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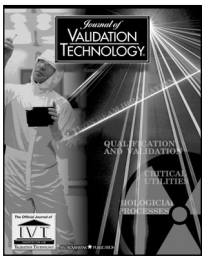

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SPECIAL EDITION

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A Case Study

By Heinz Neuhaus, Ph.D.
&
Ian K. Sykes, Ph.D.
&
Jacques-André Maring, Pharm. D.
ZLB Central Laboratory Blood Transfusion Service SRC

Validation per se is not a new requirement for pharmaceutical companies. To have validated processes is a long-standing obligation, but the interpretation of how to plan, perform, and document validation activities has evolved over time. The U.S. FDA has published its "Guidelines on General Principles of Process Validation" in 1987.[1] This guideline has been followed by more specific publications from both the regulatory authorities, e.g., FDA inspection guides, and the regulated industries. The Pharmaceutical Inspection Convention (PIC) has followed in 1996 with a publication on principles of qualification and validation.[2]

"...the interpretation of how to plan, perform, and document validation activities has evolved over time."

The Central Laboratory Blood Transfusion Service Swiss Red Cross (ZLB) is an internationally active pharmaceutical company manufacturing pharmaceutical products derived from blood plasma. Today it is the world's fifth largest company in the plasma-processing sector and has one of the largest facilities for the fractionation of human plasma into its main components. At ZLB, small and large volume parenterals – mainly Human Serum Albumin, Immunoglobulin for intravenous use and clotting factors – are manufactured under controlled conditions, including aseptic filling and lyophilization. The main processes were developed and standardized more than 20 years ago, with continuous improvements and adaptations. The facility and the plant equipment, however, have been expanded and upgraded over the years. Although basic validation requirements have not changed, due to the continually evolving state-of-the-art technology, the validation documentation at ZLB was of a variable standard depending upon when a given equipment or aggregate (e.g., a

Figure 1

Policy and SOP Documents for Qualification / Validation

(Documentation hierarchy as implemented at ZLB. Double shaded areas represent current documents.)

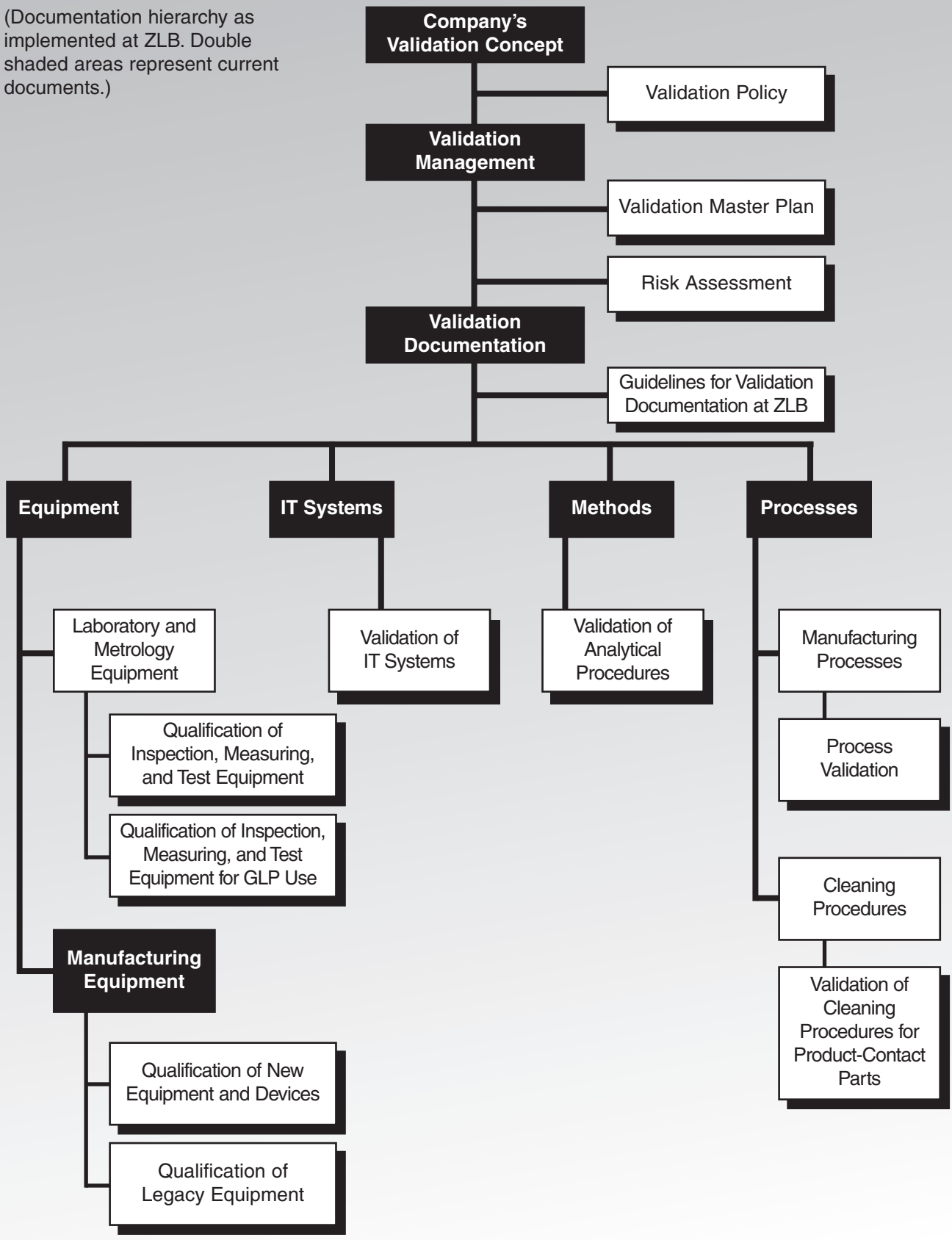
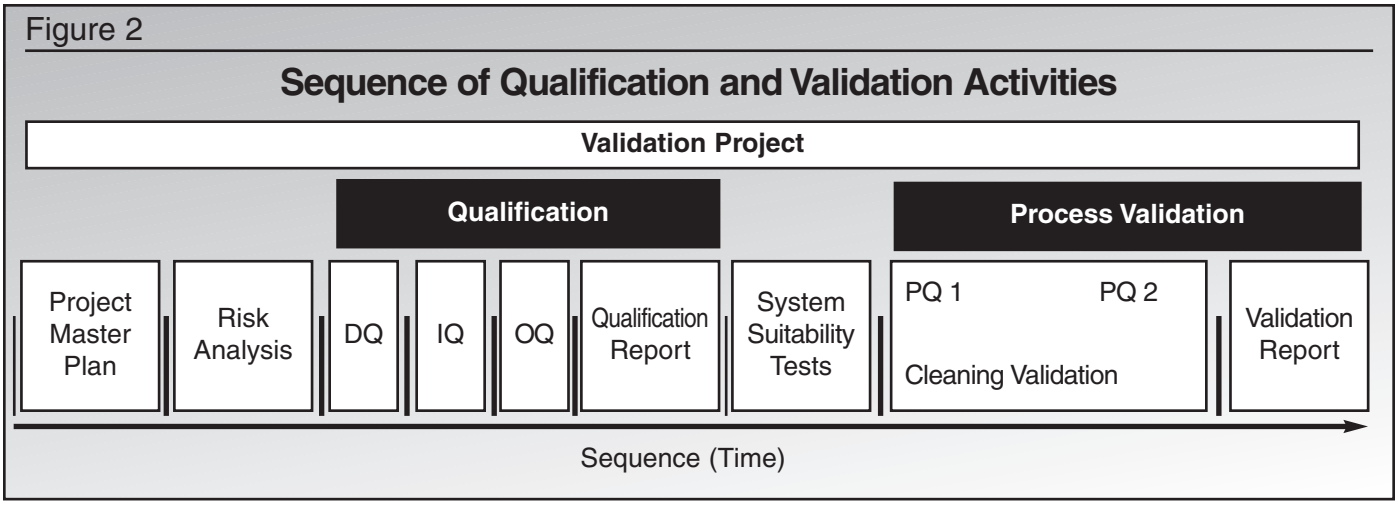


Figure 2



lyophilizer or a filling line) was originally qualified and taken into operation.

Since current interpretation of the U.S. CFR or EC GMP guidelines does not distinguish between validation requirements for "old" or "new" equipment, it was decided to establish a validation concept that would take into consideration both legacy and new equipment. In addition, this concept was also required to address requirements for information technology (IT) system validations, process, cleaning, and method validations.

Validation Policy

The general validation concept is described in a policy document which defines the terminology, responsibilities, validation approach, and applicable SOPs. Specific instructions for validation planning, performance, and documentation are described in the appropriate SOPs (see *Figure 1*).

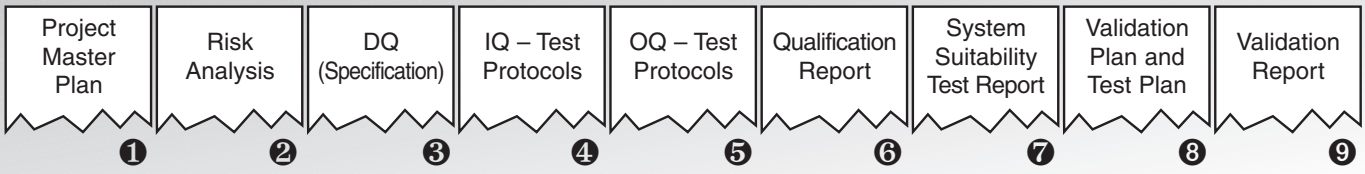
The qualification and validation activities should be performed in a predetermined sequence, as shown in *Figure 2*. For the design qualification (DQ), the performance specification/user requirements are identified. For new equipment, this also includes dimensional, installation, and operating requirements. Installation and operational qualifications (IQ, OQ) are performed without actual product being used (instead, if required, water may be used as a medium). After the qualification and before the validation, a system suitability and optimization phase may be included. This is especially recommended for important projects (e.g., installation of a new filling line). The optimization phase is used to fine tune operating parameters, train operators, and establish the required documentation (instructions, SOPs) before the actual validation begins. The process validation is divided into two separate phases: The validation phase 1 is called the performance qualification (PQ1) using e.g., placebo. PQ1 should provide evidence that the optimizations identified during the system suitability testing have been successfully implemented. The validation phase 2 (PQ2) is the actual process validation, usually to be performed as three consecutive manufacturing batches.

For equipment including an automated process control system, the qualification activities (DQ, IQ, OQ) may be performed separately for the automation system and the equipment (including e.g., sensors, actors, connections, etc.). The validation activities (PQ1, PQ2, cleaning validation) are then performed including all functions of the equipment and automation system. If necessary, the analytical validation has to be performed before testing samples. For each step, i.e., qualification or validation activity, appropriate plans/test protocols have to be established, including test methods and acceptance criteria. The results of the performed validation runs are then summarized and evaluated in a qualification and/or validation report. *Figure 3* shows the documentation according to the established validation concept.

A full validation according to this concept is required only for critical manufacturing equipment. For other equipment or instruments/devices, a limited qualification/validation may be sufficient. The required validation activities and documentation are defined in the individual validation plans. The level of validation can be approached in general as

Figure 3

Required Documentation for the Validation of Manufacturing Equipment



described in *Figure 4*.

To perform PQ1, the following activities and/or documents must be previously completed and approved:

- DQ/IQ/OQ
- Calibration of probes and test instruments
- Operating instructions, SOPs, batch records as final drafts
- Training of personnel
- Qualification of rooms and utilities (appropriate environmental conditions)
- Risk analysis of the process. This is used to identify the critical process steps, for which testing is required during the validation.
- Analytical validation
- Validation plan

For PQ2, the following requirements must be met additionally:

- PQ1 (if performed) completed
- Cleaning validation, if necessary
- SOPs and manufacturing instructions approved

Figure 4

Required Level of Validation

Simple Device or Instrument (e.g., pH Meter)	3) – 6)#
Simple Equipment (e.g., Refrigerator, Incubator)	2) – 6), [8) – 9)]*
IT Peripheral Equipment	4)
Process Change on Existing Equipment	2) and 8) – 9)
Existing Process on New Equipment	1) – 9)
New Process on Existing Equipment	2) and 8) – 9)
New Process on New Equipment	1) – 9)

 # Numbers refer to documents according to Figure 3
** For qualification of simple equipment, generally a qualification plan and a qualification report are sufficient*

Validation Master Plan

All the planned validation activities at ZLB are listed in a central Site Validation Master Plan (VMP) (*Figure 5*). This master plan is regularly updated and used to manage all the different validation activities. All validations and validation documents are approved by the "Change and Validation Committee." Each of the technical departments is represented in this committee, which is chaired by QA. Validation documents are reviewed by members of the committee and approved by QA after consultation with the committee. The VMP as structured at ZLB is a list of all validation activities planned, currently ongoing, or completed. The validations can be prospective, concurrent, or retrospective (P, C, or R in *Figure 5*). The responsibilities, planned dates, and actual completion dates are shown as well. There are clear benefits to using this master plan concept. The individual technical departments are represented in the Change and Validation Committee. Therefore, the decisions of this committee represent the opinion of the departments involved. In addition, the VMP is the steering instrument for the Change and Validation Committee. This requires, however, that the master plan is indeed containing current information, is updated regularly, and new entries should only be made prospectively (what is planned rather than what was done).

Project Master Plan

For complex validation activities, e.g., a new production line, a project master plan is established (document 1 in *Figure 3*). This master plan will describe the system, system boundaries, deliverables, milestones, overall validation planning, responsibilities etc., for this project only. It is used as a roadmap for the validation team and can also be used for resource planning. The individual validation activities (and, by analogy, the required documents) are listed in this

Figure 5

Example of Validation Master Plan

Validation*	Type[1]	Responsibility	Scope (DQ, IQ, OQ, PQ2) (Qualitative Quantitative)	Due Dates Planned*		Approval		Val. Nr.	Inv. Nr.*
				Begin	End	Plan	Report		
Planned / Ongoing									
1. Equipment									
New Autoclave	P		DQ, IQ, OQ, PQ1	Dec. 97	Mar 98	11 Dec. 97	15 Apr .98	97116	23539
Filling Line	P		DQ, IQ, OQ, PQ1, PQ2	May 98	Dec. 98	03 Jul 98		98009	24698
Bulk Manufacturing Plant 1	P		DQ, IQ, OQ, PQ1, PQ2	Jun. 98	Dec. 98	18 Jun. 98		97030	
Bulk Manufacturing Plant 2	P		DQ, IQ, OQ, PQ1, PQ2	Jun. 97	Nov. 98	24 Jun.97		97019	24565
Mobile Vessel	P		DQ, IQ, PQ	Oct. 98	Mar. 99				N/A
Filling Piston	P		DQ, PQ2	Apr. 98	Sep. 98	20 Apr. 98		98022	N/A
2. Systems									
PVIG System	P		IQ, OQ, PQ1, PQ2	Aug. 98				98002	N/A
NSR (Backup)	R		IQ, OQ	Sep. 98	Jun. 99				
Process Control System 2	P		DQ, IQ, OQ, PQ1, PQ2	Aug. 98	Aug. 99	14 Aug. 98		98094	N/A
3. Processes									
Cleaning Validation Small Parts	P		PQ1	Sep. 98	Dec. 98	07 Aug. 98		97024	N/A
4. Methods									
SDS Page	P		Quantitative	Sep. 98	Dec. 98			98080	N/A
Anti-HAV	P		Quantitative	Nov. 97	Sep. 98	03 Nov. 97		97079	N/A
Na in Product A	P		Quantitative	Jul. 98	Dec. 98	22 Jun. 98		98053	N/A
Additive in Product B	R		Quantitative	Oct. 98	Dec. 98	20 Oct. 98		98072	N/A
COMPLETED									
1. Equipment									
Lyophilizer 1	R		DQ, IQ, OQ, PQ2			N/A	03 Apr. 98	N/A	02837
Steam Sterilizer	R		IQ, OQ, PQ1			30 Mar. 98	30 Jun. 98	98000	22854
Code Reader	P		IQ, OQ, PQ1			05 Jun. 98	20 Jul. 98	98008	25019

1. P = Prospective R = Retrospective
** Does not reflect actual validation performed/code used at ZLB*

Figure 6

Example of Validation Documents Included in Project Master Plan

Validation Project New Production Line*	DQ	Risk Analysis	IQ	OQ	PQ1	PQ 2 3 Validation Lots	Extended Monitoring
1. **Infrastructure**							
Classified Rooms	✓		✓				✓
HVAC System	✓		✓	✓			✓
WFI System	✓		✓	✓			✓
DI Water System	✓		✓	✓			✓
2. **Autoclave**	✓		✓	✓	✓		
3. **Lyophilizer**	✓		✓	✓	✓		
4. **Production Process**	✓	✓			✓	✓	
5. **Cleaning Process**	✓	✓			✓	✓	

** Does not reflect actual project/equipment at ZLB*

project master plan, an example of which is shown in *Figure 6*. For each of the individual boxes, at the end of the validation project, a set of approved documents (i.e., plan, test protocols, and/or report as appropriate) must be available. Revalidation requirements arising out of this Project Master Plan are then transferred to the Site VMP.

Equipment Qualification

Equipment, devices and instruments that may influence the safety, quality, and efficacy of the manufactured products must be qualified. A checklist was developed to help the users decide if qualification is required or not. This checklist was also used to evaluate the necessity to retrospectively qualify already existing equipment. The documentation for the qualification of new and legacy equipment is established according to the same principles. The difference is that for new equipment, the qualification documentation must be established before taking it into operation (or, under exceptional circumstances, concurrent to production activities), whereas for the retrospective activities a review and update of already existing data and documents is performed, and if required, the documentation is completed by additional tests. The equipment qualification and maintenance documentation is then maintained in two separate volumes, as shown in *Figure 7*, whereas Volume I includes the qualification/validation documentation.

Prospective Qualification

For new equipment, the appropriate qualification and validation activities are planned, performed, and documented as per the validation policy and applicable SOPs. Completion of DQ is required before the equipment is purchased. The IQ is performed on site, and consists of equipment identification, check of appropriate utilities installation (e.g., power, water, cooling media), major components and materials, and required documentation is available (manuals, drawings). For the OQ, the calibration requirements and equipment control functions are checked as well as the satisfactory equipment operation according to the operating manual. For PQ1 and PQ2, the equipment is run under routine operating conditions.

Retrospective Qualification

For existing equipment, a DQ is not performed (not relevant). IQ is only an analysis of the "as built" status, i.e., the existing P&I diagrams are verified. For OQ (review of current calibration and mainte-

Figure 7

Index of Equipment Qualification and Maintenance Dossiers

Volume I: Qualification Documentation

1. Qualification Certificate
2. DQ Documentation
3. IQ Documentation
4. OQ Documentation
5. PQ Documentation
6. Change Control

Volume II: Maintenance Documentation

7. Supplier List
8. Operating Manuals
9. P&I Diagram
10. Maintenance Schedules
11. SOP List
12. Spare Parts List
13. Technical Drawings
14. Wiring Diagrams
15. Software Documentation
16. Safety Documentation

nance data) and PQ1/2, available data are used (i.e., reviewed and evaluated) as far as possible. For critical equipment, e.g., steam sterilizers and lyophilizers, it was decided to perform a complete IQ, OQ, and PQ of the existing equipment in order to have the documentation available according to the required standards. Retrospective qualification establishes the baseline for change control.

Analytical Validation

The SOP for analytical method validation was developed based on the ICH guidelines.[3] In essence, based on the type of analytical procedure (e.g., identification, testing for impurities or assay), the following parameters may be tested: accuracy, precision (repeatability, intermediary precision), specificity, detection limit, quantification limit, linearity, and range. The validation procedure is the same as described: A validation plan is established, the validation performed according to the plan, and the results summarized and discussed in the validation report.

Cleaning Validation

Cleaning validation of production equipment is usually performed concurrent to process validation (PQ1/2). At ZLB, cleaning validation routinely consists of an analysis of final rinse samples, since all manufactured products are processed liquid. Currently, we are validating a method for swab testing production vessels and other product contact surfaces.

Discussion

The described validation concept has been established to adequately plan, perform, and document validation activities for existing and new equipment, for manufacturing and cleaning processes, for IT systems, and for analytical methods. The concept, i.e., the policy and SOPs describing it, was implemented in January 1998. New validation activities since then are performed according to this concept. In addition, a list of production equipment requiring a retrospective qualification was established following a risk assessment and priorities assigned for the establishment of the corresponding validation and maintenance dossiers (volumes I and II). The difficulties we have experienced with retrospective qualification consist mainly of unstructured data that accumulated over the years and was not analyzed. These data are sometimes split and stored in different departments. Therefore, the review of available documentation and data was more time consuming than originally planned. Because the retrospective data was weak, and in order to have a more consistent documentation, it was decided to perform some qualification activities for new equipment. These activities have been set forth in an action plan.

A key to the success of this validation concept is the management of all validation activities that are ongoing in a company. The VMP is established as the management tool in order to allocate the available resources according to a priority list. Initially, all the available information to establish the VMP (validation administration) has been used. What validations they would perform and to what extent were determined by the individual departments. The corresponding documents (plans, reports) were submitted to QA and the Change and Validation Committee

almost at random. The meetings of the Change and Validation Committee are structured, an agenda is distributed to the members, all changes to the VMP (including new entries) are discussed, and only those documents will be reviewed that have been accepted per the VMP.

Conclusion

Our experience has shown that the established concept is very helpful for the planning and documentation of validation activities. At ZLB, there is no centralized validation team, but the process owners have kept responsibility for their validation tasks. QA's responsibility is to establish the validation concept according to standards that are accepted by regulatory authorities, coordinate validation activities, chair the Change and Validation Committee, and review and approve all validation documents (plans, reports). Due to this decentralized validation organization and the different functions involved, it requires considerable effort to go from validation administration to validation management. In this respect, sufficient time is required for consulting activities from Quality Assurance to the respective users in the other departments in order to have scientifically sound and appropriate validation activities and documents. A centralized validation team may be the answer to these problems, but may take too much responsibility away from the users. ❑

Acknowledgements

The authors thank all managers and personnel involved with validation at ZLB for their patience during the long and challenging discussions and for their willingness to make the system work.

References

1. Guideline on General Principles of Process Validation, FDA Division of Manufacturing and Product Quality, 1987.
2. Principles of Qualification and Validation in Pharmaceutical Manufacture, PIC-Document PH 1/96.
3. Validation of Analytical Procedures: Methodology, CPMP/ICH/281/95.

Validation of A Consumer Healthcare Facility

A Case Study in Time & Cost Reduction

By R.J. Noy, Ph.D.
SmithKline Beecham Consumer Healthcare

A recent upgrade at SmithKline Beecham's facility in the UK raised the age-old validation battle of approved methodologies versus their cost.

As national health services throughout the world have become starved of cash and more reliant on patient self-medication, OTC healthcare products have become increasingly important to the healthcare and pharmaceutical industries. SmithKline Beecham's Maidenhead facility specializes in consumer healthcare products, particularly oral care medications. Since 1994, the site has undergone a major refurbishment to upgrade its facilities. At the same time, it was necessary to continue production to meet the demands of the marketplace.

In conjunction with this major renovation, validation was included in the remit and steps were taken to validate the process equipment and facilities for all licensed products manufactured on-site. However, since the Maidenhead site manufactures mostly unlicensed consumer healthcare products, no validation in the true pharmaceutical sense was required.

While the site was undergoing its upgrade, it was decided to introduce a dedicated facility to produce medicated mouthwash. Consequently, true validation was needed for the process equipment and associated infrastructure.

The EC-GMP guidelines do not distinguish validation requirements between sterile injectables and a medicated mouthwash. As a result, the full force of a validation exercise was required. Certain standards, which clearly could not be compromised, had to be the same as they are for pharmaceuticals. Still, both internal and external sources advised us that while validation documentation is a prerequisite for compliance, certain facets of the validation process need not be as rigorous.

This paper sets out the scope, philosophy, schedule, time and cost savings for the validation of an oral healthcare manufacturing facility in the light of these recommendations. At no time during the validation investigation did SmithKline's standards fall below the legal baseline of critical pharmaceutical quality requirements.

Scope and Strategy

Table 1 indicates the scope of the validation project required to obtain an ML from the UK MCA. Because the full validation team was not organized until late in the project, the study was partly retrospective on new equipment and facilities. Given that the manufacturers of the systems were unfamiliar with validation requirements, the validation team

was able to assemble documents and ensure the careful installation and commissioning of the facilities according to the requirements of the SmithKline validation team.

One of the most important aspects of this fast-track validation exercise was setting up an implementation team that met at regular intervals (weekly) or on a rapid-response basis. If problems became critical during the project, they were discussed quickly, and solutions were sought and responded to in minutes or hours. This proved to be an excellent strategy as major difficulties were overcome and the validation project continued unabated. *Table 2* outlines the members of the validation implementation team.

The second most important element was the formation of a validation team, which was created over the course of six weeks. One of the members was an experienced validation manager familiar with the preparation of SOPs, protocols and test sheets. The validation manager was required to direct the validation effort and have the depth of background to set standards for testing and develop the technical philosophy for the exercise. Shortly after this appointment, a validation engineer was recruited to act as a deputy to the validation manager. The technicians who actually performed the testing were chosen soon after the validation manager had been appointed. *Table 3* shows the type of personnel sought for these vital responsibilities.

We adopted the systems and subsystems method of approach, and the validation master plan submitted to the MCA reflected this philosophy.

Budget constraints and the overall resources required to complete the exercise were other major considerations. Senior management continually asked the same question: Why does a mouthwash facility

Table 1: Scope of the Validation Project

Purified Water Plant	• IQ, OQ and PQ requirements • 1000kg/hour required • Ring main supply • Dual ion exchange • Storage and feed water tanks • PLC control	**Training**	This was the responsibility of the Training Department
Bulk Manufacturing Facility	• IQ, OQ and PQ requirements • Mixing vessel • Three storage tanks • CIP set and pipe work • PLC and C/I System • HVAC IQ and combined OQ/PQ	**Calibration**	Mobile, fixed and critical/non-critical instruments–all calibrated by a third party and documented by the validation team.
Filling and Packaging Line	• IQ, OQ and PQ requirements • Seven items of equipment • PLC associated with most items • Critical items (filler and labeler) • HVAC IQ and combined OQ/PQ	**Maintenance**	Computerized asset and maintenance system
Utility and Services	• HVAC • Room environmental monitoring • Change lobby monitoring • Flame proof considerations • Gases • Power • Vacuum and cleaning water for the CIP	**Work Instructions & Operational SOPs**	Working instructions for the Production and QA/QC Department were written by a site-dedicated team.
Positive Release Warehouse System	(To be explored in an upcoming edition of the ***Journal of Validation Technology***)	**Cleaning Validation**	The Quality Improvement Manager directed this function with secondary staff.

Table 2: Validation Implementation Team

Table 3

Position	Background	Skills
Validation Manager	• Science or engineering degree • 10 years pharmaceutical experience • Five years management experience • Auditing or PQ qualification	• Organizing paper systems • Overseeing batch documentation • Knowledge of GMPs • Proven management skills • Practiced facilitator • Practical knowledge of PC software
Mechanical Technician	• Trade qualification • Apprenticeship • Five years in pharmaceuticals • GMP experience	• Experience with pipe work and ducts • Repair and fault finding • Practical knowledge of PC • Knowledge of HVAC • Extensive general knowledge of mechanical systems
Electrical Technician	• Trade qualification • Apprenticeship • GMP experience	• Knowledge of C/I systems • Electrical fault finding • PLC and computer commissioning • Process and packaging experience • Software experience • Overall knowledge of electrical systems

need to be validated to ethical manufacturing standards? In a way, this question was justified, since the product was a medication for oral use only. However, the active ingredient was a very effective biocide in large concentrations. Poor manufacturing practices could have resulted in disastrous consequences.

The underlying culture of the site was a consumer goods manufacturing plant. Site development included a major upgrade in cGMPs and the transition to a healthcare culture. These goals called for a massive change in culture and the creation of validation procedures to satisfy an inspection from the MCA.

Documentation

Documentation was the starting point of the project. Without validation SOPs to drive the validation protocols, it was impossible to begin the study. Most of the project team had to agree to, approve and sign all SOPs and protocols, which was a major achievement in itself. *Table 4* gives a summary of the major levels of documentation used to define, initiate and record validation data.

The next major decision regarding the reduction of time and expense involved determining which tests to perform and to what depth and detail. (*Table 6* provides examples of some of the savings adopted during this study.)

The validation master plan was written first and submitted to the MCA for overall "approval" of the methodology and approach. This document was submitted in July 1995 and approved shortly after. Validation work began in August 1995 with the preparation of SOPs and protocols.

The water plant and ring main were the first systems to be validated using the documents and test sheets described in this paper. The water plan was chosen because we had all of the O/M manuals from the suppliers, as well as SAT and installation documentation, such as weld details, passivation data and other information.

The next system to be validated was the bulk manufacturing plant. (As luck would have it, obtaining the vendor documentation followed according to plan.) By October or November 1995, we started on the filling and packaging hall, which was dedicated for all mouthwash products and used mostly for unlicensed products. The licensed mouthwash was secondarily packed on this line, but it was not labeled there. Dedicated equipment was used for this job.

Test sheets were largely devised from the vendor's O/M manuals, though SmithKline's own in-house expertise in packaging technology was of benefit. PLC validation of all equipment was compared against the URS and FDS (information supplied from the user and the vendor respectively). By the end of January 1996, we were in position to request an inspection from the MCA.

Depth of Validation

In order to complete the schedule by the end of January 1996, a certain amount of fast-tracking was required. As indicated earlier, the biggest

Table 4: Amount of Documentation Used During Project

TITLE		PURPOSE
Validation Master Plan	(1)	Overall Plan
Validation SOPs	(35)	Drives Generic Methodology
Validation Protocols	(54	Specific Methodology
Test Sheets	(Many)	Data Gathering
O/M Manuals	(12)	Data From Vendors
Technical Files	(10)	Additional Data
Work Instructions	(102)	Site and Facility Instructions (Equivalent to SOPs used at the plant)
Validation Reports	(15)	Reporting to the Validation Work
Remedial Action Reports	(1)	Description of Remedial Action Required
System Error/Failure Sheets	(26)	Identifying Errors
Master Index	(1)	Ease of Documentation Location
Certificates	(3)	Final Approval
Review Protocols	(3)	Annual Review
Change Control Dossier	(3)	Recording Technical Changes
Training Records	(1)	Training of Staff
Maintenance Records	(3)	Maintenance and Asset Register

(The figures in parentheses indicate the number of versions of each document.)

Table 5: Depth of Requirements

Qualification Level	Consumer Healthcare Validation	Prescription Medicine Validation
Installation Qualification	• Major vessels treated as associated equipment • Details of welds only to identification level • Lubricant detail only to supplier's literature • Materials certificates only supplied • Minimum DQ and SQ	• Major vessels treated as separate protocols • Full traceability of welds plus x-ray, dye, & photographic documentation • Full details including in-house testing • Full materials traceability • Full DQ and SQ
Operational Qualification	• Full testing of system only	• Full testing of systems & subsystems
Performance Qualification	• Full testing of system	• Full testing of systems

questions were how far to carry out the validation, particularly in terms of testing, and how to keep the cost and time at a minimum. The use of a master index, which cross-referenced all of the SOPs and protocols, was very advantageous in keeping track of the work. It also provided a quick reference while an inspector was on-site. *Table 5* offers a summary of the depth of requirements required for this exercise.

The URS was not officially written at the kick-off of the project, as the validation team arrived fairly late in the proceedings. However, upon arrival, the validation team worked according to the following URS:

- Materials of construction philosophy
- Cleanability
- Maintenance
- Performance of equipment and processes
- Critical parameters identified
- Operating ranges of critical parameters defined
- Essential design criteria defined
- Requirements of the PLC, PC and C/I
- Training requirements identified
- Documentation unambiguous

Test Sheets and Forms

Design Qualification (DQ) - Minimal DQ was undertaken as the project was well into the construction phase when the validation team arrived. Still, a DQ retrospective validation review was performed quickly, and the following record forms were completed:

- Design safety form
- Layout review record form
- GMP review record form
- PLC, PC, C/I review record form
- Commissioning and start-up review record form

Installation Qualification - The IQ test sheets and forms were reduced to the list shown below by combining common parameters, such as materials of construction, lubricants and elastomers. Similarly, the utilities and services test sheets and forms were combined to include electrics, water, gases, drains, etc. IQ also incorporated the following:

- Associated items form
- Critical information form
- Consumable information form
- Drawing information and verification form
- Specification information form

- Lubricant, materials of construction, and elastomer form
- Weld information form
- Vessel and tank information form
- Controls, instrumentation, indicators and safety devices check sheet
- Utilities and services information and test sheet
- Error/failure log form

Operational Qualification - The OQ test and information sheets were rationalized and made easier to complete by the test engineer. These sheets, which were very similar to those for IQ, were composed of objective, method, acceptance criteria, results and pass/fail blocks. OQ included in the following documents:

- Prerequisites form (all IQ errors must be closed out before continuation to OQ)
- FDS comparison form
- SOP information form
- Noise level test form
- Speed and rotation test form
- Flow rate test form
- Critical devices and interlocks test form
- Screen identification form
- Leak and tank capacity test form
- Stirrer efficiency test form
- Error/failure log form

The error/failure forms were generated for both IQ and OQ because errors and failures inevitably are found during testing. In all cases remedial action was taken to rectify the faults. This activity was a prerequisite for both OQ and PQ investigations, as well as for PLC validation.

Performance Qualification - The PQ test sheets were similar to the OQ test sheets. They largely referred to the technical report prepared by R&D on the three consecutive batches of two different variants of the formulation which had been prepared during the experimental work batch phase of the project. The following documents were included:

- Prerequisites form (All OQ errors and failures must be closed out before PQ starts)
- Measurement devices form
- Raw materials requirements form
- Instrumentation and devices form
- Cleaning verification form
- Critical process steps form
- Critical operating parameters form
- Controls form
- Product composition form
- Quality of product produced form
- Disaster recovery form
- Integrated line testing form

Finally, a validation report was written summarizing these results in about two pages.

Cleaning Qualification - The test and information sheet approach was undertaken. The definition of cleaning at SmithKline is taken in the broadest of terms, ranging from chemical sanitization of the purified water plant storage tank, feed tank and ring main to CIP of the bulk manufacturing tanks and manual cleaning of the line items. Due to this diversity, the decision was made to use detailed validation reports, which took the form of technical reports that included acceptance criteria.

PLC Qualification and Validation - The protocol was called the "Validation Qualification Protocol" and comprised the following test and information sheets:

- Specification test sheet for URS and FDS comparison
- Control system data form
- Input test form
- Timer, counter and data register test form
- Output test form
- PLC module test form
- Blackout/disaster recovery test form
- Critical device calibration test form
- PLC incident form
- Error/failure form

Not all of the test and information sheets were applicable. A summary sheet was added to the front of the documents to indicate which forms were used and the number of pages of each.

HVAC and Room Environment Qualification - Test and information sheets similar to those for the process systems were used for HVAC and room environmental qualification. However, extra test sheets, along with a specialized OQ sheet, were added for room data. The PQ of the bulk manufacturing area was a daily

logging of environmental parameters, such as temperature, particles, RH, oxygen and air flow characteristics.

General Qualification - This area is defined as the daily, weekly or monthly logging of equipment, utilities, production processes and other data. Daily logs of pressures, UV lamp intensities, temperatures, air flow, etc., were recorded manually to ensure the facility remained in control. For its part, the QA/QC Department prepared daily logs of raw materials, such as water, actives, excipients, packaging components, batch records and out-of-spec results. However, it proved to be difficult to fully educate the Engineering and Production Departments, as they were not fully conversant with the daily logging of data. The education and training of this personnel is an ongoing exercise by both the QA/QC and Validation Departments.

Change Control

Change control often frightens many of the established and older personnel on the production floor. To them, it means slowing production schedules, more paperwork, etc. For an FMCG factory, this is even more pronounced and obvious. However, the need for change control in a cGMP facility is essential to keep compliant with required standards. The change control procedures again were rationalized to make the system user-friendly.

Validation Reports

These reports were written at the end of the full validation of process equipment or utilities. They proved to be an excellent way of summarizing the exercise, describing what went wrong and how it was remedied. The inspectorate also found this an excellent way of understanding the project and its faults. It was in no way detrimental to our application for a license. In fact, it helped us a great deal.

Validation Reviews

This will occur in October 1996 at the anniversary of the OQ sign-off. The check list approach will be used to complete the following major categories:

- Validation master plan review
- Validation reports, protocols and SOPs review
- Trend and daily log analysis
- Change control dossier review
- SOPs and work instructions review
- Batch records review
- Customer complaint review
- Reject materials review
- Process changes and deviations review
- Maintenance and calibration record review
- Audit and self-inspection review
- Retained sample and stability record review
- Out-of-spec results review
- Training records review

Certification and Hand-Over

At the end of the validation project, the facility was "handed over" to the new owners of the facility, namely the Production Department. This involved the acknowledgement and transfer of a formal certificate verifying that validation had met cGMP and GEP standards. Time will tell if the new owners of the facility are able to run a cGMP facility to the level required by the inspectorate.

Overall Cost and Time Reduction

Table 6 summarizes how much time and money were saved using the fast-track validation methodology described in this paper. Although subjective in its content, this table gives an accurate picture of the validation project and the ways expenditures of time and money were kept in check.

The overall costs were probably half to two-thirds the costs normally associated with an ethical pharmaceutical product (prescription-only medicine). The total time taken to obtain the license, up to and including PQ, was 17 weeks at a cost of 3% of the book value of the facility.

Conclusion

The result of the exercise was a good one for the SmithKline Validation Department. The company

Table 6: Estimated Time & Cost Reductions

Activity	Subjective Cost Reduction	Subjective Time Reduction	Downsize
Highly trained validation personnel	Medium	High	May get bored with low tech product
Agency validation personnel	Medium	High	Loss of company expertise
Quality critical testing only	Low to Medium	Medium	May miss vital aspects & secondary critical testing
Combining some test sheets	Low	Medium	Cramped presentation
Combining tests	Low to Medium	Low to Medium	Loss of detail
Secondary in-house help from untrained staff	Medium	Low	Errors may develop
Minimum hand-writing of test data	Medium	Low	Typed data may look suspicious
Validation implementation team	Medium to High	Medium	Too many meetings
Rapid-response meeting	Low	Medium	Many breaks during the job
Decision not to use engineering contractors to perform validation	High	High	None
Extensive spread of knowledge within the validation team	Medium	High	None
Engineering drawings kept to a minimum	Medium	Medium	May miss a vital change
Work instructions instead of SOPs	High	Medium	Lack of detail
Use of in-house PLC experts	Medium	Low to Medium	None
All documentation on WORD v2	Low	High	None
Use of technical file for extra data	Medium	Low	None
Color-coding of protocols	Medium	Medium	None

received its first license for the new site. The team involved in the inspection requirements was truly a "dream team," the dynamics of which will be difficult to assemble again. The team's meeting and planning strategy was excellent, as was the communication between members. The project was within budget due to the rational and targeted validation strategy that was adopted.

