratios); process interruption (system fault); re-sterilization and grouping by process or product families with similar chemical and physical properties (may reduce validation work load).

Design of Experiment (DOE) techniques or mathematical models can be used to establish and optimize critical sterilization process parameters. DOE requires controlled experimentation work and empirical analysis of the process. Real data is generated. On the other hand, mathematical models predict results (approximations) faster, but errors in any input parameter for the calculation can result in errors in the calculated results or predictions. Confirmation of predictions via experimental work is recommended to de-

tect potential error or miscalculations.

One of the most common modeling methods used in electron beam irradiators is the *Monte Carlo Method*.[9] In this method, the transport of each photon or electron from the source through the product and irradiator materials is simulated by the use of random numbers to determine the energy deposition and change of path following different interactions. The probability for each interaction is obtained from published tables. Theoretically, this method can accurately simulate the actual transport of the photons and electrons.

Cost, time, workload, and accuracy of results are important elements to consider when making a decision on the best method to use. There are several consultants that specialize in modeling techniques that can help you to do so. These are very powerful statistical approaches to effectively model the validation experiments, and establish the number of experimental replications, as well as complete in-depth data analysis. In order to be successful in the implementation of an e-beam project, it should be kept as simple and practical as possible. No rocket science is needed.

In the initial validation, the Food and Drug Administration (FDA) states in its aseptic guidelines, that at least three separate runs are needed. The manufacturer will establish and maintain procedures to monitor and control the process parameters for the validated process to ensure that the specified requirements continue to be met. The key element to in-process control of radiation sterilization is to include calibrated dosimeters within the load. These dosimeters are used as a measure of the radiation received by the load and should be placed in scientifically determined locations established during the sterilization cycle design and characterized in the validation program.

The validation program should be delineated in a comprehensive Master Validation Plan, which describes the various protocols, procedures, methodologies, scientific approaches, test functions, acceptance criteria, regulatory requirements, timelines, resources, and responsibilities. The protocols give details of the critical parts of the process, the parameters that should be measured, the allowable range of variability, and the manner in which the system will be tested.

CONCLUSION

Electron beam technology has being scientifically studied and implemented by the Medical Devices and Pharmaceutical Industry for many years, and the potential use of ionizing radiation as a lethal agent against microorganisms has being demonstrated with satisfactory results. Most relevant advantages include: no load preconditioning needed, shorter sterilization exposure time, no chemical residuals, no degassing or aeration process needed after sterilization, environmentally friendly process, faster process, less expensive than other radiation techniques in some cases, and the materials or components can be re-sterilized under certain circumstances. On the other hand, some points of concern should be noted including: short penetration, depending on material density; dose uniformity; the importance of the orientation of components; and the fact that discoloration may occur on some materials.

The most important element in the irradiation process is in the dose delivered to the product. Appropriate process parameters should be established during validation exercises. Process control methods should be in place to ensure that the dose is obtained in a reliable, accurate, and reproducible manner. Also, process qualification, routine process monitoring, re-qualification, and maintenance of validation are critical elements to ensure the reliability and consistency of the sterilization process. The validation program is a key and important factor in the successful implementation of this technology. Inappropriate process design, or lack of a solid, robust, and scientifically based validation program, will potentially result in costly quality failures or regulatory issues. ❑

ARTICLE DEFINITIONS

Anode:	An electrode to which a principle electron stream flows
Bioburden:	Natural population of viable organisms on a product
Beta radiation:	Radiation by energetic electrons
Cathode:	An electrode that is the primary source of an electron stream
Degradation:	Reduction of polymers to smaller molecules
Dosimetry:	Measurement of absorbed dose by the use of dosimeter
Dosimeter:	Device or system having a reproducible, measurable response to radiation, which can be used to measure the absorbed dose in a given material

Electron:	Component of atoms with negative electrical charge (0.16×10^{-18} A.s per electron)
Electron Beam:	Continuous or pulsed stream of high-energy electrons
Electron Emission:	Liberation of electrons from an electrode into the surrounding space
Ion:	An atomic nucleus with a charge
Irradiator:	Assembly that permits safe and reliable sterilization processing, including the source of radiation, conveyor and source mechanisms, control systems (PC, automation devices), and safety devices
Loading Pattern :	Geometric configuration of the product in the irradiation container
Mathematical Modeling :	Use of mathematical methods to determine dose distribution
Monte Carlo Method :	Mathematical modeling method used in the design of irradiators. Calculations are performed to optimize the irradiation geometry to achieve the desired throughputs and dose homogeneity
Rodotron:	Circular type electron accelerator. Usually this accelerator is more powerful, compact, and versatile than classic linear accelerators
Sterilization:	A process that kills or inactivates all forms of life
Velocity of Light :	$c = 0.299 \times 10^9$ m/s

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Article Acronym Listing

AECL	Atomic Energy of Canada Limited.
CGXP	Term inclusive of all current good manufacturing, clinical, laboratory, and documentation practices
DOE	Design of Experiment
ETO	Ethylene Oxide
FDA	Food and Drug Administration
MeV	Million electron Volts
RF	Radio Frequency

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Commissioning Issues and Considerations

Louis A. Angelucci, III
Aker Kvaerner

Commissioning, as a validation-related activity, is a recent practice in the Pharmaceutical industry. As with other initiatives related to facility and system qualification, it too has developed into an industry of its own. The term was not an invention of this industry, it is a military term. More exactly, it is a Navy term. It was, and is, a procedure that is performed on new construction to ensure functionality. (*Figure 1*.)

Commissioning as a documented activity, was introduced to the pharmaceutical industry in 1994 in an article that was published in the *Pharmaceutical Engineering*.[1] It was presented as a means of organizing the complicated and expensive process of licensing a pharmaceutical facility. This process was the verification, qualification, and validation of a pharmaceutical facility. The focus of the article is to demonstrate that a properly orchestrated construction and testing effort could lead to a more streamlined and cost-effective project. This conclusion was true at the time of the article publication date in 1994, and is still true today. There are those in the pharmaceutical industry who decided that by taking the methodology of commissioning and incorporating it with the concept of Good Engineering Practice (GEP), it was possible to reduce the burden of validation.

"...by taking the methodology of commissioning and incorporating it with the concept of Good Engineering Practice (GEP), it was possible to reduce the burden of validation."

The merits of validation are well-known and publicized. Its purpose is to offer rationalization and verification of a manufacturing process. To many, validation is a costly and time consuming undertaking. It is viewed as a paper chase, and a government sponsored "pass-go" initiative. Commissioning offered an avenue to reduce duplication of testing, as well as eliminate the activity of process validation from specified systems and equipment.

The International Society of Pharmaceutical Engineers (ISPE) took up the lead by publicizing the methodology, which stressed the commissioning approach.[2] Commissioning in conjunction with the concept of GEP would be used to justify certain tests and systems standing on their own merit. These systems would have no need of qualification as presented by the validation approach.

Validation

The term and practice of validation has now existed in the pharmaceutical industry for almost thirty years. The word appeared in the original version of the Code of Federal Regulations (CFR), but did not hold the distinction that it does today. It was a term devised by the Food and Drug Administration (FDA) to obligate pharmaceutical companies to demonstrate the control and reproducibility of their manufacturing process 'with a high degree assurance.' (*Figure 1*.)

Non-compliance carried the threat of litigation and imprisonment. For a few years, industry struggled to define the term and understand FDA requirements. In 1987, the FDA published a guideline that presented a much clearer picture of expectations. This document was the *Guideline on Process Validation*.[3]

Over the years, the concept of validation has grown into an industry unto itself with consultants and specialists offering their services. The practice has developed its own set of standards and documentation (Installation Qualification [IQ], Operational Qualification [OQ] and Performance Qualification [PQ]). All aspects of validation have been sanctioned by the FDA. In 1996, the FDA proposed a rewrite to the CFR, to more thoroughly cover the practice of validation. In Europe the EC Guidance on GMP Annex 15, define and describes in detail the topic of quality and validation.

"The FDA has over the years clarified the term and the meaning of validation"

The concept of validation was introduced by the FDA because sampling, even though statistically-based, was not sufficient to demonstrate process control. The FDA wanted industry to demonstrate statistically and with a scientific basis, that the process was sound, reproducible, and under control. This did include an application of statistics, but it also included quality testing, as well as stress testing. Validation was intended to be the mechanism by which quality could verify manufacturing. It would accomplish this through documentation review, accountability, and process testing. Validation was to be autonomous to manufacturing, and considered a function of the quality organization.

The original application of validation was to verify the actual process. To insure that the process was under control, the systems and equipment had to be qualified. The task for validation was to verify not only the process, but the manufacture of equipment, and construction of the facility. The construction verification involved testing and fabrication documentation verification. At times, specific tests had to be repeated.

Figure 1

Industry Terms and Definitions

Term	Definition
Validation[3]	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.
Commissioning[2]	A well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.
Good Engineering Practice (GEP)[2]	Proven, accepted methods that ensure that engineering solutions meet stakeholder requirements and are cost-effective, compliant with regulations and are well documented.

Commissioning

The application of pharmaceutical commissioning and GEP are industry-derived terms and practices. As was the case with current Good Manufacturing Practice (cGMP), GEP is also a term subject to interpretation and philosophical discussion. The use and practice of these concepts has not been officially accepted by the FDA. The FDA has unofficially sanctioned commissioning and GEP by participating in industry association volunteer committees that are developing industry guides which have introduced these terms. In most, if not all cases, the FDA helped to author the introductory letter, and provided commentary to these guides. Because of this, the practice of commissioning in the pharmaceutical environment has been likened to the latest fashion trend. Many firms and organizations are attempting to be included as part of this moving caravan, whether the FDA officially recognizes the practice or not. With the use of industry sponsored and developed guides, the activity has been determined to be defensible.

Commissioning has evolved from a mere equipment activity during construction to actual commissioning plans and test protocols. Operating firms utilizing the concepts of commissioning and GEP, now not only develop validation plans and the associated validation protocol documentation (IQ, OQ and PQ), but also develop commissioning plans and commissioning

test protocols. Though the practice of commissioning and application of GEP was originally limited to specific systems, today it is applied to almost every system, regardless of its importance to the process.

There were aspects of construction and installation, which could not easily be performed by the validation team due to the specialties of the crafts involved. Commissioning evolved within the pharmaceutical industry because of these specific requirements, and is more closely aligned with construction and installation than validation. Commissioning is not a replacement for validation or the quality functional testing of IQ and OQ, but embodies those tests and verifications which can only correctly be performed by the construction and installation. There are certain test functions, which until recently, have been performed in the validation IQ and OQ documentation. Among these tests of the past have been such things as, slope verification, point-to-point contact verification, and loop testing. Certainly these tests can be better described and performed by those professionals trained in such activities.

A current role of validation is to verify that these tests and checks were properly performed by the commissioning group. This might very well involve repeat tests, and alternate testing. The current role of validation is to verify the completeness and validity of all documentation inclusive of those generated by commissioning. Validation is not just limited to the process or the product; it has a definite and well-defined role in verification, as the CFR states, that equipment and systems are suitable and properly designed for their intended use. Tests such as worst-case limit testing, and capacity testing of equipment, are well within the realm of validation.

Commissioning must take on a quality function. If the activity is to allow the testing of these systems and equipment to stand on their own without the benefit of validation, then commissioning must be quality-oriented. A commissioning protocol should be generated, stipulating what is to be tested. In order to give structure and proper closure to the commissioning process, a commissioning plan should be developed, as well. Those performing the task of commissioning must show proper evidence of training, as implied in the cGMP regulations.[5] In addition, commissioning test functions should have supporting Standard Operating Procedures (SOPs) that document how standard testing is to be performed. SOPs should be required of all who are involved with facility validation. Those performing calibration functions are often third-party organizations, and they too, must demonstrate evidence of their quality systems through the proper application of required SOPs.

All systems can be subjected to a commissioning process. Even computer control systems have an aspect of commissioning associated with them. Commissioning without proper quality control, or the application of the concepts embodied within the precepts of the cGMP, cannot stand alone. For those systems that utilize commissioning, you must still demonstrate that proper testing and quality were a part of their construction and installation.

This leads us once again to the all encompassing term of GEP. It appears to be a common sense topic that needs no introduction or definition. The same was attributed to cGMP when it was first introduced, who wouldn't want to properly engineer a system? By the same token, when cGMP was introduced, who wouldn't want to do good manufacturing? It took a number of years and regulatory rewrites, as well as FDA inspections, issuance of FD-483's and consent decrees, to insure that industry had the same understanding of cGMP as the FDA. To date, no such official definition, guideline, or regulation exists to help us better understand GEP. GEP has been used as the basis to justify the commissioning of certain systems without the benefit of validation proving their suitability for a particular process.

Risk

The industry guides, mentioned earlier, promote the use of impact assessments to determine which systems are to be fully validated, and which are to be only commissioned. The application of an impact assessment to demonstrate the need for full qualification can be justified and should be done. It should be recognized that an impact assessment, is in essence, a risk analysis without the benefit of statistical verification.

Recently, the FDA has introduced another initiative, this new initiative has been termed 'Risk Assessment.'[6] The details and expectations from the FDA have yet to be announced or addressed, and there possibly may be another rewrite of CFR 210 and 211 as a result. This risk assessment initiative is obviously