The URS was in compliance, and although a formal DQ was not written, cGMP compliance was achieved, specifications were attained, documents from vendors were forthcoming and cGMP boundaries were well defined. Additionally, in most cases, design changes were recorded and vendors audited. Finally, SmithKline proved to a high degree of assurance that the oral healthcare facility was in control. All that remains is that the company continue to operate accordingly over the lifetime of the facility. ❑

Journal of Validation Technology Related Articles

May 1996

1. Wayne T. Flaherty, "Facility Validation: Management Issues." February 1995
2. Patricia Stewart, "New vs. Existing Facilities: Two Approaches for Developing IQs."

Validation Without Tears: Getting Started

By Tanya Fletcher & Melvin R. Smith
Almedica Services Corporation

Although there are many articles and treatises on the various aspects of validation, very few, if any, address the people who are getting the job done. The validation person often find themselves in a hostile environment faced with overwhelming demands, unrealistic expectations, and expected to accomplish tasks within a totally impossible time frame. This is often coupled with an almost total lack of support staff, appropriate test equipment, and inability to identify the movers and shakers who can lend support in accomplish tasks.

"This article is devoted to the subject of getting started, organized and launching validation activity."

Often too, this individual(s) finds a culture initially hostile to their activities, not understanding, nor accepting that regulatory and cGMP validations are often requirements. Validation is often seen as an intrusion on production, and something extra to do, in addition to the normal workload. Since validation efforts do not initially produce any additional profits, they may be seen as a cost center.

Often, the problem of, "but we've always done it that way" inertia is seen as an obstacle that must be overcome. When the firm sees how that new methodologies can accomplish goals, resistance will crumble. More staff will want to get involved, and climb on the validation bandwagon.

This article is devoted to the subject of getting started, organized, and launching validation activity.

Why Validation?

For discussion's sake, let's say your company has been finally forced to commence validation activity. Forced is the operative word today, not only because of the changes in the new cGMPs and CFR's, but also because of the increased sophistication and knowledge in the field. Many senior field staff of the FDA (the enforcement and compliance staffs) have recently retired and moved into senior QA industry staff positions. Their experience and training have increased the auditor inspection acumen, and validation status is at the top of their list.

Validation activities, as with all quality activities, must be supported from the top. Every level of management must permit and support your activities. Validation is the company's responsibility, not an individual, or department.

Whom Do I Report To?

Interestingly, whom the validation person should report to is of great interest, and even subject to controversy. Should it be QA? Regulatory affairs? Operations? President of the company?

Because of various levels of bureaucracy that can exist in a firm, and the Byzantine reporting structures that may exist, the validation person might want to have defined, in writing, to whom he/she

reports to. In some companies, validation is a QA department function. This can be a questionable practice since QA would then be signing off on the work for approvals. This raises all sorts of conflict-of-interest issues. The regulatory affairs department is an option, if the department has the technical expertise and the time. Operations might also be a viable option. Operations affords access to all production activities being accomplished including equipment, processes and products. Reporting directly to the President/CEO sounds great, but priority setting, and other management support might not always be present because of constraints on the chief executive's time.

Determining The Culture

You are dealing with people as well as machines, process and products. They have needs and feelings, and seek job security, sense of accomplishment, praise, a sense of structure and order, and financial remuneration. People always want to learn new things. However, if you or your work is perceived as a threat to any of the aforementioned attributes, you will have problems until that perceived threat is removed. It will be helpful if you can demonstrate how they will personally benefit from lending you a hand and learning what has to be done.

One of the pitfalls that many validation staffs fall into is their own education and training. They are so used to a higher technical knowledge level for themselves and their peers, they fail to take into account the average experience, training, education and background levels of those they must communicate with. Understand and reach everyone's level of validation expertise. When the validation professional discusses the subject in unfamiliar jargon and technical terms, he must realize that his target audience is lost. Two areas of advice can be given. First, watch the eyes of the knowledge recipient for the "aha" light to go on. Second, be guided by the dictum that "God must have loved the common man, he made so many of them." Communicate and instruct to everyone employed at your firm.

Validation should not be interpreted as a threat to job security by staff and workers, but rather viewed as a way to increase their understanding of what they are doing, and why they are doing it.

Determining The Firm's Needs

Let us assume you are the first validation person employed at your firm. Take time to walk the floors, poke into the rooms. See what is going on. Look through production batch records, instructions, and procedures. See what is there already. Talk to people, and hear what they are saying to you.

If possible, start making a list of all processes and equipment. If one already exists, keep it as a checklist as you walk around. It may need to be updated for your purposes. Don't worry at this time about prioritizing the list, you are now just being all-encompassing and getting oriented.

Validation will be broken up into six areas:

❶ Facilities commissioning/qualification.
❷ Equipment validation.
❸ Computer system validation.
❹ Process validation.
❺ Cleaning validation and,
❻ Product validation.

Because of this, take the time to list what needs to be done.

Once a preliminary list of equipment and processes is made, you will need to determine what test equipment is necessary. Some basic test equipment used for validation includes a multimeter, data acquisition device, temperature probes and tachometer. It is critical to ensure all of your test equipment is initially and continually calibrated in a scheduled manner. If it is required to obtain test equipment, learn how to cut a purchase order, or utilize other methods of procuring needed supplies. Determine if you need a budget citation. If needed, who helps you get it.

With these six "laundry lists" in hand, seek out the reporting supervisor, and determine prioritization within each category. Remember that you are a limited resource, and your talents have to be put to immediate use, where it will produce the most quality results in the shortest amount of time. Be a rifle, rather than a shotgun in your approach. If possible, determine realistic time lines along with the priorities.

Many times the easier validation tasks will not

produce any major benefits. The same goes for attacking those types of validations which are near and dear to your heart, and which in other situations, you may have done well. As this is a new situation, let your superiors outline, with your input, a reasonable prioritization. Remember, your supervisor needs to demonstrate results to the next reporting level. Furthermore, your supervisor probably knows the firm better than you, knows what the short and long term goals are, and knows the department's role in meeting them.

Get The Proper Training

It would be nice if there was a single format, and single approach, to validation activities. Sadly, there is not. But there are guiding principles and general approaches that can help you sort out what you have to do, how you're going to do it, and what your work product will be.

Therefore, besides education and training, love of detail and documentation, you must be able to write. Written communication skills are developed by practice and use. You must communicate with all employee levels. Succinct writing is a skill to be developed. Not only must data be accumulated, entered, analyzed and reviewed, but trends, forecasts and proof statements must be able to be drawn or inferred from them.

Next, it would be useful to hone your validation skills by registering for courses on basic validation principles. Join professional organizations, and order journal subscriptions to organizations that specialize in addressing validation issues. A deep working knowledge of all cGMPs, ISO9000 series, and other laws and regulations must be possessed. You are operating not as an isolated worker, but rather as part of the larger system professionally, as well as company-wise. There is much help out in industry. Seek it out. Network.

Now that the skills, knowledge of your milieu, your reporting strategies and knowledge of the organization chart are all in hand, and knowing where you want to get to (validated products, processes, and equipment) let us see how we will take the first step in validation and what you will do on the journey.

The Journey

The first thing you need to have is a master validation plan (MVP) in place. Although there is no regulation or guideline that requires this document, it is crucial. With the master validation plan in hand, one can then approach the reporting supervisor for assistance in developing strategies, priorities, as well as budgeting.

The best MVP and priorities, however, are subject to changes and other exigencies existing in the organization. This requires flexibility, so don't be too rigid against changing the MVP. Remember, you are working for a commercial firm, where facility, computer system, and equipment changes and additions are commonplace.

The master validation plan should not be viewed by management, or presented by the validation staff, as causing interference in work flow, or other negative connotations. It should also not be seen as being intrusive on other department's turf. The plan should view validation as codifying, rationalizing and legitimizing the current equipment, methods, processes and products for all to see and understand.

Once you have completed a master validation plan, listed your job priorities, realize a possible time line may be altered by exigencies within the firm, with a promise of support and backing, you are ready to start.

At this point, you need a format to do the work. No one format works for every task, but there are some general guidelines to follow.

Format

For the most part, when dealing with equipment and computer system validation, one relies upon the IQ-OQ-PQ (installation qualification, operational qualification and performance qualification). As a guideline, IQ is everything you do before powering the equipment or system. OQ is what you do after you power it to determine parameter limits of operation, and demonstrate that the equipment or system works. PQ is where the equipment or system software is subjected to the stresses of "everyday" production use. The documents or protocols must be pre-approved before executing them.

For equipment, computer system validation and other validations, the best approach, and the one most easily executed is the "fill in the blanks" pro-

Figure 1

Approvals

Document Prepared by:
Printed: _____
Signature: _____ Date: _____

Technical Reviewed By:
Printed: _____
Signature: _____ Date: _____

Approved By:

Individual Department(s):
Printed: _____
Signature: _____ Date: _____

Quality Assurance:
Printed: _____
Signature: _____ Date: _____

tocol. Here you determine what you have to do, and have it reviewed and approved by management and QA. They must sign off before you perform the study (see *Figure 1*). They sign off in designated approval sections of the documents individually.

It is best to construct the protocols based on user manuals, drawings and formalized design specifications. The needs of your firm, and intended use also dictate the content of your documents. A well constructed protocol is the easiest one to execute. Take the time and expend the effort here. In fact, constructing the format, will be the most time consuming.

There are many articles and courses available that detail how to go about writing a validation protocol for equipment, computer systems, cleaning, facility, product and process validation. Research them and find the style you are most comfortable with.

Execution

Armed with a well thought out, written and approved protocol, you are ready to execute the protocol and record results. Carefully read through the protocol and determine a tentative schedule for completion. Your schedule is dependent on details, such as testing time and turn-around of laboratory results. Also, allow downtime on equipment or processes.

Proceed step-by-step through the protocol and record the results. Any noteworthy observations should be documented in your protocol. If a test fails, this should be noted as a deviation. A deviation is where you report those findings or results which are at variance with what you expected or predicted. This may be anything from a constant tripping of electric breakers, to negative pressure in your clean room. Perhaps, inadvertently you discover that the capsule filling machine has difficulty counting black colored capsules. A distinction must be made as to what deviations are critical and non-critical. Critical deviations affect the operational status. Deviations must be reviewed and approved by appropriate personnel. For an example of a formal deviation form, see *Figure 2*.

With the protocol completed, and deviations addressed, you are ready to summarize your findings. Your summary should compare the goals that were set out in the protocol against the results.

These goals should be addressed in the protocol introduction. After comparing and summarizing the goals and results, discuss the variances and deviations encountered. If these deviations were critical, discuss how they were addressed. The summary is also an opportunity to make recommendations. For example, suppose you discover in an ultra-low freezer that the top shelf has an operating temperature a few degrees warmer than the rest. A recommendation derived from this deviation loading that shelf last when filling the freezer with drug product.

Cleaning Validations

Included with the responsibility of equipment validation is cleaning validation. In short, cleaning validation inspects your company's equipment cleaning methods to ensure both product and detergent removal. In some cases, this could involve detection for microbial load. Cleaning validation demonstrates there is no cross contamination.

Before venturing into this area, a list of equipment that comes in direct contact with product should be determined. For each product in question,

Figure 2

Validation Deviation Report

Deviation number:

Document number:

Document title:

Details of deviation:

Documented by: Date:

Response

The deviation is: Critical ❑ Non-Critical ❑

If the deviation is critical (operational status is affected) describe the impact:

Is corrective action required (Yes/No): _____ (If Yes, describe below)

Action plan:

By: Date:

Action plan approved by: Date:

Date of implementation:

Person responsible for implementation:

recovery studies must be performed. Therefore, it is necessary to employ the services of a laboratory. It is strongly advised to do research via other professionals, courses and articles before embarking on a cleaning validation program. Laboratory costs are expensive.

Once recovery studies and sampling plans have been researched and performed, a cleaning validation protocol can be written and subsequently approved. Cleaning validation typically is performed for three lots or batches of the same product in contact with the same equipment. After the typical three lots or batches are complete, and results are returned from the laboratory, a summary report can be written. As discussed, the summary should include results and any deviations found. The report should express if the validation was successful or not, based on the goals set forth in the cleaning validation protocol.

Facility Qualification/Commissioning

Commissioning involves identifying and verifying the facility floor plan, utilities, maintenance program, security/alarms system, and back up systems. The existing facility and support programs must be compared against design specifications, drawings and standard operating procedures.

Floor plan verification involves documenting walls, ceilings, floor finishes, room dimensions and lighting. This verification is based on drawings and design specifications. Utilities verification will verify use points for electricity, water systems, compressed air systems and HVAC systems. “As-found” information should be compared against design specifications. Maintenance and routine testing of these systems should also be documented. The operation of back-up systems must be documented, and tested for response time.

Alarm systems must be verified for entry, as well as out of range environmental conditions. For example, if a humidity controlled room rises above its specification of 50% or less relative humidity, appropriate personnel must be contacted. This alarm and response system must be verified and documented on a scheduled basis.

When planning to commission a facility, it is critical to identify the crucial processes carried out in the facility. Do the processes in the facility require aseptic, temperature or humidity controlled conditions? If they do, then these will be the critical aspects of your facility commissioning. If the facility is aseptic, the HVAC system must be designed to effectively filter clean air and remove dirty air. If aseptic, the cleanest area must have the lowest traffic.

As with equipment validation, adequate test equipment must be utilized. To continue the example of an aseptic area, test equipment, such as a particle counter, or manometer need to be utilized. Equipment, such as a DOP detector, can be used to determine the efficiency of a HEPA filter. As stated in the previous section, test equipment needs to be initially and then continually calibrated in a scheduled manner.

Product Validation

In this type of validation, a history of product development must be developed. It is initially assumed the equipment used and environmental conditions are validated. For example, in experimental batch #1, we mixed x with y in the following amounts with a total weight of, and kneaded it in a plastic bag. After that step was completed, we attempted to tablet it, and it fell apart. We noted the results and destroyed the mix. We then proceeded on to experimental batches two through as many as needed. Your final experimental batch will yield the desired results, and should be ready for initial scale-up.

Also included is a discussion of the final components, their sources, reasons for inclusion and intrinsic quality (USP, NF, etc.), as well as their relative mixing proportions and contents.

The final product must be described in its physical, chemical and laboratory test results. The equipment (validated) must be described, as well as required operating parameters.

The ultimate goal is describing a validated product based upon source and quality of components, method of mixing, processing and blending, final processing to get it into its dosage form testing to assure meeting its pre-determined required specification, and capability of being scaled up and manufactured on a routine and repetitive basis.

Once again, we work with a predetermined and signed off protocol, which is then filled in, and a summary is written. The history of development is

one of the major differences, as will be a discussion of the laboratory testing. But it is basically the same methodology used; plan, write, approve, execute, write, and approve.

Process Validation

This is often a variation of equipment validation, coupled with a product validation. Process validation assumes all equipment, process rooms and storage areas are validated. In order to perform a successful process validation, the process must be broken down into discrete steps. Critical parameters of the process steps must be determined and then tied together. A process validation typically involves three lots of the same product exposed to the same equipment and process. Once again, approve the protocol, fill it in and summarize. Document any deviations. Where required, determine a set of laboratory measured parameters.

Things To Remember

In conducting validation you have to decide on many things which are currently taking place, as well as future considerations, such as:

- Change control and distribution notifications.
- What triggers revalidation?
- SOPs that legitimize what you are doing, and what is required to maintain a validated state.
- Training requirements and re-training needs.
- Where is the library of manuals (operator, repair/maintenance, schematics) located?
- When will you periodically review the state of validations done? A recommendation might be two years after the original or restudy was done.

Staffing

Depending on your current responsibilities, and the amount of tasks ahead, it may be advantageous to hire additional staff. If the projects are considered a priority, or if the technical expertise is not available, it may be useful to contract the work through a validation consulting firm. If you contract the work out, you must be aware that whatever you have validated must remain in a validated state. That means if changes are made, your firm, not the consultant, is responsible for documentation, retesting or even revalidation.

Whomever you hire, it is important to assess their technical proficiency, and capabilities to perform your validation tasks.

Conclusion

When we started on this journey, the aim was to remove the mystery of validation, and encourage staff not to be afraid of it. Validation is here to stay, and its requirements will continue to expand through industry.

Validation is not difficult when critical equipment, systems, processes are identified, broken down and prioritized. Once you determine your format, focus on critical content, and get input from individual departments as well as QA, this will help the validation run more smoothly.

Once you have a basic understanding of validation and its role in industry, you will embark on effectively determining your company's needs and successfully fulfilling them. ❑

The opinions expressed in this article are strictly those of the authors. They in no way represent the views of Almedica Services Corporation.

Front-End Planning for cGMP Facility Expansion

Each year, new regulations are added to the long list of existing environmental, safety and health concerns that must be incorporated into the design of renovated or new facilities.

by
Jeffrey Broadhead
Director of Technology
BE&K Engineering
and
Edward Pedersen
Director of Facility Planning
Sear-Brown,
Bio-Pharmaceutical Group

Today's business environment in FDA-regulated industries forces facility planners, engineers, and designers to increase their efficiency and effectiveness in the planning and construction of new facilities. We are in an era characterized by exploding technology and expanding regulation. This coupled with escalating competition and increasing technical costs, forces planners to make responsible decisions that benefit their company's position in the marketplace. No longer can a current Good Manufacturing Practice (cGMP) facility be planned and implemented by a firm's internal staff group, no matter how knowledgeable and experienced they are. The complexity of modern plant technology requires that the planning process be a multi-disciplinary effort combining the expert knowledge of process architecture and engineering, materials handling, control systems, automation, compliance, validation, and construction with staff experienced in operations, maintenance, quality assurance, safety, environmental issues, and production. The requirements to be competitive in a global market, and to maintain control over increasing scope and facility costs, drive the need for early cost control. This is a critical element of the project.

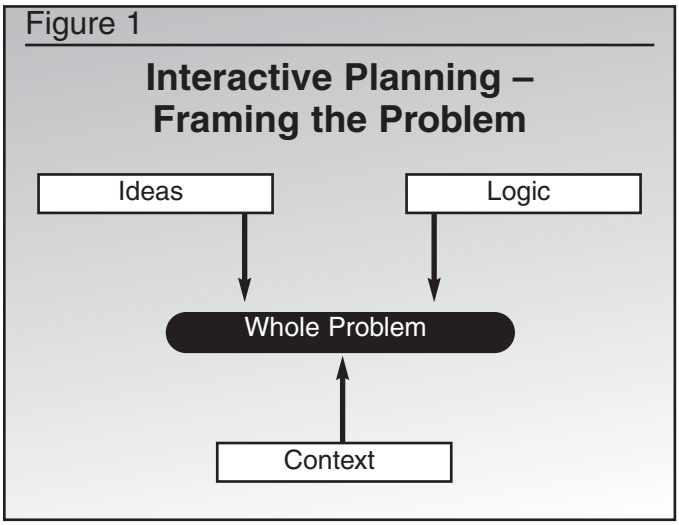
Each year, new regulations are added to the long list of existing environmental, safety and health concerns that must be incorporated into the design of renovated or new facilities. Front-end planning, as described in this article, is a critical part of a firm's compliance strategy. By documenting the design approach as the process unfolds and recording the input of all involved, those who will eventually assume the responsibility for maintaining a compliant state per 21CFR Parts 210-211, 606-680, and 820 will have a distinct advantage. Their needs and limitations are already considered, and the transfer of design documentation to construction teams ensures a compliant facility.

Decisions at each stage of project development have to be as responsive and accurate as possible. Often, major decisions are made too early without fully understanding the nature of the project or the implications they may have on the project development. The project scope and budget can become undefined and underestimated, requiring expensive adjustment after the design has started or, expensive technologies can be unnecessarily incorporated into the design. Without an organized planning and evaluation method, errors will multiply in the process, often leading to cost overruns or worse, dysfunctional/non-compliant facilities.

Getting Started

The initial step in any planning process is to define the problem: "You can't solve it, if you don't know what it is." This expression stresses the need for achieving a complete understanding of the problems that confront the expansion or design of cGMP facilities. Refer to *Figure 1*. Facility planning consists of three basic steps:

Figure 1



- Analysis, known as facility programming, investigates and clearly states the problems that must be solved, the goals that must be reached, and the issues that must be resolved in the design process.
- Synthesis or design evaluation develops the solution for these problems.
- Implementation is the ongoing process of acting upon the decisions made in the Analysis and Synthesis steps and reevaluating the consequences.

Facility programming not only seeks to identify and understand the problems that must be solved, it also establishes realistic constraints for the project and conceptually explores the potential of alternative approaches. Programming enables the planning team to frame the problem within its objectives, thereby setting priorities for later design decisions. The objectives of the project may consist of the budget, implications for change in the future, legal and regulatory requirements, and management's commitment to the project. Programming helps the owner/consultant team to organize all the relevant information about the project into a meaningful form. All problem solving, especially the design of complex production facilities, consist of resolving numerous small conditions toward some collective end. In order to do so, the planning team needs to develop a methodology for systematic organization of the information that it generates through the problem seeking and information gathering efforts.

Understanding the Client Goals and Needs

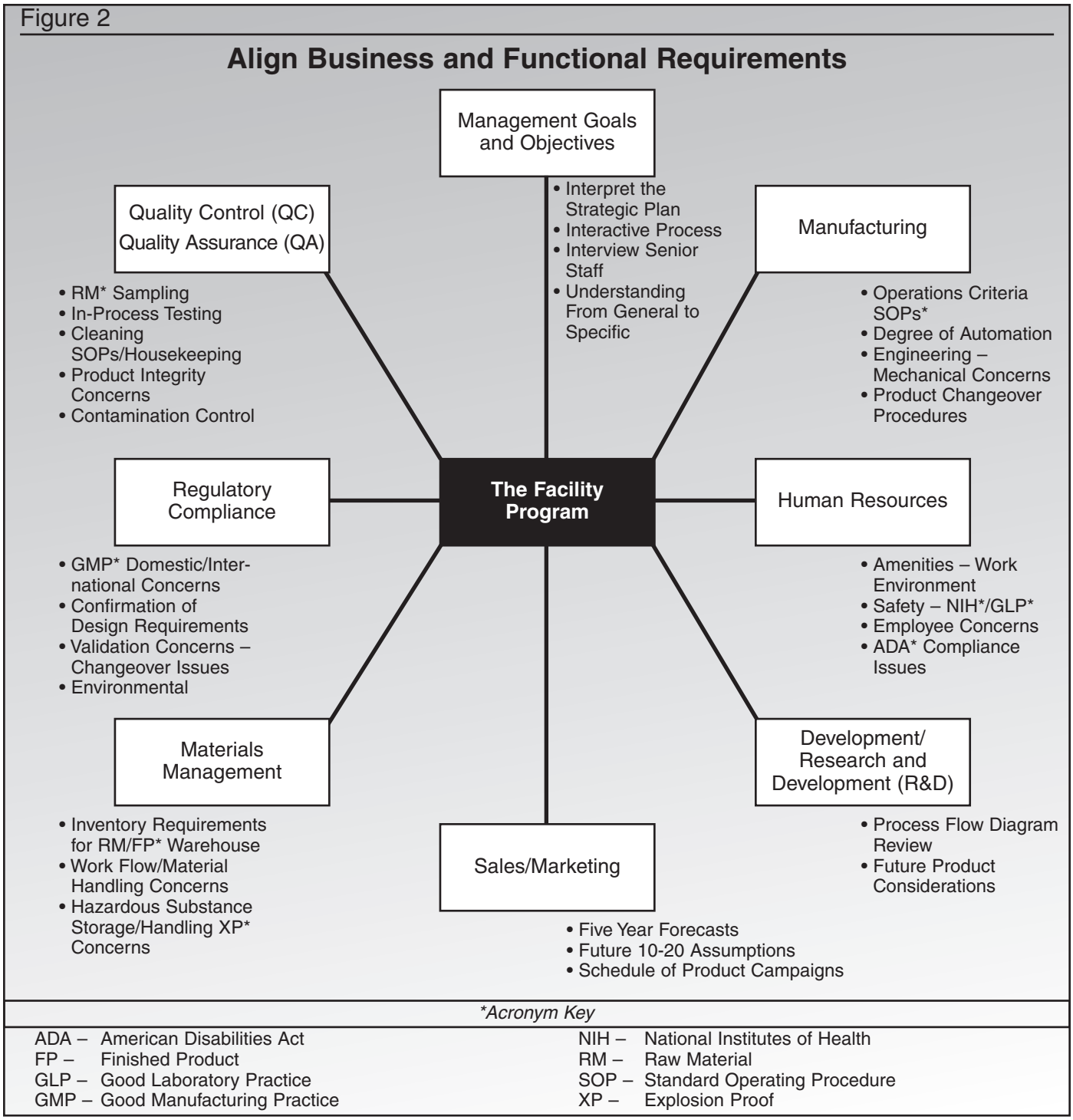
A facility must be responsive and supportive of the business goals. The business strategy, organizational structure and individual work environments must be defined, and understood for successful planning. The programming and planning sessions need to establish an open dialogue between all participants. Upper Management, Finance, Production, Human Resources (HR), Material Handling, Research and Development (R&D), Quality Assurance (QA), Safety, Information Technology (IT), Regulatory, Maintenance, and Operations must all provide input that is meaningful and defendable. *Figure 2* illustrates the general requirements to define the building project.

Structure the Client Relationship and the Team Resources

An interactive planning approach relies on the knowledge of both the client team and the consultant team. Each of these groups brings to the programming and planning process valuable insights and experience. The objective of programming is to share this special knowledge and bring it to bear on the solution of the client's problems. Three key groups are involved in the programming process: client and users, consulting architects and engineers, the Construction Manager with a facilitator and recorder.

The client and user group consists of executives, project managers, and operations staff. Each of these has different focuses, values, and objectives for the facility that must be incorporated into the project. The executives and managers are more concerned with broad questions concerning market strategy, management problems, and operating costs. The project managers will be concerned with the specifics of the project in terms of schedule, quality, and budget. The operations staff will focus on solving the day-to-day technical and operational problems of their respective areas of responsibility.

Figure 2



The consultant team, including the construction manager, provides the expertise that goes beyond the day-to-day operations of a particular plant. This group consists of a lead process engineer, process architect, equipment/materials handling engineer, automation and controls engineer, and the construction estimator. Their value is in their experience with state-of-the-art technology, gained from involvement with many current projects. Their role is to distill information and recommendations, provide realism and objectivity, and to be generally familiar with costs.

An important entity, the program facilitator/recorder, sets the tempo of the process. The facilitator must be knowledgeable in cGMP, have good communication skills, and relevant experience. His role is to focus on addressing concerns of all participants and communicating ideas with the group including discussing controversial issues without causing problems. Refer to *Figure 3*. He must bring divergent points of view together, keep the process

Figure 3

Rules of the Game

- Actively Involve Everyone
- Openly Discuss All Ideas
- Keep All Participants Informed
- Separate Decision Making

focused on the project at hand, and referee the process to prevent the takeover by any one point of view. To keep the process moving and the participants informed, the facilitator should be assisted in recording each individual's suggestion.

Define the Programming Approach

To increase the effectiveness of the programming effort, it is important to encourage interaction whereby all participants feel that they are actively involved and that their ideas are being considered. A quick way to reduce participation is for the project team to close off discussion on an idea too quickly. In one session in which ideas were constantly challenged by management, a participant made the statement that this was brainwashing not brainstorming. The process must allow for the open discussion of conflicting ideas.

Since the programming sessions may last for several days and different groups may be involved, the participants should be kept informed and visualize the results of the process as it grows and develops. To encourage idea generation and recall, dynamic graphic documentation should be used to record ideas and information. Graphic images are a much more powerful means to convey conceptual ideas than verbal statements. To avoid the sense of being locked-in, the process and documentation should be kept informal to encourage change.

The structure of the programming sessions should separate information gathering and idea generation from conclusion and decision-making. All ideas should be presented and kept active until the final decisions are made. The decision-making sessions should follow work sessions in which the consultants develop and evaluate the information and ideas presented during the interactive sessions. In the work sessions, the consultant team investigates the validity of these ideas in terms of equipment and space needs and calculates the effects of their implementation on the budget and schedule. Based on their investigations, options can be evaluated and decisions made in the subsequent review sessions.

Separate Wants from Needs

A clear understanding of the production forecast and process technologies forms the logical starting points for quantifying the facility's needs in a "block flow diagram" as shown in *Figure 4*. The team, during the interactive sessions, develops functional flow diagrams. These diagrams clarify the issues and objectives raised in the sessions, support cGMP decisions, and form the basis for subsequent discussions with the FDA for pre-validation concept reviews. Functional flow diagrams graphically interpret the complex relationships in biopharmaceutical production. They may specifically address such issues as safety, material handling, personnel movement, staging, QC testing, cleaning, and waste collection. To begin functional diagramming, the team needs to have block diagrams of all processes and a preliminary equipment list. In addition, the team must understand the client's operating and control philosophies, as well as the validation strategy.

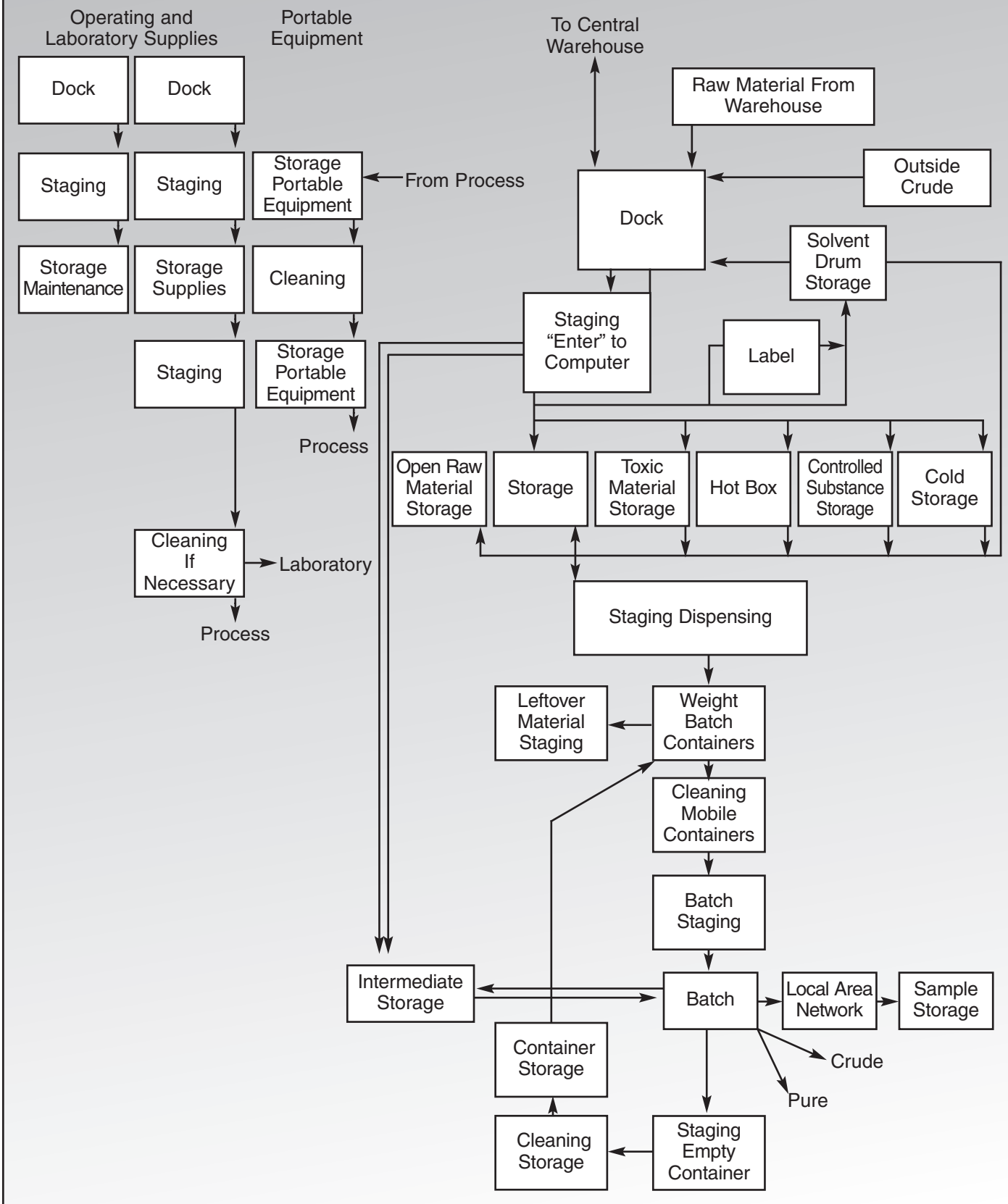
Information needed for diagramming:

- Processes
  - Present operations and quantities
  - Future operations and quantities
  - Material flows
  - People flow
  - Waste flows
  - Safety issues
  - Equipment/material handling
- Operating Philosophy
  - Materials management
  - Level of automation
  - Maintenance capability
  - Environmental concerns
  - Energy policy
  - QA/QC procedures
- Control Philosophy
  - Instrumentation
  - Automation
  - Logging
  - Inventory control
- Validation Strategy
  - Documentation
  - Regulatory issues
  - QA policies

Based on the complete understanding of the processes, the team will finalize an equipment list and establish equipment layout diagrams or modules. Then, they list functional space that will house

Figure 4

Functional or Block Flow Diagram



the required equipment, people, materials, and movement patterns. Space allocations must also encompass infrastructure support and distribution spaces. Infrastructure support space includes laboratories, control rooms, weigh rooms, and maintenance areas. Distribution space includes piping corridors, locker rooms, storage and staging areas, quarantine areas, shipping, and receiving. In addition to assigning space for specific functions, allocations have to be made for unassigned spaces such as mechanical rooms and chases, structure, corridors, and vertical circulation. This space allocation is derived from the consultant team's understanding of similar buildings, regulations, and specific project objectives. The final functional space listing with typical room sheets quantifies the design performance characteristics and technical requirements for each space including Heating Ventilation and Air Conditioning (HVAC), plumbing, electrical, finishes, and relationships to other spaces, equipment, and utility needs.

Pitfalls to Avoid

To maintain the effectiveness of the programming and planning process, several pitfalls must be avoided. For programming, the client has to be committed to the effort and willing to support it with staff involvement and time. Part of this commitment must be that Management be open to the staffs' ideas about day-to-day operational issues. The process must not be viewed as a means to sell a plan to anyone. It should be remembered that the process involves brainstorming, not brainwashing, so a single mind-set should be minimized. Too often, facility construction reflects one individual's point of view and technical background to the dissatisfaction of a wide range of individuals who will be involved in its operation and management. Secondly, both the client and the consultants should not lose touch with reality in addressing problems. In many cases, clients will expect that a project can be accomplished with far too little money and time. Pushing either is a formula for disaster. The consultants, on the other hand, must be cognizant of the client's operations, corporate culture, budget, and schedule so as not to propose inappropriate technology. To be effective, the program/planning effort must maintain a reasonable schedule. If time is too short, solutions will be truncated, requirements will be underestimated, and issues will slip between the cracks. If the time period is drawn out, the intensity will dissipate, and the participants will lose interest. Finally, considering too much detail early in the process may bog down the resolution of conceptual issues that will determine the outcome of many smaller questions. *Figure 5* lists some general pitfalls to avoid.

The success of any planning effort requires that the client group prepare for the process. Their first effort is to select a Project Manager who will lead the company's effort and be the contact person with the consultants and construction manager. The Project Manager should establish a planning committee comprised of users, facility operators, and management. The committee's responsibility is three-fold. The first is to generally define the scope of the project including a list of the products to be produced, estimates of the project's complexity, a target budget, and a project schedule. The second is the collection of basic information about the project: process block flow diagrams, production volumes, information requirements lists from users, site data, and applicable regulatory requirements. Finally, the committee should establish a decision-making methodology to be used throughout the process.

Figure 5

Pitfalls

- Lack of Commitment to Process
- Preconceived Solutions
- Distant Attitude
- Narrow Focus
- Unreasonable Schedule
- Too Much Detail

Approach, Method and Tools

To plan for expansion of cGMP facilities, an interactive programming approach that couples the free-wheeling idea generation of brainstorming with the logic and organization of systems analysis is recommended. The basis of this approach is the recognition that effective planning cannot be accomplished for an organization, but only with it. The approach consists of establishing the most desirable outcome, selecting the means to achieve it, determining the required resources, and planning the implementation to meet the desired outcome. This approach contrasts sharply with reactive planning in which design is undertaken to remove deficiencies rather than dealing with the project as a whole. The princi-

ples of this integrated approach are the participation of the client and their staff in the process, the involvement of all levels of plant operations in the planning efforts, and the coordination of the concerns of all participants in the final outcome. The objective of interactive planning is to combine the client's knowledge with the expertise of the consultants through a series of interview sessions. In these sessions, representatives from the company interact with the team consisting of process engineers, architects, and specialists to define the scope of the project with cost and schedule implications.

Operational, Technology, and Regulatory Decision-Making

This desired approach should seek to understand, quantify, and search for concepts. The interactive sessions should employ brainstorming techniques to search for information and ideas and establish objectives, raise issues that must be resolved, gather information from the participants, and uncover ideas and concepts for design solutions. Stating goals and defining project objectives provides the first level of structure to the process. The second level of structure comes from delineating what is known about the project. The facts of applicable codes, site conditions, process block flow diagrams, and production requirements can all be gathered before the sessions so that the consultants will be familiar with them and discuss them knowledgeably with the staff participants. The third level of organization focuses on uncovering conceptual alternatives that will achieve the objectives, resolve any planning issues, and answer the design problems. Conceptual alternatives identify how various aspects of the facility's requirements can be brought together to influence design. These conceptual alternatives provide the direction for quantifying needs.

Quantifying needs relies on systems analysis techniques to understand the operational requirements of the process and convert the processes into block flow diagrams, functional space needs, and an equipment list. From these, a program summary that establishes design and technical requirements, utilities and infrastructure support, and proximity needs is assembled. The result is a quantified set of architectural and engineering parameters that define the scope of the facility and establishes the basis for a realistic budget estimate.

Brainstorming provides a means of creating intensive interaction between the consultant team and the staff to produce as many ideas as possible within a limited time period. The idea is that intense, free interaction stimulates creativity and generates insights into problems. Participants are encouraged to expand upon the ideas of others, and that all concepts are to be fully discussed without judgement until the end. Brainstorming, in this case, does not mean uninhibited and uninformed responses, but the careful consideration of those who are familiar with the problem.

The interactive sessions should follow two principles of organization. First, discussion moves from stating the goals and objectives of the group to outlining what is known about the problem, and finally to discussing ideas and concepts for solving the problems and achieving the objectives. The second principle is that each discussion starts with the whole project, examines the parts, and ends in reviewing the effect of the parts on the whole.

Typical Schedule of Interactive Sessions

Day 1
- Shared vision session with all participants
- Executive and management input
- Technical administration and development
- Quality Assurance
- Review and consultant work session to organize management objectives and concepts

Day 2
- Production technology
- Consultant work session to review
- Operational objectives and concepts
- Materials management
- Process support requirements-HVAC, process piping
- Review and consultant work session to quantify needs – Organize flow diagrams

Day 3
- Management review session
- Maintenance and security
- Plant utilities requirements
- Architectural finishes
- Review and consultant work session to quantify needs – Develop spatial requirements

Day 4
- Automation and controls/information technology
- Electrical systems
- Consultant work session
- Review session with all participants

Flexibility

The demands made on today's production facility require that the planning team investigate how to incorporate plant flexibility. To investigate the need for flexibility, three different aspects have to be considered: expansion, conversion, and versatility. In process plant design, expansion refers to increasing the plant's capacity by enlarging the facilities and adding more equipment. Conversion adapts the existing plant to new products by changing its function. By reorganizing the space and adding new equipment, a converted facility has the flexibility to support a range of products. To consider flexibility in plant design, a host of design principles can be employed including standardizing equipment, developing modular equipment systems, and providing vessels with multi-capabilities. Architectural planning principles entail providing sufficient space to add or relocate equipment to reconfigure processes, create interstitial spaces for piping and utilities, and create process layout modules.

The planning for flexibility begins in the earliest moments of the programming process when the goals for the new facility are established. Working from the objectives for current and future production, an in-depth analysis will reveal the parameters for flexibility. Based on the equipment lists and block process diagrams of the products under consideration, the programming team creates a series of process models. Analyzing the data to find common denominators establishes the potential compatible processes. Next, the extremes of the processes are identified determining the range of possible processes to be included. Based on the experiences of the consultants and staff, successive iterations of the process functional flow diagrams refine, adjust, and zero in on the final process design.

Cost and Schedule

Realistic cost control begins in the programming phase, where it is simpler and far less costly to make changes in the project. During the interactive sessions, the desired needs should be exposed to all participants to avoid duplication and stimulate comparison. The programming team has to question each user group to explicitly define their needs and set priorities. The consultants must also identify the proposed opinions that would balance needs and budgets. Establishing a realistic budget based on a defined scope satisfying the company's goals and the staff's needs becomes a progressive process that explores and evaluates a number of alternatives during all stages of the programming and design process. Hopefully, these approaches are based on accurate historical cost data and not only on "Industry Standards." Tied together with the project budget is the implementation schedule for the project. This must reflect the client's needs and impacts the cost of the project by introducing a timeline against which money will be spent.

The Results

To ensure success in building cost effective cGMP facilities, the planning and design must begin on a strong foundation that carefully, but expediently organizes the client's requirements into a logical implementation plan that establishes the goals for the facility, determines the means of achieving those goals, and identifies the resources required to complete the project. This plan must be derived from the active participants of all that will manage or operate the facility. The plan must carefully balance budget and functional issues, and consider providing the appropriate levels of technology, accommodation, and flexibility to meet the ever-changing business goals of the company. ❑

Global GMP Regulations for Designing a Solid Dosage Form Facility

Adherence to GMPs, when engineering pharmaceutical manufacturing facilities, is a requirement of regulatory bodies throughout the world.

by
Jeffrey O. Hirschorn
Associate Validation Project Manager
and
Timothy Flanigan
Director of Validation and Regulatory Affairs
Lockwood Greene

United States (U.S.) pharmaceutical corporations are major worldwide manufacturers of various drug dosage forms. Although many are headquartered in the U.S., most have research and manufacturing facilities located throughout the world. These research facilities are utilized for chemical development and produce raw materials for clinical supplies used on a global basis. Their manufacturing plants are usually designed in accordance with Current Good Manufacturing Practices (cGMPs), as addressed in the U.S. Code of Federal Regulations (CFR) Title 21 Parts 210 and 211. Since these facilities produce solid dosage forms for global distribution, they must incorporate the design, construction, and validation requirements of international regulatory bodies in Europe, the Pacific Rim, and the U.S.

Adherence to GMPs, when engineering pharmaceutical manufacturing facilities, is a requirement of regulatory bodies throughout the world. Failure to abide by the regulatory requirements means that a facility is non-compliant and will not be approved for operation. This can result in significant financial loss. Thus, it is in the best interest of global pharmaceutical manufacturers to assure that all new facilities are designed in accordance with local regulations where they intend to market their drug products.

Regulatory bodies such as the U. S. Food and Drug Administration (FDA), the Commission of the European Communities, and the Japanese Ministry of Health and Welfare (MHW) have recently taken great strides towards harmonization. In fact, Section 40 of the Food and Drug Modernization Act of 1997 mandates the "pursuance of international cooperative agreements to reduce the burden of regulation and harmonize regulatory requirements if consistent with consumer protection requirements of the Food, Drug and Cosmetic Act." Toward this end, the U.S. and the European Union (EU) have entered into a Mutual Recognition Agreement (MRA). The MRA establishes the following principle: A manufacturer is in regulatory compliance in Europe and/or the U.S. should either party find the manufacturer in compliance with their own estab-

lished conformity assessments. Japan, Europe, the U.S., and other Pacific Rim nations convened the International Conference of Harmonization (ICH) in 1989. The purpose of this conference was to establish an expert working group whose responsibility it is to develop a GMP document that combines the existing guides and draft guides from the various regulatory bodies into a single document that will be accepted worldwide. Included in this guide will be sections on buildings, facilities, and process equipment. The draft for this document is scheduled for public comment sometime this year.

Though the worldwide pharmaceutical community is approaching harmonization it is not yet at this stage. As a result, it is still necessary for pharmaceutical companies to adhere to various worldwide regulatory requirements. A close examination of the regulations shows that there are many similarities. There are also differences through which companies must be cognizant of if they expect to sell their products globally. Even with the MRA in place between the U.S. and Europe, there are still equivalency issues such as manufacturing standards, inspection requirements, and enforcement authority. It can also be expected that there are differences in design requirements that must be addressed.

A facility is defined as a production building housed within a defined boundary. Within the facility, designed to support the various manufacturing and support systems, are the utilities. Together, these systems support the equipment used in various processes to manufacture finished solid dosage forms. The focus of this paper is on the requirements for manufacturing solid dosage form drugs. This paper will compare and contrast published regulations from the U.S., the EU, and Japan as related to various engineering aspects of solid dosage form facilities. It will identify where major differences may occur in requirements for material and personnel flow, Heating, Ventilation, and Air-conditioning (HVAC) and containment, fire and safety, waste disposal, cleaning and maintenance of manufacturing and non-manufacturing areas, and general facility utilities.

The cGMP regulations under 21 CFR, Parts 210 and 211, apply to finished dosage form drugs. Section 501 (a) (2) (b) of the Food, Drug, and Cosmetic (FD&C) Act requires that all drugs be manufactured, processed, packaged, and warehoused in accordance with cGMP.

Solid Dosage Form Facility

Solid dosage form drugs include tablets, capsules, and suppositories intended for the diagnosis, treatment, mitigation, and cure of disease conditions in humans or animals. Measurable quantities of solid dosage forms are manufactured as a batch process. Within each batch there are discrete unit operations, that when combined into a logical sequence, result in the finished dosage form. It is common practice for a solid dosage form facility to be used for the manufacture of multiple, non-related products. Separation of products from the initial unit operation of weighing through final compression, encapsulation, or molding is required by regulation.

Solid dosage form facilities in the U.S. must comply with FDA cGMP guidelines and various sections of the CFR. Where U.S. manufactured products are to be sold in either Europe or Japan, the conditions of manufacture must also meet these nations' requirements as well.

Process Flow of Materials and Personnel

- The U.S. GMPs state that "the flow of materials shall be designed to prevent contamination," Sec.211.42 (b).
- The EU GMP further mentions that "the adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components; to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps," EU-3.8.
- The translated Japanese GMP mentions that, "The facilities for a drug manufacturing plant shall have adequate facilities for the sanitary and safe storage of raw materials, labeling and packaging materials, and products," Ordinance No. 29Art5.

It is recognized that personnel are integral to manufacturing, but only those trained and required should have access to the various unit operations being performed.

- U.S. GMPs state that "only personnel authorized by supervisory personnel shall enter those areas of the building and facilities designated as limited-access areas," Sec. 211.28(c).

- The EU GMP mentions that, "Steps should be taken in order to prevent the entry of unauthorized people. Additionally, production, storage, and quality control areas should not be used as a right of way by personnel who do not work in them," EU-3.5.
- The Japanese GMP states that "the work-room shall be constructed so as not to allow passage for personnel other than those working in the room. Note: This provision shall not apply when there is no risk of contamination by personnel other than those working in the room," Ordinance No. 29, Art. 5, Par. 3, Item B.

HVAC and Containment

Solid dosage form facilities must contain ventilation suitable to support manufacturing personnel, while designed to prevent cross-contamination between products being manufactured in various locations within the facility. There are several methods to accomplish this objective. One way is to use ventilation systems dedicated to specific areas constructed with floor-to-ceiling partitions, and containing airlocks for separation. These areas could be designated as either classified or non-classified areas with respect to the number and size of particles per cubic foot or cubic meter. Another way is to employ dedicated ventilation systems for totally enclosed workstations. This includes glove boxes and containment booths. Another alternative is to employ pressure differentials between areas designed to prevent cross-contamination.

- The U.S. GMPs state that, "Air filtration systems shall be used when appropriate on air supplies to production areas. If air is recirculated to other production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs from production, there shall be adequate exhaust systems," Sec. 211.46(c).
- The EU GMP specifically mentions dust. "In cases where dust is generated, specific provisions should be taken to avoid cross-contamination and facilitate cleaning," EU-3.14.
- The Japanese GMP specifically covers dust, microorganisms, and the potential for worker anaphylaxis from inhaled material. "The work-room shall be provided with facilities and equipment for the prevention of contamination by dust and microorganisms, depending on the type, dosage form, and manufacturing process of intended drug. Provision: This shall not apply when the same effects are obtained from the functions of the manufacturing facilities. When a drug which is easy to disperse and cause anaphylaxis in small quantities or a drug which has serious effects on other drugs by cross-contamination is manufactured simultaneously with other drugs, the work room and air handling system shall be separated from those used for other drugs," No. 29, Art. 5-2, Par. 3, Items H, I.

Humidity and dehumidification of ventilated areas are used for both worker health and safety (Occupational Safety and Health Administration [OSHA], National Institute of Occupational Safety and Health [NIOSH]), and to meet environmental limitations to insure material and product stability. HVAC systems in the U.S. usually incorporate humidity and dehumidification equipment as part of their air-handling units.

- The U.S. GMPs state that, "Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product," Sec. 211.46(b).
- The EU GMP states that, "Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment," EU 3.12.
- No mention is made in the Japanese GMP regarding control over temperature and humidity.

Classified areas with respect to the number and size of particles per square foot or square meter are designed to protect the unpacked product from the environment. They range from walk-in suites through air locks to glove boxes, or isolators, to fume hoods. For non-sterile pharmaceutical manufacturing areas in the U.S., the usual classifications are: unclassified, Class 100K, Class 10K, and Class 1000. *Figure 1* compares the particulate requirements for classified areas for the U.S., EU, and Japanese regulations. Note that the International Organization of

Figure 1

Particulate Requirements for Classified Areas

U.S.	EU	Japan	ISO
Unclassified	Not mentioned	Not mentioned	Not mentioned
Class 100,000	Grade D	Class 8	Class 8
Class 10,000	Grade C	Class 7	Class 7
Class 1,000	Not mentioned	Class 6	Class 6
Class 100	Grade A + B	Class 5	Class 5

Standardization (ISO) uses the same classification as the Japanese.

- The U.S. GMPs state that, "Air is generally of acceptable particulate quality if it has a per cubic foot particle count of not more than 100,000 in a size range of 0.5 micron or larger (Class 100,000)." For unclassified areas, only the U.S. GMPs list recommendations: "A minimum of 30% ASHRAE [American Society of Heating, Refrigerating, and Air-Conditioning Engineers] filtration is recommended."
- No specific mention is found in the EU GMP regarding classified or unclassified areas.
- Similarly, no specific mention is found in the Japanese GMP for classified or unclassified areas.

Airlocks and separation of the workplace, where solid dosage forms are manufactured and packaged, are designed to prevent airborne contamination and physical mix-ups, respectively. These areas are addressed by both the U.S. and EU GMPs. They are not specifically mentioned in the Japanese GMP.

- The U.S. GMPs state that, "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups…" Sec. 211.42(c).
- The EU GMP addresses this topic saying, "Cross-contamination should be avoided by appropriate technical or organizational measures. For example (a) production in segregated areas or by campaign (b) providing appropriate airlocks and air extraction (c) minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air," EU 5.19.

Figure 2

Focus of Each Regulation on Airlocks and Cross-contamination

U.S.	EU	Japan
Separate, defined areas of adequate size to prevent cross-contamination	Avoid by running single product campaigns; and use appropriate airlocks	Not mentioned

Fire and Safety

Although not specifically mentioned in the GMP of all three regions, in the U.S., compliance with the National Fire Protection Association (NFPA) or equivalent code is considered by the authorities that issue Certificates of Occupancy.

According to the International Society for Pharmaceutical Engineering (ISPE) Baseline Guide for Oral Solid Dosage form facilities, design considerations include:

- The need for pressurization of exits and stairwells whenever emergency ventilation or a fire alarm is actuated
- Smoke purge and control systems
- Impact of fire damper placement on emergency ventilation and smoke control
- Air system operation in the event of a hazardous spill

Waste Disposal

Globally, the proper disposal of various classes of waste has led to the promulgation and enforcement of regulations to insure the safety and health of the local population and ecology of the surrounding surface and underground source of potable water. In the U.S., almost all construction permits are preceded by preparation, review, and favorable analysis of the environmental impact that a new or renovated solid dosage form facility will have. Waste disposal is an integral component of the environmental impact study. The three classes of waste addressed are solid waste, sanitary waste, and process waste.

- The U.S. GMPs state that, "Sewage, trash and other refuse in and from the building and

immediate premises shall be disposed of in a safe and sanitary manner," Sec. 211.50. In addition, "Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner," Sec. 211.56(a). Sec. 211.48(b) indicates that, "Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent backsiphonage."

- The EU GMP primarily addresses drains. "Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection," EU 3.11.
- The Japanese GMP includes three statements with the added requirement to prevent contamination of the workroom. (1) "The area for manufacturing operations shall have facilities or equipment for the disposal of sewage and waste," Ordinance No. 29, Art. 5, Par. 2, Item F. (2) "The area for manufacturing operations shall have facilities for the disposal of poisonous gases if generated in manufacturing any particular item," Ordinance No. 29, Art. 5 Par. 2, Item H. (3) "The work room for weighing raw materials, formulating, filling or sealing drugs in the work area shall meet the following requirements: the sewage disposal facilities in the room shall be constructed so as to prevent contamination of the work room," No. 29, Art. 5-2, Par 3, Item K.

Housekeeping/Cleaning and Maintenance of Manufacturing and Non-Manufacturing Areas

Tablets, and to a lesser degree, capsules often contain sucrose and other refined sugars. Refined sugars are used as sweeteners, fillers, and in tablet coatings. Pallets of sucrose and other sugars attract rodents and other vermin. These materials must be protected against infiltration by rodents and other insects. If they contain rodent droppings, and are used in the manufacture of solid dosage forms, the resulting products would be considered adulterated, and in violation of the FD&C Act. Recognizing the potential for non-compliance, the U.S., EU, and Japan have included regulations pertaining to the control of insects and rodents.

- The U.S. GMPs state that, "Any building used in the manufacture, processing, packing, or holding of a drug product shall be free of infestation by rodents, birds, insects, and other vermin," Sec. 211.56. "There shall be written procedures for using suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents in a manner that will prevent contamination," Sec. 211.56(c).
- The EU GMP states that, "Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals," EU-3.4.
- The Japanese GMP addresses this issue as, "The area for manufacturing operations shall have facilities for the control of dust, insects, and rodents," Ordinance No. 29, Article 5, Par. 2, Item D.

Building maintenance includes housekeeping, in addition to the physical cleanliness of ceilings, walls, and surfaces. Surfaces are further subdivided into product contact and non-product contact surfaces. Product contact surfaces include manufacturing, packaging, and testing (laboratory) equipment. Written procedures, usually in the form of Standard Operating Procedures (SOPs), are prepared and referenced for the various classes of equipment that require both cleaning and maintenance.

- The U.S. GMPs state that, "Any building used in the manufacture, processing, packing or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations," Sec. 211.42(a). "Any building used in the manufacture, processing, packing or holding of a drug product shall be maintained in a good state of repair," Sec. 211.58.
- The EU GMP addresses this issue with the following statement: "Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where appropriate, disinfected according to detailed written procedures," EU-3.2. Further clarification is given. "Layout, design and operation must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross contamination, and any adverse effect on the quality of the product," Article 8, Par. 2.

- The Japanese GMP addresses the issue too. "The area for manufacturing operations shall be adequately lighted, illuminated, ventilated and cleaned," Ordinance No. 29, Art.5, Par.2, Item A.

Facility Utilities

A solid dosage form facility houses numerous pieces of automated, mechanical equipment used in the manufacture, filling, and packaging of drug products. As designed, these pieces of equipment require the support of utilities.

According to the ISPE Baseline Guide for Oral Solid Dosage form facilities, "utility systems that come into direct product contact should be designed, constructed and commissioned to provide material which meets a predetermined specification and prevents contamination. Utility systems which do not come into direct product contact should be designed and constructed in compliance with applicable codes and standards." Each of the three GMP guides address utilities as set forth below.

Lighting

- The U.S. GMPs state that, "Adequate lighting shall be provided in all areas," Sec. 211.44.
- The EU GMP addresses this with the following statement: "Production areas should be well lit, particularly where visual online controls are carried out," EU-3.16.
- The Japanese GMP states that, "The area for manufacturing operations shall be adequately lighted, illuminated, ventilated and cleaned," Ordinance No. 29, Art.5, Par.2, Item A.

Water System

- The U.S. GMPs state that, "Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the EPA's Drinking Water regulations," Sec. 211.48(a).
- The EU GMP states that, "Distilled, Deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken," EU-3.43.
- The Japanese GMP states that, "The manufacturing facility shall have facilities for supply water of the quality or quantity needed to manufacture the drug (including cleaning water for facilities, equipment and containers)," Ordinance No. 29, Art. 5-2, Par. 5.

Though not specifically mentioned in the GMPs, in the U.S., compliance with NFPA, OSHA, NIOSH, or equivalent code is necessary to obtain a Certificate of Occupancy

Summary

Solid dosage form facilities are used for the manufacture of multiple, non-related products. The equipment is usually not dedicated to one product. Validated cleaning procedures containing documented cleaning methods by trained personnel is mandated by U.S. GMPs. Validated analytical test methods, documenting the lowest level of detection and lowest level of quantitation, are a necessary prerequisite to a sound cleaning validation plan. Physical separation of products to prevent mix-up is required by global GMPs. HVAC provides ventilation for personnel and must be designed to prevent cross-contamination between product through airborne transmission of particulates. Where fine particle dust is generated, specific precautions must be in place to avoid cross-contamination and facilitate cleaning.

For facilities where known cytotoxic drugs and radio pharmaceuticals are to be manufactured, the manufacturing areas and their air handling (HVAC) systems need to be separated from those used for other drugs. Exhaust ducts on facility roofs must be checked to insure that the exhaust from one system does not feed the intake duct of another system. Though not specifically mentioned in the GMPs, in the U.S., compliance with NFPA, OSHA, NIOSH, or equivalent code is necessary to obtain a Certificate

of Occupancy. In-process material, finished products, and packaging materials must be protected against infiltration by rodents and other insects. A documented housekeeping, cleaning, and maintenance plan are necessary for regulatory compliance. Written procedures in the form of SOPs are necessary for reference to cleaning and maintenance procedures for equipment and the facility.

The overall conclusion that can be drawn from this paper is that reliance on the GMP regulations of a single governing body is not sufficient to assure adherence to all global requirements. It is recognized that, for the most part, the global regulations do closely match but there are enough differences that all of the regulations should be given due consideration when designing and constructing a facility to meet global cGMPs. Failure to do so could potentially result in a facility that is not compliant with one or more of the global regulations. The financial implications of non-compliance can be significant.

The pharmaceutical industry can truly be considered a global rather than a regional industry. Very few of the major pharmaceutical companies have all of their facilities within a single geographic location such as the U.S., Europe, or the Pacific Rim. Rather, Industry, in general, has facilities located throughout the world. As a result, it is a necessity that Industry be cognizant of the appropriate regulations not only where they are headquartered but also where they have facilities located worldwide. This should provide the pharmaceutical companies with the advantage of having a basis of regulatory knowledge that is global in its scope. This in turn should enable these firms to minimize the risk of any facility they construct anywhere in the world.

Because the pharmaceutical industry is a global industry, logic would dictate that uniform regulations apply. The need for uniformity in regulatory requirements has been recognized by the worldwide regulatory bodies, as well as Industry. It can be assumed that uniformity is not far-off based on such advances as the ICH, ISO, the MRA, etc. However each nation, or group of nations, still have their own idiosyncrasies that must be overcome before true uniformity can be achieved. Until this point is reached, it is important to acknowledge that there are different regulatory bodies throughout the world that must be satisfied in order for global compliance to be realized.❑

The authors would like to acknowledge the contributions of Alicia Sardar and Carl Sullivan in the preparation of this paper.

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FACILITY VALIDATION: MANAGEMENT ISSUES

Wayne T. Flaherty

With costs always escalating, managing the validation of an entire facility is no easy task. This article offers tips for organizing such an effort and keeping expenses in check.

Facility validation represents the last phase of the design and construction of a pharmaceutical or biotech facility. With the total cost of facility construction and validation often exceeding $200 per square foot and nearly five to 10 percent of that cost supporting the validation effort, it becomes increasingly important to utilize project resources wisely. This article provides suggestions for the successful implementation of facility validation by establishing "good validation management practices." The concepts presented apply to both contracted and owner validation teams and are based upon traditional project management approaches and the author's personal experiences.

It is imperative that companies new to validation establish a reasonable approach for their facilities.

VALIDATION PLANNING

It is imperative that companies new to validation establish a reasonable approach for their facilities. An all too common mistake for many in this situation is described by one word: overkill. With the vast supply of information regarding validation, it is easy to become too reliant on books and articles for establishing test plans, approaches, and criteria. When developing a plan and procedures for validation, be careful not to commit to procedures which cannot be accommodated reasonably.

Many articles are authored by employees of large corporations with the systems and resources to manage more complicated policies. However, start-up firms typically do not have access to these kinds of resources. Remember, there are many ways to qualify or validate equipment and systems.

Be sure to allow sufficient time for development of a facility validation master plan and its associated procedures. Not only is a master plan strongly recommended, it is often requested by the FDA during inspections. This document defines a company's validation approach and provides a description of project scope, philosophies, and general expectations of a validation effort. A master plan is a living document which contains lists of procedures, protocols, key personnel and resources, project timelines, drawings, and other pertinent project materials.

One way to learn about establishing a master plan for a facility is to get in touch with others in the industry through professional societies and/or associations. Consider consulting a reputable provider of validation services for assistance. The

Internet also is becoming a valuable source of information.

Those in the pharmaceutical and biotech industries seem to limit themselves to their own industry. However, it is worth noting that some aircraft and automobile manufacturers have been using the principles of validation for many years, For example, Boeing utilized validation procedures to help expedite the launch of the new 777. An interesting point to consider is that these industries are not necessarily required to have and use validation programs. They seem to have realized what some pharmaceutical and biotech companies are only beginning to understand: a properly designed and managed validation program saves money, time, and maybe even lives.

VALIDATION: "OLD HAT"

For those who have well established validation programs, it is a good idea to reflect on past experiences to correct weaknesses in a program or procedures. SOPs should be evaluated and updated as necessary following the completion of every project. Remember that policies and procedures are intended to be changed; otherwise, why go through the trouble of having change control programs? There is no excuse for stagnation in validation procedures and approaches. As scientists, validation professionals should never allow themselves to become complacent about investigating and employing new technologies. Many tend to be too conservative when trying new products and ideas.

Most validation personnel know that the majority of validation groups use essentially the same testing equipment and often the same validation and design criteria. Some refer to these as "industry standards." The problem with this mindset is that companies may avoid differing from the norm with the fear that someone might notice non-conformance with an industry standard. If, however, a firm has confidence in its technical abilities, it should have no difficulty identifying better (and probably lower) cost alternatives.

Still, companies must be prepared to defend their choices, which should not be a drawback for well equipped engineers and scientists. In fact, the FDA encourages industry to continuously investigate new and improved approaches for certifying equipment and facilities.

WHERE DOES VALIDATION FIT IN?

A common and often controversial topic of discussion among validation professionals is "Where should the validation department reside within a corporation?" There are many points of view on this subject and more than one correct answer. Since many validation departments are dominated by engineers, some argue that the validation department should be combined with the engineering department. Other companies prefer validation personnel report to QA. (Though not recommended, some even feel validation should operate through manufacturing or operations.)

The FDA encourages industry to continuously investigate new and improved approaches for certifying equipment and facilities.

The author's experience has shown that a combination of the engineering and QA strategies provides the best solution. Of course, this strategy requires a great deal of coordination between the groups, as well as a "Matrix Management" type support structure. This concept works well if lines of responsibility are defined clearly between groups. In this arrangement, the engineering department is responsible primarily for completing installation qualification (IQ) while the validation department (which reports through QA) is responsible for operational and performance qualification (OQ and PQ) phases. In this approach, engineering has a "dotted line" to QA. One benefit is that the engineering department is more involved in the GMP process.

Engineering departments sometimes do not see themselves as having direct responsibility for quality assurance and overall GMP compliance.

By making them an integral part of this process, they tend to exhibit improved control over associated engineering documentation. An additional benefit involves the development and maintenance of equipment and systems specifications. In most IQ formats, system or equipment specifications are incorporated into protocols. With the engineering department responsible for the development and execution of IQ protocols, the document itself can serve as a detailed specification, thereby eliminating the potential for duplicate efforts. This does not, however, eliminate the need for general system design specifications.

The key to successful project implementation is a well defined project scope.

DEFINING PROJECT SCOPE

The key to successful project implementation is a well defined project scope, which enables the validation team or department to focus on its defined responsibilities. To define the project scope, first denote the process and facility to be qualified. For larger projects, this may require input for the project manager, other key project team members, process design engineers, scientists, and other QA and regulatory affairs personnel.

Scope definition should be completed by the project team leader and reviewed and, in some cases, approved by the project manager, key project leaders, or management. At a minimum, this information should include the following:

- List of all services, utilities, and equipment to be qualified
- List of all required qualification documents
- Discussion of responsibilities, assumptions, and project procedures

All too often, validation groups become involved in issues which should be handled by other teams or departments. Though intentions may be good and results oriented, involvement in outside issues limit a team's long-term effectiveness. More importantly, this course of action may set precedent regarding future responsibilities and accountability. Validation managers who have experienced this error in judgment may find that they have become extensions of manufacturing, QA, engineering or other teams. Unless prepared for this dilution of the team, it can become problematic as project loads increase and management has to pull back the reins.

Typically, the validation project scope is defined during the final phase of conceptual design. The facility master plan also should be started at the end of the conceptual phase. This allows key validation team members need to be involved in a project as early as possible.

When developing the project scope, it is necessary to define project procedures, an often overlooked and underrated tool. These procedures help to clarify the responsibilities of team members and establish the process by which a project will be managed. Project procedures also describe the methods that monitor progress.

VALIDATION PROJECT TEAM

Since validation is often the last phase of a much larger project, pressure and tension can become extreme. The last thing a manager needs is a team that falls apart when the going gets tough. Good validation engineers and technicians are not easy to come by, so there seems little excuse for the high turnover rates currently seen in the industry. Turnover means inefficiency and, therefore, undue added project or departmental costs. Given the time and effort devoted to training new employees, it makes much better sense to ensure that a validation team or department is "healthy." Make certain that team members work well together and within other departments in a facility.

One key to ensuring the success of a validation team is through good, frequent communication. Validation managers are often in such demand that they arrive at the office, run off to a meeting, and reemerge at the end of the day. Still, validation managers should attempt to put some time aside each day for interaction with team

members and supervisors. If possible, they also should try to take the time to visit team members at the site of a project.

Validation teams should meet at least once a week to discuss project progress. In these meetings, set goals for the coming week or days and discuss any goals which have not been realized. The validation team also should hold regular meetings with engineering, manufacturing and other departments involved in a project. In addition, it is often desirable to conduct a general validation meeting with all interested departments at the start of the project. This meeting should convey the basics of validation while discussing the project scope and responsibilities in general terms.

For long term projects, be sensitive to the needs of team members. Most people need, and want, to develop new skills to broaden their horizons. Don't fall into the trap of relying on one individual to perform certain types of validation activities. This practice serves no benefit for individuals, and it certainly is not good for a company. In the long term, it is of great advantage to a company, as well as a project team, to encourage cross-training.

When forming a validation team, there are a few points to consider:

1. Establish a well-rounded team.

For example, a team for an aseptic manufacturing facility should include a microbiologist, mechanical or chemical engineer, electrical or controls/automation engineer, pharmacist, clerical assistant, and several general technicians. For some, this may sound a bit extravagant, but a wide knowledge and experience base is valuable due the vast array of issues surrounding validation.

2. Since budgets almost never accommodate all of management's needs, be aware of costs.

The total salary of the small group outlined above can exceed $200,000 per year. For an average start-up facility with approximately 30,000 sq. ft. of manufacturing area, the annual budget for a typical validation team may be more than $1,000,000 for the first few years. Budgets may be lowered eventually as facility start-up is completed and most equipment purchases are made.

Winning approval for budgets is not always an easy task. There are a couple of general "helpful hints" in this area. First of all, always provide options regarding how a project will be staffed, which typically includes a combination of internal and external resources. Keep in mind that the average rates for validation consultants can range from $50/hour to $90/hour. Next, offer an estimate or summary of the scope for current and future projects, including the approximate total work hours and peak demand periods. This will help determine resource requirements and provide a sense of timing and scheduling. Finally, include benefits and drawbacks for each option listed. For example, a project that is budgeted exclusively for contracted or temporary personnel usually will have higher "up front" costs, and the efficiency with which this personnel will perform depends on their experience.

The most useful tool in validation project management is a timeline or Gannt Chart.

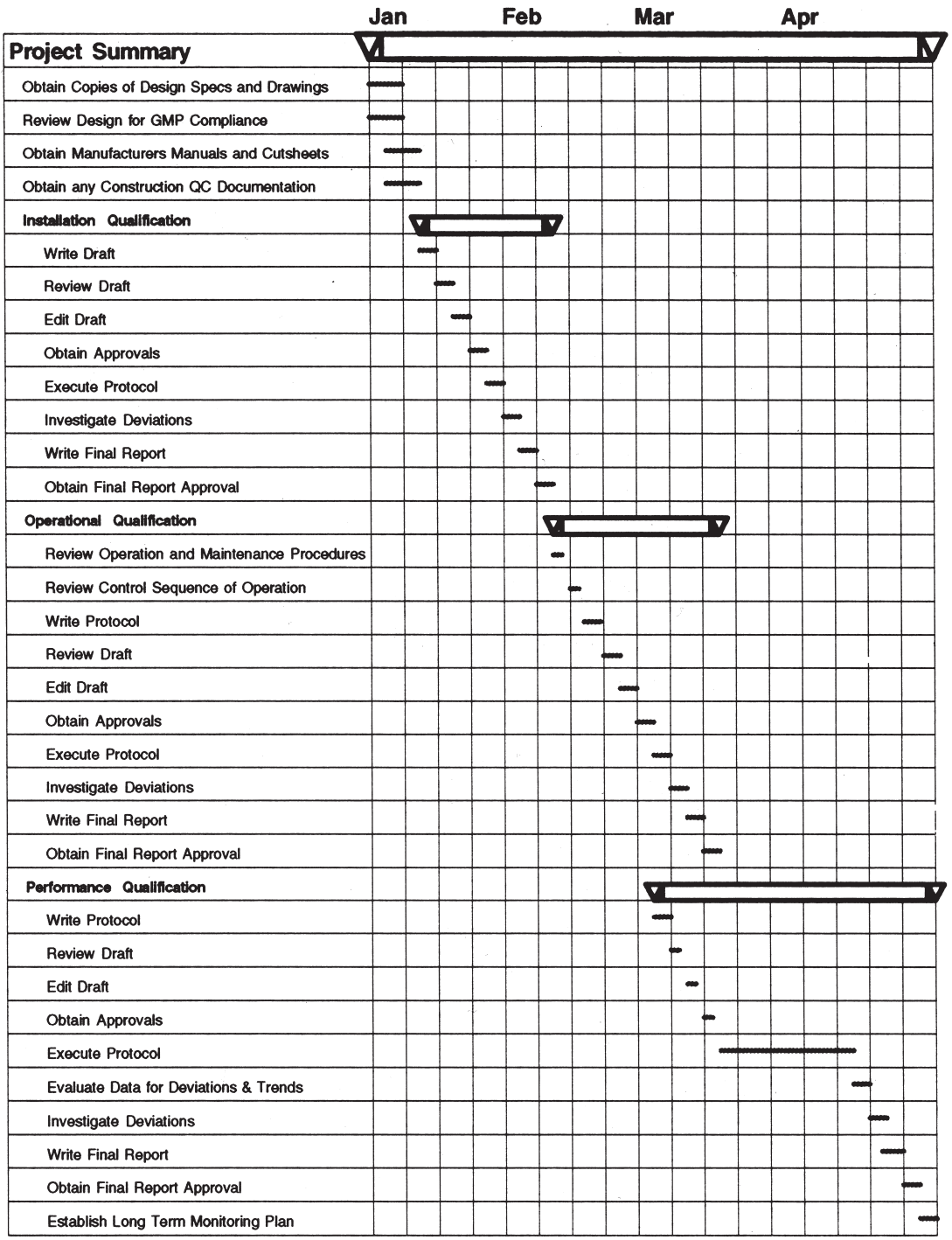
PROJECT SCHEDULING

The most useful tool in validation project management is a timeline or Gannt Chart. Timelines have been severely underrated by many validation project managers, especially those overseeing larger projects. While many feel that timelines "just don't work," failures in most situations are due to poor development and utilization of a schedule. There is always time to create a timeline; not forming one can be extremely costly to the project owner. Remember that a timeline must convey realistic goals with realistic task-oriented milestones.

Figure 1 illustrates a detailed generic Gannt Chart which identifies most of the tasks and subtasks associated with the qualification of a Water-For-Injection system. This timeline may appear impractical in that it contains a great level of detail. However, if all of the activities associated with the qualification process are not at least considered, a

Figure 1

GENERIC GANNT CHART FOR QUALIFICATION OF A WFI SYSTEM



false prediction of project duration will result. The consequences may be devastating to a contract company with a fixed-price contract or for a client company with a "fast-track" project.

Estimating task durations can be a tricky business. Every company has different processes for different tasks. For example, the document review process is often a source of difficulty. (A typical document review process should take about a week.) For this reason, development of a project timeline should involve input from all project team members. If project members are consultants or contract employees, be sure someone who has experience with company procedures and standard culture is involved. By the time a project is begun, all team members should be familiar with, and more importantly, have bought into the project schedule.

A good project schedule requires little maintenance. If project team members are familiar with a schedule and if the schedule was given proper attention during development, there should be little reason for a project manager to have to intervene during project execution. In other words, a project can almost run itself as long as team members maintain their focus and direction.

Remember the value of rewards. Typical management styles do not always provide incentives for a validation team. Those who really understand validation know it can be a dry, thankless, and often stressful process. Thus, a few small benefits can go a long way. For example, establish perks for the on-time completion of major milestones.

CONCLUSION

As facility construction costs continue to escalate, the search must continue for methods which reduce costs and improve efficiency. Start by providing realistic goals in project plans, establishing reasonable working approaches and policies, assembling and maintaining strong project teams, and learning to effectively utilize the proven tools of project management. Placing the emphasis on good validation management practices early in the project development phase establishes validation as a true cost-control device while providing assurance of product and process quality.

For related articles, see the following issues of the Journal:

February 1996

1. Brian Scott, PE, Jeff Hargroves & Jerry Bauers, PE, *Validation of HVAC Systems in Pharmaceutical & Biotechnology Facilities, Part 1*

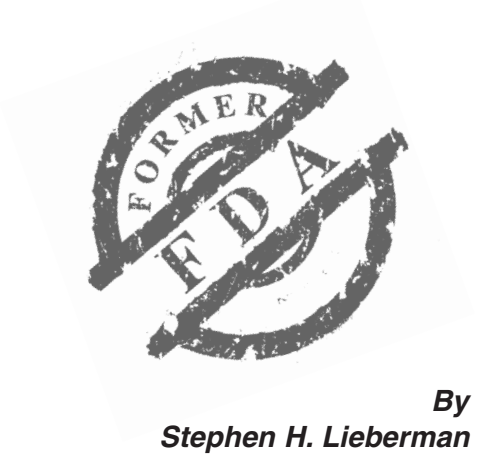
February 1995

1. Patricia Stewart, *New Vs. Existing Facilities: Two Approaches for Developing IQs*

ISO vs. FDA Auditing

At A Medical Device Facility

The ISO Standards are voluntary in nature.



By
Stephen H. Lieberman

President
Quality Systems Associates

Is the era of harmonized surveillance of the medical device industry upon us? The European community has already embraced the ISO 9000 series of standards as the benchmark for quality system requirements in their *Medical Device Directive.*[1] In addition, they have issued an International Standard, ISO 10011-2,[2] to set guidelines for the qualification criteria for quality system auditors. The U.S. Food and Drug Administration's (FDA) latest draft revisions to the current Good Manufacturing Practices (cGMP) Regulations[3] have followed most of the ISO 9000 principles. The U.S. Congress and the FDA are talking about allowing certified third-party auditors to perform FDA regulatory inspections.

With all this harmonized activity taking place and when the new FDA regulations become effective, should we expect a future FDA inspection to be similar to, and have the same results as, an ISO audit? I think not! The following are my reasons why.

The Standards

The International Organization for Standardization (ISO), an international federation of standard developers, produced the ISO 9000 series of standards. These broad-based standards are designed to be universally applicable to all enterprises that manufacture or perform services. They encompass widespread quality principles that include management involvement, design controls, purchasing units assessing vendors' capabilities to meet predefined requirements,

and communications with customers. This is in addition to the previously monitored areas of documentation, process control, inspection and testing, calibration, auditing, training and product identification and traceability. The ISO standards are voluntary in nature, with businesses allowed to follow them with or without having a third party (independent auditor) assess compliance.

The European Union has written additional requirements (EN46001[4]) to tailor the ISO standards to the medical device industry. When an ISO audit of a medical device facility is performed, that company's quality systems will be compared to both standards. The ISO 9000 standards do not specify the frequency of third-party certifying audits, but the industry practice is to recertify on a six-month or annual basis. The ISO has recently written a draft guideline[5] for medical device manufacturers which has been distributed for industry comment in December 1995.

The FDA's revision to its current Good Manufacturing Practice (cGMP) regulation for medical devices (21 CFR 820), which will be called the Quality Systems Regulation (QSR), is promised for publication in September 1996. This is a comprehensive revision of the existing cGMP regulations that codifies some of the interpretations the FDA has made over the years, does away with the distinction and special requirements for critical devices, and attempts to harmonize the regulation with most of the contents in the ISO 9001 standard and the EN 46001 document. The QSR will only be applicable to finished device manufacturers (including refurbishes) and will not be applicable to component manufacturers.