Figure 2

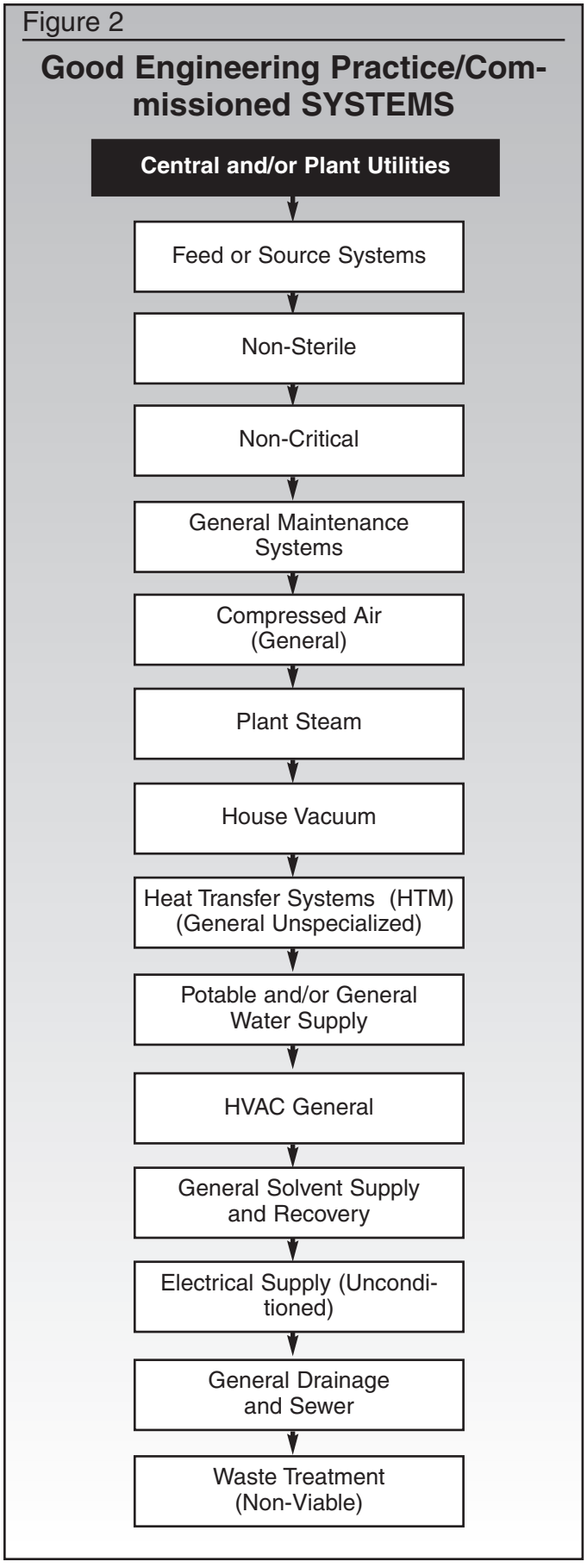
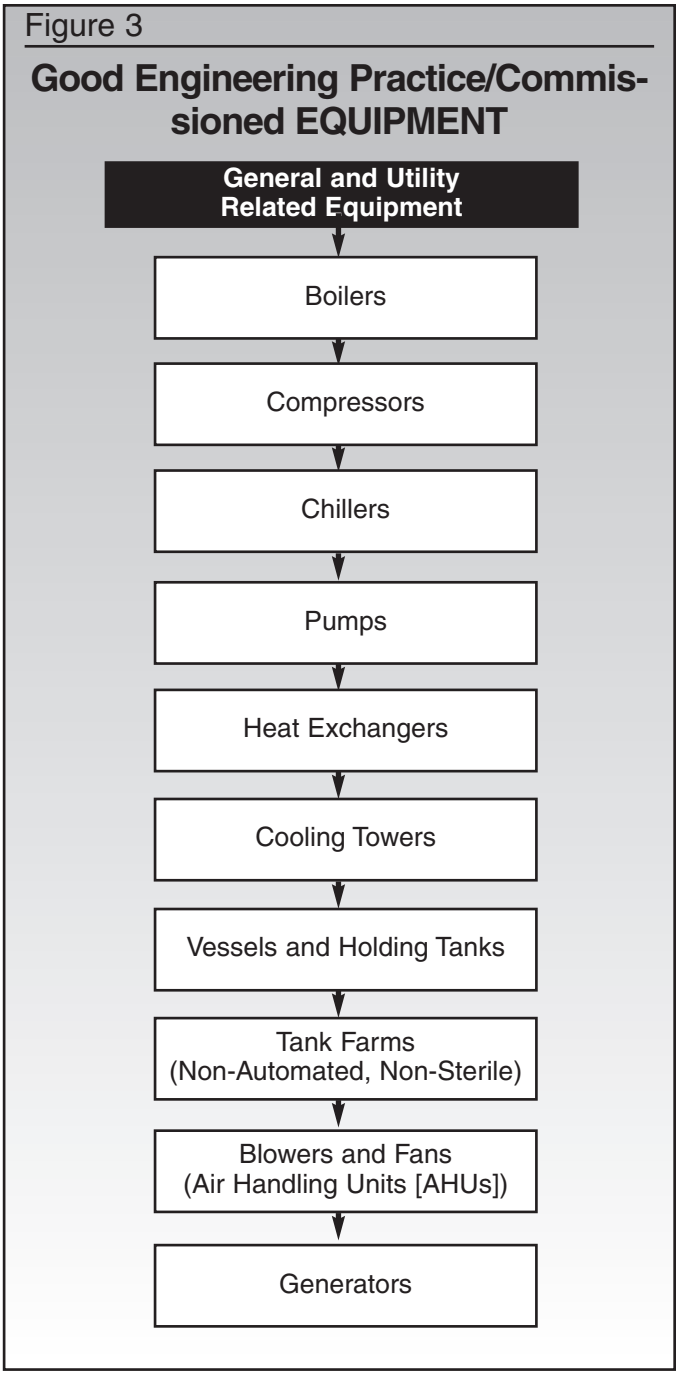


Figure 3



being driven by the current activity within industry, as well as the demands of increased inspections and the limited budget of the FDA. *Figures 2, 3, 4* and *5* show the general trend for various systems and equipment.

The concepts of commissioning and GEP are related to the concept of risk assessment. A critical aspect of this activity is an equipment and system impact assessment. The risk aspect of this is whether the lack of validation for a system or equipment will adversely affect the process or its end product. The im-

Figure 4

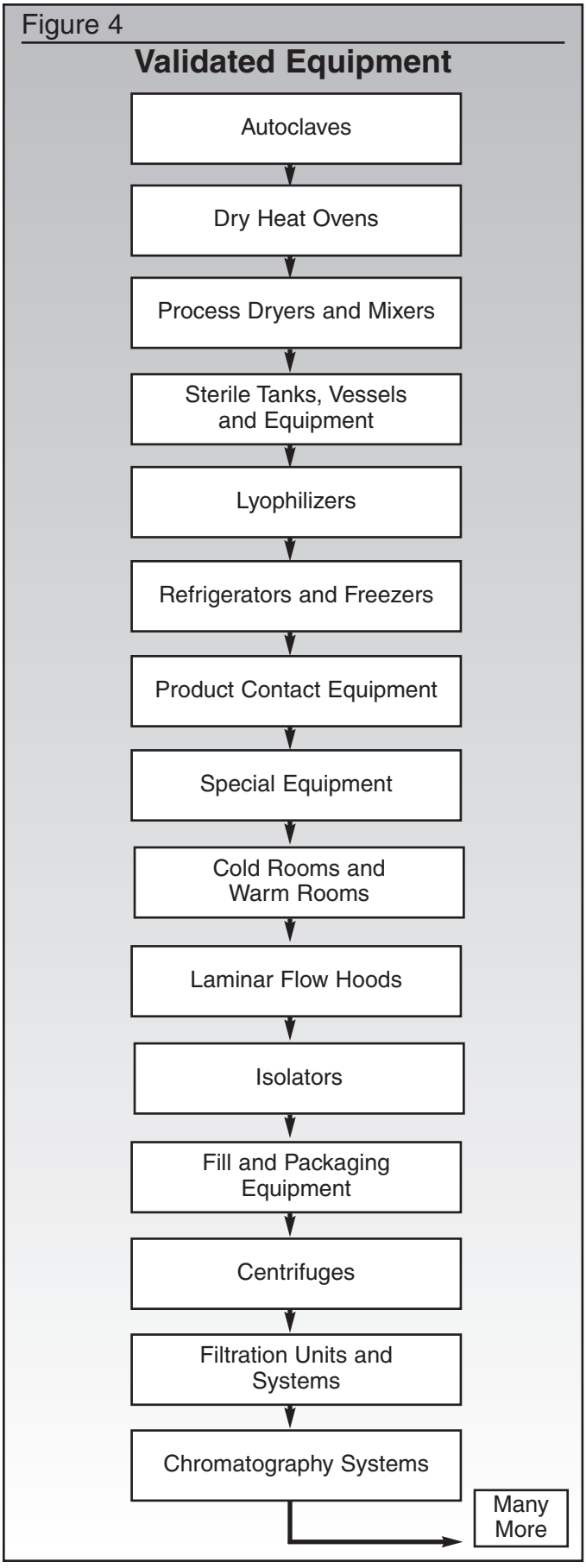
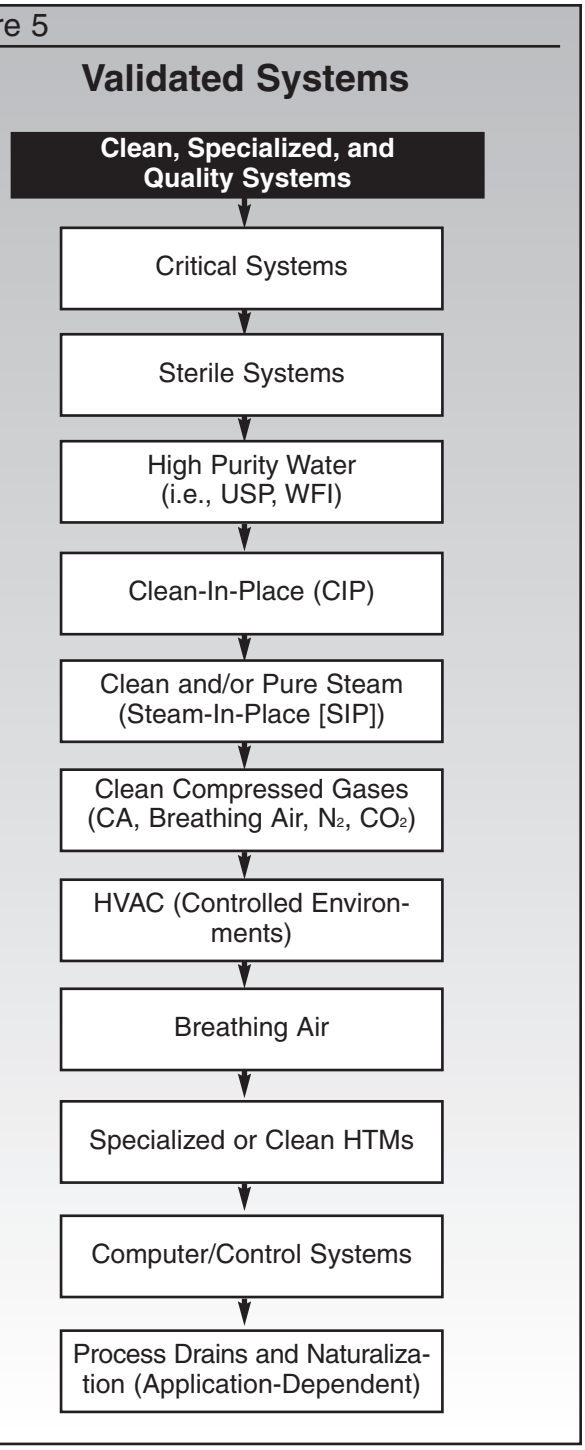


Figure 5



pact assessment is based upon the operation of a system or related equipment. The analysis will determine if either the equipment will be in direct contact with the product, or have a direct impact on the manufacture of the product. As an example, systems such as United States Pharmacopeia (USP) or Water-For-Injection (WFI) grade water, indeed come into product contact, and stainless steel surface vessels and piping also come into direct product contact, while systems,

such as chilled water and plant steam, do not. The later types of systems are usually left to be commissioned, but not validated. On the other hand, USP and WFI systems, depending on company policies, may very well be commissioned, but are definitely validated. The probability of the indirect impact systems affecting the product or its properties, is a lower probability than that of a direct impact system.

If an indirect impact system does fail, it still could have a profound impact on the manufacture or quality attributes of the final product.[4] The impact/risk assessment should demonstrate the reduced concern of failure and recall of manufactured product.

Another risk at hand is that of an FDA inspection on the so called indirect systems, as opposed to the direct impact systems. The FDA is more likely to conduct an audit and inspection of systems, such as WFI, rather than a chilled water system. Because of this fact and the impact assessment, firms have determined that following the recommendations of industry guides, written on commissioning and qualification, will be a defensible practice.

Conclusion

The role of validation and qualification needs to be defined at the very onset of the project. The first thoughts, regardless of the facility or the specifics of the process, should be how the end product will be validated. Commissioning and validation need to be close working partners in this entire effort. The results and findings of commissioning need to feed and dove tail into the recommended testing and role of validation. Commissioning has forced much of the required installation testing to be properly documented. Commissioning activities need to be performed in a quality manner which will support and augment the validation verifications and testing to be performed. As with the need for a Validation Master Plan (VMP), there should also be a commissioning plan. Again, the two need to augment and support each other.

Commissioning needs to be a quality function, and performed in a way that resists the need to have validation retest or repeat for proper verification. Validation can repeat certain tests or procedures, if necessary. Though the role of the validation IQ and OQ may appear to be somewhat diminished, there still is a place for documentation verification, and the additional testing required to insure functional and qualified equipment/systems. Validation documentation should verify that commissioning was performed properly with line items for this within the validation protocol. This would document the fact that commissioning was properly performed.

Commissioning is not just paper chase of construction and installation documentation, while validation is not a paper chase of commissioning and vendor documentation. Firms must decide upfront to define the roles of commissioning and validation. Overall policy guidelines and procedures should be developed that give adequate definition and direction to the activities of commissioning and validation. These practices and procedures need to be followed by all involved, and most especially, by the various manufacturing sites of a pharmaceutical organization. ❑

About the Author

Louis A. Angelucci III is Vice President of Validation Operations for Aker Kvaerner USA Corporation. Lou has over 18 years of experience in various aspects of validation. He has many years of blood product experience having started his career with Extracorporeal a Johnson & Johnson company. Lou is a frequent lecturer to various industry associations on the topics of cGMP compliance and validation. He also has authored numerous articles on these subjects, and serves as an Editorial Advising Board Member for the Journal of Validation Technology*. Lou has a BS in Biology, an M.S.E in Biomedical Engineering M.S.E. in Engineering Management. He can be reached by phone at 908-429-4923, by fax at 908-429-3969, and e-mail at louis.angelucci@akerkvaerner.com.*

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Article Acronym Listing

AHU:	Air Handling Unit
cGMP:	Current Good Manufacturing Practice
CFR:	Code of Federal Regulations
CIP:	Clean-In-Place
CA:	Compressed Air
FDA:	Food and Drug Administration
GEP:	Good Engineering Practice
HTM:	Heat Transfer Media
HVAC:	Heat and Ventilation and Air Conditioning
IQ:	Installation Qualification
ISPE:	International Society of Pharmaceutical Engineers
OQ:	Operation Qualification
PQ:	Performance Qualification
SIP:	Steam-In-Place
SOP:	Standard Operating Procedure
USP:	United States Pharmacopeia
VMP:	Validation Master Plan
WFI:	Water-For-Injection

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Validation of Time Synchronization

BY RICH COLVIN

syn·chro·nize *(sing' kre niz), v., -nized, -niz·ing.*
–v.t. to cause to indicate the same time, as one timepiece with another: Synchronize your watches.
— Webster's Unabridged Dictionary

Time synchronization, the action of synchronizing one timepiece with another, is an issue that needs to be considered within the overall scope of an infrastructure validation program.

This article is intended to provide background on the accuracy of timepieces and how timepiece synchronization typically works, then outline issues that need to be considered when including time synchronization in your company's infrastructure validation program. The background information may be of particular use when defending the approach used for your validation program.

For this article, validation is defined as:

… a formal, systematic approach that provides documented evidence, demonstrating with a high degree of assurance, that the software or system will consistently achieve its predetermined, specified requirements and quality attributes.

Validation ensures accuracy, reliability, and consistent intended performance.