The ISO 9000 standards were written to be applicable to all manufacturers who choose to utilize them. The QSR is silent on the ISO 9000 requirements of having a Quality Manual, preparing quality plans, reviewing contracts with a customer, and special controls for customer supplied product.

Other differences include the lack of accessibility of internal and vendor audit records to FDA investigators (these records are looked at by ISO auditors) and the absence of a written requirement in the ISO 9000 standards for the timely review of complaints. Section 510(h) of the Food, Drug, and Cosmetic Act[6] (FDC Act) requires that medical device firms be inspected every two years. However, the resources of the Agency are such that reinspection on a three- or four-year cycle is not uncommon.

Auditor Qualifications and Training

There are two well recognized credentialing authorities for ISO auditors: the Registrar Accreditation Board[7] (RAB) in the U.S.A. and the International Register of Certificated Auditors[8] (IRCA) in the United Kingdom. The RAB will certify an individual as a Quality Systems Auditor if he or she has a bachelor's degree with six qualifying audits that total at least 30 audit days (other combinations of education and audit experience exist), at least four years of relevant work experience (with at least two years in quality assurance related activities), and successful completion of the examination of a registered auditor course.

IRCA registration for an auditor requires 600 hours of study (an undergraduate degree will normally be acceptable), at least four years of relevant work experience (with at least two years in quality), successful completion of the examination of a registered auditor course, and completion of at least five audits.

Conversely, there is only one recognized authority for certifying FDA investigators – the Commis-sioner, Dr. David A. Kessler, or his delegated designate. The Agency has used an in-house program managed at their districts for training its newly hired medical device investigators. The foundation of this program was the continual nurturing of inexperienced employees with the interchange of ideas by their mentors (the experienced investigators) and the detailed review of written work by supervisors.

The program has had critics suggesting that there is a lack of uniformity in training, and that there have been discrepancies in FDA 483s (Inspectional Observations) issued to the industry.

> Most ISO auditors walk into an establishment with the hopes of finding compliance with the standards.

The Agency has heard these comments and has recently embarked on a performance certification program for investigators.

The plan proposes to certify three levels of investigators: new employees; program area specialists (e.g. medical device); and advanced program area specialists (e.g. regional or national device experts).

The program consists of: a combination of specified courses (with examinations); specified on-the-job training; participation in certification audits at the new employee level; specified advanced course work (with exams); additional audits at the specialist level; and for the advanced program, additional audits and a self-assessment examination.

This program does not characterize all the training that a typical investigator receives, but verifies, through documentation, some of the essential curriculum.

The Agency also plans to issue a series of video tapes and to have interactive teleconferences to prepare their investigators and inform the industry about quality system auditing.

All of the above is an ambitious undertaking, especially during a time of diminishing resources. If the Agency is successful, it hopes to attain a credible baseline of training and experience for its investigators.

The Agency is also planning ways to educate both its investigators and manufacturers in cGMP design controls. Part of this includes the March 1996 draft guidance documents on the design control portion of the QSR – one is entitled, *Do It By Design* and the other, *Design Control Guidance For Medical Device Manufacturers*. The FDA plans to set up an industry/FDA ad-hoc committee to develop a strategy for the training.

Finally, the Agency has had preliminary news releases, and Congress has initiated FDA reform legislation to allow third-party personnel to perform inspections for the FDA. In the Medical Device Reform Act of 1996 (HR 3201), there is language to have the Agency develop procedures for accrediting an independent organization (and later to implement those procedures) to conduct cGMP inspections. When an accredited person performs an inspection, he or she will be able to issue a certificate of compliance which will allow the FDA not to inspect that facility for a two-year period. Currently, there are no thoughts to change the FDA two-year reinspection mandate.

Additional provisions require accredited investigators to immediately notify the Agency if they find a situation that involves a probability that a device could cause serious health consequences or an unreasonable risk to the public. The notification provision of this type of third-party review differs from the confidential nature of ISO auditor or independent consultant findings.

Attitudes and Motivations

ISO auditors, although independent, are working for a registrar or a notified body who is trying to maintain a long-term relationship with the audited medical device company. Most of these auditors walk into an establishment with the hopes of finding compliance with the standards.

In the past, FDA investigators have made their reputations with management by showing that they can discover deviations from cGMP regulations and document them. The more serious the cited deviation (ones that lead to Warning Letters, civil

penalties, seizures, injunctions or criminal prosecutions), the better an investigator was rated. Many FDA investigators have the opinion that the device industry is full of hidden compliance problems, and that it is their job to find them.

However, there is a new class of FDA investigator. These investigators believe the establishments they inspect are in compliance, and their job is to verify that fact. During an FDA inspection, one such investigator defined this position by stating, "I am most satisfied to find firms in compliance; but I'm obligated to pursue consumer protection when I encounter problems."

He compared his role of problem identification to that of a programmer testing software. He stated, "If your viewpoint is to demonstrate that the program can work, then no doubt your testing will demonstrate that it does. If your intent lies in eliminating bugs, the accepted attitude of software testing is 'this program has bugs,' and I must find them. Any other approach is a waste of time."

The Agency has changed its way of rating an investigator, by revising its evaluation forms. Investigators are now reviewed for improvements in compliance by the industry and not on the number of regulatory actions initiated as a result of their inspections. However, old habits of the supervisors and mid-level managers will probably still be a factor in decisions concerning the future promotion of two equally qualified investigators. With a fundamental goal of assuring that their investigators remain capable of recognizing problems (if they do exist), it will be difficult for the FDA to instantaneously change its 'cop' culture.

Conduct of an Audit

The main difference in an ISO audit vs. an FDA inspection exists in the philosophical distinction between the mission of the two entities. Those involved with an ISO auditing belong to a non-governmental third party whose mission is to assure that there is a level playing field among ISO certified companies, and to assess a firm's conformance with the voluntary ISO 9000 quality standards. Specific written guidance is often not available, and positive results (registration or certification) can be achieved in some instances by negotiating (e.g.: "Yes, we can accept that interpretation, and we will implement it by your next audit.") on minor requirements.

Conversely, the FDA (not to be confused with the Agency that promulgates fear, depression, and aggravation) is a regulatory agency that is part of the Department of Health and Human Services. The FDA is not in the business of quality systems improvement for medical device firms. It is charged with the mission of assuring the safety and efficacy of such devices when they are used by the public.

> In the past, FDA investigators have made their reputations with management by showing that they can discover deviations from cGMP regulations and document them.

Section 301(a) of the Food, Drug and Cosmetic Act[9] defines as a Prohibitive Act - "The introduction...into interstate commerce of any...device that is adulterated or misbranded." Section 501(a)(2)(B) of the FDC Act[10] states that drugs manufactured in a manner that does not conform to cGMP are adulterated. The courts have consistently construed that good manufacturing practice in the context of drugs applies equally to medical devices.[11]

Courts have also found a device to be adulterated, as a matter of law, if there is a single instance of failing to conform to cGMP regulations.[12] For domestic device manufacturers, the FDA has an arsenal of regulatory persuaders at its disposal for violators of Prohibited Acts, including monetary fines, seizing products, halting production or shipments, and imprisonment. For foreign manufacturers of medical devices, the Agency can seize devices that are within its jurisdiction and/or request the U.S. Customs Service to refuse imports from a medical device company that is not found to manufacture in accordance with cGMP.

In the past, the FDA has always utilized surprise, namely unannounced visits, as their *modis operandi* for conducting routine inspections of domestic med-

ical device firms. (Compare this to an always announced ISO audit or FDA inspections conducted in foreign countries.) The Agency just changed this procedure in April with the initiation of a pilot program of pre-announced inspections of medical device manufacturers (at a district's discretion for non-violative firms). Please note that this pilot program is only for manufacturers of medical devices.

Additional provisions of this pilot program include:

- Having the investigators annotate promised or completed corrective action(s) on the FDA 483 at the time of issuance.
- Requiring FDA investigators to discuss observations with the inspected firm's management as they are observed or on a daily basis.
- Having post-inspection correspondence which states that a company is either in substantial compliance or that the observations did not warrant any regulatory follow-up. This will be in addition to the "gotcha" Warning Letter for those with violative findings requiring regulatory or administrative follow-up.

ISO audits, once started, adhere to a rigid, predetermined time schedule that is shared with the audited firm. The schedule will show when each ISO 9000 quality system requirement (e.g. Design Control, Purchasing, Training, etc.) is to be audited, and by which member of the audit team. ISO auditors may, upon agreement with the audited firm, discontinue an audit when the audit objective is determined to be unattainable. Otherwise, their audit will cover all of the applicable elements of the ISO standard regardless of any adverse findings uncovered during the audit. They will work from a checklist which is usually shared with the audited firm. The checklist will assure that they cover each mandatory element (designated by the word "shall") in the standard.

Immediately after the audit is completed, the auditors will present a firm with written non-conformances (if any exist) between the implementation of the quality system and the written ISO standard.

Similarly, the FDA has a collection of guidance documents from which their investigators work. (By the way, try not to call the FDA officials "inspectors;" it refers to an FDA employee with less responsibilities and less formal education.) The most important is their *Compliance Program 7382.830 Inspection of Medical Device Manufacturers,*[13] which details the following areas that must be reviewed during an inspection. Please note that this *Compliance Program* also requires the investigator to check a firm's adherence to the Medical Device Reporting [MDR] regulation. No such counterpart exists for an ISO audit.

The following areas are required to be covered in a medical device inspection:

- Complaint Handling System
- MDR Compliance
- Medical Device Tracking[14]
- Failure Investigation
- In-Process & Finished Device Rejects & Rework
- Evaluation of Procedures for Change Control
- Validation
- Components
- Audits
- PMA Devices

FDA investigators are trained to concentrate his or her inspection time on those cGMP areas, if problems exist, that will "likely produce nonconforming and/or defective finished devices."[15] As soon as such system-wide deficiencies are found and documented, the FDA investigator is instructed to discontinue the inspection and not to inspect any other areas of the firm. Firms are told via a statement on an Inspectional Observations form (FDA 483) that they are "Responsible for conducting internal self-audits to identify and correct any and all violations of the cGMP regulation."[16]

Other FDA guidance documents that may be utilized by the investigator include:

- *Compliance Program 7382.830A Sterilization of Medical Devices*, dated October, 1, 1989[17]
- *The Investigations Operations Manual*[18]
- *A Pocket Guide To Device GMP Inspection*[19]
- *Guideline On General Principle Of Process Validation*[20]
- *The Medical Device Good Manufacturing Practices Manual*[21]

Both an ISO auditor and an FDA investigator will ask to see documentation to support promised corrective actions from their last visit. Since the experience with the ISO standard is relatively new, this will not be applicable for a first ISO audit. However, the FDA's files are very extensive with

inspection reports and correspondence which may contain promises of corrections. Failure to keep any promise is the beginning of a deteriorating relationship with your investigator or auditor.

Different Audit Results

Is it possible to be in compliance with an FDA inspection and fail an ISO audit, or vice versa?

Differences exist between the two standards. For example, a firm could be cited for failing to have in place an essential element of an FDA regulation (i.e.: never reporting MDRs for incidents in which your product was associated with a patient death). Since this is not an ISO 9000 requirement, it would not be cited as a nonconformance on an ISO audit. Similarly, not having a Quality Manual or failing to review your customer contracts would be cited as major non-conformance during an ISO audit. This would prohibit certification for an ISO Standard, but would not be a deviation from the FDA regulations.

Another example would be that a medical device manufacturer could contract with an ISO registrar for ISO 9001 (the broadest certification containing quality systems in design, development, production, installation and servicing) certification. If, during the audit they were found to have well written design control procedures, but never put an existing product through that procedure, then they may not be certified for ISO 9001. (The registrar could elect to certify to ISO 9002 until design control implementation could be substantiated.) Yet, when the QSR is in place, firms will not have to retrospectively document their existing designs, but they will need to have new procedures in place and implemented at a later date.

Other situations that might lead an FDA inspection towards the issuance of an FDA 483 and would not reflect on an ISO audit could occur in the areas of validation or complaint review. The ISO and the FDA directives address both issues. However, an ISO auditor will focus on whether you investigated the complaint and attempted to develop a corrective action. Depending on the severity of the complaint, and its implications to public health and safety, an FDA investigator could find that an inadequate investigation was performed, or the investigation conclusions were not supported by adequate documentation.

Similarly, an ISO auditor will look for the validation of a sterilization process, but might not question a firm's lack of validating a solvent bonding or injection molding process. Unless you have a trainee or a visually impaired FDA investigator, you probably will see the familiar FDA 483 for failing to validate such processes.

Audit Findings and Appeals

What about the ISO auditor or FDA inspector who misinterprets the requirements of the standard or regulation? The best tact is to reach an understanding with the auditor on what they perceived as the requirements of the standard or regulation, what their observation was, and how it differed from the requirements. The difficulty is to keep the discussions at the professional level. Avoid comments like "Any idiot can see..." or "You must not understand our industry."

Avoid Confrontation

This may be easier to do if communications are established during the audit and the adverse observations do not come as a surprise. Most ISO and FDA auditors will communicate their concerns, if asked, at the conclusion of each day during their visit.

It is more difficult to deal directly with over-zealous FDA investigators if they take it upon themselves to liberally interpret the requirements of the regulations. But I guess there could be a worse nightmare for a Quality Assurance or a Regulatory Affairs Manager, such as having three armed FDA criminal investigators issuing a Notice Of Inspection.

If discussions fail to resolve the differences in viewpoints, you should send a timely written communication to your registrar or your FDA district office, explaining your view. It is important to support your position with appropriate documentation. A well-presented description of the facts, your understanding of the standards and/or regulations could end up with a finding supporting your viewpoint. This could save you time and resources in correcting a situation that did not require modification.

Competition

With the international marketplace becoming extremely competitive, and regulators being pressured to eliminate non-value added events, the time for redundant, expensive audits (FDA and ISO) will

not be long-lived. Presently, the FDA has allowed employees of some states to perform FDA inspections. What makes a state employee easier to train and less impartial than an independent ISO auditor? How can the medical device community support almost identical inspections of its facilities by two different organizations? Can the European and United States consumers really afford two slightly different approaches to the same quality system to cause an escalation in health care costs?

The first step of harmonizing most of the quality system standards will lead us to one standard. This will eventually lead the way for one criterion of inspecting medical device facilities. The second step will be having well-trained, independent and accredited individuals not merely ISO accredited or U.S. government hired auditors and investigators. The last step will be the recognition of the equivalency in the training and abilities of these individuals.

We are experiencing a journey to this more efficient type of third-party review, but will there be any stumbling blocks placed in our way by bureaucrats trying to protect their empires? Will FDA investigators or ISO auditors exercise unprofessional behavior by attempting to protect their existence by competing between themselves? Will management of the two systems work together to help complete the harmonization, or will differences cause a wider rift?

I believe there will be some individuals attempting to find the faults between the two different approaches to the same problem. From my experience with the Agency and being a professional auditor, I find that the vast majority of FDA investigators, their managers, the ISO auditors and their employers are above that type of unworthy conduct.

Both the ISO and the FDA are customer-oriented or are changing their philosophy in that direction. However, it will take some time for the differences to be worked out. I anticipate seeing this evolution to take a few years, perhaps near the beginning of the 21st Century. In the meantime, don't expect identical results from ISO and FDA visits. ❑

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Omeo Chatterjee

PERFORMANCE QUALIFICATION OF A CLEAN ROOM FROM A QUALITY PERSPECTIVE

Every facility design is unique for its specific needs, and validation programs must be customized to meet these challenges. While there is no one right way to write a clean room validation protocol, the key is to develop documentation using common sense and according to the specific requirements for an operation and established regulatory standards. After a brief discussion of important validation concerns, this paper will focus strictly on the performance of clean room facilities.

FUNDAMENTAL VALIDATION ISSUES

There basically are two types of validation:

- *Initial Start-Up* - A facility that is brand new or an existing facility that has gone through major renovation or very specific changes.
- *Concurrent* - Ongoing validation that takes place during normal day-to-day activities.

In the case of start-up validation, challenge the clean room thoroughly and document evidence to illustrate that the clean room facility is capable of delivering the required quality standards prior to actual process implementation. Production is not to take place until such demonstrable confidence is evident. In concurrent validation, however, generate and collect data during the actual production operation. Analysis of this historical data must support the required performance standard. Once detailed and clear protocols are complete, it is essential that they are followed as written.

Two basic elements decide the success or failure of any validation project:

- *People* - Organize a validation team that includes members from various academic disciplines, such as Engineering, Pharmacy, Chemistry, Microbiology. These team members must have a thorough understanding of the current and future needs of the company, hands-on experience in production, engineering/maintenance, quality control/quality assurance, as well as good knowledge of validation. Without practical experience very little will be achieved.
- *Plan* - Without effective planning, senior management support, and on-going follow up, a project is bound to suffer. Total support from senior management is essential; they must understand a given project without necessarily knowing scientific detail. Inform them about the impact that validation will have on finances, manpower, product availability, as well as about a backup plan in case problems arise with the initial plan. The importance of senior management's understanding and support of the validation process cannot be over emphasized.

GETTING STARTED

Beginning any validation project is a crucial issue because companies do not want to do a lot of work only to find out it is not acceptable. With an adequate plan or procedure, carrying out a validation program becomes a matter of time and people resources.

Initially, during the drafting stage, make sure that the validation plan is flexible so that changes and team input can be incorporated. The goal is to achieve the best design and ensure successful results. Once the plan is finalized, it must be capable of withstanding critical review and satisfy future company needs.

The validation team must start working at ground level to establish specifications, guidelines, schedules, as well as to identify appropriate in-house expertise and outside resources, such as contractors, subcontractors, and vendors. These outside resources must have prior knowledge and experience in clean room construction. Without such knowledge, projects will become bogged down by mistakes, additional costs, and delays.

The validation team jointly should establish a validation program as follows:

1. Establish Parameters
2. Draft Protocols
3. Review and Approve Protocols
4. Conduct Tests and Collect Data
5. Evaluate Data
6. Document Results
7. Approve and File Results

Protocols must cover the following sections:

1. Purpose and Objective
2. Design Characteristics
3. Procedure
4. Acceptance Criteria
5. Test Methods
6. Standard Operating Procedures
7. Preventive Maintenance Plan
8. Acceptance Responsibility

Incorporate these items so that protocols are understood easily by all responsible personnel, including outside contractors. Some validation tests are carried out by contractors and must be reviewed thoroughly and approved by the validation team. In addition, the validation team must review and approve changes to the original plan and specifications which take place during construction of a clean room. Otherwise, there may be a significant negative impact on end results.

PERFORMANCE QUALIFICATION

Once architectural design and actual construction is complete, the PQ of a clean room facility begins. Some tasks are conducted by certified/licensed contractors, while others are performed by in-house technical personnel.

Protocols for a clean room should cover the following items:

1. HEPA Filter Performance Test and Certification
   - In-place HEPA Filter, Housing, and Frame Leak Tests
   - Airflow Velocity Profile of HEPA Filter
   - Certification Label
2. Pressure Control Test
3. Temperature Control Test
4. Humidity Control Test
5. Smoke Profile Test
6. Inter-Room Air Velocity Test
7. Detection/Monitoring of Particulate Matter
8. Sanitation
9. Clean Room Employee Training

1. HEPA Filter Performance Test and Certification

• *In-Place HEPA Filter, Housing, and Frame Leak Tests* – Confirm that the HEPA Filter, or its frame, is not damaged or improperly placed during installation. A properly applied HEPA Filter produces a fairly uniform discharge of air velocity and direction. The HEPA filter test should be performed only by certified personnel.

Conduct the leaker test using a DOP (Dioctyl Phthalate) aerosol generator of the Laskin

Nozzle(s) type. An aerosol of DOP is created by flowing air through liquid DOP at room temperature. The instrument used should have a threshold sensitivity of 1 x 10^{-3} micrograms per litre for 0.3 micrometer DOP particles and a capacity for measuring a concentration of 80 - 120 micrograms per litre. The sample rate of air should be 1 cubic foot per minute. Calibrate the aerosol photometer at least once during each calendar year according to the manufacturer's recommended procedure.

The next step is to introduce the DOP Aerosol into the upstream of the HEPA Filter. Adjust the instrument until a DOP challenge concentration of 100 gm/litre of air is reached. Scan the downstream side of the HEPA filter and the perimeter of each filter pack by passing the photometer probe in slightly overlapping strokes over the entire surface of the HEPA Filter. The nozzle of the probe should not be more than one inch from the surface. The entire periphery of the filter, the junction between the filter, and the filter mounting frame should be scanned. Perform scanning at a traverse rate of not more than two inches per second.

A unit is considered acceptable when no significant leakers exist or all significant leaks are repaired. A significant leak is defined as a photometer reading greater than 0.01 percent of the upstream concentration. Repairs may be made to significant leaks by caulking with silicone sealant. (However, no more than five percent of the effective area of a filter should be caulked.) The sealant is forced over the filter medium between the separators and must be smoothed flush with them. The filter should be rechecked for leaks as specified above. If more than five percent of the filter face caulking is required, the filter must be rejected and a new one installed. It is important that all repaired and non-repairable leaks are depicted pictorially on a diagram and kept as part of the final report.

• *Airflow Velocity Profile of HEPA Filter* – A thermoanemometer with a sensitivity of ±2 feet per minute or three percent indicated velocity normally is used. The instrument should be calibrated according to the manufacturer's instructions and within a maximum of six months. Ensure that this calibration is traceable to the National Bureau of Standards.

Starting six inches from the inner edge of the filter perimeter, take and record the air velocity test at multiple points on a grid scale to give approximately nine readings per square foot of area. Use a small ring stand and clamping mechanism to hold the anemometer probe stationary during all velocity measurements; a hand-held anemometer probe is prohibited.

Acceptable mean air velocity is 90 (±10) fpm. All measured values should fall within ±20 percent of the resulting mean velocity. If necessary, the variable blower motor speed can be adjusted to achieve the acceptable mean air velocity. The recording of the air velocity reading should be repeated. Submit a pictorial representation of the air velocity measurement grid, documenting all actual velocity readings (before and after air flow adjustment), as part of the final report.

• *Certification Label* - Affix a label bearing the name and address of the company conducting the test, date of test, test criteria for the Performance Certification (e.g., Federal Standard 209E, etc.), and the signature of the individual who performed the test. The test number and recommended date for recertification should be entered on the label.

2. Pressure Control Test

The purpose of this test is to confirm the capability of the air system to control pressure levels within preestablished specifications. An inclined pressure gauge with a resolution of 0.02 inches of water is required.

In order to conduct this test, all HVAC and Laminar Airflow Systems must be in continuous operation. To establish a baseline, all doors must remain closed and no traffic is allowed through the facility during the test. Pressure readings are to be taken with the high and low pressure tubing at each location. Once the baseline reading is established, then readings should be taken under stress conditions by opening various doors within the clean room facility.

Acceptance criteria is as follows:

- *Pressure differentials should be within design tolerances under static and simulated operating conditions.*
- *The system is not acceptable if, at any time during static, stress, or dynamic conditions, the pressure in the primary environments becomes less than zero or negative. The report from these readings is to be kept as part of the validation documentation.*

Keep the following points in mind for clean room air handling systems:

- Always purchase systems from a reputable manufacturer and hire well-experienced technicians to perform installation and certification. These measures will reduce the risk of potential major disruption of systems and the possibility of product failure due to environmental contaminants.
- Do not cut costs on a prefiltration system. Use a high grade prefilter which will extend the life span of expensive final HEPA filters. Ultimately, there will be less down time in production.
- In clean room laminar airflow, parallel streaming of air is an important factor for effective removal of contaminants. The presence of non-unidirectional flow of air within the laminar air system can impose a substantial risk. Most standards for laminar flow systems take this into account and impose definite requirements on velocity distribution. Watch for uneven air distribution. It is caused by a poorly designed ventilation systems or by uneven flow of air from the filter.

3. Temperature Control Test

Proper control of temperature within the parenteral filling facility is a key factor. Temperature specifications established in qualification documents must relate to product and personnel requirements. Recirculating air from the Laminar Air System, heat generated by equipment and flames, along with a fully enclosed gowning system for all operators, governs the system, which must be capable of providing a comfortable temperature (65°C, ±5°C during the activity stage). Take temperature readings at static and dynamic states. Leave on all air handling systems and lights for at least 24 hours prior to conducting the tests. Temperature readings should be recorded at various locations every 15 minutes for two hours over a period of ten days. A summary of results for each room tested should be prepared. Make sure that the system is capable of maintaining the desired temperature range (65°C, ±5°C or other preset specification) at all times.

4. Humidity Control Test

The objective of this test is to verify the air handling system's ability to control humidity in the clean room at a preestablished specification. This test, which is conducted after balancing the air system, uses a dry and wet bulb thermometer or automatic humidity recording instrument. Readings are taken and recorded during static and active conditions within a clean room.

It is advisable to take readings throughout the year. The relative humidity should fall within the company's required tolerance range.

5. Smoke Profile Test

The objective of this test is to check the HEPA ceiling area for proper air pattern. Such tests use commercially produced smoke sticks, cotton swabs dipped in Titanium Tetrachloride, or an equivalent smoke source to indicate air flow profiles. Visually divide the areas to be tested into squares of approximately 60 cm x 60 cm (24" x 24"). Introduce smoke into the grid pattern, and then observe and record the directional flow of the smoke. The smoke profile should support the air flow design criteria. Record, correct, and retest any observed reverse air flow or dead air space to confirm compliance to specifications.

6. Inter-Room Air Velocity Test

This test verifies the air flow velocity between connecting rooms in a clean room facility. A list and/or diagram of all rooms and areas interconnecting the main facility should be prepared. Note the direction and rated design velocity of air flow

at each interconnection. Turn on all applicable air handling systems at least fifteen minutes prior to conducting the test. Measurements of air velocity should be taken with a calibrated velocity meter at each room door and/or pass-thru. Visually divide each of these areas into three equal horizontal sections. Measure and record air velocity at the center of each section. Average inter-room air velocity should not be less than design specifications.

Inter-room air velocity problems often are observed near conveyor lines where empty containers enter and filled containers exit from the clean room area. This situation can be rectified by adjusting the air balancing system.

7. Detection/Monitoring of Particulate Matter

Determining and controlling particulate matter in clean room filling areas are extremely important for product quality control. Air supply, equipment, personnel, and the activities inside the work area are generally the major sources of airborne particulates. Federal Standard 209E describes the various air cleanliness classes in terms of the number of particulates per cubic foot of air. For example, in a Class 100 environment, where any sterilized product or material is exposed to the working environment, the number of particulates must not exceed 0.5 µm in diameter per cubic foot of air.

Prior to monitoring particulate matter, ensure that the following items have been addressed:

- Air handling systems have been certified in accordance with their specific rating or classification.
- Clean room facility and its equipment have been cleaned thoroughly and are devoid of any dust or lint.

In addition, personnel present in clean rooms must be trained and dressed in appropriate garments.

Protocols should identify all rooms and/or areas to be monitored, giving general descriptions, such as sterile filling area or sterile storage area. Companies may choose the type of air sampler to be used. However, the number and position of sampling points to be monitored must be decided and indicated in the protocol.

Take the particulate measurement first at static and then while either actual work or acceptable simulated activities are being carried out in the clean room. During the initial validation, particulate count is recorded when normal operations are not taking place. However, continuous monitoring is required, including during high activity periods, to capture the total particulate status of specific classified sections. Investigate, rectify, and validate "out of spec" trends immediately.

The following are common causes of increased particulate counts in a clean room when moving from a static to dynamic state:

- Excessive number of personnel and their activities
- Rapid personal movement
- Improperly cleaned equipment (e.g., particulate counter, production equipment, tools, etc.)
- Material disposition
- Open flame, aerosols, steam, compressed gas, equipment, etc.

8. Sanitation

Properly designed sanitation procedures and their organized execution are key to bringing sterile areas into acceptable operating conditions. For example, in one particular new start-up of a clean room facility in which airborne viable and nonviable particulate counts were outside acceptable limits, an investigation revealed that everything in the clean room was cleaned thoroughly except for the ceiling. This white ceiling had a layer of white construction dust, which contributed to the sporadic release of excessive numbers of particulates into the area.

Select cleaning solutions that contain antimicrobial agents very carefully since many chemical sanitizers are available. During the selection process, make sure that the agent to be used is effective and will not cause or pose risks to products. The role of an experienced microbiologist is crucial in this area. Sanitation procedures, including the frequency of cleaning, should be written in detail for each specific area.

• *Evaluation of Sanitation Program* - Begin the testing program immediately before and after an area has been restricted to aseptic operations and subjected to microbial decontamination. The evaluation should include the following:

1. Inspection for physical cleanliness and orderly conditions
2. Microbial exposure and air sample plate test
3. Contact plate test
4. Swab test

Record and evaluate all laboratory test procedures and then attach them to the protocol. Major deviations from the plan and "out of spec" test data must be explained. Corrective actions must be carried out and included in the report.

Remember the following points:

• Select cleaning/sanitizing agents that do not leave sticky or powdery residues and that are non-corrosive to stainless steel.

• Alternate sanitizers to avoid developing resistant strains of organisms.

• Prepare detailed, written instructions for the measurement, mixing, and use of specific cleaning and sanitizing agents. Often employees fail to measure sanitizing agents prior to dilution and are unaware of temperature requirements for certain agents.

• Cleaning equipment itself should always be properly cleaned, sanitized, and stored. Failure to do so may result in increased bioburden in sponges and mops. It also may introduce heavy contamination in clean room areas.

9. Clean Room Employee Training

It is common knowledge that personnel present in clean rooms are major contributors of particulate contaminants. However, many businesses concentrate on the validation of mechanical systems and put very little emphasis on clean room personnel. Proper training of these employees and their use of appropriate garments are crucial.

Personnel must receive classroom and hands-on training prior to receiving approval to work in clean room areas. Such training programs should be part of clean room validation requirements. They should include the following areas:

- Classification and description of clean room areas
- GMP requirements in clean room areas
- Acceptable and non-acceptable practices in the clean room areas
- Recognition and use of special clean room clothing
- Basic microbiology
- Review of various types of sanitizers and their specific function in clean room areas
- Review of various types of sterilization processes
- Depyrogenation methods
- Hands-on training of product manufacturing equipment, set-up and handling of goods, in-process sampling and checks, and transfer of product in and out of the clean room facility
- Evaluation plan to establish the degree of success of the training program

Keep the following points in mind:

• Employee training is an important investment for building quality products. Without documented formal training, trends towards batch failures and higher rejection rates will develop.

• Training based on in-house standard operating procedures, rather than "prepackaged" training, will provide a higher rate of success in product quality and improved employee morale.

CONCLUSION

The subject of validation continues to be of major interest in the pharmaceutical industry. The proper execution of protocols during PQ is an important part of validation efforts. Today companies are serving the global market. Therefore, they need to satisfy various countries' regulatory needs. Executing validation "right the first time and all the

time" can be achieved by having experienced, forward-thinking validation team members and a good scientific plan.

Validation of Existing Facilities:

A Systematic Approach to Facility Qualification

By Edyth L. Fitzgerald
A & E Validation, Inc.

The 1987 FDA Guideline for process validation clearly states that air and water handling systems, and environmental controls will be evaluated during process validation.[1] Ideally, qualification tasks are performed as part of the start-up and commissioning of a new facility. But in some cases, it may be necessary to qualify an existing facility. For example, a company engaged primarily in research and development must produce clinical supplies in accordance with good manufacturing practice. A section of their facility was suitable for this purpose, but the building was not qualified at the time that it was constructed. Another small company built their first manufacturing facility. The need for facility qualification was considered, but not formally included in the design, construction and start-up phases of the project. After the issuance of the certificate of occupancy, the validation department was brought in to qualify the facility.

"Ideally, qualification tasks are performed as part of the start-up and commissioning of a new facility."

In the first example, as the research and development company's operating and maintenance data was collected in a controlled manner, it was available to support the qualification protocols. This data included start-up and routine testing of all major systems, including HVAC and process utilities. In the second example, where the building was recently completed, operating data had not been generated. Qualification of this facility applied techniques associated with prospective validation. Since the existing documentation was acceptable (items, such as system specifications and as-built drawings), this company began prospective validation.

Facility Qualification

Where do you begin? Facility qualification involves large, complex mechanical and electrical systems that most scientists take for granted, as long as the air conditioning works in their office. But, facility qualification is the foundation for assuring success in further process validation. Before you begin qualifying a process, an acceptable facility and the utilities to support manufacturing operations must be in place. So, what should be included in facility validation? The main components of a facility qualification program include verifying the suitability of the building itself, and qualification of air handling systems, electrical systems and process utilities. The "building system" encompasses materials of construction, room finish schedules, and the facility layout with respect to the flow of personnel, materials and processes. Built-in equipment, such as fume hoods and walk-in storage areas, which are an integral part of the facility, are also included. HVAC, electrical and process utilities typically include all utilities distributed from a central plant, or the equivalent. Point

of use utilities, (such as an individual vacuum pump used in a specific process) would be qualified separately from the facility. (See *Figure 1*.)

Figure 1

Examples of Utilities Requiring Qualification

Water-for-injection	Standard power
Deionized or Purified water	Emergency/back-up power
Process solvent systems	Instrument air
Process fluids (saline, etc.)	Purified air
Nitrogen	HVAC systems
Oxygen	Fume hoods and biological safety cabinets
Carbon dioxide	Laminar flow work stations
Argon	
Natural gas	Vacuum systems
Specialty gases	Product transfer systems
Plant steam	Process drain systems
Clean steam	Acid dilution systems
Humidification systems	Hazardous emissions systems

There are two main issues associated with performing facility qualification that are not normally experienced when qualifying manufacturing equipment. The qualification of facility equipment and systems requires working with many different vendors and contractors. Many of these contractors may have limited experience with GMP requirements for the pharmaceutical and medical device industries. In addition, the terminology used in the construction industry varies significantly from the nomenclature used to describe qualification or validation tasks. For example, the commissioning of an HVAC system as described in ASHRAE Guideline 12 includes the terms "verification inspection", "functional performance testing" and "post-acceptance testing" which can be loosely correlated to installation qualification, operational qualification and performance qualification. Because this testing and documentation is provided by contractors, it must be clearly stated, in terms which are understood by all parties, and documented as "deliverables" within a written contract.

Qualification of an existing facility presents additional challenges that typically do not apply to the qualification of a new facility. It requires beginning in the middle. Documentation must be assembled to catch up to a point where the performance qualifications can proceed. Qualification of an existing facility requires facility down time for verification of installations and functional performance testing. A major problem in qualifying existing systems may include inadequate testing, and/or documentation, during the design, construction and start-up phases of the project, the lack of verified as-built information, and incomplete operation and maintenance manuals. There are also logistics issues in performing qualification testing in a facility that is "up and running". Ideally, the installation inspections are performed before walls are completed or ceilings installed. The validation schedule should include allowances for the time needed to physically access various systems for inspection. Other factors which may add time to the schedule include reworking the HVAC or utility systems to add test or sampling ports. Obtaining documentation retrospectively can often be a frustrating, if not impossible task. Taking all of this into consideration, qualifying an existing facility may not be as practical or efficient as performing prospective validation.

Figure 2

Qualifying an Existing Facility

- Define the areas and systems to be validated.
- Classify equipment and systems.
- Determine the documentation and testing requirements.
- Review existing documentation.
- Create the facility validation plan and schedule.
- Write and execute the qualification protocols.
- Implement a change control program.

Define What is to be Validated

The project should begin by defining what is to be validated. (See *Figure 2*) In order to perform facility qualification, you must first define what will

be validated. The facility and operations that are conducted within the facility must be evaluated. All activities subject to current Good Manufacturing Practices must be considered when determining validation needs. This includes not only the manufacturing areas, but support functions, such as material storage and analytical labs. Non-GMP areas (offices, research labs, general storage) should be considered only if there is a potential impact to the GMP areas of the building. It is acceptable for a single facility to have both GMP and non-GMP areas, as long as each area is clearly defined, and it can be demonstrated that the non-qualified areas do not affect the function of the qualified sections of the building.

The evaluation should begin by mapping out the flow of personnel, materials and products within the facility, and determining what sections of the facility will be included in the validation project. The easiest way of completing this task is obtaining several copies of the drawings which show the layout of the facility. For this purpose, the drawing should have minimal detail, other than room layout. The architectural room designation drawing is usually a good choice. Use highlighting markers or colored pens to show each of the following: (Use separate drawings for each).

❶ **Flow of personnel in the facility.** This should include entry to, and exit from, the manufacturing or finishing areas, as well as general traffic in the facility. Indicate the locations which are restricted to one-way movement of personnel.

❷ **Flow of manufacturing materials**. Include details showing receipt, sampling, and storage of incoming raw materials, the transfer of materials to manufacturing or packaging areas, and the storage of in-process materials and finished products.

For example: Bulk active ingredients and excipients are held in a controlled room temperature warehouse, one active drug substance is stored in a designated refrigerator, sampling is performed in a laminar flow chamber adjacent to the warehouse, raw materials are staged as needed to a holding area immediately outside the manufacturing area, in-process materials are held in the manufacturing suites pending test results, and finished products are stored in either the controlled temperature warehouse, or a walk-in refrigerated storage area.

❸ **Flow of process and related equipment.** This should be a general diagram of the process flow. The sequence and flow direction of the process and related equipment are of primary interest. Extensive process details are not needed at this point. Include only major equipment, and designate as clean-in-place, or show equipment cleaning rooms.

For example: Show the areas for weigh-out of raw materials, processing areas, blend transfer, further processing, bulk product transfer to packaging, the finishing area, and the delivery of the finished product to the storage area.

❹ **Critical areas of the facility.** After determining the flow of personnel, materials and the process(es), highlight or outline all areas of the building which have specific requirements for temperature, relative humidity, air flow or pressure differentials, and cleanliness. Be sure to include any support areas which are subject to cGMP requirements.

For example: Each manufacturing suite is maintained at 69 – 75ºC, 30 – 50% RH, requires a minimum of 20 air changes per hour (ACH), 90% dust spot efficiency air filtration, and negative pressure to the central corridor of 0.05" wg. The finishing areas (no open product) require 67 – 77ºC, 30 – 60% RH, a minimum of six ACH, and a positive pressure of 0.025" wg to the adjacent warehouse. The quality control laboratories call for 68 – 76ºC, 30 - 60% RH, a minimum of 15 ACH, and negative pressure to the common hallway of 0.05" wg. Material storage areas include a warehouse at 15 - 30ºC, 30 - 60% RH, with six ACH and neutral pressure, refrigerated storage (2 – 8ºC), and controlled room temperature stability storage rooms (23 – 27ºC, 55 – 65% RH). A vivarium housing rodents used in GLP studies must be maintained at 64 – 79ºC, 40 – 70% RH, requires a minimum of 15 ACH, and negative pressure to the common corridor of 0.05" wg.

❺ **Non-GMP areas.** Indicate any areas of the building which are used exclusively for non-GMP activities. This may include offices, research labs, or warehousing for non-GMP materials.

Note: Non-GMP areas have comfort requirements, and therefore it is good business practice to qualify these areas, but they should not be considered critical unless the air handling, or other utilities

for these areas affect the quality of the service to the manufacturing areas.

❻ **HVAC systems.** Outline the areas of the building served by each air handling system. Highlighting markers of various colors are helpful in showing the different systems. Indicate the air flow direction for adjacent areas. A current test and balance report (if available), should be used as the primary source for the air flow information. The goal at this point is determining what sections of the building are served by common air handling systems, and how the systems function with respect to building pressurization. Identify the air handling systems that must be validated.

For example: The primary air handling system (AHU1) for a small facility provides single pass, filtered air to the manufacturing area. A secondary system (AHU2) provides controlled room temperature storage for GMP materials. AHU3 is a self-contained system serving two stability storage rooms. AHU4 serves office areas, and is supplemented by supply air from AHU1 to provide positive pressure between the office area, and the manufacturing section of the building. In this case, AHU1, AHU2 and AHU3 should be included in the validation program, and AHU4 requires only routine start-up and maintenance, since a failure of this system would not affect the performance of the critical systems.

❼ **Critical utilities.** Process utilities generated from a central plant, should be included in the facility validation program. The flow of each process utility in the facility should be indicated. Typical process utilities include purified water, compressed air, process steam, and vacuum systems. Other critical utilities vary with different processes. Some utilities may be used for more than one purpose. A compressed air system used for the pneumatic controls on the HVAC system, may also be used for manufacturing equipment operation.

Electrical. Electrical systems are always considered a critical utility. Power quality can have a significant influence on the performance of equipment, and can create havoc on solid-state electronics. Designate incoming electrical service which requires transient surge suppression. Indicate all areas which must be provided with emergency lighting and emergency power. Critical equipment varies for each facility, but may include exhaust systems for containment areas, low or critical temperature storage chambers, and process utility equipment, such as the circulating pump on a purified water system. Specifications for power supply, voltage regulation, and uninterruptible power supplies (UPS), should be included in individual equipment protocols.

Classify Equipment and Systems According to Qualification Requirements

After completing facility evaluation, the next step is listing all the systems and equipment to be included in the validation program, and then classifying the equipment according to qualification requirements. Facility validation is a costly and time consuming process. Classifying equipment reduces unnecessary testing during the facility qualification, and also minimizes the testing required when changes or repairs are made to a qualified system.[3] Equipment and equipment systems can be classified by the qualification requirements for each:

IQ Only. Test or measuring equipment which can be confirmed reliably with calibration and preventive maintenance programs, may be considered for installation qualification only. Examples include anemometers, thermometers, pH or conductivity meters. Non-mechanical components of equipment systems which cannot be tested without other components, may also be appropriate for IQ only. Examples include: piping and valves for a chilled water system, and coalescing filters for a compressed air system.

IQ/OQ. Individual components in a larger system should be considered for having only installation and operational qualifications if the performance qualification will be performed on the system as a whole. Examples include: boilers or chillers for a HVAC system, UV sanitization lights or pumps on a water system.

IQ/OQ/PQ: Individual equipment designed to perform a specific, independent function should be subjected to a performance qualification (as well as IQ/OQ). Examples include a fume hood or laminar flow work station. In addition, equipment systems (HVAC and other utilities) will have a PQ performed on each system as a whole. Some systems may

Figure 3

Equipment Classification

Equipment	IQ	OQ	PQ
HVAC System #1	X	X	X
AHU-1 (Air Handling Unit)	X	X	
Heating Water System		X	X
BLR-1 (Hot Water Boiler)	X	X	
BLR-2 (Hot Water Boiler)	X	X	
HWP-1 (Hot Water Pump)	X		
HWP-2 (Hot Water Pump)	X		
Hot Water System Piping/ Valve Schedule	X		
BLR-3 (Steam Boiler)	X	X	
HMD-1 (Pure Steam Humidifier)	X	X	X
Chilled Water System		X	X
CLR-1 (Chiller)	X	X	
CWP-1 (Chilled Water Pump)	X		
CWP-2 (Chilled Water Pump)	X		
Chilled Water Systems Piping/Valve Schedule	X		
Terminal Devices	X	X	
Duct System	X		
HVAC Monitoring & Control System	X	X	X
USP Purified Water System #1		X	X
Carbon Beds	X		
DI (Mixed) Beds – Worker	X		
DI (Mixed) Beds – Polishing	X		
UV Sanitization	X		
Final Filter	X		
Recirculating Pump	X	X	
Storage Tank	X		
Purified Water System Piping and Valve Schedule	X		

require an IQ/OQ on the whole system, as well as each component.

Figure 3 gives some examples of equipment classifications.

Determine the Documentation and Testing Requirements

The testing and documentation requirements for each type of equipment or equipment system must be defined. This task (which is normally performed at the design stage of a prospective validation project), provides the basis for IQ and OQ protocols. Although the completion of the protocols in not necessary until testing is initiated, this is a good time to begin writing these documents. *Figure 4* provides an example of the testing and documentation requirements for a HVAC system. A similar checklist should be created for each equipment system. The descriptions used in the checklist should contain terminology common to both construction and pharmaceutical-/medical device industries. This practice is helpful when contacting vendors or contractors to obtain missing documentation or test reports.

Review Existing Documentation

Once the documentation list and testing requirements has been compiled, a review of existing documentation must be performed. This includes all relevant drawings, manuals, test reports, and if available, historical operating, repair and maintenance data. This review is a time consuming task, and must be performed by personnel capable of assessing both the content and quality of the documentation. It is not enough to check off the presence of an operating and maintenance manual. The manual must be evaluated to insure that it contains all information necessary to operate and maintain equipment. *Figure 5* provides a checklist for the content of HVAC operating and maintenance manuals.

Create the Facility Qualification Plan and Schedule

Upon completion of the documentation review, you should have a reasonable idea of where you are, and what is needed to complete the facility valida-

Figure 4

Documentation and Testing Requirements for Qualification of HVAC Systems

- ❑ Mechanical Design Drawings
- ❑ Mechanical As-Built Drawings
- ❑ Electrical As-Built Drawings
- ❑ Control System Drawings/Schematics
- ❑ Verification Report (Installation Qualification)
- ❑ Certificate of Readiness
- ❑ Functional Performance Report (Operational Qualification)
- ❑ System Operation Description/Final Design Intent
- ❑ Commissioning Report (Validation Summary Report)
- ❑ Operation and Maintenance Manuals
- ❑ System Manual
- ❑ Training of Operations and Maintenance Staff
- ❑ Post-Acceptance Procedures (Change Control)
- ❑ Post-Acceptance Testing (Performance Qualification)

Comments: _____

_____

_____

Verified By: _____ Date: _____

tion project. The next step is outlining the tasks necessary to complete the qualification of all facility equipment and equipment systems, and creating the facility qualification plan. The successful completion of the preceding steps will give you most of the information necessary to complete the plan. Project planning software is helpful when creating the tasks list and the schedule.

The following information should be included in the facility qualification plan:

❶ **Facility summary.** Describe the facility in terms of size, layout and intended use. This is an overview of the whole facility, and should include a narrative description, as well as drawings showing the layout of the building. Indicate the designated GMP areas, and the flow of personnel, materials and processes. The drawings created at the beginning of the project can be used for this purpose.

❷ **Utility systems.** Describe the HVAC systems and critical utilities in a narrative format. List all equipment included in facility validation, and the testing and documentation for each. The spreadsheet showing equipment classifications and qualification requirements is a good summary of this information.

❸ **Other facility requirements.** Outline the finish schedule for all critical areas of the building. This includes floor, wall and ceiling finishes, door schedules, and lighting requirements.

❹ **Specialty equipment.** List or describe all other equipment, such as fume hoods, laminar flow work stations and walk-in refrigerated or stability storage areas, and the qualification requirements for each. Once again, the equipment classification spreadsheet may be used for this purpose.

❺ **Documentation requirements.** Specify the formats to be used for IQ, OQ and PQ protocols and summary reports. Indicate what departments will review and approve protocols and test reports. Also include information about where the completed protocols and supporting documentation is stored. If this information is included in the validation master plan, reference this document.

❻ **Control procedures.** List the standard operating procedures used for document control, deviation and change control, personnel training, calibration and maintenance, and quality assurance programs.

❼ **Qualification schedule.** List the schedule of events for completion of the facility qualification, and include the estimated time and schedule dates for each task.

❽ **Acceptance criteria.** Describe the procedure for the review and approval of the qualification documents, and indicate what constitutes the acceptable completion of the facility qualification project.

Figure 5

HVAC Operation and Maintenance Manuals Include the Following

Detailed description of each system and system component.	❑ Yes	❑ No	❑ N/A
Wiring and control diagrams with operation/control of each component.	❑ Yes	❑ No	❑ N/A
Control sequences for start-up, all modes of operation, and shut-down.	❑ Yes	❑ No	❑ N/A
Installation instructions.	❑ Yes	❑ No	❑ N/A
Procedures for start-up, operation, and shut-down.	❑ Yes	❑ No	❑ N/A
Maintenance and overhaul instructions.	❑ Yes	❑ No	❑ N/A
Lubrication schedule (type, grade, temperature, frequency range).	❑ Yes	❑ No	❑ N/A
Corrected shop drawing.	❑ Yes	❑ No	❑ N/A
Product information (performance curves, ratings, features).	❑ Yes	❑ No	❑ N/A
Copies of approved certifications or lab test reports (if applicable).	❑ Yes	❑ No	❑ N/A
Copies of warranties.	❑ Yes	❑ No	❑ N/A
Test procedures.	❑ Yes	❑ No	❑ N/A
Parts list, including source of supply and recommended spare parts.	❑ Yes	❑ No	❑ N/A
Contact information for each subcontractor/equipment supplier.	❑ Yes	❑ No	❑ N/A
Other technical data as specified.	❑ Yes	❑ No	❑ N/A
Impact testing of fire/life safety systems on HVAC systems.	❑ Yes	❑ No	❑ N/A
Uninterruptible power supplies. (Include list of equipment and design kW load on each.)	❑ Yes	❑ No	❑ N/A
Emergency power generation. (Include list of equipment and design kW load on each.)	❑ Yes	❑ No	❑ N/A

Note: This checklist was adapted from ASHRAE Guideline 1: The HVAC Commissioning Process.[2]

Write and Execute the Qualification Protocols

Once the items listed above have been completed, the writing of the qualification protocols should be a straight forward task. The testing and documentation requirements have been determined for all equipment and equipment systems. The checklists and test requirements should transfer easily into standard protocol formats. The completion of the protocols marks the beginning of a validation life-cycle, which continues until the facility is taken out of service. ❑

References

1. FDA Guideline on General Principals of Process Validation. May 1987
2. ASHREA Guideline 1: The HVAC Commissioning Process. 1996
3. Desain, Carol and Sutton, Charmaine, *Validation for Medical Device and Diagnostic Manufacturers*, Interpharm Press, Inc., 1994.

Validating Building Controls Systems

By Jeffrey L. Waters
Landis & Staefa

Why should a company validate its Building Controls System? Today's international competition and wary consumers mandate some kind of quality control in almost every industry. Voluntary compliance with the International Organization for Standardization (ISO) is one of the hallmarks of many successful businesses. The ISO 9000 standard is even recognized by the Food and Drug Administration (FDA) in its internet file (ftp://ftp.fda.gov/CBER/ misc/cgmp.txt). "The principles and practices elucidated in the ISO standards are not in conflict with those provided by the cGMP (current Good Manufacturing Practices) regulations," the FDA states in the file. "Indeed, the voluntary ISO standards share common principles with FDA's cGMP requirements."

"Environmental control in drug manufacturing facilities has drawn increased attention from the FDA in the 1990s."

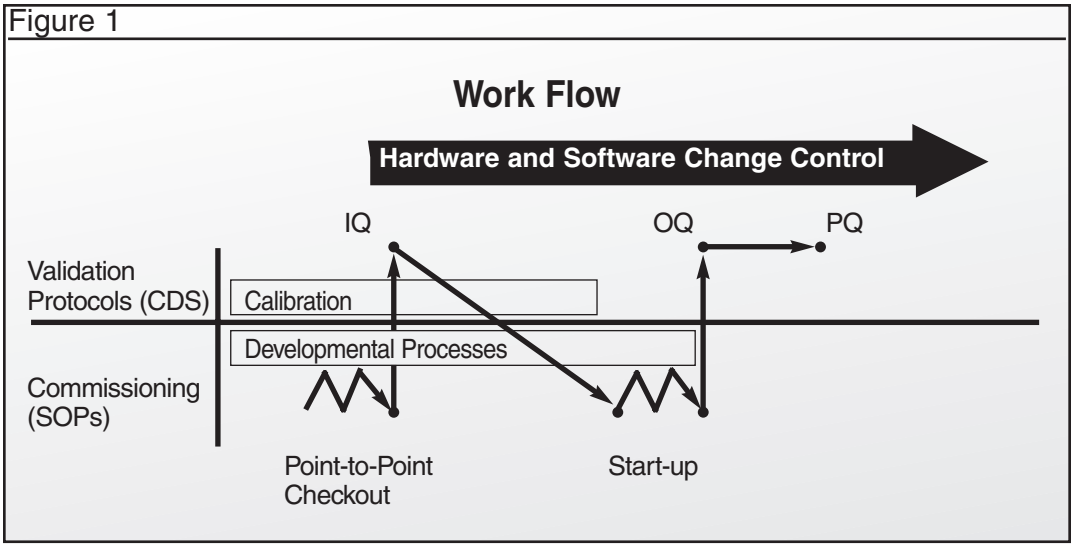
Environmental control in drug manufacturing facilities has drawn increased attention from the FDA in the 1990s. The cGMP (21CFR 211.46), last modified in 1995, says in part:

(a) Adequate ventilation shall be provided.
(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used on air supplies to production areas when appropriate.

These recommendations must be interpreted and implemented by the individual facility operators, but other industry guidelines are more specific. The ASHRAE 1995 Handbook – *HVAC Applications* (pg. 13.8), [for chemical] *Laboratory Ventilation Systems*, states, "Minimum ventilation rates are generally in the range of 6 to 10 air changes per hour [ACPH] when occupied." Actual air change rates may be significantly higher in labs with a high concentration of fume hoods. For example, a 30-by-50-foot lab with 10-foot ceilings (15,000 square feet) containing 10 fume hoods exhausting 1000 cubic feet per minute each (a total of 10,000 CFM) would experience a ventilation rate of 40 ACPH. On the other hand, labs with a single fume hood or bio-safety cabinet may require supplementary general exhaust ducts to provide adequate air changes. Simple mechanical Constant Air Volume (CAV) systems are less expensive to install and start up, but a computerized Building Controls System (BCS) provides dynamic control and monitoring of parameters such as air pressure and humidity. Variable Air Volume (VAV) controls minimize energy usage by reducing supply and exhaust flow when fume hoods are closed or the facility is unoccupied.

Air filtration in most critical applications is provided by High Efficiency Particulate Air (HEPA) filters. Strict specifications (such as Military Standard MIL-F-51079B for fire resistant biological filters)

Figure 1



define the properties of a HEPA filter. The National Sanitation Foundation requires (in its NSF-49 standard for biohazard cabinetry) that aerosol penetration not exceed 0.01% at any point on the filter, so NSF-49 certified HEPAs are at least 99.99% efficient. Pre-filters (to prevent loading the more expensive HEPAs) are simple bag or box filters that trap dust and large particulates such as animal hair. Alternatives for less critical applications include High Efficiency filters (95% efficient), and charcoal filters for organic vapor or odor control.

The cGMPs have governed drug manufacturing facilities since 1963. According to the FDA's World Wide Web site (www.cgmp.com), proposed changes may require construction of separate facilities and control systems for highly toxic agents:

"Penicillin has long been subject to specific cGMP regulations designed to reduce the danger of cross-contamination. Because other substances [cephalosporins, cytotoxic anti-cancer agents, and infectious agents] pose at least as great a risk of toxicity due to cross-contamination, FDA is proposing to expand the contamination control requirements. Section 211.240(b) would require dedicated production, which may include facilities, air handling, or process equipment, in those circumstances in which contaminants pose a special danger to human or animal health."

Fear of FDA intervention certainly is a compelling reason for a company to validate its environmental controls. Accomplishing business goals may be a better reason. According to Landis & Staefa validation consultant Irene Miess, "It just makes good business sense to make sure the facility operates as designed to ensure quality products are consistently produced."

Sean Chuckas, Landis & Staefa's operations manager for validation, explains it this way, "Aside from the risk to the life and health of employees, the cost of product failure due to not meeting quality standards can be very high. Years ago, humidity, pressure, and temperature were not considered part of quality control. Today we realize that production yield is boosted by controlling the environment. It's not just the process (that must be validated)."

Now that we have established the necessity of validating HVAC equipment, it is vital to understand the difference between commissioning environmental controls and validating their performance. A chart will help explain the difference.

The purpose of *Figure 1* is to show the work flow in a linear fashion while separating the Validation Protocols (contained in the Controlled Documents System) from the Commissioning Process. Standard Operating Procedures (SOPs) are used in the commissioning of everyday projects. After the HVAC mechanical equipment and controls are installed, the process should begin with a point-to-point check-out of every component (i.e, verifying that every input and output device is connected to the proper terminals). The jagged line on the chart represents the ups and downs of a typical construction project. A method that reduces cost and time is utilization of commissioning documentation to support validation. For example, commissioning checklists can be referenced in the Installation Qualification (IQ). According to Sean Chuckas, "The alternative is to do them separately and duplicate a lot of paperwork." If calibration is required, the procedures and documentation must be referenced in the validation protocols.

Once Installation Qualification is satisfactorily

completed, start-up of the HVAC system can begin, in accordance with the company's SOPs. The mechanical equipment must be up and running before Operational Qualification (OQ) can begin. This is where verification that the various mechanisms operate as intended must be done (for example, when the room thermostat calls for heat, does the hot water valve open?).

Performance Qualification (PQ) must be carried out by the owner. This is where verification is done to insure that all systems work together under as-used conditions to meet the User Requirement Specification. Do room temperature, humidity, and pressure stay in spec with production under way and people entering and leaving the facility? All systems must be operational to complete PQ.

Cooperation between the various contractors (mechanical, controls, etc.) is vital to completing PQ in a timely and cost-effective manner. Sean Chuckas stresses, "The owner and the designer must sit down at the beginning of the project and determine critical [validated] and non-critical areas. You don't want to waste resources and dollars validating non-critical areas."

To help make this determination, one should ask, "Which areas are critical to the production and storage of the product?" and validate only those areas. If more than one building will be constructed, all processes that must be validated by Good Laboratory Practice (GLP) or Current Good Manufacturing Practice (cGMP) should be segregated to the same building, and non-critical facilities housed in the other. If critical and non-critical areas are mixed within the building, the critical processes should be segregated to one area. Do offices, research-and development-labs, storage areas, and corridors really need to be validated? And finally, are only the rooms critical, or should the HVAC equipment be validated as well (air handling units, filters, temperature sensors, etc.)? One should be sure to coordinate these decisions with the supervisors of each affected area.

Hardware and software change control also must be addressed early on, because it will affect the entire process. If thermistors are specified (they must be replaced when they are out of specification) and then sealed behind drywall during construction, calibration will be a very expensive and time-consuming process. RTDs, which can be calibrated in place and have field replaceable parts, may be more cost effective in the long run even though the initial cost is higher. If the software change control procedure requires re-validation with every minor modification, updates will be very difficult and costly. One should remember that the maintenance staff must live with the change control procedures for the life of the facility. Flexibility should be built in, and subcontractors also must be trained on proper procedures. Change control procedures should address such issues as scheduling and documentation of maintenance, and re-certification of calibrated sensors. How will one insure that a calibrated sensor is available if one fails, or that the control program changes stick to standard formats? This is the nature of Building Control System Change Control.

The following quote from the Proposed Changes file of the cGMP web site emphasizes the FDA's viewpoint: "To preserve the validated status of a process, measures must be taken that will allow any significant process changes to be recognized and addressed promptly. Such change control measures can apply to equipment, standard operating procedures, manufacturing instructions, environmental conditions, or any other aspect of the process system that has an effect on its state of control, and therefore on the state of validation."

"Cooperation between the various contractors (mechanical, controls, etc.) is vital to completing PQ in a timely and cost-effective manner."

An auditor must be able to evaluate the current status of a facility based on the owner's documentation, and compare it to the specifications, but the processes also have to work smoothly and allow improvement. Irene Miess has this advice for anyone responsible for validated processes; "The owner should get involved as early as possible and look at what the desired end result will be, not just the 'cor-

rectness' of the specification. The User Requirement Specification is not always exactly what he wants, and what he wants is not always what he gets."

Some aspects of validation are unique to HVAC control systems. Sean Chuckas elaborates, "Although the controls are one of the last things to go in on new construction, they must not be planned last. The owner must make many decisions before the controls are installed and there should be meetings early in the process. Quality can't be tested into a process. It has to be designed into each system."

The HVAC controls for critical (validated) areas should be grouped in specified field panels. One may want to label these panels, "Critical Process Controls: Please follow Change Control Procedures," or something similar. This will prevent the necessity of having to validate non-critical controls.

Electric and other utilities must also be evaluated. One may need an Uninterrupted Power Supply (UPS) for critical field panels and PC workstations to continuously monitor critical equipment – such as refrigerators, incubators, and particle counters – with the Building Controls System.

When choosing an HVAC controls vendor, one should have experience in the validation process as a prerequisite. A close working relationship can save time and money beyond the initial cost of installation. Irene Miess sums it up thusly, "A primary criterion for choosing a building automation vendor should be the ability to provide support for the life of the facility. Their attitude should be, 'We don't walk away after commissioning.'" ❑

Validation Commissioning Documents:

A Checklist Approach for Facility Validation

By Daniel J. Tisak, Bala Consulting Engineers
&
Robert E. Koster, SmithKline Beecham Pharmaceuticals

Qui non est hodie cras minus aptus erit.

He who is not prepared today will be less so tomorrow. – Ovid

When pursuing the facility validation process, it is essential to be prepared. Part of the preparation involves securing documentation, testing assistance and other services from vendors for the success of the project. Even those in the industry who lack expertise in pharmaceutical validation nonetheless understand and appreciate the value of reliability, and the need to incorporate the aid and expertise of the contractors and vendors for testing and documentation. Yet the preparation and planning required to make sure that necessary documentation and services are provided can become a difficult, logistical challenge. A practical, effective way to ensure the provision of services is through the use of a Validation Commissioning Document (VCD). The VCD designates document and testing requirements. The VCD identifies the shared responsibility and cooperation that must occur between the owner, construction manager and vendor for documentation and testing.

"Successful completion of the VCD supplies the basis for IQ/OQ development and execution."

Objective

The VCD is a planning tool for the commissioning program. A commissioning program that is well-planned and executed will facilitate the validation process, accelerate start-up, enhance documentation and ensure that the pharmaceutical product is produced in a GMP-compliant facility. The objective of the VCD is to clearly and concisely identify the documentation and services that the vendor must provide for the commissioning program, including the facility validation process. Successful completion of the VCD supplies the basis for IQ/OQ development and execution. Using VCDs has an added benefit: Through coordination of testing, repetition of work between related commissioning and qualification activities is minimized, thereby reducing costs. Thus, VCD use can enhance a reasonable approach to validation. This is especially significant for start-up firms that do not have the resources to manage complex policies.

Procedure

During a project's design phase, a VCD is filled out for each system or piece of equipment and sent to the vendor as part of the bid package. Inclusion of VCDs in the bid package fosters early planning and preparation. It also helps the vendor to more realistically anticipate and assess the installation, testing and documentation costs of the system or equipment to be provided, based on the needs of the owner. One VCD may cover a number of similar equipment pieces.

VCD Checklist

The VCD contains a simple checklist that is prepared by the validation contractor and approved by the pharmaceutical firm's project manager or representative. The checklist is divided into seven sections. Each section lists many related types of documentation and services. Tasks required for individual equipment pieces are checked. The following list is an example that identifies the sections and some of the tasks that the VCD should contain:

1. General Documents
- Specifications.
- Purchase Orders.
- Engineering Documentation.
- Process Flow Diagrams (PFD).
- Piping and Instrumentation Diagrams (P&ID).
- Operation and Maintenance Manuals Warranties.

2. Construction/Installation/Certification Documents
- Installation Requirements.
- Quality Standards.
- QA/QC Reports from Subcontractors or Vendors.
- Material Certification.
- Welding Procedure.
- Welding Inspection.
- Weld Map.
- Noise Data Sheets.

3. Testing and Commissioning Activities
- Factory Acceptance Testing.
- Site Acceptance Testing.
- As-Built Drawings.
- Air Balance Report.
- Duct Pressure Test.
- Filter Certification.
- Megger Testing for Power Cables.
- Motor Rotation Verification.
- Ground Continuing Testing IEEE/ANSI/ASME/NEMA/ASTM Certification.

4. Equipment Data
- Component Listing.
- Spare Parts List.
- Lubrication List.
- Motor List.
- Single Line Diagram.
- Motor Wiring Diagram.

5. Instrumentation/Calibration
- Instrumentation Checklist.
- Calibration Certificates with NIST Traceability.
- Calibration Procedures.

6. Computerized Systems
- Quality Program Software Development Standards.
- Functional Specification.
- Flow Diagrams.
- Pseudocode.
- Source Code.
- Annotated Ladder Logic.
- Programming Manuals.
- I/O Rack Address Verification.
- Control Panel Hardware and Set-up Document.
- Component Location Verification.
- Automatic Valve Operation Check.

7. Training
- Factory Training.
- Site Training.
- Certificates of Completion.

When filling out the VCD checklist, the validation contractor refers to the engineering design specifications, the owner acceptance criteria, and FDA regulatory guidelines to determine the requirements. For example, if the specification indicates the requirement "SA-240, Grade 316L Stainless Steel," then the requirement named "material certification," listed in Section 2, Construction/Installation/Certification, is checked. Once the checklist has been completed, it is routed to the owner's project manager for approval. After approval, the checklist is distributed to the construction manager and vendors. *Figure 1* is a sample from one section of a VCD.

Figure 1

VCD Sample

VCD Number	VCD007	Date:	March 25, 1997
Equipment Number:	3-CENT-7501, 3 CENT-8501	Revision:	01
		Protocol:	BFP08011
Description:	Building 3 Centrifuge		
Material Requisition Number:	1-7-97-0000057	Page:	5

Section 3: Testing and Commissioning	Subcontractor	Vendor	Owner	Comments
Factory Acceptance Testing (FAT)		x	x	
FAT Methodology in Bid Package		x		
Approved FAT Procedure		x		
FAT Acceptance		x		
Tester CVs				
Dye Leak Test Report				
Start-up Procedures Data Sheet		x		
Site Acceptance Testing (SAT)	x	x	x	
Approved SAT Procedure		x		
SAT Results	x			
Tester CVs				
Installed Setpoint/Operating Data Documented	x			

Cases to Consider

Recurrent FDA-483 observations include "inadequate documentation" and "incomplete test cases." In some cases, the vendor and owner may perform the reliability tests but fail to document them in sufficient detail. In other cases, the test procedures overlook assumptions that were made during the development of functional requirements. Several approaches may be taken to address documentation and testing requirements. One approach uses a qualification protocol during the design phase to identify documentation and testing requirements. The qualification protocol typically was previously written for a similar project, system or set of equipment. However, this approach may be insufficient for developing as-built test packages, especially for new equipment and systems such as those that are computerized. For example, suitable test procedures for computerized systems identify operator actions and test results, but these may not be known in detail early in the design phase. A more practical approach uses the VCD to identify the requirements for documented factory and site acceptance testing. The test procedures can be evaluated for detail and accuracy later, during the construction phase, and incorporated in the qualification protocol before actual testing.

Industry Comparison

The VCD uses a conceptual approach that has been employed by other industries with different regulatory concerns. For example, the planning process for software development includes a state-

ment of what the customer wants the seller to do, called a Statement of Work (SOW). The SOW indicates deliverables and testing requirements. The Nuclear Regulatory Commission (NRC) has its own detailed testing requirements for the nuclear industry, and the Department of Defense (DOD) has military specifications that indicate the procurement and task requirements for establishing reliability of systems and equipment.

Summary

The VCD is an organizational tool and a major communication path for the project. Its use in the facility validation process is important, therefore, because organization builds consistency and consistency yields reliability. Moreover, the VCD identifies the shared responsibility and coordination that must occur between the vendor, subcontractor and owner. Finally, the use of VCDs supports Good Engineering Practice (GEP), for GEP suggests that the vendor documents be organized, properly witnessed and approved.

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Validation/Qualification and Commissioning Strategies for Major Capital Projects: A Case Study

Chris Wernimont, P.E.
Eli Lilly and Company

Brett Conaway
ValSource

Validating, Qualifying and Commissioning (V/Q&C) for a major capital project in the pharmaceutical industry is a daunting task, especially in today's environment of increased focus on compliance, and the business benefit of trouble-free facility startup.

What follows are key V/Q&C concepts, and a description of their application in the delivery of a major capital project in the pharmaceutical industry. The following case study involved a major modification to an existing bulk Active Pharmaceutical Ingredients (API) manufacturing plant during a defined shutdown period.

"The following case study involved a major modification to an existing bulk Active Pharmaceutical Ingredients (API) manufacturing plant during a defined shutdown period."

Part I: Governing Document (The Validation Master Plan), Project Structure, and Training

The Validation Master Plan (VMP) is a summary document prepared as part of project planning that describes overall philosophies, approaches, and objectives to all aspects of V/Q&C (e.g., facilities, utilities, equipment, process). The document defines responsibilities and expectations for the various components of the V/Q&C exercises, and also establishes target timelines for completion of each component.

A VMP was generated for the major capital project with the following purposes:

- To provide the strategy to be used for planning, execution, and completion of V/Q&C activities for the project.
- To outline the organization for the V/Q&C aspects of the project and associated individual responsibilities.
- To define specific tasks or expectations, including major project milestones, which upon completion, will serve as evidence of completion.

Validation/Qualification and Commissioning Strategy Team

The VMP calls for the formation of a Validation/ Qualification & Commissioning Strategy Team (V/Q&CST) that has the overall responsibility of developing the master plan, and coordinating subsequent V/Q&C activities.

The V/Q&CST was composed of representatives of the following groups:

- V/Q&C Leader
- Quality Control for the Project
- Corporate Engineering VQ&C Specialist
- Process Automation
- V/Q&C Tech
- Technical Services Department Head
- User Representative (Typically an owner, Design Engineer)
- Quality Control (QC)
- Technical Services Specialist for Cleaning Validation and Process Validation
- Contract Firm V/Q&C Leader
- Operations Team Leader

Many of the decisions that guided project delivery were documented in the meeting minutes of this team. It is very important that the V/Q&C leader, or his/her designate, keep detailed and accurate meeting minutes. It is recommended that the meeting minutes be filed as a historical record upon project completion.

Roles and responsibilities beyond the V/Q&C team were also defined within the VMP. An overview of the V/Q&C project team's mission and key relationships included the following:

V/Q&C Team Mission Statement

❶ Apply good engineering fundamentals to qualification.
❷ Determine design intent (if not available, must require design to provide it) and develop testing to prove or disprove said intent.
❸ Document evidence of said testing in a manner compliant with Food and Drug Administration (FDA) requirements.

V/Q&C Relationships

❶ The handshakes between V/Q&C and the Design/Engineering team was the user requirements, design intent to meet these requirements, and developing and executing the testing plan to prove or disprove the design intent. The User Rep (Design Engineer) was responsible for developing the design intent, and V/Q&C was responsible for test planning and its execution.
❷ The handshake between V/Q&C and mechanical construction was the Process and Instrumentation Diagrams (P&ID) field verification.
❸ The handshake between V/Q&C and electrical construction was the instrument installation, dry loop, and calibration execution.
❹ The handshake between V/Q&C and the end user was the post execution approval of the qualification package. This also served as the overall project and plant handshakes.

Training

Training was conducted for all employees, contractors, consultants, and other persons involved in V/Q&C, as required by the VMP and applicable corporate quality procedures and policies. The documentation must show that the individuals involved have the proper education, experience, and training to perform their job function. The training documentation must be filed in the permanent record.

V/Q&C Contractor Qualifications and Hiring Process

Contract V/Q&C support was necessary throughout the project. The V/Q&C scope of work did not allow for in-house staffing of resources. The V/Q&C leader took responsibility for contractor hiring decisions. This is not always done, and is a key recommendation for other projects. Direct oversight over the hiring process, and the contract staff qualifications, is imperative for building a competent staff that can accomplish project goals.

The V/Q&C lead and the V/Q&C staff retained throughout the project, screened resumes of potential contract V/Q&C resources. If the individual had sufficient qualifications, an in-person or phone interview was conducted. The project screened approximately 25 resumes during the process of retaining eight V/Q&C contractors for execution support. A copy of the contractor resumes were filed with the training documentation.

Part II: Generation of the System Qualification (SQ) Package

The System Qualification (SQ) package is a qualification package inclusive of Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) activities, as appropriate. Generation of an SQ package for a unit operation or

utility system is a multi-step process that requires the participation of a cross functional group. The VMP places the responsibility of SQ package development with the Contract V/Q&C lead engineer. In a project of this size, development activities are delegated appropriately. The composition of an SQ package is described below.

SQ Protocol Composition

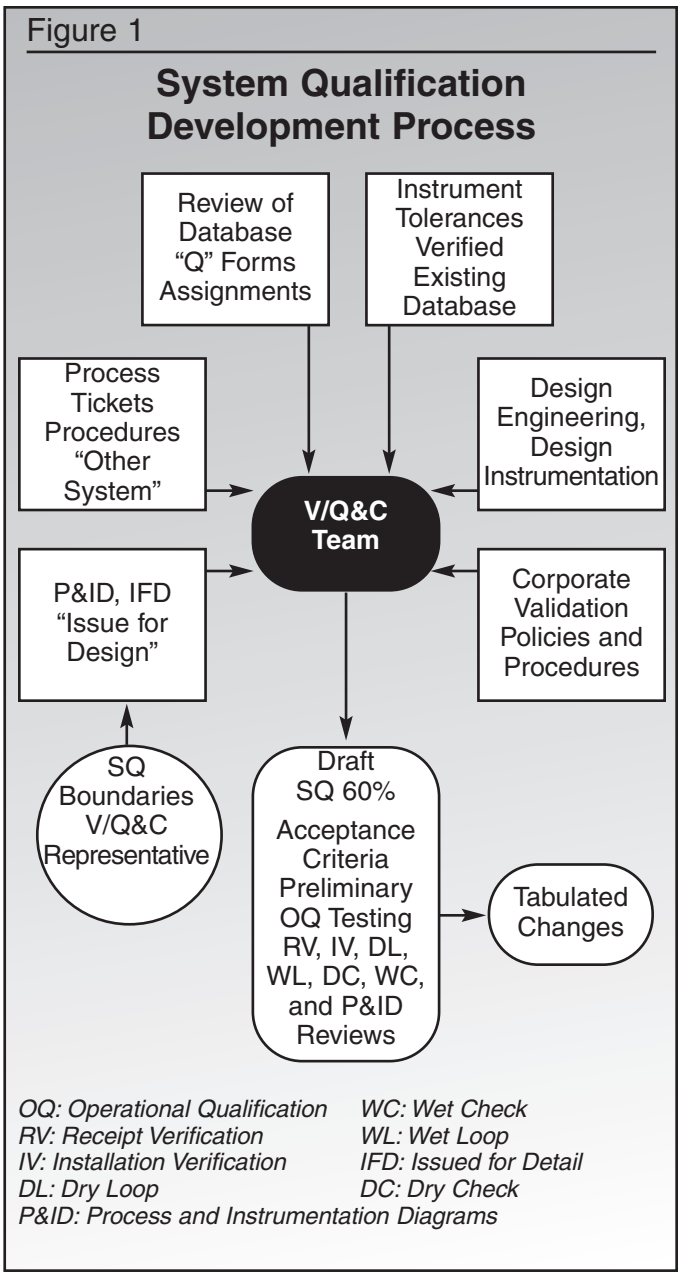
❶ Individual components of a system, instruments, equipment, and piping must be checked with appropriate procedures and practices to insure they are installed, and function as designed. (IQ/OQ methods for instruments and equipment, and P&ID verification for piping). (IQ and component OQ testing).

❷ The system subparts must be checked, as well. This includes, but is not limited to, loop tuning tests, waterbatch transfer testing, sequence testing, vacuum testing on empty equipment, etc.

❸ Once all individual components and subsystem testing is complete and results satisfactory, a check of the entire system must be performed. This is referred to as a full system check, and is consistent with the definition for PQ.

The V/Q&C team developed a flow diagram of SQ package development, pre-execution, and post-execution approval (see *Figures 1, 2*, and *3)*. These diagrams describe the process that was used to generate the SQ packages. The detailed V/Q&C project schedule was generated directly from the flowchart. The following will elaborate on each step of SQ generation, as described in *Figures 1, 2*, and *3*.

Figure 1



Overview

SQ package generation was divided and tracked by three milestones. The first milestone was denoted as a "60% complete draft based on design." A second milestone was the "80% complete draft based on construction." The final milestone in package generation was the pre-execution approved SQ package. The percentage complete description of these documents is a guide only, and should not be viewed as real estimates on protocol generation duration. These SQ package milestones reflect the process of V/Q&C interfacing with design, construction, and system owner groups. The system described below is only efficient if all parties are in attendance, and engaged fully with their roles and responsibilities as described in the VMP.

60 Percent Complete Draft Based on Design

The generation of this initial draft of the SQ package was accomplished typically in parallel with the detailed design effort. *Figure 1*, *SQ Development Process*, is a description of the SQ package development flowchart. An assumption has been made that the project scope has been defined and described in the VMP, and an initial Issued For Review (IFR) version of process P&IDs have been issued.

The goal of this draft was to define the component

IQ/OQ methods, (Receipt Verification [RV], Installation Verification [IV], Dry Loop [DL], Dry Check [DC], Wet Check [WC], Wet Loop [WL]) requirements, incorporate the Issued For Detailed (IFD) P&IDs, and define the preliminary OQ testing requirements and acceptance criteria.

SQ Boundaries V/Q&C Representative

This describes the process of defining the scope of V/Q&C on the initial revisions of the process P&IDs. System boundaries were defined, and used to generate the equipment, instrument, and materials lists utilized throughout the project. This process is captured as "V/Q&C Boundaries on IFR P&IDs" activity on the project schedule. This project chose to define system boundaries using P&ID drawings. IFR P&IDs are redlined in accordance with boundaries of new piping and/or equipment installations. Care was taken to be exact in the definition of boundaries, as this defined the limits to which installed system verification were performed. Each boundary is denoted with an SQ package number, as dictated by the V/Q&C matrix assignment that resided in the VMP. Upon completion of system boundary redlines, the drawings were sent to the contract Architecture and Engineering Firm (A/E) firm design team to be designed in Computer Aided Design (CAD).

P&ID, IFD (Issue for Design)

The release of IFD design was an important milestone in the SQ package delivery. A prerequisite to release of IFD drawings was the V/Q&C review of CADed system boundaries for accuracy, and any additional V/Q&C instrumentation/piping requirements from the IFR drawings. This process was captured as "V/Q&C Release P&IDs for Detail Design" activity on the project schedule. An example of V/Q&C input into the IFD drawings was the required addition of a glycol flow transmitter for heat duty calculations for an evaporator heater. Consideration should also be given to accessibility requirements during OQ testing. The addition of spool pieces or access points may be incorporated into the design at this point. V/Q&C input to design at this stage is essential in minimizing design re-work later in the project. Exploring these issues of V/Q&C needs early in the process is also essential to facilitate timely and accurate execution of OQ testing.