For the validation of time synchronization, the biggest issues that need to be addressed include:

1. Defining the accuracy requirements
2. Testing the accuracy of a system
3. Ensuring accuracy, reliability, and consistent intended performance

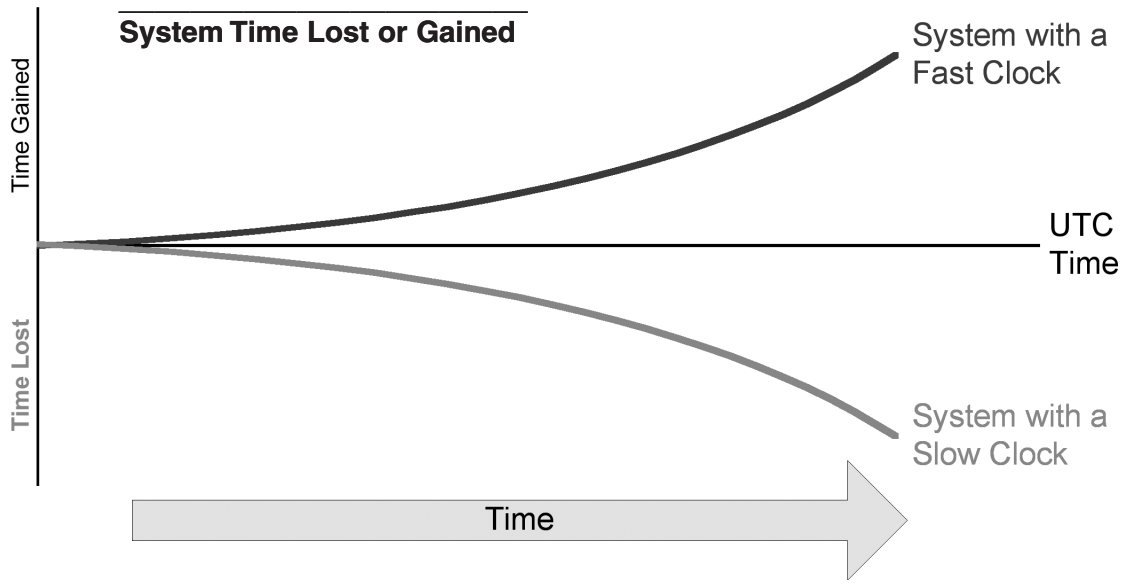
Each of these issues is detailed in this article.

Accuracy of a Computer System's Timepiece

Computers maintain their time using an internal, crystal-based clock. This basis for maintaining time is considered

Figure 1

System Time Lost or Gained



accurate to a point,[1] but the system's measure will vary over time. One way to visualize this is shown in *Figure 1.*

In this figure, the time on the computer is either faster (above the line) or slower (below the line) than the accepted standard (Coordinated Universal Time {UTC} is the international standard).[2] The amount of time lost or gained will continue to increase over time to the point where the system's measure will be noticeably wrong.

Many system administrators have setup their network systems so that the client PC's (Personal Computer) time is reset when a user logs on. This action is commendable, however, it probably won't hold much weight in an audit. What is needed is defensible proof that the system's time is accurate.

How Time Is Distributed

The Internet community has created many new and wonderful technologies, one of which is the Network Time Protocol (NTP).[3] The definitions for these protocols are public, and are maintained online by the Internet Engineering Task Force (IETF).[4] Following is a list of the latest versions:

PROTOCOL	DEFINITION
NTP version 3	RFC 1305
SNTP version 4	RFC 2030

NTP is a pull system, not a push system. This means, that each system gets its time from an NTP server. A common configuration is shown in *Figure 2*

Figure 2

Timepiece Accuracy w/Correction Applied

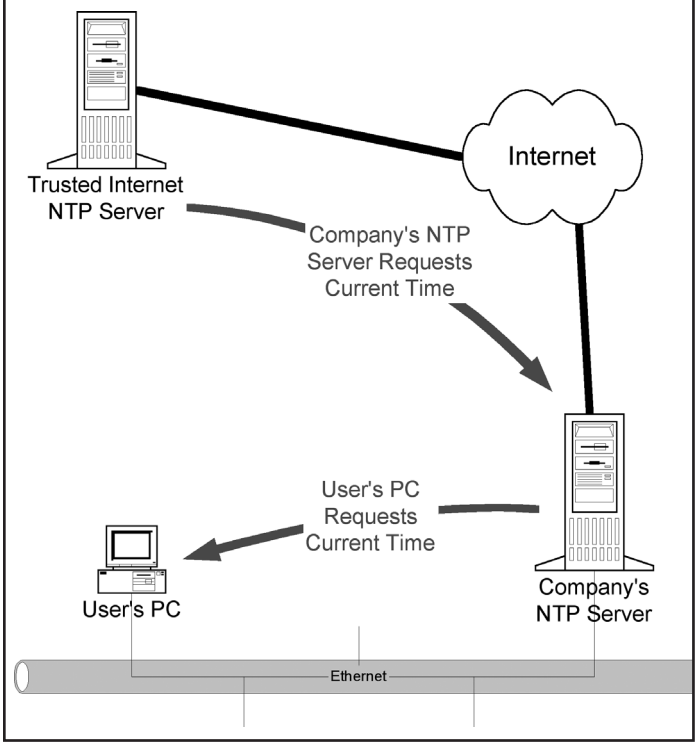


Figure 3

Time Resets Over Time

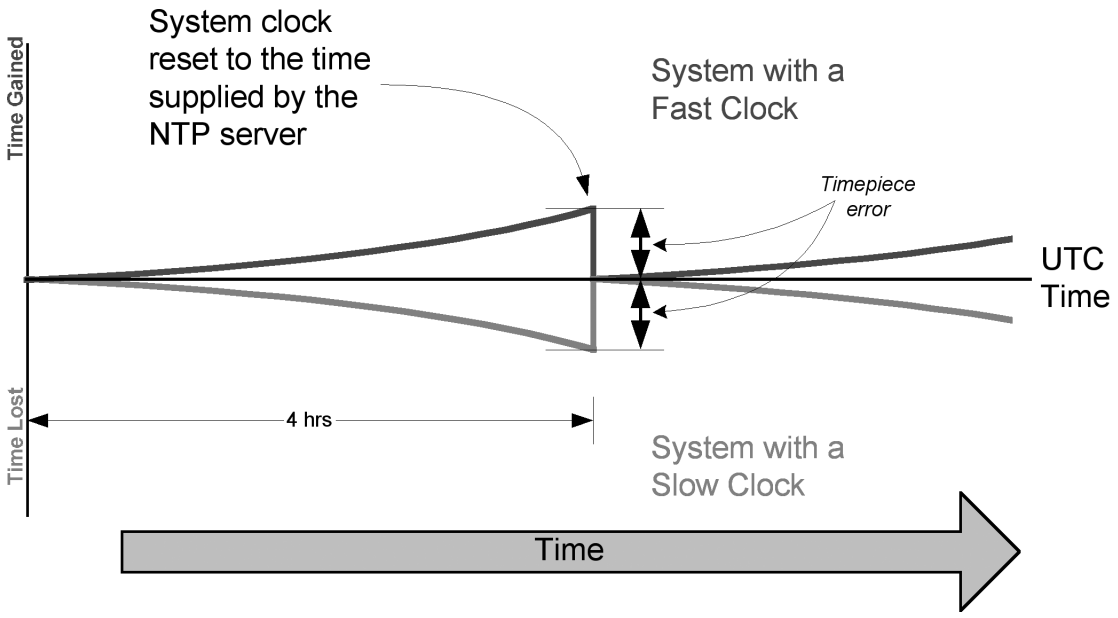
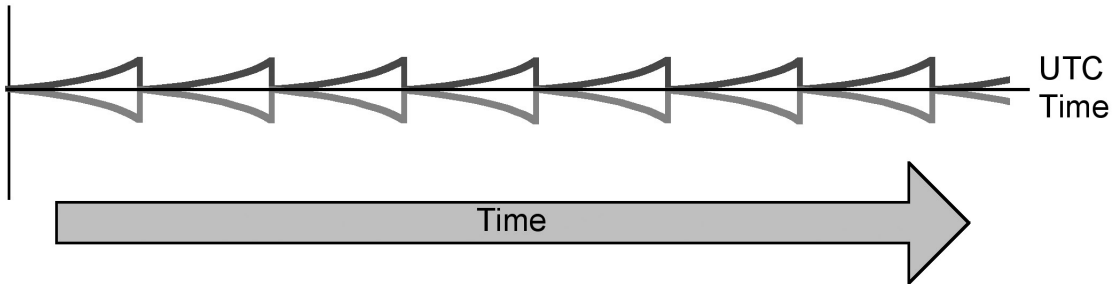


Figure 4

Time Resets Over Time



Typically, the client system (e.g., user's PC) sends the request for an update based on a schedule (e.g., every 4 hours). In such a system, the chart for the client system's timepiece accuracy is shown in *Figure 3*. Over time, this will look like *Figure 4*.

The frequency at which the timepiece is reset can be increased, decreasing the timepiece error. At some point, however, the resetting process would reach a point of diminishing returns, and could, potentially, overtax the NTP server or the network.

How Accurate Must the System's Timepiece Be?

The most accurate timepieces in America are the U.S. Naval Observatory's[5] (USNO) Master Clock and the National Institute of Standards and Technology's[6] (NIST) NIST-F1 clock.

Figure 5

Time Service Department in the USNO

The present USNO Master Clock is currently based on a system of 50 independently operating cesium fountain atomic clocks and 9 hydrogen maser clocks. It is considered accurate to ± 10 nanoseconds (± 0.000 000 010 seconds); however, the Naval Observatory is constantly looking at new ways to improve the accuracy of timekeeping.

NIST's F1 clock is a cesium fountain atomic clock, and is the primary time and frequency standard for the United States. It is the eighth in a series of increasingly accurate clocks emplaced by NIST, and is predicted to be accurate to ± 1 second in 20 million years.

That level of accuracy is needed for some functions (e.g., frequency measurements at very short wavelengths); however, it probably isn't needed for maintaining audit log accuracy in computer systems. In addition, the cost of such a clock is prohibitively high for every company to utilize. For commercial computer systems, other sources may be more useful.

The United States (U.S.) Global Positioning System (GPS) gets its time from the USNO Master Clock. As a system, GPS' time is designed to stay within ± 1 microsecond (± 0.000 001 seconds). In practice, however, the time is more accurate than that.

GPS provides two signals: one for anyone to use (the standard positioning service {SPS}) and one for the military's use (precise positioning service {PPS}). The accuracy of both GPS signal times are measured and published on the Internet. A recent review of the data collected showed the SPS system is correct to within ± 340 nanoseconds (± 0.000 000 340 seconds), while the time on the PPS is correct to ± 200 nanoseconds (±0.000 000 200 seconds).[7]

Various manufacturers sell GPS receivers that can be setup as an NTP timeserver on a company's network; however, they can be relatively expensive to install. If nothing else, the GPS receiver's antenna must be installed outside the building. A typical configuration is shown in *Figure 6*.

One option that's less expensive is to install an NTP timeserver that gets its time signal from the cell phone network. The cells in a digital phone network [e.g., Code Division Multiple Access (CDMA)] must be kept within a certain level of accuracy or the phones in the network won't work

correctly. To achieve the required accuracy, most digital phone towers are kept within ± 10 microseconds (± 0.000 010 seconds). A typical digital phone signal receiver could also provide reasonable accuracy as an NTP timeserver. This is shown in *Figure 7*.

A company's Internet firewall generally gets its time from a timeserver on the Internet. Many firewalls can also act as an NTP server for the company, and the use of this option may have value to the company. (This is the configuration shown in *Figure 2*.)

Wall Clocks Matter Too !

The accuracy of a company's wall clocks is important, and should also be considered. Code of Federal Regulations 21 (CFR) 11 makes a vague reference to this in §11.10:

> *Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and* ***to ensure that the signer cannot readily repudiate the signed record as not genuine.***
>
> *— 21 CFR 11.10*

The goal here is to prevent an individual from denying that he or she signed a record because the wall clock's time is different from the system's time. Fortunately, the National Institute of Standards and Technology (NIST) has a solution (see also, *Figure 9*).

The system (WWVB[8]) was originally constructed in 1962; however, in the late 1990's, NIST refurbished their low frequency (60 kHz) time transmission system. Now, radio-controlled clocks that can utilize that transmission to ensure they maintain the correct

Figure 6

Typical GPS-Based Configuration

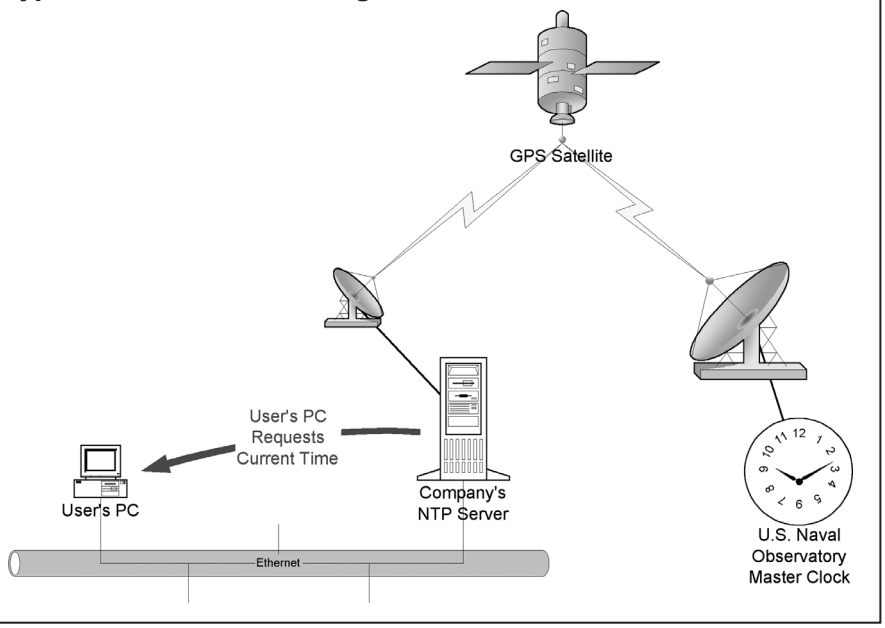


Figure 7

Typical Digital Cell Phone-Based NTP Configuration

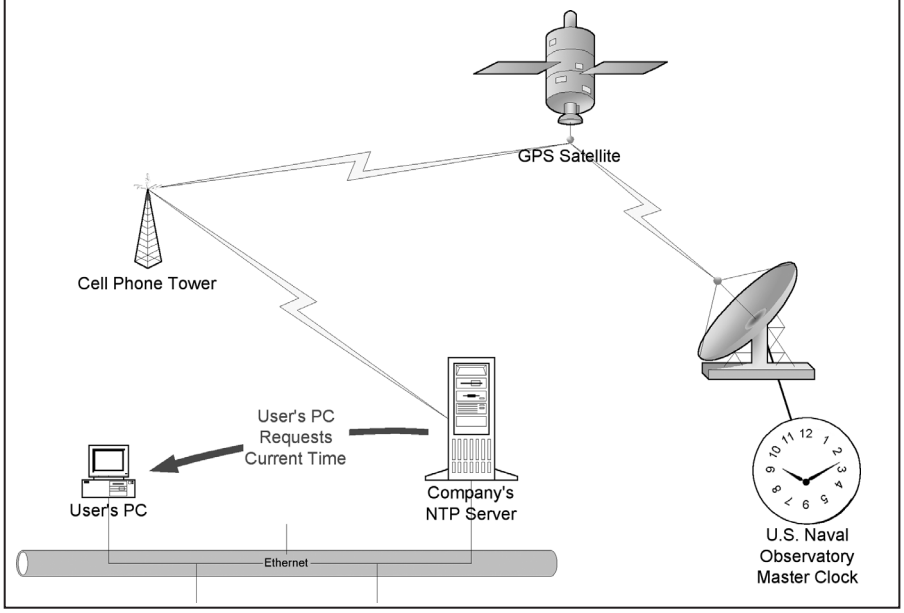


Figure 8

NIST's Radio Stations WWV & WWVB

time[9] are available at reasonable costs.

The transmission originates near Ft. Collins, Colorado, and is best received at night. The low frequency radio transmission does not allow for high transmission of data,[10] so the time information takes a full minute to transmit. The clocks have a receiver that receives the signal continuously, but decodes it on a set schedule. Some, like the watch I own, decode it (and set themselves appropriately) only once daily (my watch sets itself at 2300). Others decode the signal every 4-6 hours.

If the company has a centralized, master clock system, another option might be available. A system such as shown in *Figure 10* could possibly be implemented to synchronize the time.

A typical configuration implemented this way might have the master clock updated on a once per day basis.

Accuracy Requirements

21 CFR Part 11 addresses time synchronization to a limited extent in the following areas:

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

Figure 9

WWVB Time Transmission

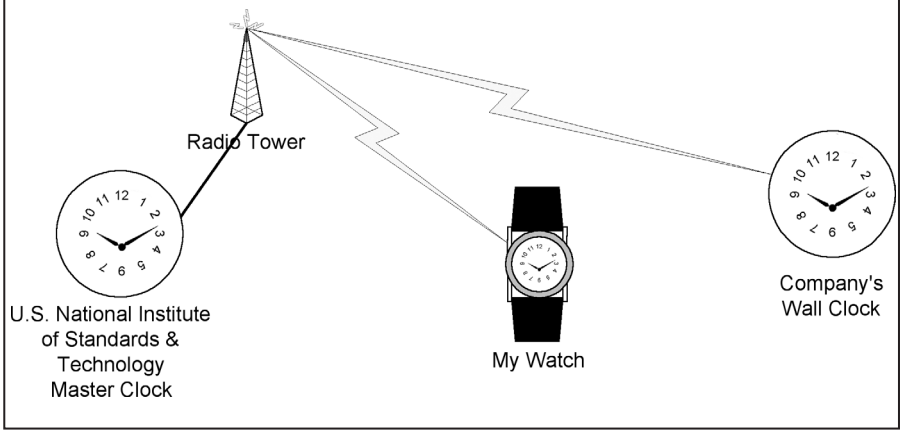
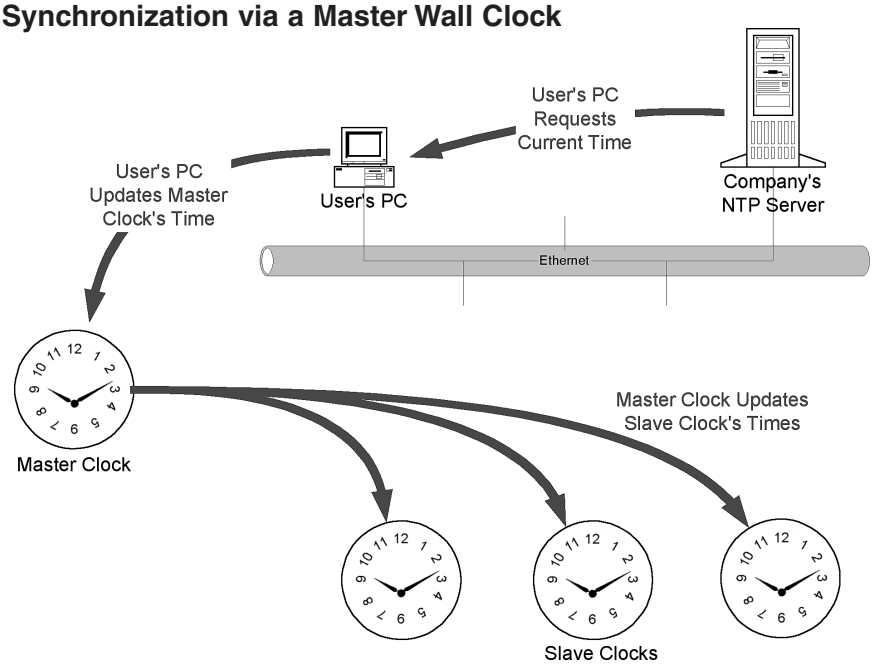


Figure 10

Synchronization via a Master Wall Clock



(k) Use of appropriate controls over systems documentation including:

(2) Revision and change control procedures to maintain ***an audit trail that documents time-sequenced*** *development and modification of systems documentation. — 21 CFR 11.10*

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(2) ***The date and time when the signature was executed*** *— 21 CFR 11.50*

The FDA's guidance on time stamps for audit trails was withdrawn, however, the accuracy requirements for the audit trail (based on 21 CFR 11) are generally accepted to be precise to the hour and minute. Ensuring accuracy beyond that may not be needed for meeting Part 11 requirements; however, general validation requirements may require higher levels of accuracy. In particular, validation of plant-floor systems may require accuracy to the millisecond level.

Accuracy Requirements

Defining the accuracy requirements is probably one of the biggest problems in the validation efforts for infrastructure systems. Defining a testing strategy is a manageable task – if the requirements are known. In the case of time, we know that the time needs to be "right;" however, we haven't defined what that means.

Within the manufacturing environment, sensors are used for many parts of the process. These sensors must be shown to be accurate for the process in which they are used. A typical approach is to ensure the sensor is four times as accurate as needed for the process specification. Therefore, if a process temperature must be measured to within 1˚C, the sensor measuring that temperature is tested to ensure it is accurate to at least 0.25˚C.

The difficulty in applying this logic to time is that we don't typically define how accurate our clocks must be. If we were to say that our clocks must be accurate to within one minute, then we could (theoretically) test to ensure it was accurate to within 15 seconds.

For some applications (e.g., data historians), data is sampled on periods of 100 – 500 milliseconds (0.1 – 0.5 seconds). If this is the requirement, then the clocks must be accurate to 25 – 125 milliseconds (0.025 – 0.125 seconds).

Some applications on the plant floor run even faster. Typical PLC (Programmable Logic Controller)-based applications run sensor sample cycles on the order of 10 – 25 milliseconds. This requirement for accuracy would then be 2.5 – 12.5 milliseconds (0.002 5 – 0.012 5 seconds).

Testing Accuracy

We must be extremely careful with the accuracy we specify, because we must be able to measure the accuracy we require. If a system must be accurate to 100 milliseconds, then we must find a way to ensure the computer system's clock is accurate to 25 milliseconds. Since that is 0.025 second, we must have an application that logs accuracy of the time to three or four decimal places.

The systems I've used only record time adjustments to one decimal place. Given that, my system could only be considered accurate to 0.4 seconds. In actuality, the official system updates on my system are 0.2 – 2.3 seconds, with a mean of 1.45 seconds and a median of 1.7 seconds. Therefore, I'd expect my system to be considered accurate in the range of ± 10 seconds.

For higher accuracy requirements, I recommend a solution I learned in the Army. I call it the Pacing Solution.

The Pacing Solution

Prior to the invention of GPS, a field soldier had to use dead reckoning for navigation. The direction he or she moved from a fixed point was determined using a compass, but the distance traveled is more difficult to accurately pinpoint. Each soldier has a different stride length, so the number of steps walked between the two points will differ with the soldier.

To solve this problem, a known distance is marked (usually 100 meters). Each soldier walks the distance, counting his or her steps between the two points. This exercise is repeated until the soldier gets three counts that are the same. The step count then becomes that soldier's personal multiplier for distance measurements.

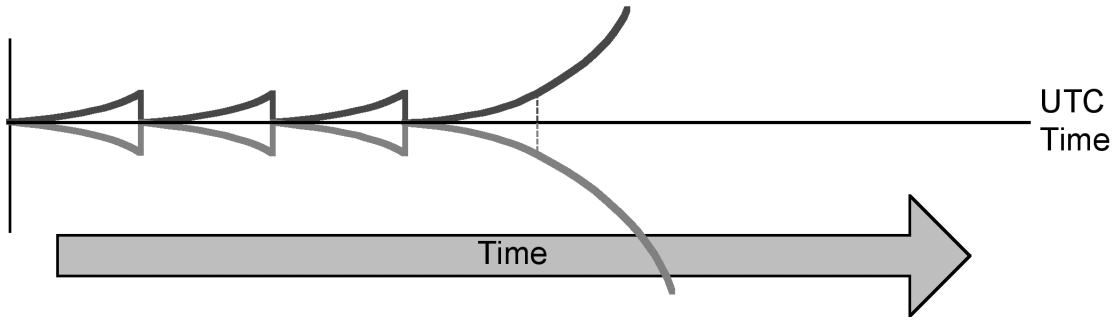
So, if some soldier's step count is 130 steps per 100 meters, and he or she must travel three kilometers, then the required step count would be 3,900. That sounds fine on paper; however, the soldier would probably lose count somewhere around 100. To solve that, the soldier was taught two things:

1. Count every other step, essentially making the count 65 steps per 100 meters
2. Every 100 meters, tie a knot in a string, then start counting over

Using this method, when 30 knots were in the string, he'd traveled 3,000 meters. That's the theory, but some soldiers are better at it than others are. Their accuracy is measured by having them travel long distances during training

Figure 11

Exaggeration of Timepiece Error When Not Reset



exercises. An accurate soldier would have 43 knots when he has traveled 4,300 meters.

The Pacing Solution Applied

This method may be applied to our problem as follows:

1. Synchronize the computer timepiece (the measured clock) with a known, calibrated system (the reference clock).
2. After a relatively long time period, compare the two timepieces. The time delta can then be used to calculate the accuracy.

For this example, let's assume the measured clock must be accurate to ± 2.5 milliseconds (0.0025 seconds) over a one-minute period. If they start from the same point and are observed over a period of 100 hours, then at the end of the period, the measured clock should be within 15 seconds of the time measured by the reference clock.

Ensuring Intended Performance

NTP is an excellent method by which a system's timepiece may be reset to a standard time. However, it only works when invoked. If the NTP time update is not invoked, then the client PC's time won't be accurate. In this case, the system will act as shown in *Figure 11*.

For this reason, client system timepieces will have to be inspected on a periodic basis to ensure the corrections are occurring on a regular basis. One method for performing this inspection is to include the time monitoring systems as part of the company's PM (Preventive Maintenance) or calibration program.

Conclusion

Timepiece synchronization should be performed, and the accuracy of the timepieces should be validated. This is not a difficult process, and it should be undertaken to provide evidence that the systems meet regulatory requirements. To perform the validation, your organization should apply due diligence in its research to ensure their expectations and efforts are appropriate. ❑

Article Acronym Listing

CDMA:	Code Division Multiple Access
CFR:	Code of Federal Regulations
GPS:	Global Positioning System
IETF:	Internet Engineering Task Force
kHz:	Kilohertz
mHz	Megahertz
NIST:	National Institute of Standards and Technology
NTP:	Network Time Protocol
PC:	Personal Computer
PLC:	Programmable Logic Controller
PM:	Preventive Maintenance
PPS:	Precise Positioning Service
RFC:	Request For Comment
SNTP:	Simple Network Time Protocol
SPS:	Standard Positioning Service
U.S.:	United States
USNO:	U.S. Naval Observatory
UTC:	Coordinated Universal Time
WWV and WWVB:	NIST [low frequency time transmission systems (radio stations)]

Aknowledgements

Facility pictures shown in this article are courtesy of the U.S. Government agencies indicated in the captions. They were taken from the agencies' web sites.

Accuracy of the NIST and USNO timekeeping systems were taken from their respective web sites.

About the Author

Rich Colvin is the manager of the Quality Implementation Services Department within corporate IT at Abbott Laboratories. Mr. Colvin may be contacted by email at richard.colvin@abbott.com.

References

1. Crystal-based computer clock accuracy is on the order of ±1 minute per month.
2. Greenwich Mean Time (GMT) is not the standard as is commonly believed. For more information on UTC, see also the U.S. Naval Observatory's web site (http://tycho.usno.navy.mil).
3. Information about NTP is available online (http://www.ntp.org). This site also has information about NTP's little brother, Simple Network Time Protocol (SNTP), another product of the Internet community.
4. http://www.ietf.org.
5. The U.S. Naval Observatory, part of the Department of Defense, has an excellent web site with great information (http://tycho.usno.navy.mil).
6. The National Institute of Standards and Technology, part of the Department of Commerce, has an excellent web site with helpful information (http://www.nist.gov).
7. Taken from the USNO's GPS Time Transfer information (http://tycho.usno.navy.mil/gpstt.html) on 25 June 2003.
8. The WWV series of transmissions have long been used by the military and amateur radio enthusiasts for ensuring they have the correct time. The long distance transmissions on the HF radio band (2.5, 5, 10, 15, & 20 MHz) are affected by many factors, including sun spot activity. They are most reliable at the start of the night.
9. A list of manufacturers is available at NIST's web site (http://www.boulder.nist.gov/timefreq/general/receiverlist.htm).
10. The speed of data transmission is 1 bit/second.

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Qualification of Quality Control Laboratories

By Mowafak Nassani, Ph.D.
International Clean Rooms Control Engineering

The basic concepts of Quality Assurance (QA), Good Manufacturing Practice (GMP), and Quality Control (QC) are interrelated. QA is responsible for ensuring defective product does not reach the market, they assist production in running a satisfactory process, assist production in trouble shooting, and provide the final independent judgement of a product's suitability for sale. The responsibility for quality is shared between production, QA, and QC.

As mentioned in the European Guide for GMPs (Pharmaceutical Legislation volume four [4])[1]

"Each holder of a manufacturing authorization should have a QC department. This department should be independent from other departments and under the authority of a person with appropriate qualifications and experience." The QC department is concerned with sampling, specification, and testing, as well as the organization, documentation and release procedures that ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

The important and vital role of the QC department make it the first target of quality compliance inspectors. The QC laboratories inspection requires the use of observations of the laboratories in operation, and of the raw data to evaluate compliance with current Good Manufacturing Practices (cGMPs).

"By using the validation/ qualification approach, the QC laboratories can achieve the highest product control."

In the Food and Drug Administration's (FDA) inspection of QC laboratories, they evaluate raw laboratory equipment and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with cGMP regulations.

By using the validation/qualification approach, the QC laboratories can achieve the highest product control. Pharmaceutical process validation/qualification defines the types of procedures needed to assure that product quality is maintained.