Process Tickets, Procedures, and "Other Systems"

This input to the SQ 60% draft describes the documentation required in generation of the initial drafts of the SQ package. Existing Process Flow Documents (PFD), Standard Operating Procedures (SOP), and Tickets are an excellent resource in understanding the operation of a system when additional capacity is being added by "cloning" or modifying existing systems. This documentation was used in the generation of the system description portion of the SQ package. For additions of new equipment without a "sister" system, resources such as draft SOP's and tickets can be a resource into understanding the functionality of the system, and incorporating a description into the SQ package.

Review of Database "Q" Forms (IQ/OQ Methods) Assignments

A database of IQ/OQ methods (RV, IV, DL, DC, WL, WC forms), as described in the VMP, defines the IQ/OQ methods assignments for each type of instrument. These IQ/OQ method form (Q form) assignments are reviewed for compliance with this documentation prior to inclusion in the SQ package. This process continues through the design and construction effort, as instrumentation and equipment requirements evolve. Particular attention should be given to vendor skid-based equipment. Corporate or site procedures should give guidance on how to handle the RV and IV process for skid-mounted packages.

Instrument Tolerances Verified from Existing Instrument Database

Instrument information that resides in the Instrument Database and used in generation of IQ/OQ Method forms is input and verified by the project instrument group.

This process continues through the design and construction effort as new instruments are added to the database, and existing instrumentation is identified that requires being removed, relocated, or replaced.

Design Process Engineering and Design Instrumentation

Documentation generated by Process Design and Instrumentation Engineering groups should demonstrate that system functionality, user requirements, and design intent have been incorporated in the design. The SQ package is a testing plan that, when executed, demonstrates that the system performs to the

design intent. V/Q&C involvement in the review process of major equipment procurement and P&ID review is essential to ensure success during the execution phase of the SQ.

Corporate Quality and Engineering Policies and Procedures

Corporate policies and procedures may change on a timescale that is shorter than large capital projects. Decisions on how to implement policy and procedural changes into a project are documented through cross-functional discussions in the V/Q&C Strategy Team (V/Q&CST) meetings. The mandate for this team is discussed in the VMP. V/Q&CST meeting minutes are filed in the Good Manufacturing Practice (GMP) Library for historical reference.

Other Inputs Pertaining to *Figure 1* But Not Shown in *Figure 1*

Design Qualification (DQ)

Formal DQ was not required when the project scope was developed. A DQ procedure became effective in between two distinct phases of the project. The V/Q&CST decided and documented a path forward for this issue. Some systems did receive design qualification, as the design was not completed prior to the effective date of the procedure. The DQ documentation was attached to SQ packages of these systems.

To comply with the intent of the DQ procedure, and as Good Engineering Practice (GEP) for systems designed prior to the effective date of the procedure, a cover page was added to each SQ package for GMP systems to catalogue design criteria for the system. Changes to design were tracked through the tabulated changes (described below) documentation, and the final system design was summarized in the appropriate change control. This was done for GMP, as well as non-GMP systems for GEP reasons. GMP and non-GMP designations for systems were described in the VMP.

Part III

80 Percent Complete Draft Based on Construction

Figure 2 illustrates the SQ development and pre-execution approval process.

Tabulated Changes Meeting

The tabulated changes document that was generated by the project user representative was an attempt to capture a detailed list of all changes that occurred for a given system. This document was a direct input into the building change control document, but in itself is not a GMP document. It was developed as a communication and tracking tool used by the user representatives. This document was used to present a tabulated list of changes to a cross functional group during the "Tabulated Changes Meeting." Other inputs to the tabulated changes document were V/Q&C and automation requirements for each detailed change.

P&ID, IFC (Issue for Construction)

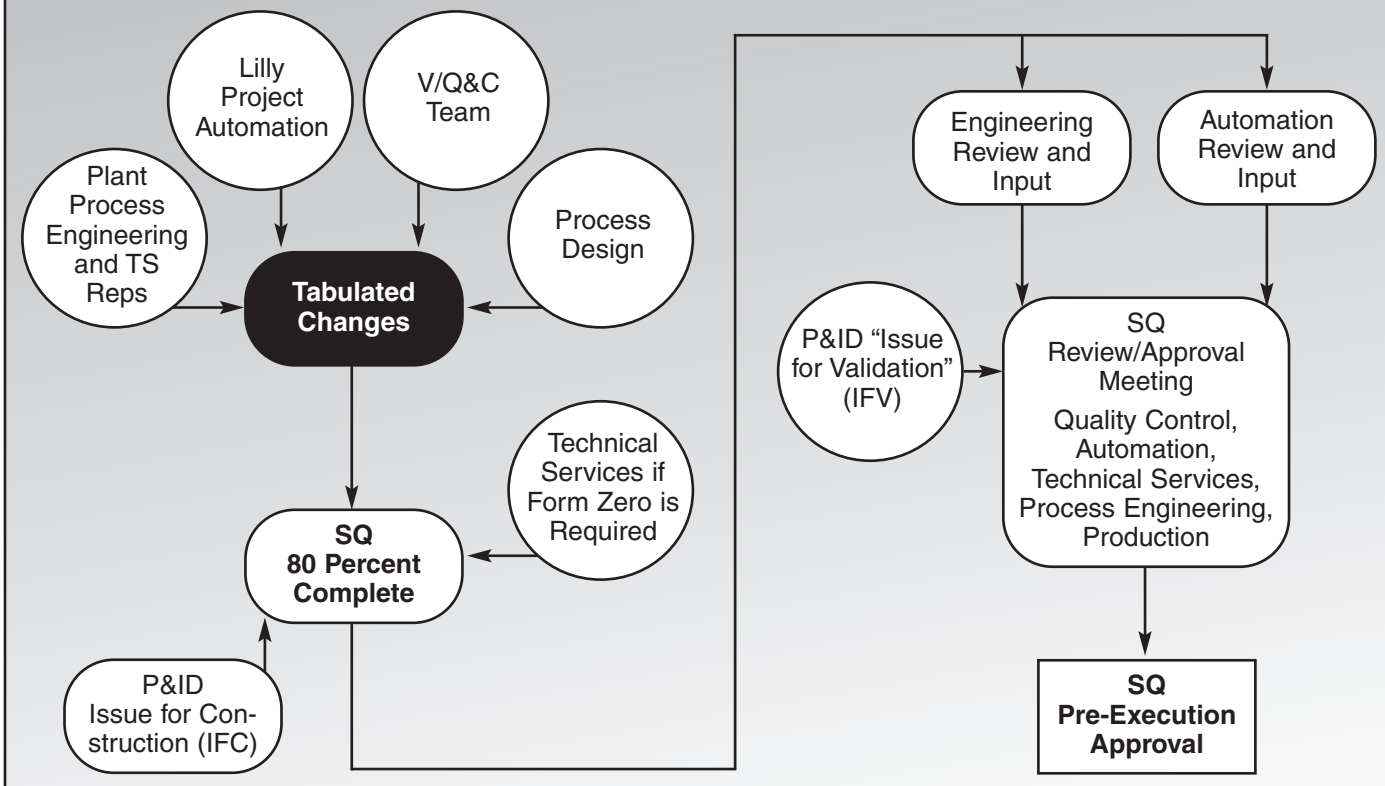
The Issue for Construction (IFC) version of the P&ID captured all changes to the IFD P&ID, and any input related to modifications required by construction. An example of a construction-related modification would be the removal and replacement of instrumentation to allow enough space to bring a new piece of equipment into a processing area. These assessments can only happen after the scope is clearly defined, and the major pieces of equipment are far enough along in the procurement process to obtain dimensional data, etc. When construction management identified equipment or instrumentation that had to be altered, a project P&ID change notice was completed. The change notice may also include V/Q&C boundary additions, or V/Q&C may fill out a separate change notification. This change notification allowed the contract instrument and equipment engineers to add newly scoped changes to the appropriate database. The revision showing design and construction input was included in the 80% draft of the SQ package. This activity was listed as "Validation Boundaries on IFC P&IDs" on the Validation Schedule.

Full System Check (Form Zero) Generation

The full system check assured that all components, when operating together, functioned as designed. It is typically the last OQ test, and its successful completion gives as much confidence as possible that the system will work once product is introduced to the equipment. A form zero ticket (a ticket without product) was used to accomplish the full system check, where applicable. The idea is to prove that the automation, equipment, process/chemistry, and operations

Figure 2

System Qualification Development and Pre-Execution Approval



P&ID: Process and Instrumentation Diagrams
TS: Technical Services

work as intended. As stated in the VMP, Technical Services (typically a chemist who supports the manufacturing operation) was responsible for the form zero test. Technical Services was accountable for supplying a form zero ticket for inclusion into the 80% draft version of the SQ package. The ticket resided in the SQ package, and was incorporated as an OQ test. It was essential that all parties understood that the form zero ticket was attached as an OQ test, and should be treated as such. It resided with the SQ package after pre-execution approval, and was the document that was executed during SQ. The full system check, as described above, was in alignment with the corporate definition of PQ.

P&ID, IFV (Issue for Validation)

If not all the constructability input is received prior to issuing IFC P&IDs, an IFC rev 1 or "IFV" can be issued. The inclusion of this scope is critical to completely define the scope of the V/Q&C effort. To accommodate the inclusion of this information to the P&IDs on an earlier project, a P&ID draft "IFV" was issued. This version is not required if constructability requirements are inputted prior to the issuance of the IFC.

Upon completion of the 80% draft, additional items were attached to the package to aid in the review process. Typical attachments were the Rev. 0 IFC versions of the applicable P&IDs, pertinent copies of VMP addenda, and relevant equipment/instrument design documentation.

The 80% draft of the SQ package was sent to the appropriate Process Engineering, Project Management, Automation, Technical Services, Production, and Quality groups. Review responsibilities for each party were documented in the VMP.

The SQ Package Pre-Execution Approval Cycle

- The 80% draft of SQ package was published to reviewers and approvers.
- Five business days later, the review meeting was held.
- SQ author had three business days to incorporate

input from review meeting.
- Some follow-up was required, and appropriate parties had three days to provide input to the SQ author.
- The revised SQ, based on this input, is published electronically to reviewers and approvers with changes noted.
- Five business days later, the approver meeting was held.
- Approval was expected at this approval meeting.

The above cycle was reflected on the V/Q&C schedule. Actual results were very close to this expectation.

Review Meeting

Attendees to the review meetings represented a cross functional group from the Project, Process Engineering, Automation, Technical Services, Production, and Quality groups. Meetings were typically scheduled for two hours, and were a working lunch. The lunch hours were typically the only realistic time to bring together such a diverse group. The cost to the project of providing a lunch was far less than the opportunity cost of even one person not being able to attend this highly cross-functional discussion. All attendees were expected to have reviewed the document and participate in the meeting. The meetings were largely a working format where the contract V/Q&C engineer, responsible for the SQ package, lead the discussion of the package. A page-by-page approach of review with all groups present was the only realistic way to expedite the pre-execution approval cycle to meet the aggressive project schedule. The SQ author was responsible for incorporating the groups' comments and revising the package. Meeting minutes were drafted in a timely manner to document important decisions, and any follow-up from groups that was necessary to the completion of the package. On this project, this approach was effective in meeting the aggressive timelines, while still maintaining quality.

Approval Meeting

Meetings were typically scheduled for three hours and were a working lunch. The meetings are largely a working format where the contract V/Q&C Engineer responsible for the SQ package leads discussion of the package. The SQ package is typically projected on a conference room screen, so any final edits can be made during the meeting. The meeting only addresses changes to the document from the previous review meeting. The expectation is that all outstanding items have been resolved and that the SQ package will be approved during this meeting.

Upon pre-execution approval of the SQ package, it was transmitted to document control to be controlled until execution.

Other Inputs Pertaining to *Figure 2*

Acceptance Criteria Generation

Acceptance criteria must be developed using good engineering and scientific principles based on process requirements. Inattention to detail will often lead to unnecessary deviations during protocol execution. It also abdicates an excellent opportunity for the design engineer, who typically works for a contract A&E firm, to clearly communicate with the owner/user engineer. Generally, when failures of poorly developed acceptance criteria occur, the criteria is evaluated against process requirements, and revised through documented failures in the qualification package. This is not only inefficient, but demonstrates a lack of understanding and forethought during the qualification package generation process. This is one of the most important aspects of efficient execution of qualification studies.

This major capital project relied on the cross-functional review of Process Engineering, Technical Services, and Design Engineering to develop criteria that were related to process requirements. Two examples of acceptance criteria rationale are discussed below.

The first example used an existing chromatography column's historical data and Statistical Process Control (SPC) analysis that determined the acceptance criteria of key operating parameters. The data and SPC analysis was conducted by an user/owner engineer, as the system was a "sister" system to an existing process. The analysis allowed the project to set process-related acceptance criteria that were successfully met during the execution phase.

The second example used an evaporator system modification. It differs from the previous example in that it was a completely redesigned system that had no "sister" process. The acceptance criteria was generated by the design engineer. The incorporation of this type of rationale into the SQ package demonstrated control during SQ package development, and acted as a future reference during audit and review. This evaporator sys-

tem produced a solvent buffer that was subsequently used in a manufacturing step for an API intermediate.

Part IV

System Qualification (SQ) Execution

Figure 3 illustrates the SQ execution and post-execution approval process.

IQ Execution

Two key components of IQ were execution of installed system verification and IQ/OQ methods (RV, IV, DL/WL, DC/WC) execution for equipment and instruments.

P&ID Verification

The term P&ID Verification is a misnomer. The process was better described as Installed System Verification (ISV) using the P&ID. An ISV form was printed for each P&ID that included the attributes, as described in the Non Hygienic ISV attributes (*Table 1*) and Hygienic ISV attributes (*Table 2*), respectively following on the following page. In some cases, a

Figure 3

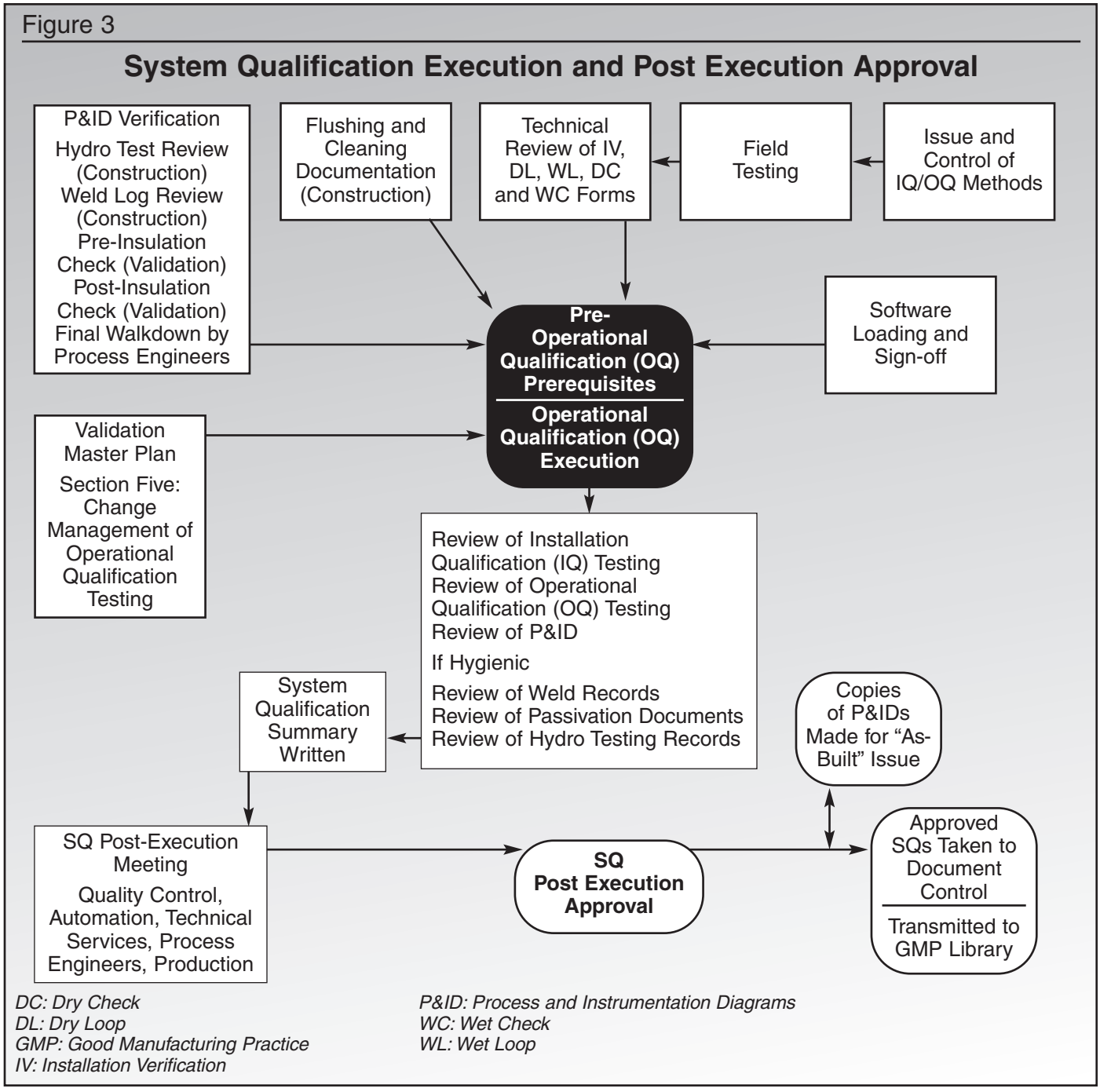


Table 1

Non-Hygienic ISV Attributes

1. Verify piping, valves, and devices were installed in the correct sequence
2. Pre-insulation check: Verify piping, valves, and devices were installed per specifications. Verify pipe, valves size, type, and Material of Construction (MOC).
3. Post insulation check: Verify piping, valves, and devices have not been damaged by the insulation process. Verify insulation type and heat trace, if applicable.
4. Pressure test and flushing were completed per specifications.
5. Weld inspections were completed per specifications.
6. Attach field verified P&ID to form and file with the appropriate SQ package.

Table 2

Hygienic ISV Attributes

1. Verify piping, valves, and devices were installed in the correct sequence
2. Pre-insulation check: Verify piping, valves, and devices are installed per specifications. Verify pipe, valves, size, type, and MOC.
3. Post insulation check: Verify piping, valves, and devices have not been damaged by the insulation process. Verify insulation type and heat trace, if applicable.
4. Pressure test and flushing were completed per specifications.
5. Isometrics, weld maps, weld logs were completed per specifications.
6. Slope verification maps and heat number maps were completed per specifications.
7. Passivation and cleaning were completed per specifications.
8. Material inspection forms and material certifications were completed per specifications.
9. Welder, welder operator qualifications, weld gas certifications completed per specifications.
10. Sign logs were completed per specifications.
11. Attach field verified P&ID to form and were filed with the appropriate SQ package.

P&ID will have two forms if it contains both non-hygienic and hygienic piping. Often, it will have one or the other.

The formal statement of mechanical completion was in the form of a "Transfer of Care, Custody, and Control" letter that was transmitted to the V/Q&C Lead from the Construction Manager. Any items that were not completed at the transfer, were captured under a formal punch list. Upon receiving the "Transfer of Care, Custody, and Control" letter and associated punch list, the V/Q&C lead released the validation staff to begin ISV of the system. Punch list items include items that may affect IQ/OQ testing (e.g., pump coupling not installed – these types of items must be resolved prior to IQ/OQ testing – typically there were few of these listed on the punch list), as well as items that do not affect the functionality of the system (e.g., painting of insulation). However, they must not be items that affect the installed system, as defined on the P&ID. It is critical that ISV not begin until construction is complete with their work, and has documented punch list items. If ISV is performed in parallel with construction, risk of construction rework after ISV must be mitigated. Any rework to piping systems requires a re-execution of ISV. In cases where insulation will obscure piping systems, some aspects of ISV must be accomplished prior to construction completion. The process used to maintain control over the integrity of the ISV process is described below.

Piping can be divided into two categories, insulated piping, and non-insulated piping.

ISV Process for Insulated Piping

Systems that required insulated piping required special attention to the timing of ISV to minimize rework, and/or removal of insulation for the verification process. Construction management must be aware that ISV requires validation personnel to verify items, such as line size and material of construction of components, prior to being insulated. The project managed this process jointly between validation and construction management resources.

As construction of the system progressed, Construction Management (CM) handed over a document to the validation group detailing piping line numbers, hydrotest data, and a highlighted P&ID detailing hydrotest boundaries. At this time, CM requested that the validation begin the ISV process. The validation group required that hydrotesting be performed on the portion of piping prior to begin-

ning ISV execution. This gives reasonable assurance that the piping will not be reworked. If rework does occur, a new hydrotest is performed, documented, and the system is reverified.

The validation group performed ISV on lines that required insulation only. Lines that met the specification listed in attributes one and two of the ISV forms were highlighted in yellow (Note: attributes 1 and 2 are the same for either Hygienic or Non-hygienic piping). Items that did not meet the specifications were noted in blue, and a "construction open item list" was generated to inform CM. The validation group then documented which lines were acceptable per specification, and released these lines to CM for insulation.

Upon ISV and release for insulation of any line that required it, the validation group ceased the ISV process until a "Transfer of Care, Custody, and Control" letter and an associated punch list were generated by the construction manager, and handed over to the V/Q & C lead. Upon construction completion, the system was verified as outlined on the ISV form. Insulation was verified according to line three of the ISV form and color coded as listed below.

"Acceptance criteria must be developed using good engineering and scientific principles based on process requirements."

ISV Process for Non-Insulated Piping

All piping that did not require insulation did not receive ISV until a "Transfer of Care, Custody, and Control" letter and punch list were received for the system. This assured that construction work did not occur after ISV had been initiated, unless in response to the findings of the ISV, or pre-existing punch list items.

ISV Color-Coding

Yellow – Piping had been verified as meeting requirements of Sections one and two of the ISV form, and was released to be insulated.

Blue – The validation group found an item that did not match specifications, and required follow-up.

Green – Piping had been verified in meeting all specifications listed in Sections one, two, and three of the ISV form. Yellow marks were highlighted in blue upon completion of ISV Section three to show green for completion. Items that were marked blue were highlighted over in yellow after resolution to show green for completion.

Verification of Other GMP Drawings

Verification of non-P&ID GMP drawing types was conducted following a similar approach.

Construction Documentation – Hydrotesting, Weld, Cleaning, etc.

The following piping specifications were used.

Project Piping Specification Non-hygienic

This specification detailed installation, cleaning, component specification, and construction documentation requirements of non-hygienic piping within the project. The latest revision of this specification was used during ISV execution.

Verification of aspects of this specification was verified in line two of the ISV form (listed as attribute 2 in *Table 2*.)

Construction-related documentation, as required by the non-hygienic specification, was verified on lines four and five of the ISV form (listed as attribute 4 and 5 in *Table 1*). The responsibility of review and approval of this documentation was with the construction management team.

Construction documentation from non-hygienic specification was submitted upon completion of the project, and was stored separately from the SQ package in a construction Turn Over Package (TOP).

Project Piping Specification Hygienic

This specification detailed installation, cleaning, component specification, and construction documentation requirements of hygienic piping within the project. The latest revision of this specification was used during ISV execution.

Verification of aspects of this specification was verified in line two of the ISV form (listed as attribute 2 in *Table 1*).

Construction-related documentation, as required by the hygienic specification, was verified on lines four through 10 of the ISV form (listed as attribute 4 through 10 in *Table 2*). The responsibility of review and approval of this documentation was the construction management and the pharmaceutical manufacturer's project manager (in lieu of Construction Engineer).

The reviewed and approved construction documentation from hygienic specifications was transmitted to the V/Q&C team's custody after the project manager's approval for reference by the SQ package, prior to post-execution approval.

All 316L stainless steel tubing purchased for installation under specifications, non-hygienic or hygienic, met the hygienic specification standards for material of construction and polish. Purchasing all material to meet the highest-grade requirement allowed for elimination of risk of incorporation of lesser materials into hygienic systems. This approach may have increased construction cost, but risk of material mixing during construction was eliminated. This approach was also used in hygienic gasket specification. All hygienic gaskets installed were virgin teflon. Certificates of compliance for hygienic gasket materials were located in the material inspection and material certification binders for hygienic piping.

Material inspection forms, material certifications, isometrics, slope maps, weld logs, heat maps, hydrotest, passivation, and cleaning documentation were located in the hygienic construction turnover documentation.

Engineered Items Specification

This specification detailed important aspects of items that fell outside the normal piping specifications, non-hygienic and hygienic. Items, such as specialty valves and hoses were captured under this specification. The items covered by the Engineered Items list were noted on the appropriate P&ID with unique identifiers (e.g., EI/FH0504204).

Verification of aspects of this specification were verified in line two of the appropriate ISV form.

Location of Specifications Used During ISV

The most current project piping specifications were located in the IQ reference notes that were part of the validation contractor training binder, located in the GMP library. Revision history was documented on the cover page and within specifications.

Approved Alternates to Piping Specifications

During execution of the ISV, there were two types of issues that needed to be addressed.

Items (valves, flanges, gaskets, etc.) that were unable to be fully field verified to meet specification due to lack of sufficient markings were detailed on an "open items" list, and submitted to construction management. If construction management believed the item met specification, sufficient documentation (cut-sheet, purchase order, etc.) would be handed over to allow document and/or field verification of the installed component.

Some items did not meet specifications listed in the project piping specifications. These items were identified on an "open items" list, as submitted to construction management. If the inclusion of the item was unintentional, the item was replaced with an in-spec item. If the item was included intentionally by the construction team, an approved alternate evaluation was initiated by the API manufacturer's design engineer and project manager. A listing of items approved as alternates to the piping specification was generated and inserted into each "IQ Execution Reference" binder for reference during subsequent ISV. The original documentation for approved alternates resides in the permanent record. These items were described in the appropriate SQ summary report that received cross functional review and approval, including the quality unit as part of the post-execution approval step.

Piping specifications were drafted in such a way that there should be no approved alternates necessary. The breakdown occurs when contractors procure items that are different than the specified item. There may be good reason for deviation from the piping specification, but the project team must be informed of the need to deviate from the spec. The process of approving alternate items during a shutdown window requires resources that are already stretched. The mechanical contractors must be informed, before beginning procurement, that any items that do not explicitly meet the required specification need to be formally reviewed and incorporated into the piping specification in question. Lack of adherence to piping specifications can greatly increase time required for ISV during the execution window.

Punch List Resolution

Punch list items were divided into two groups; items that may affect OQ testing, and items that do not. Items that did not effect OQ testing were tracked on the punch list contained within the "Transfer of Care, Custody, and Control" letter, and closed out as part of the governing change control as an action item. This action item was listed as "Complete punch-list generated during project installation," and is under the Equipment/Facility Impact Area. Items that could have affected OQ testing (i.e., missing insulation on a heat exchanger, incorrect line slope, etc.) must be resolved prior to execution of OQ testing. Prerequisites for OQ testing were detailed and approved in each SQ package.

IQ/OQ Methods Execution

Issue and Control of IQ/OQ Methods

It is essential to have a central document control group that issues and controls the flow of IQ/OQ methods (RV, IV, DL, DC, WL, WC). On this project there were thousands of documents, and it was paramount that IV not be executed prior to RV, DLs not executed before IV, etc. The central document control group would not issue an IQ/OQ method until the prerequisite form was executed and approved.

Field Testing/Technical Review of IV, DL, WL, DC and WC Forms

Personnel trained for the execution of IQ/OQ methods obtained the appropriate form from document control, executed it, and returned the form for appropriate technical review, which was typically their trained supervision. Supervision would then review, take corrective action as necessary, and then approve the form. The approved form was then submitted to document control, and the subsequent form was issued.

OQ Execution

Prerequisites

Prerequisites for beginning OQ testing were documented within each SQ package. The status of these prerequisite activities were monitored twice each day during validation and commissioning turnover meetings between contractor shifts. Each SQ package contained the following language:

Before OQ testing, confirm the following items are complete or in progress to the point that OQ testing will not be affected:

- RV/IV and loop checks are complete.
- P&ID verification is complete and outstanding punch list items identified.
- Software has been tested and loaded.

Prerequisites for individual OQ tests were documented within the testing plan of each SQ package. Shutdown meetings were also held twice daily. Representatives from Maintenance, Operations, User Representatives, Process Engineering, Technical Service, QC, Production Management, Project Validation, Project Construction, and Plant and Project Health and Safety attended these meetings. OQ testing did not commence until verbally authorized by the V/Q&C lead, typically done during these meetings.

OQ Execution Roles and Responsibilities

It is important to design the division of roles and responsibilities in a fashion that allows for reduced project resources, and more involvement of the end-user in the qualification effort. The following are examples of key groups' responsibilities during this time in the project:

Process Engineering – This group had the role of direct supervision of the execution of OQ testing, documentation results, and troubleshooting efforts.

Operations – This group was responsible for execution and setup of OQ testing under the direct supervision of process engineering.

These roles allow the physical testing and operation of equipment to be performed by the end user groups, not validation resources. The great benefit of this approach is that it allowed familiarization of the end user with all new systems. These groups will be operating, maintaining, and troubleshooting these systems in the future, and knowledge gained during the OQ testing phase will become a valuable asset in future operations.

The V/Q&C group played a crucial role in OQ testing execution. The roles defined in this project included:

- Consultation/Clarification of written protocol
- Integrity of documentation

- Writing of system summary report
- Troubleshooting assistance

This integrated approach of placing execution responsibility with the end-user allowed for V/Q&C staffing levels to be minimized. V/Q&C staffing should allow full-time coverage of all OQ testing activities, but in an oversight/support role, rather than a directing role. Staff that was retained during OQ testing communicated quality concerns to Process Engineering when issues arose. The sensitivity that the validation group has to documentation issues was not always felt across other groups. Validation was still responsible for the end product, and to guide the qualification effort when problems were encountered.

Change Management of OQ Testing

The most likely area of qualification execution to require a change management procedure is OQ testing. OQ testing, is by nature, the application of the scientific method. The pre-execution approved test plan represents the hypothesis. The executed test protocol represents the experimentation that proves or disproves the hypothesis. If the results are unacceptable, the test protocol must be rewritten and approved by the technical content expert, which is typically process engineering. To satisfy the legal requirements of our regulated industry, this must also be approved by QC. It may be necessary for all signatories of the SQ package to approve the "retest plan," depending on the extent of the change. A change management procedure that is well-defined must be in place as a reference during test execution. This system will guide how change is documented and approved in an orderly manner. A change management procedure must also not be overly cumbersome. Having a clearly defined change management system will yield efficient resolution of issues, and allow for a clearly documented path of decisions. Change management during OQ execution of the project was documented in the VMP.

The VMP defined two types of change:

❶ Test plans that are modified strictly for clarification purposes need only be signed and dated by the person responsible for execution.

❷ Test plans that are modified to reflect a new approach or execution strategy must be signed and dated by the person responsible for execution, and an individual representing the QC Unit.

Examples of the first type of change may include items such as, protocol generation errors for instrument numbers. Items, such as this, do not affect the intent of the test, but clarify and/or correct the test execution.

Changes that modify the testing approach may be necessary during OQ testing.

System Summary Generation

The summary reports generated for the project included items that did not meet specifications listed in the SQ protocol, items that deviated from acceptance criteria, and items of exception or special note. The goal of the summary report was not to restate confirmation that each test acceptance criteria had been met. The report was generated by the responsible validation resource. During the generation of the report, the validation resource verified each page within the compiled SQ package. Items that did not meet acceptance criteria were noted in the summary. Any justification regarding system parameters not meeting pre-approved criteria were documented and approved as part of the SQ package approval. Items that clarify execution details were also noted. An example of clarification was the inclusion of two Installation Verification (IV) forms for a pump. The summary report detailed that two forms are included for the pump, and the reason for the second form (e.g., pump motor was removed and reinstalled after the initial IV for rework of the pump base).

"Having a clearly defined change management system will yield efficient resolution of issues, and allow for a clearly documented path of decisions"

Post-Execution Approval Process

The following steps occurred after testing was completed:

- The validation group compiled and reviewed all

SQ documentation
- A meeting was held with the responsible process engineer, and the project quality representative to close out any final details
- The SQ package was turned over to the project quality representative for a detailed review and GMP drawing verification approval
- A summary report was drafted by the validation group
- A meeting was called for all SQ package approvers
- The summary report was presented. Any changes to the summary report were made during the approval meeting.
- The post-execution approval signature page was completed.

Copies of P&ID's Made for "As-Built" Issues

Each system qualification package contained a reference to the VMP concerning GMP drawing management. Upon post execution approval of the SQ package, copies of the GMP drawings were sent to the CAD operator to incorporate the field markups. Upon receipt of the CAD versions of the field markups, the responsible process engineer and quality control resource approved the drawing. The scope of the process was clearly defined by the SQ package boundary on the drawing.

Approved SQ Package Transmitted to GMP Library

The following documentation was submitted to the GMP library as part of the closeout of the project:

- Project Validation Master Plan
- V/Q&C Strategy Team Meeting Minutes
- Training Documentation
  - – Validation Contractor Training
  - – Construction Contractor Training for IQ/OQ Methods
- Project Signature Log
- IQ/OQ Methods
  - – RV and IV
  - – DL and DC
  - – WL and WC
- Design Turnover Packages
- System Qualification Packages
- Non-hygienic and Hygienic Piping Specifications, Approved Alternates List, and Hygienic Pipe Slope Justification
- Non-hygienic Piping Specification Documentation
  - – Hydrotest Records
  - – Material Inspection and Material Certification
  - – Weld Documents
- Hygienic Piping Specification Documentation
  - – Hydrotest, Passivation, and Cleaning
  - – Material Inspection and Material Certification
  - – Other Piping Documentation Organized by the SQ Package
- Vendor-Supplied Calibration Documentation
- Vendor-Supplied Certificates of Compliance
- Miscellaneous Vendor Documents by System
- Project Validation and Commissioning Handbook/Project Summary.

Summary

This concludes the discussion of V/Q & C project structure, protocol generation, protocol pre-execution approval, and IQ/OQ/PQ execution. These are concepts critical to the success of a major capital project in the pharmaceutical industry. In this particular project, there were no factory losses or unplanned downtime upon startup. ❑

Article Acronym Listing

A/E:	Architecture/Engineering
API:	Active Pharmaceutical Ingredient
CAD:	Computer-Aided Design
CM:	Construction Management
DC:	Dry Check
DL:	Dry Loop
DQ:	Design Qualification
FDA:	Food and Drug Administration
GEP:	Good Engineering Practice
GMP:	Good Manufacturing Practice
IFC:	Issue for Construction
IFD:	Issued for Detail (Design)
IFR:	Issued for Review
IQ:	Installation Qualification
ISV:	Installed System Verification
IV:	Installation Verification
IQ:	Installation Qualification
MOC:	Material of Construction
OQ:	Operational Qualification
PFD:	Process Flow Documents
PQ:	Performance Qualification
P&ID:	Process and Instrumentation Diagrams
QC:	Quality Control
RV:	Receipt Verification
SOP:	Standard Operating Procedure
SPC:	Statistical Process Control
SQ:	System Qualification
TOP:	Turn Over Package
TS:	Technical Services
VMP:	Validation Master Plan
V/Q&C:	Validating, Qualifying and Commissioning
V/Q&CST:	Validation/Qualification & Commissioning Strategy Team
WC:	Wet Check
WL:	Wet Loop

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*.)

"...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."

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.