Figure 1 illustrates the main critical areas submitted to the validation/qualification approach:

- Analytical methods (physical, chemical, and microbiological)
- Equipment
- Procedures
- Document control
- Reference standards and reagents
- Statistics and data treatment

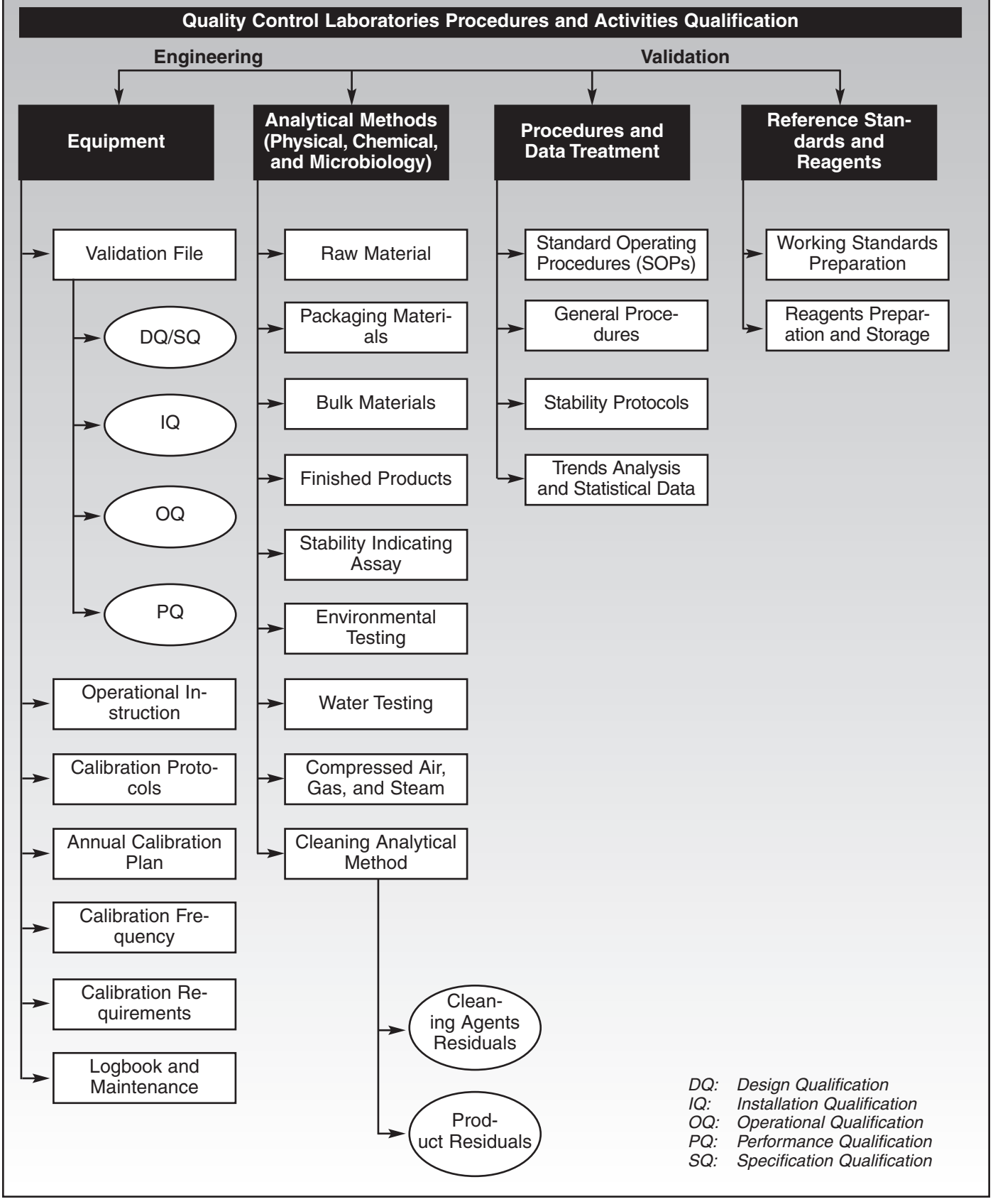
Analytical Methods Validation

Standard Requirements

The objective of method validation is to demonstrate through systematic evaluation that an analytical method is adequate for its intended use. In particular, validation is useful in ensuring that when the method is applied in different laboratories, it is capable of giving reproducible and reliable results.

Figure 1

Main Qualification/Validation Areas in Quality Control Laboratories



The FDA, the International Conference on Harmonization (ICH) and European Union (EU) have clearly defined requirements for validation of all processes and analytical methods used in the production, formulation, and distribution of finished pharmaceuticals.

The method validation or method performance applies for all material testing methods of any material in relation to product manufacturing including; raw materials and packaging materials, intermediate and bulk products, finished products, stability indicating assays, environmental testing (swabs, air samples, etc.), water testing, compressed air, gases, steam, and cleaning methods (chemical residuals of drug formula, cleaning agent residuals).

Validation of analytical methods ensures conformance to corporate and regulatory standards established for individual analytical methods.

The requirements for method validation will depend upon the particular test being conducted, and the particular technique being applied. In fact, method validation is the final step in a dynamic process, similar to that which a drug undergoes from discovery through final product approval.

Method validation starts with the definition of the technical objective. It proceeds from its selection through the development necessary to ensure that the method meets the technical objective.

Progressing to the preparation of the final testing procedure, and the protocol defining the specifics of the validation experiments, it concludes with the performance of the formal validation. A successful validation guarantees that both technical and regulatory objectives of the analytical method have been fulfilled.

Since a successful validation requires the cooperative efforts of several departments including; Regulatory Affairs, QC, and Analytical Research and Development, it is essential that the organization has a well defined Validation Master Plan (VMP) for analytical methods. Therefore, successful fulfillment of the regulatory and technical objectives requires total management support.

Scope

A minority of analytical methods may require very little validation (e.g., pH measurement, appearance, conductivity measurement). Where reduced validation is carried out, the justification should be documented.

Under certain circumstances, it may not be necessary to examine all aspects of method validation. In this instance, several stages may be reduced if:

- Only one analyst is ever likely to apply the final method
- The method is applied only to intermediate or starting materials and not finished product
- The sample matrix is very simple (e.g., water, compressed air, gases, etc.)
- The requirements of the method are judged to reduce validation requirements
- Compendial pharmacopoeial methods must be validated for formulation and/or matrix effects, or must be verified for their suitability under the actual conditions of use

Analytical method validation is applied to all analytical methods developed for the analysis of:

- Major components of bulk substances or actives ingredients, including preservatives in finished pharmaceutical products
- Impurities or degradation compounds in bulk drug substances or in finished products
- Performance characteristics, such as dissolution, disintegration, etc.
- Cleaning validation

System Requirements

Criteria

Establishing Criteria

Criteria for validation of an assay is established by the developer with consideration of the stage of development and the analytical test method; and for conformance to corporate and regulatory standards.

Guidelines for validation can be found in chapter 1225 of the United States Pharmacopeia (USP).[2]

A detailed guideline by analytical test is detailed in *Figure 2*.

Performance Criteria

Selectivity/Specificity

Few techniques are specific (i.e., each analyte will produce a totally unique response).

Many techniques are selective (i.e., High Performance Liquid Chromatography [HPLC], Gas Chromatography [GC], Capillary Electrophoresis [CE], Spectro Fluoro-

Figure 2

Analytical Method Validation Parameters

Method	*Analytical Method Validation Parameters*								
	Accuracy	Precision (Repeatability)	Linearity	Reproducibility	Selectivity	Specificity	Limit of Detection	Limit of Quantitation	Ruggedness/ Robustness
Loss of Drying	Yes	Yes							
Water by KF Titration	Yes	Yes							
Solvent by ^{1}H NMR					Yes		Yes		
Related Impurities By:									
HPLC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TLC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anions/Cations:									
IC	Yes	Yes		Yes	Yes	Yes	Yes	Yes	
CE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Wet Chemical Test	Yes	Yes		Yes	Yes	Yes	Yes	Yes	
A (One Percent, One cm)		Yes							
Metals by ICP-AES	Yes	Yes	Yes		Yes		Yes	Yes	
Swab Analysis	Yes	Yes	Yes		Yes	Yes	Yes	Yes	
Dust Analysis	Yes	Yes	Yes		Yes	Yes	Yes	Yes	

CE: *Capillary Electrophoresis*
GC: *Gas Chromatography*
HPLC: *High Performance Liquid Chromatography*
IC: *Ion Chromatography*
ICP: *Inductively Coupled Plasma*
KF: *Karl Fischer Titration*
NMR: *Nuclear Magnetic Resonance*
ICP-AES: *Inductively Coupled Plasma-Atomic Emission Spectrometry*
TLC: *Thin Layer Chromatography*

photometry Chromatography [SFC], Thin Layer Chromatography [TLC], Ultra Violet [UV] – spectroscopy, mass spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, etc.), and demonstrate an ability to discriminate between analytes. It should be noted that the terms specificity and selectivity are not the same. It must therefore be clearly defined in the method objectives whether specificity or selectivity is the required parameter.

In the selectivity, the analytical method must be shown to be capable of accurate, selective measurement of the analyte in the presence of other components that may be expected to be present. These may include: impurities of synthesis, degradation products, excipients, preservation, internal standards, and their degradants, and finally any other active ingredients in a formulation.

At the 95% confidence level, the procedure should not have a significant bias. Specificity is demonstrated if:

- The assay shows no significant interference from known degradation products
- There is no significant interference from the product excipients with the potency assay
- Bulk drug assays have no significant interference attributable to known degradation products and process impurities

When the potential interfering substances are spiked into the method, recovery should be at least 90%, and Relative Standard Deviation (RSD) should not exceed two percent.[3]

Precision (Repeatability)

Precision is a measure of the degree of reproducibility of the analytical methods under normal operating circumstances being an expression of the agreement between replicate measurements made on identical test material under the same conditions (same operator, same interval of time).

The precision of an analytical method is usually expressed as the standard deviation of variation) of replicate test results.

Precision is a function of the size of the acceptance range or specifications, and the consideration of the samples assayed, with consideration of the overall operational efficiency.

The RSD should be typically <1% for standards measurements, <1.5 % in precision evaluation of standard preparation, and the same value could be used as a rough guideline for precision evaluation of sample preparation. For microbiological assays, RSD five percent or less could be accepted.

The criteria for acceptability of RSD values will depend greatly on the type of method used, and may vary with sample type, for example, a higher RSD may be acceptable for blends, inhalers, trace, limit tests, etc.

Reproducibility

Reproducibility is the precision of a method as measured under certain circumstances. It is an expression of the agreement between replicate measurements made on identical test material under different conditions, operators, apparatus, laboratories, and/or times. It is termed "intermediate precision" in the ICH guidelines on validation.[4] To evaluate reproducibility of an analytical method, an exercise could be performed by two analysts on one or more sets of samples sufficient for at least three determinations to be carried out on each set. The overall RSD of less than 2.0% would be expected. Higher values may be acceptable, depending upon sample type, and significantly higher values may be acceptable for trace analysis.

Accuracy

Accuracy is a measure of the closeness of the results obtained by the true value. Accuracy is often determined from recovery studies over a given range. Acceptable tolerances for accuracy parameters are a function of the test method, and the concentration of the component being measured.

Accuracy limits and ranges are determined by the function of the test. Recovery experiments involve application of the analytical method to sample preparations where a known quantity of the analyte(s) of interest has been added to the matrix, or a synthetic copy of the matrix in which the analyte(s) is to be analyzed. The recovery may be expressed as the percentage recovered by the assay of a known added amount of analyte.

In addition to recovery studies, consideration may be given to comparison of the results from the method undergoing validation with those obtained by an alternative test procedure that should be as different as possible from the procedure being validated.

Linearity

It is an assessment of the method's ability to give results that are proportional to the concentration of analyte in the samples within a given range. Establishing the linearity of response by preparing ideally at least five reasonably distributed standards of the active(s) of interest at concentrations range from typically 20% to 150% of the theoretical. A linear regression analysis of the results is carried out versus concentration (e.g., response versus weight of analyte taken). The equation of the line, correlation coefficient, and intercept should be documented (the total number of standard curves should be 45).

Three analysts, running three separate assays using five sets of controls in each assay/linearity needs to be determined over the full range of the assay.

Typically, the correlation coefficient should be greater than 0.997 (a straight line is 1.0). The intercept (expressed as percentage of the typical response for the nominal concentration) should be typically within the range ± two percent for a main component assay.

A higher value may be acceptable for the determination of related impurities.

Ruggedness

Method ruggedness is a measure of how small changes in operational parameters affect the qualification of the analyte.

It is determined by evaluating those potential variables that result from multiple technicians, multiple laboratories, different instruments, different environmental conditions, etc.

Each of the potential variables should be listed, and then a determination made as to how experimentally each can be evaluated in a controlled experiment.

Method ruggedness can be evaluated also by making deliberate, small changes to the operating conditions, and assessing whether such changes have any significant effect upon the validity of the method.

ICH guidelines identify robustness/ruggedness as reproducibility. The robustness/ruggedness differs from reproducibility in that more than one sample is involved, and may be determined as part of the transfer of a method.

"The Code of Federal Regulations (CFR), Chapter 21, Part 211.194 concerning "Laboratory Records," requires that: "...the suitability of all testing methods shall be verified under the actual conditions of use."

Limit of Detection

The limit of detection is the lowest concentration of analyte in a sample that can be detected, but not necessarily accurately or precisely quantified under the stated experimental conditions.

The limit of detection is typically defined as the concentration giving a signal-to-noise ratio of: 3 (S/N = 3).

Sensitivity (Limit of Quantification)

Limit of quantification is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy under the stated analytical conditions. Typically, the limit of quantitation is defined as the concentration given a signal-to-noise ratio of 10 (S/N = 10).

Potential Interference

Assays may have interference from water, containers, buffers, chemical impurities, reagents, etc. A blank sample should be prepared and tested in order to identify the potential interference. This interference should then be listed, and a determination made as to how experimentally each can be evaluated in a controlled experiment.

Stability of Standard and Sample

It is always important to determine the stability of prepared samples and standards. Even if it is required that samples and standards be prepared just prior to use. Stability must be considered since these solutions may sit on an auto sampler rack for 12 to 24 hours or more when large sample volumes and long run times are involved.

The study of sample and standard solutions stability may determine the maximum interval that can be allowed between sample preparation and analysis, under the defined conditions (e.g., temperature required, light exposition).

System Suitability Checks (SSCs)

The Code of Federal Regulations (CFR), Chapter 21, Part 211.194 concerning "Laboratory Records,"[5,6] requires that: "…the suitability of all testing methods shall be verified under the actual conditions of use."

Therefore, at this stage of the method validation, the analytical chemist must experimentally demonstrate the method's ability to achieve the regulatory and technical objectives. Typical examples of the SSCs that might be applied to chromatographic methods are resolution between two closely resolved peaks, column efficiency, and peak tailing

System Sequence

During the documentation of the validated method, it is imperative to define the assay sequence.

The system or assay sequence describes the following:

- How many analyses of each standard and sample are required? How many sample analyses can be run between standard analyses? Are samples analyzed using bracketing standards, the average of all standards, or the first standards only?
- Is a standard run at the end of all analyses used to confirm that the system is still suitable? What are the requirements for the analyzed standard value?

An assay sequence is necessary to define the method precision or batch testing portion of the validation, and to confirm that once that assay sequence has been validated, it is used for all additional sample analyses.

Change Control and Revalidation

Methods should be continually appraised and any changes in performance should be noted.

Following a change to a method, additional validation will be required.

Documentation of a new method or changes to an existing method must be reviewed and approved prior to changing the actual practice. There must be a system that provides for retrieval and review of the documentation for all changes to a method.

Method Assessment and Documentation

Once a method has been developed, it must be formally documented in a final analytical test and validation protocol.

Validation experiments are designed to adequately test and optimize the method parameters.

Validation experiments are performed using established criteria to determine the acceptability of the method as appropriate. Suitable statistical evaluations of test data are utilized to determine conformance to the established criteria.

Method Validation Protocol

The validation protocol is the culmination of all the regulatory and technical accomplishments up to this point in the development of the method. Therefore, developing the validation protocol is the most important step in the validation process.

The validation protocol states how the validation will be conducted, the key variables evaluated, what analytical testing methods are required, and what constitutes acceptable results.

The validation final report analyzes the data and summarizes the findings.

The validation protocol must define which validation parameters are needed, and the specific experiments necessary to demonstrate the validity of the analytical method. The protocol must contain all of the acceptance criteria for each of the relevant validation parameters. Additionally, the protocol must define the number of replicates, reporting format, and number of significant figures. Briefly, the validation protocol instructs the analyst on how to validate the analytical method.

The validation protocol contains the following main sections:

- Approval page and signatures
- Title
- Purpose
- Introduction
- Responsibilities
- Definitions.
- Prequalification requirements:
  - Objectives
  - Configurations and conditions
  - Sample requirements and identification
  - Test parameters and methods
  - Acceptance criteria
  - Data handling
  - Results
  - Conclusion and recommendations
- Materials and equipment
- Procedure
- Test report with conclusion

Analytical Test Procedure

The analytical test procedure includes the following main sections:

- Objective/purpose
- Scope
- Test upper and lower limits
- Summary of methodology
- Instrumentation and equipment
- Reagents
  - List of reagents
  - Preparation of reagents
- Preparation of standards and samples
  - Preparation of standards
  - Preparation of samples
- Operating conditions
- Procedures
  - System suitability
  - Analyte(s) Identification
  - System Sequence
- Calculations/Result
- Approval

Laboratory Equipment

Before any method validation can begin, the relevant analytical method equipment must have satisfactorily completed the validation requirements for all critical equipment including; Design Qualification (DQ)/Specification Qualification (SQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

Equipment Validation Matrix (EVM)

A list of laboratory equipment should be prepared containing all critical and non-critical equipment. Based on this list, a validation matrix should be established to summarize the validation plan and to determine the validation requirements for each piece of equipment. *Figure 3* lists the EVM.

Validation of Laboratory Equipment

Following the EVM, the validation work starts.

A validation team should be formed to develop the equipment specification. This team should include qualified persons from the QC and engineering departments. The participation of engineers or technicians from the engineering and maintenance departments is important due to their future role in the equipment calibration and maintenance.

When developing the specifications, you should examine the following items:

- Materials used in the construction of the equipment (where applicable)
- Utilities needed for the operation of the equipment
- Operating requirements
- Safety considerations
- Vendor qualifications. Finding the right equipment from the right vendor is critical to success
- Space requirements
- Equipment measuring ranges
- Critical spare parts
- Warranty

Design Qualification (DQ) Specification Qualification (SQ)

The validation team should review the specifications outlined here to ensure all validation items are included in

Figure 3

Equipment Validation Matrix (EVM) for Some Critical Equipment

Equipment	DQ/SQ	IQ	OQ	PQ	Calibration
Atomic Absorption	Yes	Yes	Yes	Yes	Adj.*
Autoclave	Yes	Yes	Yes	Yes	Yes
Balances	Yes	Adj.*	Adj.*	**	Yes
CE	Yes	Yes	Yes	Yes	Adj.*
Conductivity Meter	–	–	Yes	Yes	Yes
Disintegration Tester	Yes	Adj.*	Yes	Yes	Yes
Dissolution Tester	Yes	Adj.*	Yes	Yes	Yes
Drying Oven	Yes	Yes	Yes	Yes	Yes
Gas Chromatography	Yes	Yes	Yes	Yes	Adj.*
High Performance Liquid Chromatography (HPLC)	Yes	Yes	Yes	Yes	Adj.*
High Performance Thin Layer Chromatography (HPTLC)	Yes	Yes	Yes	Yes	
IC	Yes	Yes	Yes	Yes	Adj.*
IR	Yes	Yes	Yes	Yes	Adj.*
Laminar Flow	Yes	Yes	Yes	Yes	Yes
Microbiological Incubator	Yes	Yes	Yes	Yes	Yes
IR	Yes	Yes	Yes	Yes	Yes
NMR	Yes	Yes	Yes	Yes	Adj.*
pH Meter				Yes	Yes
Potentiometer	Yes	Adj.*	Adj.*	Yes	Yes
Tablet Friability Tester	–	Adj.*	Adj.*	Yes	Yes
Tablet Hardness and Thickness Measurement	Yes	Yes	Yes	Yes	Yes
Ultra Violet (UV): Vis Spectrophotometer	Yes	Yes	Yes	Yes	Adj.*
Vacuum Oven	Yes	Yes	Yes	Yes	Yes
Viscometer	Yes	Yes	Yes	Adj.*	Yes

*ADJ.** *Periodic adjustment required by specialist engineer or the manufacturer*
***:* *Depends upon the complexity of the balances, i.e., attached to device that performs calculations or stores data*
DQ: *Design Qualification*
IC: *Ion Chromatography*
IR: *Infra Red Spectrophotometer*
IQ: *Installation Qualification*
OQ: *Operational Qualification*
PQ: *Performance Qualification*

the specification. This team should prepare a DQ or SQ protocol, and generate a DQ or SQ summary report. The DQ or SQ protocol and summary report should include the following items:

- Title
- Approval and signatures
- Objective
- Scope
- Responsibilities
- Acceptance criteria
- Equipment name
- Equipment manufacturer
- Type
- Model
- Tag number
- Specification
- Measurement limits or ranges
- Accuracy
- Precision
- Critical parts
- Calibration requirements and frequencies (if applicable, proposed by the vendor)
- Maintenance and cleaning
- Operational instructions
- Maintenance manual
- Certificates of calibration (if applicable)
- Warranty

Installation Qualification (IQ)

The IQ stage is usually done by engineering and maintenance department engineers in conjunction with the vendor (for complicated equipment).

The IQ includes installing the equipment, ensuring the services are connected and working according to specification. Also, all drawings, purchased parts details, spare parts, manuals, and purchase orders must be part of the package.

The IQ protocol and summary report must include the following typical sections and attachments:

- Title
- Approval and signatures
- Responsibilities
- Definition
- Equipment Identification
- Instruments used for installation
- Procedure
  - Description
  - Documentation
  - Test Forms
- Acceptance criteria
- List of documents to be included
- Archiving
- References
- Attachments (as test forms where applicable):
  - Personnel performing IQ
  - Observations and comments
  - Documentation verification
  - General arrangement verification
  - Power, electrical utilities verification
  - Non-electrical utilities verification
  - Critical instruments list verification
  - Consumables list
  - Spare parts list
  - Logbook verification
  - IQ deviation form and recommendation
  - IQ completion

Operational Qualification (OQ)

Operational qualification is completed by engineering and QC personnel. This includes ensuring all operational details are checked. Operational Qualification demonstrates that the equipment functions within its specified operating parameters, and can perform reliably under routine operating conditions.

The OQ protocol and summary report must include the following typical section and attachments:

- Title
- Approval and signatures
- Objective
- Equipment identification
- Responsibilities
- Equipment and test instrumentation
- Procedure:
  - Measurement ranges and limits
  - Function tests
  - Test method/conditions
- Calibration (if applicable)
- Acceptance criteria
- Test results
- OQ deviation form and recommendations
- OQ completion

Performance Qualification (PQ)

Performance Qualification is the final test that demonstrates that the equipment performs as intended.

It determines whether the equipment is capable of providing the necessary information. Is it accurate? Are the results reproducible? What is the variability expected? Is it sensitive enough to provide the level of precision required by laboratory methods?

A PQ protocol is then developed, detailing all critical operating parameters including:

- Title
- Approval and signatures
- Objective
- Equipment identification
- Responsibilities
- Definitions
- PQ requirements
- Procedure:
  - Samples and standards preparation
  - Measurements plan
  - Measurements sequence
  - Results analysis
  - Statistics
  - Accuracy
  - Precision
  - Curves
- Acceptance criteria
- List of documents to be included
- Archiving
- Recommendations and periodic revalidation
- References
- Test data:
  - Analyst ID
  - Sample ID
- Test results
- Comments, observations, and deviations
- Final evaluation of the test
- Conclusion

Operational Instructions

Operational instructions for all laboratory equipment should be properly prepared describing equipment operating step-by-step. Instructions should be maintained near the equipment in a place accessible for all operators.

Operating instructions are based on the manufacturer's instruction manual. They should be written in a clear, detailed, and easy-to-understand language to simplify their use by the operators.

Calibration

Laboratory equipment calibration is an FDA requirement. 21 CFR 820.72 states that:

> *"…equipment used for inspection, measuring and testing of process equipment 'shall be routinely calibrated'. Calibration is also an expectation and critical in the European Pharmaceutical Legislation (Eudralex) GMP's, volume four (4), chapter three (3): '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.'"* [1]

All laboratory data should be generated using appropriately qualified calibrated instrumentation. Current, written, approved calibration procedures should be used to assure the equipment and instrumentation is suitable for its intended function while in use. Calibration will occur at established time intervals, and calibration records and related documentation should be retained for an appropriate duration.

If an instrument is repaired or moved, it must be recalibrated if it has been determined that the repair or move affects the instrument calibration. Equipment and instrumentation past due for calibration should not be used until a recalibration is performed.

A calibration protocol contains the following main sections:

- Title
- Approval and signatures
- Objective
- Equipment identification
- Responsibilities
- Test instrumentation
- Reference calibration instrumentation
- Recommendations before calibration
- Calibration procedure
- Calibration report
- Equipment labeling
- Acceptance criteria

- List of documents to be included
- Archiving
- Recommendations and calibration frequency
- References

Annual Calibration Plan

A calibration plan, for annual, quarterly, or monthly testing should be prepared, listing the equipment that required calibration versus calibration date and frequency (*Figure 4*). The plan should be prepared by a calibration specialist, and reviewed and approved by the QC Manager.

The QC laboratory's tasks are organized by a documentation system, containing groups of procedures that describe all activities and operations necessary to perform the laboratory's work, including: specifications, sampling regime, testing procedures, analytical reports and certification, reagents preparation, samples receiving, etc. Two types of procedures summarize the laboratory's activities and are followed by the laboratory's staff:

Figure 4

Examples of an Annual Equipment Calibration Plan

Year/Month	Year: 200X											
Equipment	1	2	3	4	5	6	7	8	9	10	11	12
Autoclave							■					
Balances			■			■			■			■
Conductivity Meter	*Calibrate Before Use*											
Disintegration Tester				■						■		
Dissolution Tester		■						■				
Drying Oven						■						
Microbiological Incubator								■				
Moisture Tester Balance (IR)				■						■		
pH Meter	*Calibrate Before Use*											
Potentiometer		■										
Tablet Friability Tester				■						■		
Tablet Hardness and Thickness Measurement		■						■				
Vacuum Oven				■						■		
Viscometer			■						■			

■ *Calibration Required*

❶ Standard Operating Procedures (SOPs)
❷ General Procedures.

The QC laboratory manager is responsible for issuing and implementing laboratory SOPs. Supervisors and analysts must know the SOPs and consistently operate in acceptance with them.

Analysts must be trained on the operation of SOPs, and be assessed for competence in operation of the SOPs after training. Refresher training at appropriate intervals should be given to the laboratory's staff.

Laboratory SOPs describe the following major areas including:

- Sampling regime
- Samples receiving
- Laboratory record
- Samples retaining
- Analytical method validation
- Self inspection
- Stability study policy
- Laboratory analyst notebook
- Numbering system
- SOP writing and handling
- Good Laboratory Practice (GLP), GMP deviation reporting
- Actions taken when out-of-specification results occur
- Handling of reference standards
- Cleaning validation policy
- Environmental control (sampling and testing)
- Control of recalls and returned goods
- Training policy
- Media preparation

The above SOPs outline the main critical issues and tasks. Additional SOPs could be generated according to the laboratory's needs.

A typical SOP format contains on the first page (cover page or header) the names of personnel responsible for that particular SOP. Typically, this is the writer, reviewer, and one person responsible for SOP approval. The main SOP sections are:

- Subject
- Purpose

- Definitions
- Scope
- Safety concerns
- Flowchart (if applicable)
- Procedure
- References
- Change history

Deviation from the SOPs must be properly documented at the time they occur, and assessed by management for significance for quality.

General Procedure

General procedures concern that type of laboratory general work followed and applied by the analysts, and not specific or related to the analysis of one dedicated product.

Examples for general procedures including; buffers preparation, culture and media preparation, glassware cleaning, reagents standardization, etc.

Trends Analysis

Trends analysis provide critical data on quality and laboratory work performance.

They confirm when a process or method is running well. They highlight unexpectedly good performance, a pointer to process, and yield improvement.

Trends analysis warn of a drift towards an out-of-specification result before rejectable material is produced.

The typical QC trends are; impurities, assay, moisture content, preservatives, dissolution, and pH.

Reference Standards and Laboratory Reagents

Reference Standards

Laboratory reference standards that are properly defined and characterized for a particular use should be used to measure potency, purity, and critical physical comparison tests of products and materials. This characterization should be documented and approved by the QC manager.

Reference standards are used at their labeled purity, and stored according to their label instructions.

Working standards should be prepared and treated according to written procedure. They should be periodically reevaluated to maintain their potency and integrity. This periodic characterization should be documented and approved by the QC manager.

Review of data and assessment of any apparent trends in the laboratory standards results will assure the assay performance and monitor the stability of laboratory standards.

Laboratory Reagents

As mentioned in EC pharmaceutical legislation and GMP guidelines (Eudralex), volume four (4), chapter six (6), paragraph 6.20 states that;

> *"Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and cultures media should be indicated on the label, together with specific storage conditions."*

In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

Standardization Reagents

Standardization reagent should be prepared to contain a known quantitative concentration. The concentration or factor of the reagent is used in assay calculations. Standardized reagents used in laboratory testing should be prepared according to appropriate written procedure, labeled with complete information, including reagent name, standardized concentration or standardization factor, identification of the preparer, date of preparation and the expiry date. Optimal shelf-life has been found not more than 30 days (unless otherwise documented). All outdated standardized reagents must be discarded.

Non-Standardized Reagents

Non-standardized reagents should be prepared to contain a semi-quantitative or non-quantitative concentration. The concentration or factor of the reagent is not used in assay calculations.

Non-standardized reagents used in laboratory testing should be prepared according to appropriate written preparers, and labeled with the name of the reagent, preparer-name, date of preparation, and the expiration date. Concerning the shelf life, it is recommended to not exceed one year from the date of preparation. All

outdated non-standardized reagents should be discarded.

The label on the reagent's containers should contain the following information:

- Reagent
- Strength
- Preparation method number
- Prepared by
- Preparation date
- Storage conditions
- Shelf-life or expiry date

Conclusion

GMP regulations contain several sections that deal specifically with laboratory operations (21 CFR Part 211.160, 165, and 194). However, there are other provisions of the GMPs, not listed under the headings generally covering laboratories, that apply to all operations, including analytical laboratories.

Test methods must be written, validated, specific for each product, and be readily available to all analysts. Each method must be controlled and subject to strict change control. Only pre-approved and authorized changes are permitted, and these must be documented.

Procedures covering all key laboratory activities should be written in controlled SOPs. It is important that SOPs cover all topics and activities of QC Laboratories listed in this article. There can be a tendency in some technical laboratories to assume that highly trained and competent chemists will perform these activities correctly in the absence of SOPs. This cannot occur, and is a clear violation of GMPs.