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 being driven by the current activity within industry,

Figure 2

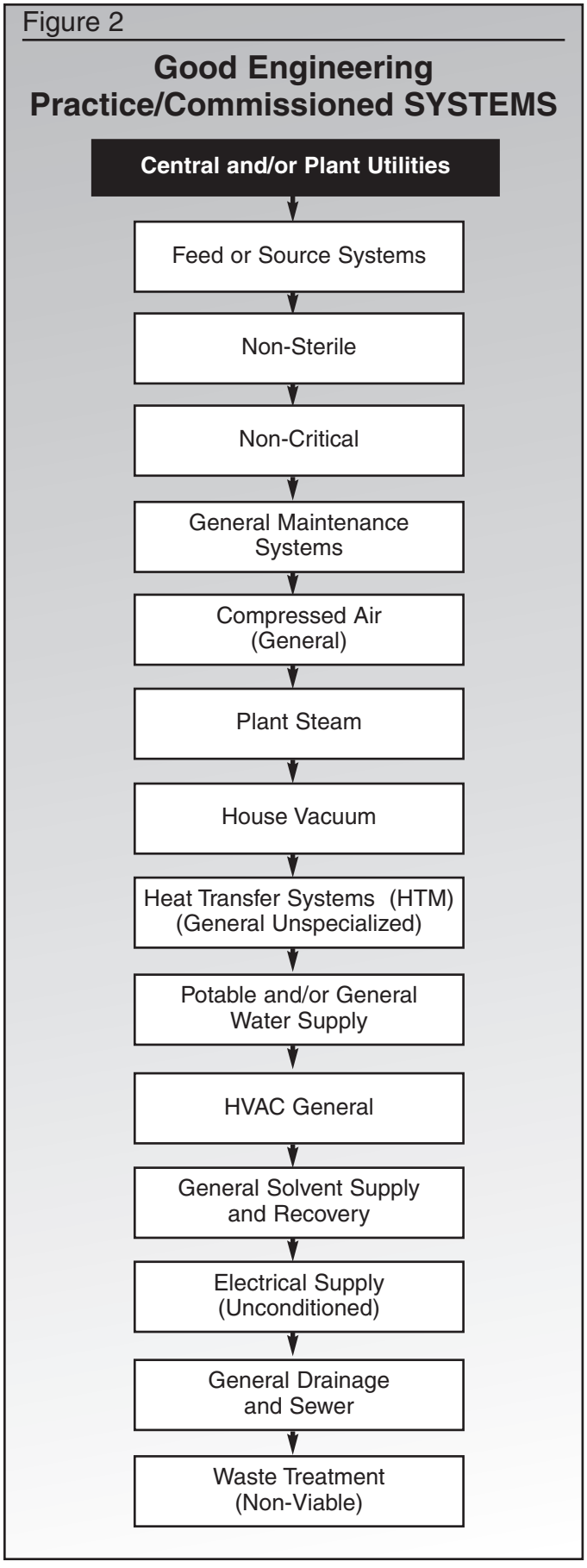
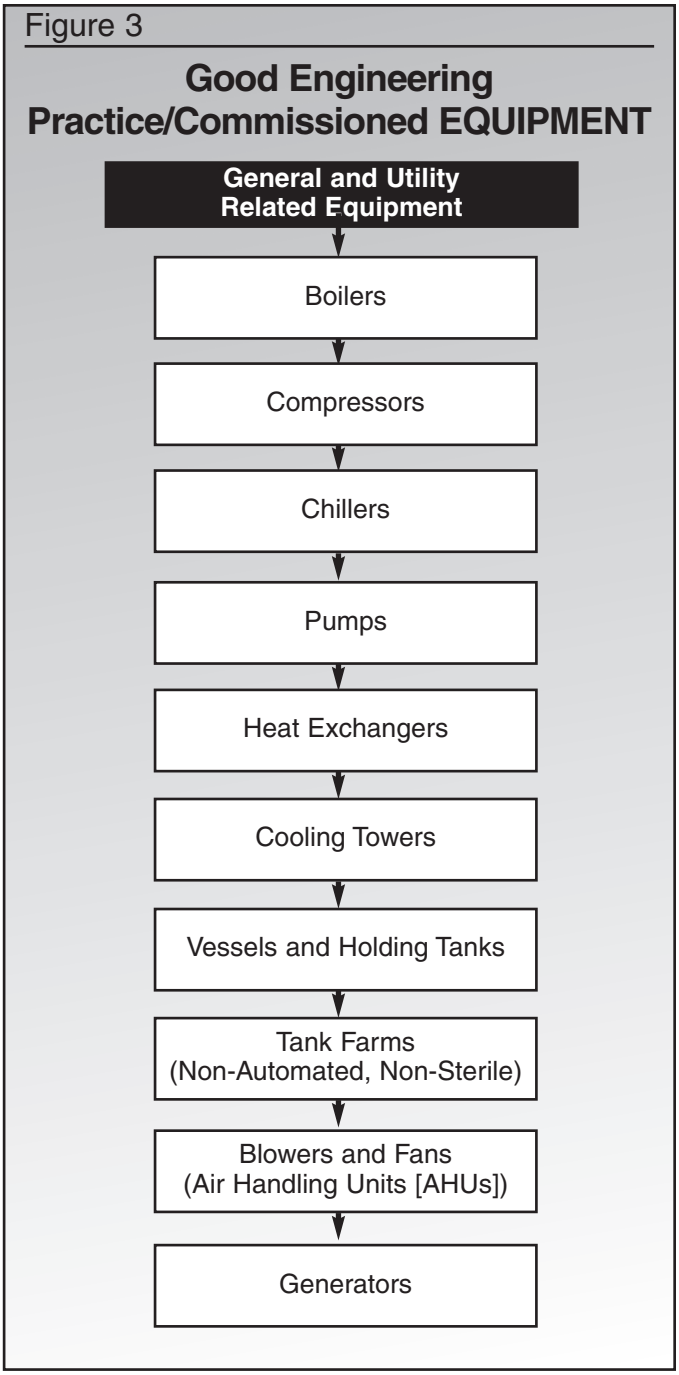


Figure 3



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 impact assessment is based upon the operation of a

Figure 4

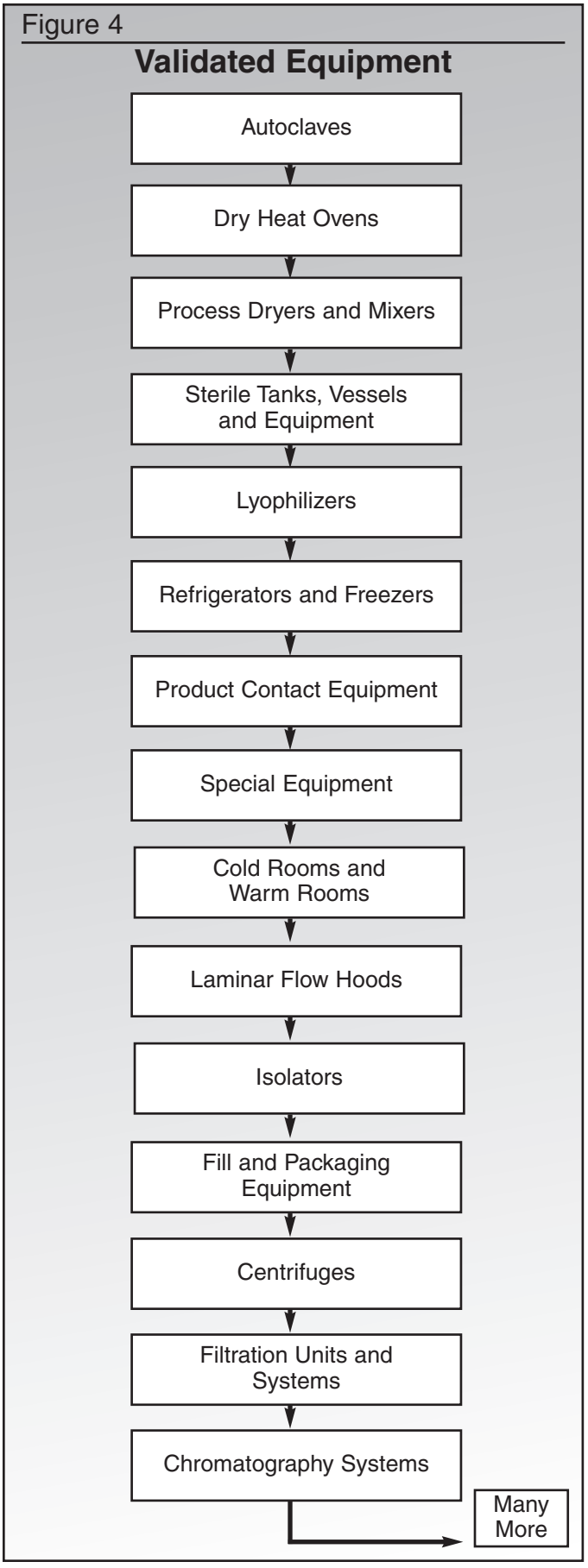
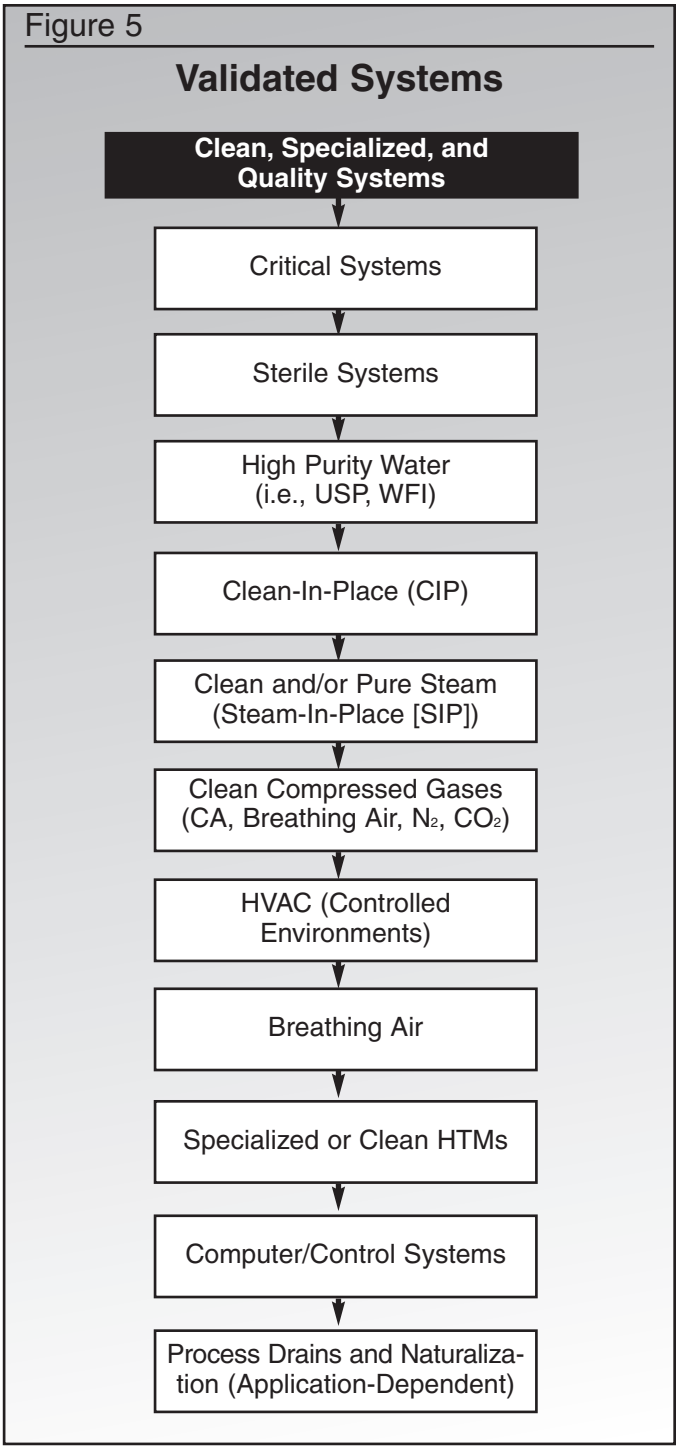


Figure 5



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. ❑

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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

Facility Validation:

A Case Study for Integrating and Streamlining the Validation Approach to Reduce Project Resources

By Graham C. Wrigley
Pfizer Global Manufacturing
and
Jan L. du Preez, Ph.D.
Research Institute for Industrial Pharmacy

Pharmaceutical companies typically require considerable resources, in terms of time, money, and specialized personnel, to validate a current Good Manufacturing Practice (cGMP) facility. This can be overwhelming to a small company or plant with limited resources. This paper identifies some of the key areas in a facility upgrade project that have been found to result in inefficiencies, project, and facility start-up delays. It seeks to demonstrate that the integration and streamlining of the design, construction, commissioning, and validation phases can accelerate the start-up effort, reduce the validation effort and costs, produce superior documentation, and ensure that product is produced in a cGMP-compliant facility. It will also prove that even though the original focus of validation was to satisfy regulatory expectations, facility validation has in fact become good business and engineering practice that enhances reliability, cost, and quality of the products.

"Before you begin validating a manufacturing process, an acceptable facility, and the utilities and equipment to support manufacturing operations must be in place."

Introduction

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

In this environment, the pharmaceutical industry also constantly seeks improved manufacturing efficiencies to attain marketplace strategic advantage with "cost of goods" and "speed to market" imperatives, and increasingly more costly capital expenditures are devoted to achieving this competitive

advantage. These strategies often include the building of new facilities or modernizing existing facilities.

The design, construction, commissioning, and validation of pharmaceutical facilities are significant challenges for project managers, engineering, and quality professionals. Constantly caught in the dilemma of budget and schedule constraints, they have to deliver an end product that complies with all building, environmental, health and safety governing codes, laws, and regulations. The facility must also comply with one very important criterion; it must be validated to meet cGMP regulations.

Historically, the legal requirement for validation of pharmaceutical manufacturing processes originated in the U.S. with the Food and Drug Administration (FDA) promulgating the cGMP regulation in 1979. This precipitated a widespread rush by pharmaceutical manufacturers to install formalized validation programs suited to their individual needs, financial capabilities, and company philosophy. These regulations have been written in such a way as to leave the interpretation to the user. Confusion and misinterpretation by industry on the scope and extent of this requirement has led to ever increasing costs of bringing pharmaceutical facilities in compliance with these cGMPs. The cost of validating a facility is determined by time spent on documentation, development of protocols and Standard Operating Procedures (SOPs), and the time spent on actual fieldwork, data collection, and analysis.[1] These costs have increased over the years reflecting higher standards required by regulatory authorities, and also because industry has adopted inefficient and costly blanket validation compliance strategies. As a result of this, there is a continuing struggle and challenge of meeting regulatory requirements, keeping overhead costs down, and running a profitable business. It is interesting to note that a good rule of thumb is that total validation costs may run from four (4) percent to eight (8) percent of the total project cost for typical pharmaceutical plant expansion projects.[2]

For a new or upgraded facility, commissioning and facility validation is the foundation for assuring success in further manufacturing process validation. Before you begin validating a manufacturing process, an acceptable facility, and the utilities and equipment to support manufacturing operations must be in place. Facility qualification (a part of validation that proves and documents that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results), and validation (establishing documented evidence that provides a high degree of assurance that the manufacturing processes, including buildings, systems, and equipment consistently produce the desired results according to predetermined specifications and quality attributes) activities will establish and provide documentary evidence that:

- The premises, supporting utilities, equipment, and processes have been designed in accordance with the requirements of GMP. This constitutes Design Qualification (DQ).
- The premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications. This constitutes Installation Qualification (IQ).
- The facilities, supporting utilities, and equipment operate in accordance with their design specifications. This constitutes Operational Qualification (OQ).
- The facilities, utilities, or equipment that can affect product quality, performs as intended meeting predetermined acceptance criteria. This constitutes Equipment Performance Qualification (EPQ) Once the facility has been validated (IQ + OQ + Performance Qualification [PQ]), then process validation can commence.
- A specific process will consistently produce a product meeting predetermined specifications and quality attributes. This constitutes Process Validation (PV) or Process Performance Qualification (PPQ).[3]

These Good Validation Practices (GVPs) thus play a crucial role in delivering operationally effective, safe, and efficient facilities, process air handling systems, utilities, equipment, and also provide the medium by which compliance is achieved, demonstrated, and retained.

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

- Plant commissioning is a vital element in the process of delivering new facilities. Often, varying commissioning practices and methodologies

result in inefficient implementation and costly delays when project teams under manage the tasks of commissioning, starting up, and turning over facilities. Too often, the validation process reveals a large burden of unfinished commissioning business, resulting in a delay in facility start-up.

- As mentioned, validation activities form a significant percentage of time and money in most pharmaceutical capital projects, and the cost of validating and maintaining facilities designed to meet cGMP requirements can be overwhelming to small pharmaceutical companies and plants with limited resources.
- Currently, the level of wastage and inefficiency in validation is spiraling out of control. For example, the cost of validation to the industry in the United States has been estimated at $50 billion dollars.[4] This is because most organizations lack a clear understanding of the reason for validation, fail to develop procedures to allow them to conduct efficient validation, and rarely allow themselves sufficient time and resource to plan for validation activities. Validation Master Plans (VMPs) are often rushed and poorly constructed. Content and presentation of documentation is frequently inadequate, and the validators themselves are regularly passed over in training and assessment routines.
- Advancing manufacturing technology also makes new facilities increasingly more complex, and bring higher expectations for output, quality and efficiency. The fear of high financial losses due to shutdowns are forcing many company's to invest in the benefits afforded by effective commissioning and validation programs.

Pharmaceutical industry, regulatory authorities, organizations (e.g., the World Health Organization [WHO]; the Pharmaceutical Inspection Cooperation Scheme [PIC/S]; and the European Community [EC]), institutions, and corporations in countries like the United States, Europe, and Japan are attempting to harmonize their regulations and practices relating to cGMP. Nations worldwide, like Australia and South Africa, are gradually adopting these rules, regulations, and practices.

As is for the GMP's, there must also be continuous quality improvement over time in the GVP concept, and ways of streamlining the process of validation, with methods that satisfy quality and business needs, and regulatory requirements must be enforced to ensure that Industry remains competitive and compliant in an effective and efficient manner.

This article presents the author's experience in validating an upgraded manufacturing facility, and proposes methodologies to improve, integrate, and streamline the facility validation approaches to address the above shortcomings, identify unnecessary validation activities, and implement new approaches to reduce costs and improve efficiency.

Project Profile and Scope

The manufacturing plant in Cape Town (South Africa) was built in 1982. The facility manufactures multiple consumer healthcare and pharmaceutical prescription products in multi-use equipment. Dosage forms manufactured include oral tablets, capsules, solutions, syrups, suspensions, lotions, creams, ointments, and suppositories. Since mid-1999, the site has undergone a phased refurbishment to improve the manufacturing efficiencies (i.e., improved workflow methods, equipment utilization, manufacturing cycle times, and increased batch sizes), and regulatory compliance (cGMP and Environment, Health and Safety [EHS]).

At the same time, it has been necessary to continue production to meet the demands of the marketplace during this construction phase. This fast-track project included:

- In Phase One, a 90 m^2 Stability Chamber, 850 m^2 office block, 120 m^2 Research and Development (R&D) Pilot Laboratory, and 285 m^2 Chemical Weighing Facility; and
- In Phases Two, Three, and Four, a 1075 m^2 Oral Solid Dose Manufacturing facility (Granulation/Blending, Compression and Encapsulation sections) and a 120 m^2 Heating, Ventilation and Air Conditioning (HVAC) utility room.

Major systems installation included fifteen new plant and process HVAC systems, a Building Management System (BMS) for control of the HVACs, new dust collection plant, new chilled water plant, with upgrades to the existing compressed air and steam sup-

ply systems. New process drying, blending, and materials handling equipment items were also installed.

Part of the scope of this particular project included the transfer of a limited number of manufacturing processes to the above new equipment. As part of the facility validation, the validation of cleaning procedures and systems in the new facility were handled as a separate project with its own VMP, and for simplicity's sake, will not be covered in this article.

The facility design was contracted out to an engineering consulting company, who subcontracted the construction work to various contractors. The consulting engineer was responsible for the coordinating and scheduling of construction. His teams of subcontractors were responsible for the construction, commissioning, and turnover of the facility. Various equipment vendors and agents were employed at certain stages of the project.

A multi-disciplinary project team was formed at the project's inception to cover regulatory and technical concerns. A team comprising of in-house representatives from Engineering, Production, Quality Assurance (QA), Validation, Product Development, EHS, and Technical Training functions, was formed at the project's inception under leadership of the Project's Engineer/Manager. These core team members headed up five sub-project teams to address the following key project deliverables:

❶ *Facility/Equipment design requirements:* This team's role was to define the product, process, operations, maintenance, and compliance requirements influencing the conceptual design of the facility (seven part-time team members assigned – full-time equivalents at 25%).

❷ *Validation:* This team's role was to ensure that the facility and system qualification requirements are communicated and met (three part-time team members assigned – full-time equivalents at 60%). The project validation scope was very extensive, so an additional temporary "backfill" validation resource was assigned to the validation manager to assist with routine non-project-related validation activities. It must be said that, here in South Africa, there are no local validation consultants for pharmaceutical companies to call on, therefore in-house expertise has always to be developed and used. All project validation deliverables were reviewed and approved by the site validation and QA functions.

❸ *Equipment and Utility Decommissioning, Relocation, and Commissioning:* This team's role was to ensure that the phased relocation, installation, commissioning, and qualification of existing equipment and utilities is executed according to plan, with minimal impact on production schedules (four part-time team members assigned – full-time equivalents at 25%).

❹ *Process Technology/Product Regulatory Compliance:* This team's role was to facilitate the process transfer to the new facility, evaluating the regulatory impact of equipment and process changes, coordinating batch size increases, process optimization, and process validation (seven part-time team members assigned – full-time equivalents at 50%).

❺ *Current Good Manufacturing Practice:* This team's role was to define workflows and garbing policies for the new facility, ensure that sufficient training had been undertaken, and that there was an understanding of the facility and equipment operation (five part-time team members assigned – full-time equivalents at 25%).

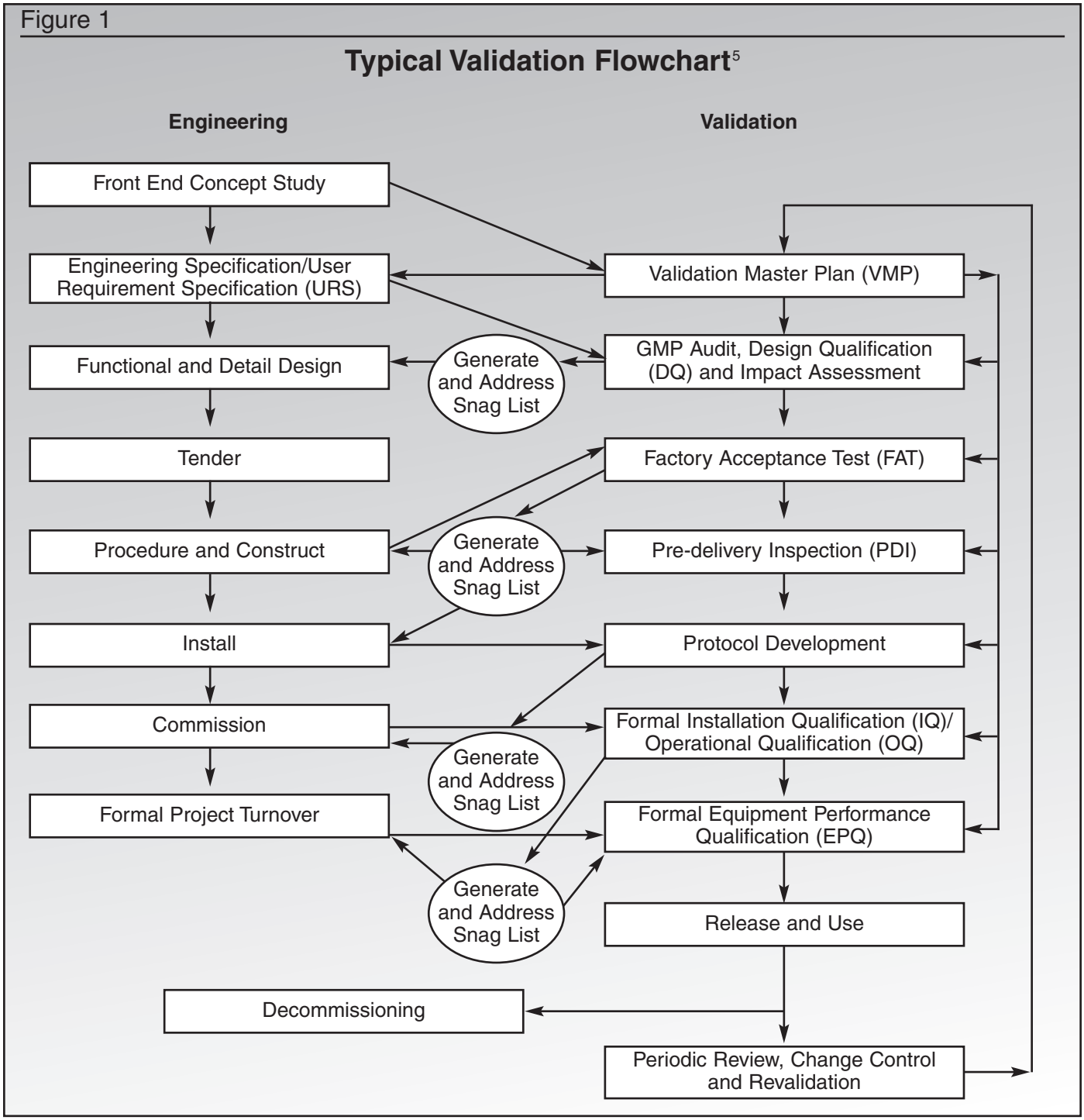
These five team leaders, project manager, and functional management group constituted the project steering committee.

The Fundamentals of Facility Validation

Facility validation provides the documentation necessary to demonstrate that facilities, utility systems, and process equipment are operationally effective, safe, and efficient.

Figure 1 shows an example of a typical validation flowchart for a pharmaceutical plant with the engineering and validation activities paralleled. The fundamental lifecycle approach to validation has been widely accepted internationally. The basic premise involves dividing the system into components or phases. The project validation lifecycle follows a structured method to plan, design, implement, test, and operate a system from its conception to the termination of its use and decommissioning, or it may reenter the cycle with change and revalidation.

Figure 1



The important aspect to note in this flowchart is the interaction and interdependency of many of the engineering and validation activities. Such as:

- DQ confirms the GMP facility design supporting utilities, and equipment. This can be conducted in parallel with development of Factory Acceptance Testing (FAT) and Site Acceptance Test (SAT) methodologies.
- Pre-Delivery Inspection (PDI) of major system components can contribute to the IQ
- Factory acceptance operational tests can contribute to the OQ
- Commissioning activities can overlap with some IQ/OQ activities, and can confirm the User Requirement Specification (URS) for "indirect impact" systems
- IQ verifies construction and installation

- OQ verifies functional design
- PQ verifies the URS, and will challenge a collection of both "direct impact" and "indirect impact" systems working together

Using *Figure 1* as a basis for further discussion, each phase of a typical validation project is presented and discussed.

■ Requirements Phase

A successful project is dependent on clear definition, communication, and understanding of the project scope and objectives, as defined by the end user and other stakeholder requirements. At the outset of the project after the front end conceptual study has been completed, the user must specify his requirements for individual aspects of the facility, equipment, utility, and systems in terms of function, throughput, operability, and applicable local compliance standards to the engineering service provider. This enables the development and assessment of specific engineering options. These requirements are normally formalized in a detailed URS document.

■ Validation Planning

For significant validation efforts involving multiple equipment and utility systems, a project VMP should be developed early in the project, as early as the conceptual engineering design phase, to define the overall validation philosophy and methodology to be used throughout the project. This allows the project and validation managers to plan resource and scheduling requirements, and ensures that design engineer specifications and detailed design are suitable for validation.

The VMP should be a structured, detailed plan defining all the testing, acceptance criteria, and documentation required to satisfy the regulatory authorities and support the validation process. Based on an impact assessment, the plan also clearly defines the scope and extent of the qualification or validation process by listing the matrix of products, processes, equipment, or systems affected.

The VMP also assigns responsibilities for developing and executing validation program activities, and gives a first look at an anticipated testing execution schedule.

At the inception of projects, it is necessary, and in fact, essential, that the project team and project sponsor approve the VMP to enable the release of sufficient financial and staffing resources to support the entire project.

■ Formation of a Project Team

Establishing a project team that has adequate skills that are appropriate for the size and complexity of the project is key to the project launch. Project team representation should be based on the project scope, resource requirements, and key stakeholders.

To ensure timely and cost-effective project completion, it is essential to have excellent communication, planning, and coordination between project team members. Organizing these teams, establishing roles, responsibilities and expectations, levels of authority, monitoring performance, and taking corrective actions are fundamental project management issues that challenge project leaders.

■ Facility Systems GMP audit, Design Qualification and Impact Assessment

Early involvement by the QA function ensures clear understanding of the project's scope, facility, processes, and equipment. Early involvement by QA, by means of a GMP audit, for example, should provide clear communication of regulatory requirements, ensuring that effective procedures and practices are established upfront for incorporation into the project. This GMP audit can be conducted in parallel with the impact assessment, if required.

The functional design of the system or equipment must be confirmed as being correct and appropriate for the requirements of the URS. This confirmation is made by detailed comparisons of the functional design with regulatory requirements, company procedures, manufacturer's documentation, and the URS in a formal DQ protocol.

Once the DQ is complete, a risk analysis or impact assessment can be conducted. The key to successful project implementation is a well-defined project scope, which enables the validation team to determine the degree of effort and level of resources required, enabling them to focus on its defined responsibilities. It is the function of the facility, equipment, or utility that determines what level of commissioning and qualification are needed. Developing the project commissioning and validation scope is normally accomplished by conducting a risk analysis or impact assessment, whereby the impact of a system on product quality is evaluated, and the critical components with-

in those systems are identified. It will separate systems and equipment into those that have direct or indirect product contact, others which have product quality impact, and finally those that do not affect the product in any way.

So called "direct impact" systems are expected to have an impact on product quality. Examples of such systems are when they are either in direct physical contact with the drug product; a system that produces data that is used to accept or reject products; or the system is a process control system that may affect product quality.

"Indirect impact" systems are not expected to have an impact on product quality. Examples here include support systems such as heat transfer systems, electric power, and non-process water sources. These are non-critical and need not be qualified. However, the monitoring and control of critical parameters, which these support systems affect, should be validated. Both types of systems will require commissioning. However, the "direct impact" systems will be subject to supplementary qualification practices to meet the additional regulatory requirements.

"No impact" systems will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned following Good Engineering Practice (GEP) only.

Decisions relating to the extent of validation using impact analysis based upon GMP significance is a major opportunity for streamlining validation. This assessment should be carried out by those with the appropriate skills and experience necessary to make an informed decision based on a comprehensive understanding of the product, process, and nature of the facility systems and components.

Typical stakeholders may include representatives with process, engineering, validation, and QA experience and responsibilities.

A typical pharmaceutical company will expect to qualify and validate the following for a new or upgraded manufacturing facility:

- Facility design, installation, and function
- Critical process support utilities e.g., HVAC, compressed air, steam, dust extraction, and water purification systems
- Process equipment design, installation, and operation

Once the facility has been validated, the following would then need to be conducted:

- Operating staff training
- Manufacturing process validation
- Equipment cleaning procedure validation

■ FAT and Pre-Delivery Inspections (PDI)

Wherever possible, advantages should be taken of the opportunity to inspect and test systems or major system components before delivery to the site. This allows a quicker and more efficient remedy of any failings, and avoids delays to the project schedule that would result from discovering problems later on-site. FAT at an equipment vendor's location prior to shipping equipment to the facility can significantly reduce overall project timelines if performed properly, in that some or all of the FAT documentation may be used to support commissioning and SAT.

FAT ensures that specified equipment performs to the manufacturer's designs, and that certification is supplied to confirm correct performance. At this stage, all safety and quality critical items should be examined and documented. All of the documentation should be reviewed and anomalies addressed, together with any issues pertaining to calibration and connected utilities. These operational FATs should contribute to the OQ effort. Pre-delivery inspection and testing of major system components before delivery to the site may also contribute to the IQ effort.

■ Commissioning

Plant commissioning efforts address the foundation of the manufacturing facility, and is a vital element in the process of delivering new facilities. It ensures that all building and process systems are designed, installed, functionally tested, and capable of operation in conformance with the design intent.

Unlike regulated qualification practices, commissioning activities do not need to meet the compliance needs imposed by regulatory authorities. For the pharmaceutical industry, commissioning may be defined as follows: "Commissioning is the process of ensuring all building and process systems are designed, installed, functionally tested, and capable of operation in conformance with the design intent."[6] Another definition is that commissioning is "a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the

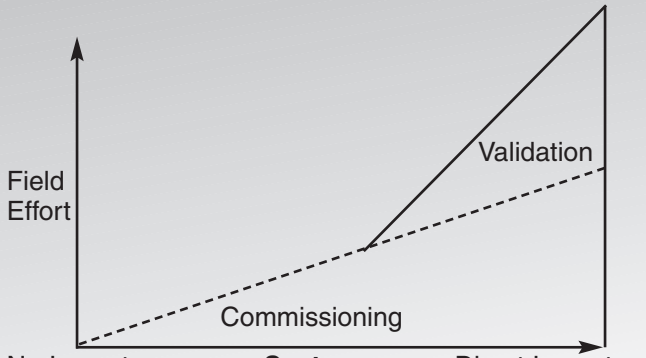
end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations." [7]

Commissioning process steps include system documentation, equipment start-up, control system calibration, testing and balancing, performance testing, and turnover.

Figure 2 depicts the interaction and interdependency between commissioning and validation activities, and shows the field effort required to validate "direct impact" critical facility systems, as opposed to no impact and non-critical facility systems.

Figure 2

Commissioning and Validation Effort Profile[6]



GMP: Good Manufacturing Practice

Commissioning incorporates a systematic method of testing and documenting of systems and equipment at the conclusion of project construction, but prior to process validation. Commissioning execution typically occurs between physical completion and turnover to either the operational user or the validation team, and entails activities, such as system inspection (visual testing), adjustment and regulation, testing (individual system tests), and performance testing (combined system tests). Commissioning also includes various activities designed to prepare equipment for startup and validation, such as installation of filters, alignment of motors, lubrication, and calibration of critical gauges and instruments.

The development of SOP, Preventive Maintenance (PM) procedures, and user training may also be conducted early on during the commissioning phase of the project. Training is a neglected element of most commissioning programs, and proper personnel training should become a part of the commissioning or qualification program (normally during OQ). Knowledge transfer and personnel training is a systematic approach designed to help operating, technical, and maintenance personnel develop the skills and knowledge to start-up and sustain new operations at high levels of performance.

On completion of the commissioning activities, there is normally a phased project turnover of the system or equipment to the user or validation team, together with the commissioning documentation (for example; drawings, design documents, test procedures, factory test evidence, field test evidence, calibration data, inspection records, and Operation and Maintenance [O&M] manuals).

Delays of many months are encountered when facilities do not have an orderly commissioning/turnover process.

■ Installation and Operational Qualification (IQ/OQ)

IQ and OQ are regulated activities that are part of final qualification activities before performance qualification or process validation begins. Commissioning and qualification testing are interrelated, and testing performed during commissioning may be used to support qualification activities.

IQ protocol execution should tie in closely with the construction schedule so that as sections or systems are completed, they are inspected, and the results documented in the IQ protocol.

Once the results of the IQ execution have been completed, the OQ execution can begin. OQ protocol execution should tie in closely with the commissioning schedule so that as sections, systems, or equipment is completed, they are tested, and the results documented in the OQ protocol. As part of equipment or system IQ/OQ activities, computer-related functionality may also be validated as part of combined or individual protocols.

Qualification protocols are normally required to be written for "direct impact" systems. These are individual documents describing the system under consideration, documentation deliverables, testing plans, acceptance criteria, and forms for recording the test results that ensure that a system is installed, and operates in accordance with predetermined specifications. IQ and OQ protocols may be combined

into one document, or the protocols may be kept as separate individual documents.

After protocol execution is complete, approval by the original protocol signatories is required before the PQ can proceed. For this approval review, a summary report may be written at the end of the OQ stage to summarize the IQ/OQ results, and provide data analysis. It also may be written at the completion of PQ.

■ **Performance Qualification (PQ)**

PQ is the final qualification activity before PV begins. Only "direct impact" systems will be subject to PQ. The PQ integrates procedures, personnel, systems, and materials to verify that the pharmaceutical utility, environment, equipment, or support system produces the required output. This output may be a product contact utility (clean compressed air, water purified etc.), or environment (HVAC system). At this stage of the qualification exercise, the commissioning activities are normally complete, IQ and OQ are complete, all deviations or snag items from IQ/OQ have been resolved, pertinent SOPs have been approved, and training in these areas are complete and documented.

OQ and PQ protocols may be combined into one document, or the protocols may be kept as separate individual documents.

On completion of the construction phase, individual systems and process areas are reviewed to satisfy compliance with the project objectives and regulatory requirements.

■ **Related Programs**

Related programs are undertaken to provide assistance and information in support of the qualification activities, for example, safety, SOPs, training, PM and calibration, and cleaning validation. The activities within these programs can be addressed and managed through the VMP, or through independent plans and programs referenced within the VMP.

Commissioning and qualification of facilities, equipment, and utilities are the foundation for process validation. Process validation includes consideration of the suitability of the materials used, and the physical plant, as well as the performance and reliability of equipment and systems. It is normally addressed separately to the facility qualification plan.

■ **Plant Release and Start-up**

Once IQ/OQ/PQ and process validation is complete, planning for the plant start-up can commence.

The facility and systems are considered acceptable for use following the review of the validation documentation that concludes the validation has met all the requirements set forth in the approved validation plan, and that all deviations incurred during this validation have been identified, documented, and resolved. Authority to release and use the facility is granted by the QA Unit.

Planning for plant start-up includes planning for technology transfer, personnel training, logistics of raw materials, finished product distribution, and technical and business systems. These elements must be in place prior to start-up to ensure seamless operation of the system.

When problems are experienced during the commissioning, qualification, and validation process, it is usually due to the lack of start-up planning at the project's scheduling stage.

■ **Periodic Review, Change Control and Revalidation**

To verify compliance with procedures and policies, validated systems should be subjected to ongoing operational audits. Review of a previously validated system is recommended to identify possible trends in the system's performance. This periodic review should be conducted according to an SOP, and in accordance with schedules established and documented in QA audit plans. The frequency of audits should be based on system importance relative to regulated operations. Upon completion of the evaluation, a report of the findings should be issued, including all actions recommended, and the corresponding supportive documentation. The result of this periodic review will then determine the need and degree of system revalidation, if necessary.

Change control is essential to the successful management of a system, and should be in-place when the system enters into service. After a system is validated and becomes operational, changes will occur during its operational lifetime, that may impact its validation status. If a change is deemed to have a potential effect on the system's validation, appropriate requalifications and/or revalidation measures should be executed, documented, and approved. Change control maintains functionality as the system evolves, and provides an audit trail that helps maintain the system in an operating and validated state

Summary of Project Performance and Outcome

In general, the plant start-up went according to schedule with strict timeline and budgetary objectives being met, and cGMP compliance was maintained in the plant throughout the construction phases.

- Phase One was built, commissioned, and validated by May 2000. (stability chambers, December 1999; pilot lab, September 1999; and chemical weighing in May 2000), Phase One was also audited and approved by the local regulatory agency in July 2000, and by corporate quality auditors in October 2000.
- Phase Two (Granulation) was built, commissioned, and validated by May 2001.
- Phase Three (Compression) was built, commissioned, and validated by June 2001.
- Phase Four (Compression and Encapsulation) was built, commissioned, and validated by January, 2002. Corporate quality auditors inspected and approved the upgraded plant in February 2002.

Certain delays were encountered due to several deficiencies and/or changes in facility or HVAC design; for example, in the Phase Two HVAC installation, with consequent delays in the commissioning, validation activities, and start-up of the granulation facility.

Various process system delays were also encountered in Phase Two due to control problems with the new Air Handling Units (AHUs) process equipment.

Delays were experienced with the commissioning and validation of the Phase Three HVAC system due to chemical de-humidifier and AHU control issues with the resultant delay in start-up of the compression facility.

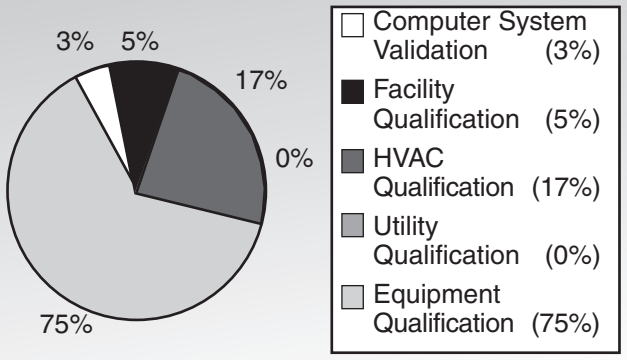
As phases were completed, knowledge, and experience gained from the design, construction, commissioning, and validation of preceding phases was used and incorporated to improve these activities in subsequent phases.

In this three-year project, the validation team, consisting of three permanent company employees, generally met all key project milestones, while writing and executing approximately fifty-four validation protocols. *Figure 3* shows a breakdown of how their time was spent until the end of Phase Two on various validation activities, including the time taken from the pre-approval of the protocol to the approval of the final validation report.

Figure 3

Breakdown of Time Spent on Validation Activities

For Phases One and Two



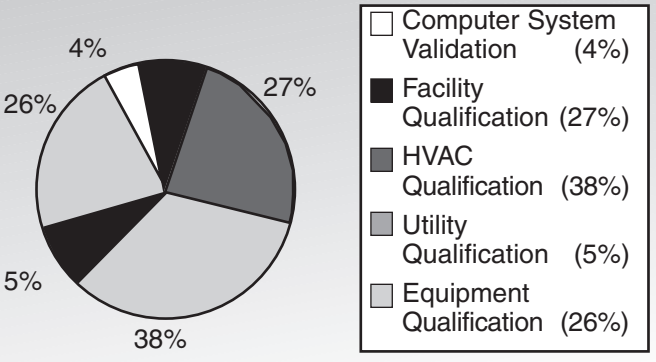
HVAC: Heating Ventilation and Air Conditioning

Phase Two of the project, as opposed to Phase Three, involved the installation and qualification/re-qualification of many process equipment items. As shown, the time spent on equipment qualification was significant, and this was due mostly to the delay in completion and approval of many protocols, and their final approval due to the late development, sign-off, and training of operating, cleaning, and maintenance SOPs, PM, calibration schedules, and turnover of commissioning documentation and O&M manuals. *Figure 4* shows a breakdown of how their time was spent until the end of Phase Four on the various qualification activities.