GMP regulations state that laboratory procedures should be written, adequate to describe the activity, and all operations must conform to these procedures.

In most laboratories, several types of documents exist. Each type of document must be controlled. That is, a mechanism must exist in which all documents are approved before they become official, and a controlled means for making changes must exist. The absence of control regarding laboratory documents indicates a significant lack of control. Without proper controls, you can never be quite sure if the methods and procedures in use are correct. ❑

About the Author

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Article Acronym Listing

CE:	Capillary Electrophoresis
CFR:	Code of Federal Regulations
cGMP:	Current Good Manufacturing Practice
DQ:	Design Qualification
EU:	European Union
EVM:	Equipment Validation Matrix
FDA:	Food and Drug Administration
GC:	Gas Chromatography
GLP:	Good Laboratory Practice
GMP:	Good Manufacturing Practice
HPLC:	High Performance Liquid Chromatography
HPTLC:	High Performance Thin Layer Chromatography
IC:	Ion Chromatography
ICH:	International Conference on Harmonization
ICP:	Inductively Coupled Plasma
ICP-AES:	Inductively Coupled Plasma-Atomic Emission Spectrometry
IQ:	Installation Qualification
IR:	Moisture Tester Balance
KF:	Karl Fischer Titration
NMR:	Nuclear Magnetic Resonance
OQ:	Operational Qualification
PQ:	Performance Qualification
QA:	Quality Assurance
QC:	Quality Control
RSD:	Relative Standard Deviation
SFC:	Spectro Fluorophotometer Chromatography
SOP:	Standard Operating Procedure
SQ:	Specification Qualification
SSC:	System Suitability Check
TLC:	Thin Layer Chromatography
USP:	United States Pharmacopeia
UV:	Ultra Violet
VMP:	Validation Master Plan

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Commentary

THE CUBIC CASE STUDY:
The Qualification/Validation of Equipment Under Changing Business Conditions

BY CHARLIE NEAL

INTRODUCTION

This paper is devoted to sharing how a validation project can sometimes go well. In actuality, it was a project that required the qualification of equipment identified for a Small Scale, Phase III project, called CUBIC. Certain approaches, i.e., combining protocols and utilizing the family approach to equipment qualification, were utilized to better ensure that the qualification timeline would be satisfied. In each case, the entire project team supported these. Perhaps better still, many of these resource-saving tactics were suggested by the Quality Assurance (QA) Validation resource, which was also the equipment qualification project leader.

Although the situation described is real, the names of the company and the project code have been changed. A detailed discussion follows.

STAGE SETTING

Company Z is a contract biotechnology manufacturer located in RTP, North Carolina. The company is less than 10 years old and has the capability of performing both development (small scale) and commercial (large scale) manufacturing. Obviously, commercial manufacturing requires process validation, and process validation requires equipment qualification, among other things.

The company had evolved to the point of having a good Validation Department consisting of Equipment and Critical Utilities Validation (EV), Computer Systems Validation (CSV), Re-qualification, Cleaning Validation, and Process Validation groups. New equipment qualification projects were typically split between the EV group (headed by one manager) and the CSV group (headed by a different manager). Each of these managers reported to a common Associate Director, who also directed Cleaning Validation activities. The Process Validation Department reported to a different Associate Director. Each Validation Department ultimately reported to Quality. This structure is illustrated in *Figure 1*.

In July of 2002, a reorganization resulted in new reporting schemes for the aforementioned validation groups. A new validation group—the Facilities Validation (FV) group—consisting of the old Equipment Qualification (EQ) group and the Re-qualification group—was formed and reported to Facilities Engineering. The CSV group reported to Systems Engineering; Cleaning and Process Validation reported to Manufacturing. This new structure is illustrated in *Figure 2*.

Within both the old and new reporting structures, project assignments were determined based upon the work involved. For example, if a project involved strictly automation related activities, the project would be handled by the CSV group. If it involved equipment qualification in the absence of automation, the project was assigned to the FV group. If it involved both automation and equipment, an agreement was reached based upon the rough percentage of automation vs. equipment qualification involved and the availability of resources in each group. It is important to note that each group had at least one resource that was ca-

Figure 1

Pre-July 2002 Departmental Alignment

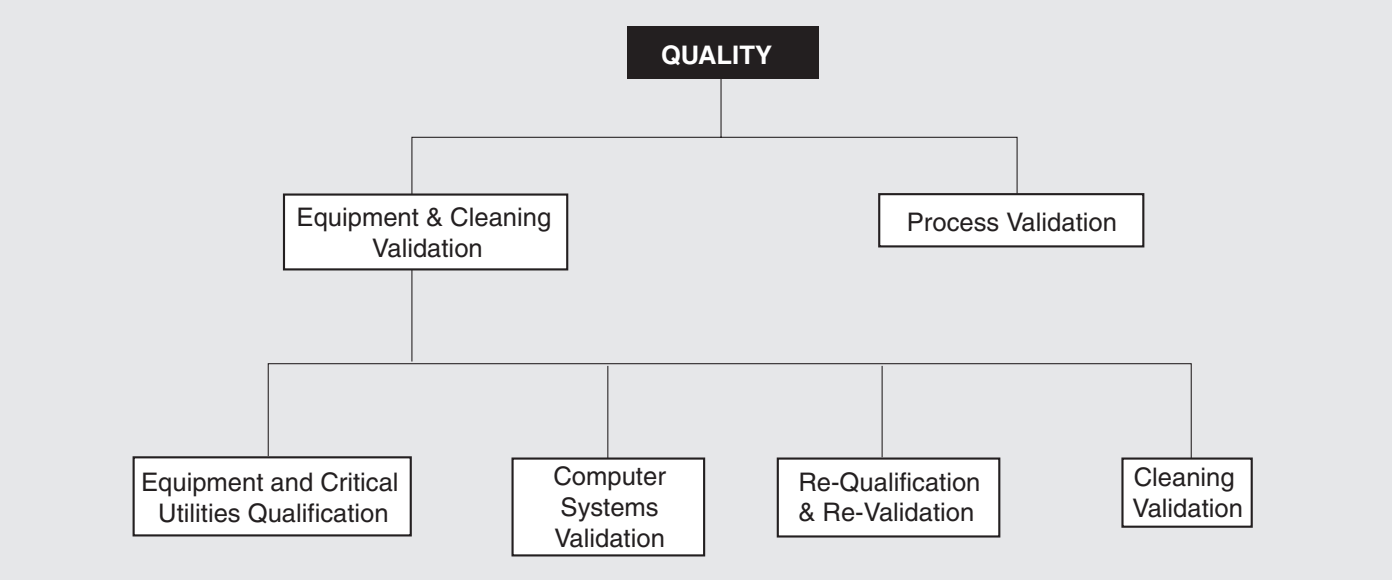
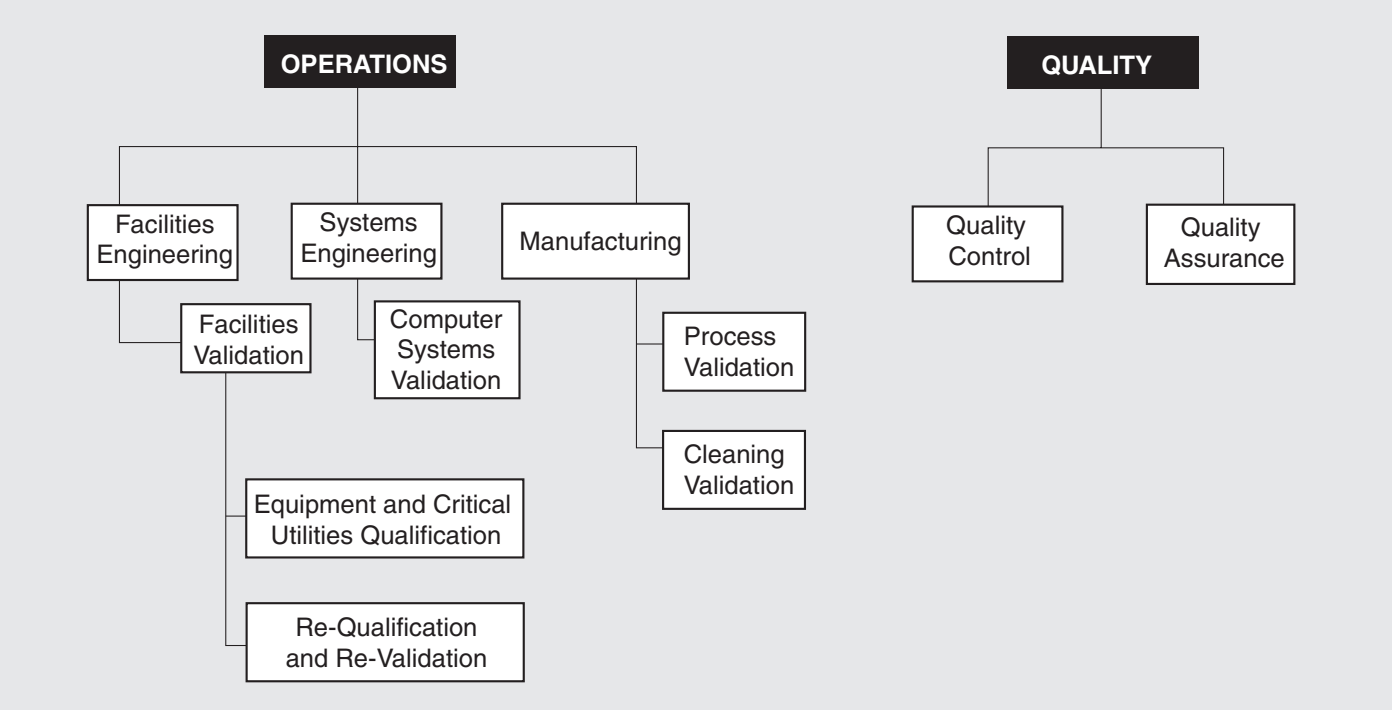


Figure 2

Post-July 2002 Departmental Alignment



pable of "crossing-over" and supporting the other. In addition, each group was willing to assist the other.

At all times, both the FV and the CSV groups were overwhelmed with project requests. Each resource within these groups often struggled to keep up with the project load. As such, external, contractor-sourced resources were routinely used to assist with key projects.

Within the FV group, new projects—meaning the introduction of new client contracts—would be a priority. However, oftentimes, these projects would have to compete with other client projects and other internal priorities. Around the summer of 2002, one such project, dubbed the "Small Scale

Up-fit" project, was introduced. At the onset, this was a multi-client project. The objective was to qualify all critical Small Scale equipment, thereby rendering the equipment Good Manufacturing Practice (GMP)-compliant. A contractor-sourced resource was assigned by the FV group. This resource also served as the equipment qualification project leader, and made some progress against the project throughout the remainder of 2002. In January 2003, this resource supporting the project left the company and an internal resource from the FV group filled the position as the new qualification project lead. Again, it should be noted that this project was competing with other project priorities, which meant that it did not receive full-time attention from the lone validation resource.

Figure 3

Post-July 2002 Departmental Alignment

EQUIPMENT NAME	QUALIFICATION REQUIRED				
	IQ	OQ	PQ	CV	SV
(2) 25L Jacketed Tanks w/mixers	X	X			
(2) 100L Tanks w/mixers	X	X			
(1) 250L Harvest Vessel	X	X			
(1) Homogenizer	X	X			
(1) Low Pressure Chromatography System	X	X			
(1) Data Acquisition Software	X	X			
(1) Chromatography Skid	X	X			
(1) DCS Operator Station	X	X			
(1) Autoclave	X	X	X		X
(1) 140 L Glass Fermentor	X	X	X	X	X
(1) Glass Washer	X	X			
(2) Centrifuges	X	X			
(1) Temperature Controller	X	X			
(1) Incubator Shaker	X	X			
(4) Refrigerators	X	X			
(1) Refrigerator/Freezer	X	X			
(2) Air Handling Units	X	X	X		
(1) Laminar Air Flow Hood	X	X			
(1) CIP Skid	X	X			
(13) Miscellaneous Pumps	X	X			
(1) Filter Housing	X	X			
(1) Portable Bench Top UF/DF System	X	X			
(4) Chromatography Columns	X	X			

Note: IQ = Installation Qualification; OQ = Operational Qualification; PQ = Performance Qualification; CV = Cleaning Validation; SV = Sterilization Validation

A New Strategy

In the first quarter of 2003, it was decided that the Small Scale Up-fit project would not involve the level of qualification that had been agreed upon in the year 2002. This decision resulted from the realization that equipment qualification for certain key clients could not be delayed by waiting for the completion of the entire Small Scale Up-fit project. This decision was based primarily upon an assessment of resources, overall project timing, the clinical phases of the client projects, and of course, economy. In essence, this decision resulted in the splitting out of client projects that had extremely tight timelines.

The Small Scale Up-fit project of old was then renamed the "*CUBIC*" project. This renaming reflected a Phase III client project having the most aggressive timeline.

The table in *Figure 3* provides a listing of the *CUBIC* equipment requiring qualification with the level of qualification required.

Bear in mind that project management for equipment qualification was the sole responsibility of a resource from the FV group. Again, this resource attempted to drive this project with many other day-to-day validation priorities. This resource constructed a project tracking system that identified *CUBIC* equipment requiring qualification and its status, convened regular meetings, and communicated with the project team regularly. Unfortunately, limited progress was made.

Reeling from a Reorganization

In May of 2003, Company Z underwent a massive reorganization in an effort to better cope with the decline in the economy. Facilities Validation, formerly consisting of the Equipment Qualification and Re-Qualification groups, was dissolved. Actually, only three of the original members, including the manager were retained. All other members, including the resource that had been leading the *CUBIC* equipment qualification project, were impacted during the downsizing. The manager was asked to report into QA Validation while the two remaining subordinates were retained and reassigned, reporting to Facilities Engineering. It should be noted that QA Validation's role was to oversee validations, to create and implement validation policy, and to ensure that validation-related actions were compliant with internal and external guidelines.

With regard to the *CUBIC* project, all project momentum was lost as a result of the reorganization. Nonetheless, the need to have the Small Scale facility qualified for the *CUBIC* client remained. The company stood to lose credibility if a qualified facility was not delivered by the agreed

Figure 4

List of Resources Available for the CUBIC Project

Departments Solicited	Primary Responsibilities	Resources Provided
Quality Assurance Validation	Qualification leadership, ensure team focus, provide protocol guidance, approve protocols	2*
Quality Control	Sample analyses, reporting results	3
Facilities Engineering	Author protocols, task execution	3
Computer Systems Validation	Author automation-related protocols, task execution	2
Systems Engineering	Commissioning of automation-based equipment, assist with task execution	1
Process Engineering	Commissioning of non-automation-based equipment, author protocols, assist with task execution	4
Project Engineering	Equipment acquisition, sub-project leadership for small scale equipment.	2
Technology Transfer	Author protocols, task execution	1
Small Scale Manufacturing	Author protocols, task executions	6

*Second QA Validation resource assisted with the oversight and approval of automation-based protocols.

upon late 3rd quarter-early 4th quarter deadline.

Fortunately, the former validation project leader who had been dismissed had done a superb job of spread-sheeting progress against the project goal. Though he had not been completely successful in rallying the troops to complete the *CUBIC* equipment qualification project, he made considerable progress towards preparing the necessary protocols.

A decision was then made to assign the equipment qualification project leadership task to the former Manager of Facilities Validation, who now reported to QA Validation. It is worthy to note that this resource brought in excess of 22 years of validation experience.

PREPARING FOR BATTLE

A key validation tool, a *CUBIC* Equipment Validation Master Plan, was not available. While a validation master plan is not an American regulatory requirement, it is often one of the first validation documents that the Food and Drug Administration (FDA) requests. It should be understood that the author is not advocating proceeding in the absence of a Validation Master Plan. However, given the situation, proceeding without a master plan was the best business choice and the only logical choice that could have been made.

The absence of this plan meant that the equipment qualification project leader (EQPL) would have to lean heavily upon the equipment lists and day-to-day communications in order to have any chance for success.

STRATEGIZING

This equipment qualification project required 51 separate protocols covering 45 pieces of equipment. The project required that the equipment be qualified and released for manufacturing by October 2003. The EQPL realized that given the amount of time to complete the equipment qualification and the loss of seasoned, dedicated validation resources, the task would be very difficult to complete. Inevitably, the EQPL realized that what the project needed more than anything else for success was resources—*human resources*.

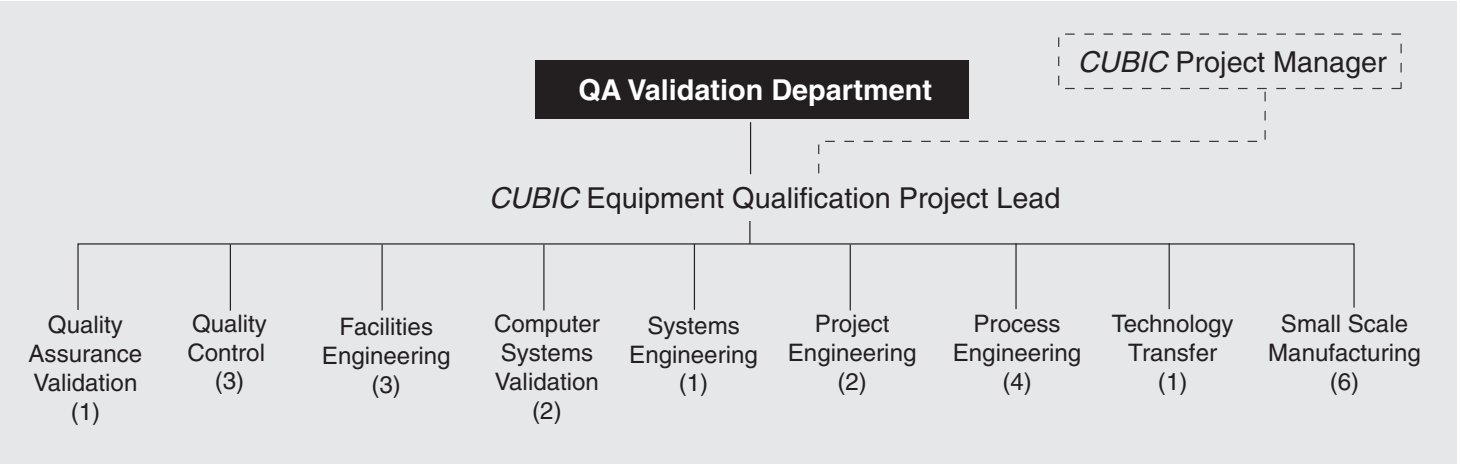
Out of necessity, efforts were made to glean available resources from the various operations groups, specifically departments that had the PROs (Persons Responsible for Ownership). In simple terms, these departments owned the equipment that required qualification, and therefore, their resources were regarded as the "equipment experts."

Conversations were initiated in June 2003 with the departments tabulated in *Figure 4* for resource commitments. The number of resources attained from these departments and their primary responsibilities are listed under the appropriate column heading.

In total, approximately 25 resources (including the EQPL and Project Management, which is not listed above) were volunteered to assist with the *CUBIC* project. Again, it should be noted that these resources were not dedicated. The point should also be mentioned that Small Scale manufacturing contributed the most resources due to the fact that they owned the majority of the equipment slated for qualification

Figure 5

QA Validation with Project Reporting Departments



(please refer to table in *Figure 3*).

To present an overview of the structure for the *CUBIC* Equipment Qualification project team, the schematic in *Figure 5* is provided.

At the start of the revised *CUBIC* project, the EQPL identified a training curriculum for the team members. This curriculum consisted of key validation-related Standard Operating Procedures (SOPs) which would ensure that each member would be equipped with the same, necessary information. The EQPL convened team meetings from the start of the project to ensure that team members were focused on the project objective. This forum also served as a place where issues, problems, and concerns were openly discussed. The EQPL made it clear that it was his responsibility to attain resolution on any open issues. It was then the responsibility of the team to perform: to identify issues and to write, execute and to position their respective qualifications for closure. These team meetings were held twice a week for the first two weeks after which the frequency was decreased to once a week.

To supplement the team meetings, satellite meetings under the leadership of the EQPL were held to attack major issues. In an effort to conserve resources, these satellite meetings purposely involved only the department that voiced the issue and those departments that were key in resolving the issue. These meetings were convened whenever an issue was identified that threatened the success of the project. From a frequency standpoint, multiple satellite meetings could be held in a given day.

DEALING WITH THE NEW PROTOCOL GENERATION SOFTWARE

As a contract manufacturer, Company Z had found it necessary to use numerous contractors in prior years to prepare and execute validations. Though the quality of work was acceptable, these contractors often introduced a variety of approaches and therefore a variety of documents resulted. Inevitably, consistency with the validation documentation was a concern. As such, efforts were underway to initiate the implementation of new protocol generation software that would result minimally in a consistent format for the validation documents. It was the responsibility of the EQPL to ensure that the approach was consistent.

Discussions around this new software began early in 2002. As previously mentioned, plans were to implement this new tool in early 2003. Realizing that there was a considerable learning curve involved, the EQPL ensured that each team member having the responsibility for protocol generation was trained on the new software. This made it possible for the entire team to assemble necessary protocols using a common approach.

Given the fact that protocols for at least 25% of the equipment had already been created and approved prior to the implementation of the new protocol generation tool, a decision had to be made whether these older protocols would be used or whether the *CUBIC* project would consist only of protocols created with the new generation tool (thereby forfeiting the monumental efforts made to complete the protocols).

The pre-2003 protocol format was GMP-compliant. Given this point and the resource constraints, a decision was made to utilize both the protocols that were approved reflecting the older format, and those that resulted from the protocol generation software, meaning that the *CUBIC* project would consist of two different protocol formats. Whatever document format is selected, it must contain those elements that result in GMP compliance.

EFFECTIVE COMMUNICATION

To capitalize on the numerous information-sharing meetings, the EQPL issued meeting minutes capturing key points discussed. To prevent loosing key discussion points, efforts were made to issue the minutes within a day of the actual communication forum. These meetings not only captured the issues of discussion, but also the action steps with the resource(s) responsible, and the due dates for resolution. These minutes were typically copied to the team members and management (team members' management and project management).

In addition, the project lead utilized numerous communication tools to share project status and key updates, i.e., Microsoft® Project, Excel, and Word. These were issued on a weekly basis, and like the meeting minutes, were often copied to the team members and management.

PERSONAL PROJECT TRACKING

In an effort to ensure that key project information was readily available, the EQPL prepared a project-tracking manual. This manual was nothing more than a white three-inch thick, three-ring binder with a presentation cover. For quick identification purposes, a cover page was prepared with the *CUBIC* logo. This cover page was inserted into the presentation cover.

This manual was then populated with section tabs that identified each piece of equipment, project meetings, Gantt charts, spreadsheets, etc. Within each of these tabs, appropriate information was arranged chronologically. For example, any emails that were related to a piece of equipment were printed and inserted in the appropriate section. The one important thing about this manual is that it was a tool prepared to aide the EQPL. There was no rhyme or reason for the section tab headings, the number of tabs, the size or configuration of the manual. In summary, this manual was simply a tool prepared by the EQPL to provide quick access to key project information.

COACHING

Consistency not only in the manner that protocols and summaries were assembled, but also in the overall approach to qualification was a goal of the Company Z organization. Realizing this, the EQPL met with those preparing and executing the protocols regularly. In addition, recommendations were provided on how to handle deviations. Again, the intent was to improve on consistency with respect to the overall qualification effort.

COMBINING PROTOCOLS

In order to maximize resources, efforts were made to minimize the impact of each qualification task. As an example, one of the methods used was to "combine protocols." This was a tactic wherein the Installation Qualification (IQ) and Operational Qualification (OQ) were combined to yield a singular document, the I/OQ. This actually decreased the number of documents that were created and handled, and as a result reduced the total approval time. The following illustrations, Scenarios 1 and 2, detail how time could be saved by using this combining technique for a piece of equipment that requires Installation and Operational Qualification.

One shortcoming of this approach is that in the absence of good oversight, it could permit an undisciplined resource to execute the OQ section prior to the IQ. However, the entire process was policed by the EQPL who made sure that the proper sequence occurred.

Family Approach

Another way of minimizing the qualification task was to reduce the number of validation documents generated. This meant that wherever multiple pieces of similar equipment required qualification, efforts were made to group the equipment under a single protocol. Prime examples would be process pumps, refrigerators, process tanks, etc. This approach significantly reduced the time required to prepare protocols and to attain approvals. As an example, consider the situation where there are three (3) "widgets" that require Installation Qualification. Time to write and approve three individual documents will be significantly longer than the time to write and approve a single protocol containing all three widgets. Scenarios 3 and 4 below illustrate this point.

While Company Z stores completed validation documents in fire-proof file cabinets, it also maintains electronically accessible PDFs of approved validation documents and a database where a search can be conducted of completed documents primarily by equipment-type. Within the com-

Scenario 1, Conventional Approach, using separate IQ and OQ

Documents	Approximate Work Hours			
	Write	Attain Approval	Execute	Total
IQ	8	8	40	56
OQ	16	8	56	80
			Grand Total	136

Note: times are presented for example purposes only

Results: 2 documents tracked and handled
136 hours consumed

Scenario 2, Combined Approach, using a single, combined I/OQ

Documents	Approximate Work Hours			
	Write	Attain Approval	Execute	Total
I/OQ	24	8	96	128
			Grand Total	128

Note: times are presented for example purposes only

Results: 1 document tracked and handled
128 hours consumed
Time saved in this example:
(Scenario 1 - Scenario 2), 136 – 128 hours: 8 work hours

Scenario 3, Conventional Approach, using separate IQ and OQ

Documents	Approximate Work Hours			
	Write	Attain Approval	Execute	Total
IQ—Widget 1	8	8	40	56
IQ—Widget 2	8	8	40	56
IQ—Widget 3	8	8	40	56
			Grand Total	168

Note: times are presented for example purposes only

Results: 3 documents tracked and handled
168 hours consumed

pany, one detriment associated with the family approach is that the validation document titles—as entered in the existing validation data-base—do not automatically list multiple pieces of equipment that are included in a given validation document. Specifically, the company's validation database lists documents by a single equipment number, then by specific document number. This creates concern in those cases where there are multiple pieces of equipment covered within a single document due to the fact that only a single piece of equipment (number) would be visible during a database search. This of course, would result in equipment masking. However, this concern can be eliminated via internal procedures.

It should be noted that the resources saved in coupling both the combined and family approaches would exceed by far the numbers shown in the aforementioned examples.

POLICING DOCUMENTS

The EQPL understood that validation documents were sacred documents. With this understanding, the entire project team was made aware that:

1. Validation documents should not be mailed but hand carried to the reviewers or approvers
2. Validation documents should not be left unattended on a chair or desk

The above rules were hammered into the project team. In addition, each document presented to the EQPL for final approval was logged in for tracking purposes. The EQPL ensured that approved documents were immediately bound and submitted to the document administrator. These efforts prevented the loss of any *CUBIC* validation documents.

RETROSPECTIVE ASSESSMENT: LESSONS LEARNED

The *CUBIC* project team had an opportunity to observe a number of Company Z's internal systems and operations. Some of these worked well while others could have benefited from some form of improvement. Noteworthy areas for improvements included:

- ➢ Inconsistent approach to Factory Acceptance Testing (FAT) of equipment
- ➢ Departmental responses not always timely
- ➢ Timeliness of specification preparations
- ➢ Qualification and release of equipment that is not critical
- ➢ Insufficient time for (Master) planning
- ➢ Better communication of client expectations

The *CUBIC* project went extremely well. The team succeeded in releasing to the Fermentation Group 100% of the equipment for manufacture by September 2003. They then succeeded in releasing 100% of the equipment required by

Scenario 4, Family Approach, using single document for multiple pieces of similar equipment

Documents	Approximate Work Hours			
	Write	Attain Approval	Execute	Total
IQ including	12	10	120	142
Widget 1				
Widget 2				
Widget 3				
			Grand Total	142

Note: times are presented for example purposes only

Results: 1 documents tracked and handled
142 hours consumed
Time saved in this example:
(Scenario 3 - Scenario 4), 168 – 142 hours: 26 work hours

Purification by October 2003. Were all qualification documents completely closed out and approved by these dates? No. However, the equipment qualified was released based upon the fact that necessary qualification efforts had been completed, the data had been reviewed, and QA Validation supported the release of the equipment based on sound justification established for each release.

CONCLUSIONS

Overall, this project went very well considering that the team consisted of many who had been unfamiliar with validation. Noteworthy factors contributing to the success of this effort include:

- Team focus
- Team dedication
- Team commitment
- Team maturity
- Project leadership

In retrospect, this project could not have been done without the elements listed above and the efforts of the team members, who each had other priorities yet did their utmost to keep the project on time.

One key element of most successful validation projects is a well-written Validation Master Plan. Unfortunately, no such document existed for the *CUBIC* Equipment Qualification Team. A search of regulations revealed that the only regulatory requirement for a VMP document is mentioned in EU Annex 15, which basically states that a Validation Master Plan should be used for validation undertakings. The Code of Federal Regulations (CFRs) do not require one, yet our FDA has grown to expect and request one. The author is not suggesting that a Validation Master Plan not be assembled prior to initiating a validation project, only that the current regulations do not require one.

In closing, though the team lacked an Equipment Qualification Master Plan, the final destination was reached. Bear in mind that Master Plans have long been considered as a guide or road map to validation. The success of this project does not contradict this theory. However, it does speak volumes for having not only a focused project team but also for having project leadership who, like those who have traveled extensively, instinctively know how to guide the team to the destination in the absence of a map. ❑

ABOUT THE AUTHOR

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Article Acronym Listing

CFR:	Code of Federal Regulations
CSV:	Computer System Validation
CV:	Cleaning Validation
EQ:	Equipment Qualification
EQPL:	Equipment Qualification Project Leader
EU:	European Union
EV:	Equipment Validation
FAT:	Factory Acceptance Testing
FDA:	Food and Drug Administration
FV:	Facilities Validation
GMP:	Good Manufacturing Practice
IQ:	Installation Qualification
OQ:	Operational Qualification
PQ:	Performance Qualification
PRO:	Person(s) Responsible for Ownership
QA:	Quality Assurance
SOP:	Standard Operating Procedure
SV:	Sterilization Validation
VMP:	Validation Master Plan

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