Figure 4

Breakdown of Project Time Spent on Validation Activities

For Phases Three and Four



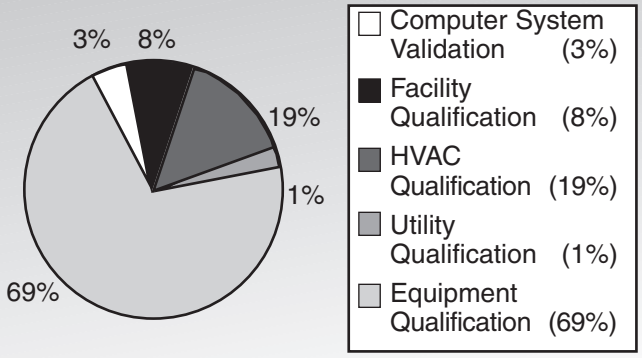
HVAC: Heating Ventilation and Air Conditioning

Figure 5 shows a final breakdown of how their entire time was spent on the various qualification activities.

Figure 5

Breakdown of Time Spent on Facility Validation Activities

Total Project



HVAC: Heating Ventilation and Air Conditioning

As part of the validation deliverables, more than sixty operating, cleaning and maintenance SOPs were written/revised, and manufacturing operators and engineering personnel were trained on them.

From the middle of Phase Two, certain strategies were introduced to improve the efficiency, and streamline the validation process for the final two project phases.

For example, working more closely and meeting regularly with the project and engineering functions, the consulting engineer and contractors ensured that the validation and documentation requirements were clearly understood early on in that particular construction phase schedule. Fieldwork was substantially reduced by integrating installation, commissioning, qualification, and engineering activities. Combining activities and minimizing resource requirements also substantially reduced the amount of fieldwork. The use of standardized documentation templates significantly reduced the time taken to write, review, and approve validation protocols and reports. Identifying SOPs, training, calibration, and maintenance requirements early on in the construction phase enabled operating, maintenance, set-up, and calibration issues to be addressed before qualification commenced.

Based upon research conducted in the U.S., it has been estimated that as much as 75% of the dollars spent on validation activities are spent on facility and equipment qualification.[8] Industry norms estimate the cost of facility validation to generally range anywhere from four percent up to 10% of the total installed cost of a project. Recent experiences also indicate that the commissioning process costs between two to four percent of the total installed cost.[6]

Figure 6 gives a breakdown of the overall costs for this particular project.

Figure 6

Project Cost Breakdown

Facility Upgrade Project

Service	Percent Total Installed Cost
Architectural/Engineering Design and Construction	51%[1]
Equipment	39%
Commissioning/Start-Up	1%
Validation	9%[2]

1 Includes project management and field supervision costs

2 Includes salaries, FAT travel costs, and vendor equipment validation documentation costs

In summary, all the major validation milestones, i.e., cost, quality, and time schedule, were met for this project. Further integrating and streamlining the validation approach has the potential to provide even more relief for overburdened validation resources, and these aspects will be discussed in this article.

The Use of an Integrated and Streamlined Validation Approach

What can be done to control the cost and time of validation? As usual, the answer lies in the management of the validation process. In this section, means to achieve total project success, by using an integrated and streamlined approach to optimize commissioning and validation activities on a project, are discussed. Total project success would mean:

- Reduced project costs
- Reduced project schedules and better overall schedule management
- Reduced start-up time needed in the field
- Less defects

- Reduced internal resource needs at the end of the project
- Adherence to all compliance requirements
- Better overall project quality

Streamlining existing commissioning and validation activities adheres to the following basic principles:

- Start the project by evaluating the impact of a system on product quality
- Focus resources on the qualification of systems with "direct impact" on product quality according to GMP
- Provide contractors, vendors, and engineers with the project validation requirements up-front to enable them to plan installations to meet these requirements
- Design and commission those systems that have no "direct impact" on product quality according to GEP
- Enhance the commissioning, qualification, and validation documentation generation, review, and approval processes
- Integrate the commissioning and qualification activities to avoid duplication of work
- Conduct training of employees, contractors, consultants, and other personnel early in the project lifecycle

The following details some strategies that could be followed to reduce project resource requirements, and improve the efficiencies of the commissioning and validation programs:

Structure the Project Team Appropriately and Define their Roles and Responsibilities

Pharmaceutical companies typically require considerable resources, in terms of time, money, and personnel, to validate a cGMP facility. This can be an overwhelming task to a small company or plant with limited resources. Therefore, fundamental project management issues, such as the organization of the project team, establishing roles, responsibilities (project ownership) and expectations, monitoring performance, especially the commissioning process, and taking corrective action are constant challenges to the project manager in achieving cost, schedule, and quality advantages. Taking full advantage of this integrated approach, and subsequently controlling cost, requires a multi-disciplinary team, effective planning and communication, management, and enforcement of the validation plan. The project manager must be capable of managing his own time and resources, the time and resources of every member of the project team, while also weighing the needs of the organization against the needs of the project. Project team representation should be based on the project scope, resource requirements, and key stakeholders impacted by the project outcome. Individual team members need to understand the roles, responsibilities, and levels of authority for both the team leader and other team members. They also must appreciate how the team will be managed e.g., meeting frequency, reports, communications, problem resolution, etc. Typical functions and roles that make up a project team include a project sponsor, project manager, engineering and maintenance, procurement, construction, commissioning leader, operations/production, validation, QA, Quality Control (QC), R&D, safety, and a technical writer.

To streamline the validation process, it is critical to form the validation team at the start of the project. This will ensure that all validation requirements are integrated into the project design specifications. Project qualification milestones and information that needs to be captured and documented are identified to ensure the completion of all validation responsibilities in a timely and effective manner. Ensure that the most technically qualified individuals or groups are empowered to lead, for example, equipment qualification efforts. Individual project team members need to be intimately involved in the project so that they gain a thorough knowledge of the intended use, design, and operational characteristics of the relevant systems.

For validation to be fully integrated into the project, it must also be the responsibility of every member of the rest of the project team to ensure that whatever work is done, it is with the validation endpoint in mind. This will help streamline the validation activities where possible, so that validation does not duplicate work carried out by other disciplines, but merely audits and identifies areas that are incomplete or non-conforming, and collects and collates relevant data.

Conduct an Impact Analysis Early on in the Project

It is imperative that companies new to validation and with limited resources, establish a reasonable

approach to their facility validation.[9] An all too common mistake for many in this situation is to "overdo it," and start-up companies typically do not have the resources to support this "all or nothing approach." Base the level of documentation and validation on the complexity of the system/facility, available resources, and the potential risk/cost.[10] Performing an impact analysis and identifying "direct impact" or GMP critical systems and processes for validation can focus resources on systems with "direct impact" on product quality. This assessment should be integrated into the overall project schedule, and be made by those with appropriate skills and experience to make an informed decision. "Indirect impact" or no impact systems and their components will not be subjected to qualification, but will be designed, installed, and commissioned according to GEP only. Decisions relating to the extent of validation using this impact analysis are a major opportunity for streamlining validation, as long as the rationale for the decisions taken are documented by the appropriate individuals and are approved.[11]

Develop a Robust Validation Master Plan (VMP)

If validation is to be integrated into the project, it must have the same status as other activities within the project schedule. The development of a robust validation master plan detailing the scope of work and schedule will ensure that validation is integrated into the project with the same status as other activities within the project schedule. The use of a VMP is an efficient way to insure the requirements for validation are understood, and agreed upon, by everyone involved.[12] The process of integration must begin when conceptual design attributes are transformed into layout drawings, equipment data sheets, and process flow diagrams.[8] The VMP should outline the overall validation philosophy and approach to be used throughout the project lifecycle and should include the following:

- The qualification rationale and strategy (the VMP could also include the commissioning strategy and plans, but this is uncommon)
- A list describing the facility, equipment, controls, and systems
- The process for determining direct, indirect, and no impact systems
- A detailed testing sequence integrated with the overall construction commissioning and start-up schedule, and reconciled with the VMP
- The documentation requirements for the project, and
- Key roles and responsibilities throughout the life of the project

The VMP is thus the key that governs the testing and documentation required to satisfy the regulatory authorities. This document will become the common thread for all parties, and thus creates integration and a common mission for the project team.

The VMP should become a living document that is periodically updated to reflect current design conditions.

Integrate Validation Schedules into the Overall Project Schedule

The project manager should ensure the development of a commissioning and validation plan as an integral part of the project plan and schedule. Integrating validation into the overall project schedule can save both time and money. Integrated schedules should be developed with input from the construction and validation project teams, and be maintained and reissued regularly.

IQ/OQ may be conducted as part of the physical completion of the facility, thus tying IQ/OQ closely to the construction contractor's scope of work that includes commissioning. To avoid the effort and inconvenience of discovering and rectifying basic problems, it is recommended that all systems go through an informal shakedown phase before IQ/OQ commences. This will help ensure a smooth transition between IQ and OQ, and minimize the number of changes during IQ and OQ.

Scheduling of PQ is particularly critical as PQ testing is often the most time consuming part of the qualification. Scheduling should take into account any prerequisites that should be achieved prior to PQ execution (such as commissioning of all support systems, availability of SOPs, system interdependencies). The PQ protocol often receives the greatest amount of scrutiny from the approval team. This often results in a lengthier authorization process, and an adequate amount of time should be allowed in the project schedule for this long approval period.

Adopt Formal Commissioning Procedures

Depending on the intent of the system, commissioning may be a precursor either to equipment qualification, and ultimately to process validation for "direct impact" systems. Otherwise, it may be the final activity for "indirect impact" systems prior to routine operations. If commissioning is not adequately performed, adjustments that would have been recorded on commissioning sheets become non-conformance at the IQ/OQ stage. This is not a desirable consequence, and makes the validation longer and less convincing when audited.

The benefits of implementing formal commissioning procedures in facility construction projects are:

- Verifies that full value is obtained for an owner's construction dollar by implementing formal inspection procedures to verify that all systems and equipment are provided, installed, and can be operated as specified and intended
- Assures system design performance by testing systems and components in all modes of operation, and verifying proper integration with other building systems
- Maximizes system operating efficiencies by assuring that design and operational intents are fully understood and implemented
- Minimizes lost use, down-time, and user inconvenience by assuring that each system is brought on-line and tested prior to system turnover.
- Avoids financial liabilities by reducing exposure to critical system failures.
- Reduces maintenance costs and improves maintenance response times by initiating formal operator training and awareness sessions, and providing necessary operating and service manuals.
- Realizes major cost savings if commissioning protocols are properly integrated into an overall validation plan.

Integrate Commissioning with Validation Activities

There are advantages of time, money, and quality in integrating many of the functions carried out by skilled resources, such as engineering contractor and validation teams. A great deal of validation work, that traditionally has been carried out separately from the engineering work, can be associated with the engineering and commissioning of a facility, and be integrated into the project sphere. The responsibility for timely and appropriate execution then becomes that of the combined validation and engineering team, so that they become indispensable to each other and reduce the time spent on validating the facility and scaling up to production. The use of a competent expert multidisciplinary team will ensure that best practice is deployed and duplication of activities is avoided.

Excellent documentation of commissioning can be conducive to a successful validation effort if it is in a form consistent with the requirements of cGMP and quality.[13]

Integrating activities such as DQ, FAT, SAT, and commissioning into the qualification and validation activities can control validation costs. Instruments and equipment can be verified at the vendor's site during FAT and PDI. This reduces delays caused by identifying problems only after equipment is delivered. If these items are not altered or dismantled in any way for transport, these checks, if properly documented, could be used in support of SAT or qualification activities.

For OQ, by identifying the critical operational criteria that require testing prior to the facility, utility, or equipment being used in production, and planning the schedule accordingly, the duration of the testing can be shortened.

If FAT is executed for equipment i.e., alarms and interlocks testing, some or all of these tests can be performed at the vendor's site, or these tests can be performed as part of commissioning, and be used in support of the OQ.

Performance testing carried out as part of commissioning can contribute to PQ if performed consistent with qualification practices.

Thus, if the integrated approach is used and proper inspections, documentation, and certain required field execution work is accomplished by the construction vendors and contractors, then the validation scope can be reduced to that of review, monitoring, and compiling. The integration of commissioning and qualification merges activities, minimizes resource requirements, and streamlines the validation effort by reducing the number of protocols and reports.

To illustrate this integrated approach, *Figure 7* shows examples of tests and verifications conducted on a new Fluid Bed Dryer (FBD) at various phases of the project.

Figure 7

Example of Integrating Commissioning and Validation Testing

FBD Tests/ Verifications	Phase Where Testing Conducted				
	Commissioning Phase		Validation Phase		
	FAT	SAT	IQ	OQ	PQ
Functional Design/Specification Verification (DQ)	X				
As-Built and Plant and Instrumentation Diagrams (PI&D) Verification	X		X		
Materials of Construction Verification	X				
Welding Information Verification	X				
Critical Component Verification	X		X		
Control System Component Verification	X		X		
Instrument Calibration Verification	X		X		
Alarms and Interlocks Testing		X		X	
FBD Sequence of Operation Testing		X		X	
FBD Recipe Handling and Recovery Testing		X	X		
Control System Security Access Testing		X		X	
FBD Operating Parameter Control Testing		X		X	X

FBD: Fluid Bed Dryer *FAT: Factory Acceptable Testing*
SAT: Site Acceptance Testing *IQ: Installation Qualification*
OQ: Operational Qualification *PQ: Performance Qualification*

Enhance the Documentation, Documentation Management, and Approval Process

The development of validation documentation is an essential part of any successful validation program.[14] In fact, documentation starts the validation process. For validation work to be integrated into the project framework, the paperwork aspects must be kept to what is strictly necessary for validation. Validation must be logical, structured, verifiable, and above all, correctly documented. The biggest problem facing most protocol writers is the lack of information and time. These problems are usually due to poor integration of validation into the project process, validation requirements not being written into the design specifications, protocol requirements not being relayed to a contractor/equipment vendor, late identification of items (e.g., calibration requirements) that should have been incorporated into the design documents, and no cGMP audit being performed on the design documents (design errors being discovered during qualification).

So to streamline the validation approach, conduct a documentation gap analysis when the project is in the design phase to define the validation documentation requirements. Then, provide the vendor or contractor with these guidelines to inform them of the documentation requirements in advance. Request that technical information becomes available for the team as detailed design proceeds. This will minimize the validation team having to struggle to obtain the documentation when under pressure during protocol writing/execution/field work.[11] This enables the team to begin developing the second level task schedules, staffing schedules, validation plans and protocols, sampling plans, test plans, training materials, etc.

Approaches to streamline the amount of paperwork required to give sufficient documented evidence of validation could include:

- Using standardized protocol and report templates wherever possible, so that reviewers become used to protocol formats and contents
- Structuring executed protocols as reports to obviate the need for writing a separate report.
- Combining IQ and OQ documents (to IOQ) will result in fewer documents to develop, track, review, and approve. Keep in mind that IQ still must be completed before OQ commences.
- Include only the critical tests in the protocol, and do not repeat non-critical ones already conducted in FAT or SAT phases.
- Setting realistic validation protocol acceptance criteria based upon the process demands for reproducibility and product quality. One of the surest ways to create unneeded work, extra cost, and headaches during the validation program is to set unfounded or unrealistic valida-

tion acceptance criteria.
- Recording deviations in the validation protocol and report rather than developing elaborate deviation systems.
- Ensuring that commissioning documentation for "Direct Impact" systems are appropriately planned, created, organized, and authorized so that they may become an integral part of the qualification support documentation.
- Combining engineering and validation information to minimize duplication. If engineering and equipment validation were fully integrated into the engineering documentation with QA review, protocols would not need to contain information that is adequately stated in the engineering documentation and specifications.

Once qualification protocols are written, they should be approved, and this may be a time consuming process. Several ways to streamline this process include:

- Minimizing the number of approvals required
- Clarifying the review process with all parties early in the project
- Collecting all comments from all parties on one master document
- Instituting a formalized protocol tracking process
- Minimizing the number of review cycles allowed by the team
- Implementing a simple review and approval procedure. However, still bear in mind that protocols should be carefully reviewed to minimize deviations and time-consuming explanations of errors in testing or reports.
- Instituting protocol review meetings for all parties involved
- Assuring the protocol review and approval process is included in the overall project schedule

No matter how well you streamline your documentation, there will still be hundreds of documents – drawings, specifications, manuals, inspection reports, and testing reports – to support the qualification effort, and a document management system needs to be in place.

Active Participation of Quality Assurance (QA)

Qualification can be greatly enhanced and streamlined by the early involvement of QA to ensure that knowledge, expertise, and input in the areas of GMP, regulatory expectations, and industry trends are incorporated into the project from design concepts forward. This involvement ensures that appropriate quality practices and procedures are adopted early in the project, and ensures those regulatory requirements and expectations are addressed and met. Practical application of regulatory requirements is key in streamlining and efficiently managing qualification activities. QA provides input to the impact analysis, provides feedback, and approves plans and protocols used to conduct qualification activities, results, and conclusions.

During the engineering phase of the project, QA may audit the approved equipment and utility system vendors to verify that they have the necessary quality systems in place to ensure quality of their product or service. Part of the integration concept also involves auditing design and construction activities for compliance with cGMPs, verifying documentation, and keeping a close eye on the installation progress throughout the project's construction phase.[8] QA should review and approve all commissioning documentation.

Appropriate documented change control should exist throughout the life of the project, and through the long-term maintenance of the validation status after the project is completed. The QA unit should be routinely involved in the engineering change management process as changes may alter the impact assessment, change the design concept, or deviate from the original user specification.

Greater End User/Stakeholder Participation

"Direct impact" systems demand closer and more comprehensive "hands on" involvement from the end-user or stakeholder group. Where appropriate, end-users should become involved in vendor audits to evaluate suitable vendors and FAT of systems prior to shipment.

The integrated approach to qualification/validation should also change the way in which protocols are executed. Making those who will be operating and maintaining the system a part of the validation procedure is beneficial because of the experience and understanding they gain. Production and engineering should be responsible for ensuring comprehensive testing of mechanical, electrical, and control functionality, and for ensuring that the documentation complies with the company's engineering standards.

Validation will then review many of the qualification activities, instead of performing all of the work themselves. This exposure also will be valuable when the need to revalidate arises because of changes or updates to the system.

Separate Related Program Verifications from the Validation Protocols

Related programs are undertaken to provide assistance and information in support of the qualification activities, for example, safety, SOPs, training, PM, and calibration. Instead of the activities within these programs being addressed and managed through the VMP, they should be handled, where appropriate, through independent plans and programs that are referenced within the VMP. These programs could be handled under the umbrella of a commissioning team represented by engineering, EHS, technical writing, and training. This will mean that these programs will need to be established early on in the project lifecycle. This will streamline the validation approach by segregating the individual qualification protocols.

Safe operation is a necessary requirement for all systems. Safety can be managed in a similar way to the qualification program, and the project team can develop a safety plan specific to the project during construction planning to manage safety.

SOPs are established to ensure that activities are performed consistently every time. They also play an important role in maintaining the validated state of a system. It is recommended that the SOP program be established early on in the project lifecycle. A project team can write SOPs detailing the operation, maintenance, set-up, and calibration of equipment, as well as SOPs for facility and equipment cleaning. These should preferably be written and finalized prior to the PQ phase.

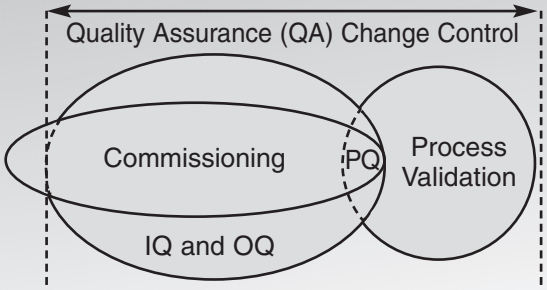
Training is listed as a requirement for compliance with cGMPs. Project training, as well as the ongoing training during the lifecycle of the facility, can be administered within a training program. Apart from operational training, relevant regulatory requirements, specifically GMP, Environmental Protection Agency (EPA), and Occupational Safety and Health Administration (OSHA) requirements should also be communicated as part of the training program. The overall PQ process can be streamlined if a proper training program has been put in place before PQ execution. Key factors that should be addressed in training personnel on a new system include; product and personnel workflow, gowning procedures, applicable equipment/system operation and maintenance, cGMP documentation training, environmental monitoring, swabbing and sampling, and change control.

Components that have been determined to be critical to product quality will most likely have more frequent calibration and maintenance schedules. In this manner, these programs are key for maintaining a "direct impact" system in a validated and controlled state. The process of setting up clear and understandable procedures and carrying out a formal criticality assessment will allow preventative maintenance and calibration activities to be managed to concentrate the resource where it is most needed. In this manner, the calibration of critical instruments will be verified in IQ before undergoing any qualification testing, to ensure that the test results in OQ are valid. This verification, along with the calibration certificates and procedures, provide the documented evidence required to demonstrate that a system operates in a controlled state.

The integrated and streamlined approach is not a complicated theory or a great technical breakthrough, but merely a logical and practical approach to facility validation. There is agreement within the pharmaceutical industry that the most effective and efficient approach to accomplishing validation is to incorporate the validation process into the engineering, procurement, construction, commissioning, and start-up activities associated with a project.[10] *Figure 8* depicts how commissioning, qualification, and validation can

Figure 8

Integrating Commissioning, Qualification, and Validation[7]



IQ: Installation Qualification
OQ: Operational Qualification
PQ: Performance Qualification

be integrated.

This integral approach, as opposed to treating validation as an event in the project lifecycle, will reduce overall project cost and schedule duration, and provide real value-added benefits in the start-up of cGMP compliant facilities. Properly executed validation pays for itself, often in non-financial ways.

In summary, the adoption of this integrated and streamlined validation approach will provide the following advantages:

- Strong management support for this cost-effective validation approach
- Uniformity of approach to commissioning, and validation issues with direct input from the project team
- Optimal usage of available personnel, and proper establishment of priorities through central planning, coordination, and monitoring
- Optimal usage of technical knowledge from all project team members
- Effective training of operators in new processes and equipment by actively involving them in validation studies
- Enhancement of the quality awareness of personnel resulting from active involvement in the project
- Positive contribution by Industry to the development of emerging cGMP industry validation standards, together with the regulator of the South African pharmaceutical industry, the Medicines Control Council.

Adopting and applying these practical, integrated, and streamlined proposals can substantially reduce total validation costs. In this case study, validation time and costs for the latter phases of the project were reduced by as much as 50%.

Conclusion

The word "validation" has a negative connotation in the pharmaceutical industry, and is still understood by some as unrestrained bureaucracy, paperwork, and procedures whose roots and logic are obscure, and that only serve to slow down progress. In a typical fast track project, this perception further reinforces the views in the minds of some project managers and senior management, governed by budgets and timelines, that validation does not provide beneficial contribution to a project.

Validation has in fact given the pharmaceutical industry many positive benefits; we have more assurance of safe and quality products, equipment and systems are more reliable, there is improved process understanding, we have more scientific data on which to base justifications and corrective actions, process-related recalls have been reduced over the last decade, and processes are more reproducible.

However, the original visions of validation making, for example, scale-ups from development to routine production more efficient, increasing production throughput, reducing in-process, and final product testing, reducing the incidence for reworks, retests, and returns, have all not been realized.

As facility construction costs continue to escalate, pharmaceutical companies will continually struggle with the challenge of meeting regulatory requirements and running a profitable business. The "current" in cGMP requires us to always improve, so Industry must continue to search for methods that reduce costs and improve efficiency. As scientists, validation professionals should never allow themselves to become complacent about investigating and employing new approaches and technologies.[9] The rate of change in technology, legislation, and professional practices is now extremely rapid. With the fields of quality assurance and regulatory compliance in a state of constant flux, validation is in a key position to take the lead, refocus, and begin to dispel the negative perceptions and reverse this disturbing trend toward unnecessary or inefficient facility validation activities to provide positive impact to the corporate bottom line.[15]

Validation is a function of risk aversion, and the cost of validation is related to the amount of risk that we wish to avert.[12] This article demonstrates that design, engineering, commissioning, and validation activities can be integrated and streamlined to accelerate the start-up effort, reduce the validation effort and costs, produce superior documentation, and ensure that product is produced in a cGMP-compliant facility. It also proves that even though the original focus of validation was to satisfy regulatory expectations, facility validation, has in fact, become good business and engineering practice that enhances reliability, cost, and quality.

Validation ultimately results in bottom line cost savings. ❑

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Suggested Reading

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Summary of Practical Advice for Facility Validation

Commissioning and validating a facility, while maintaining ongoing manufacturing operations, represents the highest order of challenge to any project team. Working with limited resources (manpower and budget) and strict implementation timelines just further complicate the project. The following summarizes some of the common areas that can be troublesome during facility validation, and suggests strategies to address them:

Project Team Planning

1. Project teams are normally always under-resourced. Resource the project team adequately by ensuring that representation is based on the project scope, resource requirements, and key stakeholders.
2. Add technical support to your validation group. Including the design engineer, contractors, and equipment vendors to the protocol review list will save a lot of effort later in the project when time is often least available. Use this resource up-front for the validation team to gain a thorough knowledge of the intended use, design, and operational characteristics of the systems and equipment requiring validation.
3. Validated facilities must be operated and maintained by the maintenance department, so maintenance should be involved at the very beginning of the project – at the master planning stage.
4. Involve the Quality Assurance (QA) unit early on in decisions concerning the design, construction or installation, commissioning, and qualification to ensure clear understanding of regulatory requirements, procedures, and practices are established that need to be incorporated up-front into the project. Also, the QA/Quality Control (QC) auditing of the design and construction activities for compliance with GMPs throughout the project's construction phase needs to be carried out formally during the project.
5. Formulate a change control procedure before construction. Change controls should be implemented not only for revisions to the design of facility systems, but also for modifications to the protocols themselves. Nearly every project will need some changes made to the validation protocols after they have been formally adopted. Having an established procedure for making these changes can avoid needless delays during construction.
6. At the start of the project, clearly define what is "in" and "out" of the project scope. There is always a tendency to allow project "scope creep" with additional direct impact systems being identified and installed, thus increasing the validation scope, workload, and resource requirements.
7. Obtain approval on system functional descriptions and design concepts from the same personnel who will be approving validation protocols and reports. This provides another check that validation requirements have been included in the design. By the time the protocols are completed and reviewed, the design may be much harder to change.

Validation Planning

8. Hold off on the completion of detailed design documents until a Validation Master Plan (VMP) has been established. The popularity of fast track projects often means that validation efforts begin after the detailed design is completed, and the project is nearing the construction phase. Considerable rework may be avoided by planning and incorporating the validation effort into the detailed design engineering phase of the project.
9. Ensure that your VMP is written early enough in the project, and in sufficient detail, to identify important resource, planning, and timeline constraints that may impact the validation team's performance. Insufficient time allocated to validation in the overall project plan can leave insufficient time for corrective action when a system or equipment fails validation tests. This places enormous pressure on the validation team to complete their activities.
10. Avoid the tendency to validate all aspects of the operation regardless of facility system criticality and "product impact" considerations. Advancing manufacturing technology makes new facilities increasingly more complex, and brings higher expectations for output, quality, and efficiency. Here, fears of plant shutdowns and possible financial losses are forcing validation teams to qualify or validate non-critical cGMP systems that really only require commissioning. Conduct an impact analysis by beginning with the needs of the process. Identify the facility systems that will impact the process and those that do not. Facility validation is often extended to include building systems that should, more appropriately, be included as part of the commissioning effort. If the building systems do not affect the quality and repeatability of the process, don't validate it. Include a list of systems that require validation and those that do not in the VMP, and clearly spell out the reasons for this justification.
11. Inform your design engineer, contractors, and equipment vendors at the start of the project of the importance of cGMP and the validation documentation deliverable requirements. It is estimated that 30% of validation time is taken in producing protocol documents, and any lack of vendor information and late delivery of documentation from vendors or contractors can lead to the inefficient writing and execution of protocols. This often results in a frustrating documentation chase, wasting precious validation time and resources when they are most in demand.

Commissioning

12. Modern pharmaceutical facilities incorporate technically complex systems, and demand expert design, installation, and operation. Facility commissioning represents the last phase of the design and construction of a pharmaceutical facility before validation, and is often beset by many problems that may delay the commencement of the validation activities and ultimately the plant start-up. To avoid costly delays, stressful implementation, and missed opportunities when project

teams under manage the tasks of starting up and turning over facilities, standardize the plant commissioning practices and methodologies, plan the activities well, and allocate realistic timelines for execution early on in the project.

13. Where the scale and complexity of a project is such that it suggests that commissioning activities have to be stringently planned and executed, the appointment of a commissioning leader or commissioning steering team may be appropriate. It is also good practice to have the contracted design engineer take an active role in the final stages of the commissioning process to inspect the completed facility, review and follow-up on commissioning items that have not been addressed, and coordinate and/or collect project deliverables to ensure that there is proper turnover of the facility for validation.
14. Integrate commissioning and validation efforts. A well-planned validation program enables contractors to fill out many validation protocols at the same time they are performing installation and start-up tasks, e.g., calibration. However, ensure that this requirement is defined in the original bid documents from the contractors.

Qualification and Validation

15. It is recommended that the Standard Operating Procedure (SOP) program is established early on in the project lifecycle. SOPs detailing the operation, maintenance, and calibration of equipment, as well as SOPs for facility and equipment cleaning should be written and finalized prior to, or during, the Operational Qualification (OQ), so they can be used and referenced during Performance Qualification (PQ). Knowing how the system will be operated assists in the development of validation protocols. Often, protocols are written based on the initial project design documentation, and in isolation of the actual design and construction. These protocols are then reworked after commissioning and start-up to reflect the as-built design conditions. This is an inefficient and time consuming approach to protocol development.
16. Inspect systems before shipping. Although much of the Installation Qualification (IQ) effort must take place in the field, many construction delays can be avoided by performing Factory Acceptance Tests (FATs) for controls, software, and equipment at the vendor's site before they arrive on site and are needed for installation. It may also be helpful to have vendor manuals shipped ahead of the equipment so that they can be referenced as validation protocols are being developed. FATs and SATs thoroughly conducted can significantly enhance the quality of the validation effort and the qualification turnaround times.
17. Cover a broad range of operating conditions in testing. Don't restrict validation protocols to the design parameters of the system. Good protocols will take into account "worst-case" extremes of operating conditions, as well as conditions with no load and fully loaded systems. System recovery after control limits has been exceeded, and during start-up, should also be tested.
18. The validation effort can cover related programs, for example, environmental, health and safety assessments, electrical installation, SOPs, training, and preventive maintenance and calibration schedule verifications. Even though these activities are undertaken as part of the facility project, and may provide assistance and information in support of qualification activities, the subject experts in these fields, in separate project teams, could better handle these compliance issues. It is these related activities that can delay the closing out and approval of validation protocols.
19. Project managers, running out of money and time at the end of the project, look towards finishing the project as quickly as possible, and find validation hindering these goals, especially when it requires more engineering input for which they have no extra funds to cover or time to spare. In fast-track projects, project managers tend to move onto their next project phase before the whole job is done, leaving validation personnel and engineering maintenance personnel with a cumbersome task: working off a snaglist, struggling to locate commissioning data, as-built documents, making equipment work, and calling vendors for training and turnover. The validation process is designed to expose non-conformance to design, and deficiencies in plant design/construction, and operation. It is imperative that the validation group meet routinely with the project manager and project team to address these issues.
20. Commissioning and validation testing can often be duplicated during a project. Integrating commissioning documentation with validation documentation can be conducive to a successful validation effort if it is in a form consistent with the requirements of cGMP and quality.
21. The setting of unclear quality acceptance criteria for the validation can lead to unnecessary extra work, extra cost, and complications during the validation program. The acceptance or rejection of equipment or systems is ideally based on the process demands for reproducibility and product quality.
22. The most common problems found during regulatory audits are not due to design deficiencies; they are inadequate documentation, or failure to follow approved procedures and protocols. The importance of good recordkeeping and proper reporting of validation results cannot be over emphasized.

Plant start-up

23. Training is a requirement for compliance with the cGMPs. It is important that time for training be included in the overall project schedule. A training matrix to support training activities should be developed. Operating personnel should become familiar with SOPs for manufacturing and support processes, cleaning, as well as proper gowning techniques. Maintenance personnel should also be trained because they will be maintaining systems, and also entering GMP process areas. ❑

Article Acronym Listing

AHU:	Air Handling Unit
BMS:	Building Management System
cGMP:	Current Good Manufacturing Practice
DQ:	Design Qualification
EC:	European Community
EHS:	Environmental, Health and Safety
EPA:	Environmental Protection Agency
EPQ:	Equipment Performance Qualification
FAT:	Factory Acceptance Testing
FBD:	Fluid Bed Dryer
FDA:	Food and Drug Administration
GEP:	Good Engineering Practice
GVP:	Good Validation Practice
HVAC:	Heating, Ventilation and Air Conditioning
IQ:	Installation Qualification
OQ:	Operational Qualification
OSHA:	Occupational Safety and Health Administration
OTC:	Over-The-Counter
O&M:	Operation and Maintenance
PDI:	Pre-Delivery Inspections
PIC:	Pharmaceutical Inspection Cooperation Scheme
P&ID:	Plant and Instrumentation Diagram
PM:	Preventive Maintenance
PPQ:	Process Performance Qualification
PQ:	Performance Qualification
PV:	Process Validation
QA:	Quality Assurance
QC:	Quality Control
R&D:	Research and Development
SAT:	Site Acceptance Test
SOP:	Standard Operating Procedures
URS:	User Requirement Specification
VMP:	Validation Master Plan
WHO:	World Health Organization

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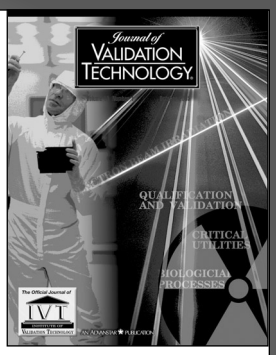

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- ◯ 0500 Other (please specify) _____

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Qualification of Environmental Chambers

By Tod E. Ransdell
Genetic Systems Corporation, a Division of Sanofi Diagnostics, Inc.

For the purposes of this article, an environmental chamber is defined as any device whose interior chamber environment is regulated or controlled to a specific set of parameters. This could be an incubator, refrigerator, freezer, isolation chamber, isolation cabinet, or anything that falls into this general type of functional category. One might even stretch the notion so far as to include autoclaves, lyophilizers, dry heat ovens, and dry heat tunnels, although there are special conditions connected with them. The general approach is universally sound enough that it can be applied in many diverse situations. Since these devices are considered to be equipment because of their control features, the regulatory view is that they need to be qualified and/or validated.

"...an environmental chamber is defined as any device whose interior chamber environment is regulated or controlled to a specific set of parameters."

The Written Word – An Approved Protocol

Following the initial project planning phase, the validation/qualification process continues on with the written document or protocol. The flow and contents of protocols have been very well covered in previous discussions, courses, and articles and can be found on diskettes provided through the ***Institute of Validation Technology***. The protocol is generally broken down into primary phases or sections. Each phase and the elements of each phase are discussed in the balance of the article. The actual organization of the elements is up to each professional or organization. One may choose to execute a long series of functionally explicit qualifications that include design qualification (DQ), commissioning or specifications qualification (SQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) as part of the validation process. One may also choose to wrap all the elements into a general equipment qualification (EQ), with only an IQ and OQ as functional components.

It does not make any difference where all the components go or what they are named, as long as each progressive step is included in the final protocol and report. Rigid thinking is the beginning of a poor validation approach. It is also more important that the documents, reports, and records within the company are consistent with each other than with any outside formats, templates, or examples one might encounter in searches of the available literature. For the purpose of simplicity in this organizational example, I will use two basic qualification sections.

The Installation Qualification

The IQ is the performance of documented verification that all key aspects of the equipment/system has been received as ordered, that installation

adheres to approved contract specifications, and has achieved design criteria. The IQ is developed from Process (Piping) and Instrumentation Diagrams (Drawings), (P&ID's), electrical drawings, mechanical drawings, purchase specifications, purchase orders, instrument lists, engineering/technical specifications, equipment operating manuals, and other necessary documentation. All draft and developmental documentation may also be included in an IQ. The manufacturer's specifications, recommendations, local and state utility and building codes, and the cGMP should also be suitably considered when conducting this phase of the validation.

It is very important that the IQ be thorough and comprehensive. This is no time to skimp on the collection of material of direct observation. The information collected during this phase of the qualification captures the initial status or condition of the equipment or system. This information is extremely useful in the future determination of process drift due to the aging of the equipment or minor process adjustments that occur over time, that cumulatively may generate an entirely new set of process control parameters. There have been occasions when the IQ portion of the validation package is the only source of original information concerning a system or piece of equipment. The IQ will contain, but not be limited to, the following set of elements: equipment identification, documentation, utility requirements, and component specifications.

Equipment Information

This section records the general information about a particular piece of equipment. Most of the information can be obtained directly from the device nameplate. Other information must be found in the associated equipment documentation. The following items should be recorded, but don't stop short with this basic list (see *Figure 1*). Add as much information as you are able to gather. A small effort now will pay off in the end.

Documentation

Hopefully, each device will be accompanied by an installation, operations, care, and maintenance manual. The manual(s) should include some basic schematics or system drawings. It is a rare case when the manuals are not included. If they are not, it would be a good idea to contact the sales representative or the manufacturer's technical service department immediately to obtain a copy for your equipment files, quality system records, and/or qualification records. Your data collection sheet can contain any number of the following information blocks or sections. (See *Figure 2*). It is important to include these items in this section of the IQ. If the listed documentation is ever inadvertently misplaced or lost, this basic information will allow you to recover it from the manufacturer.

Figure 1

System Information Summary

System Description:_____
System Location: _____
System Number: _____
Manufacturer Model No.: _____
Serial Number:_____
Purchase Order Number: _____
Manufacturer: _____
Manufacturer Address:_____
Manufacturer Phone and Fax: _____
Additional Information:_____

Figure 2

Item:_____
Item Number: _____
Revision Number: _____
Revision Date: _____
Title: _____
_____
Where Stored: _____
Parts List – Yes/No: _____

Utility Requirements

Electrical connections, compressed gasses, refrigerants, steam, hot/cold water, deionized water, glycol, exhaust/waste/effluents, etc. are a few of the types of utility connections that should be addressed in this type of data collection section. Each piece of equipment will generate its own specific utility list.

Each utility supplied for the operation of a particular piece of equipment will usually have its own separate data collection page.

In the case of a refrigerator/freezer unit, the type, amount, and relative pressures of refrigerant(s) for each chiller/compressor or evaporator should be recorded in this section of the document. The presence of a manufacturer's suggested preventive maintenance documentation should also be noted.

See the example of the data collection page (*Figure 3*) for electrical utility connections. A similar page should be included for each utility identified for the individual piece of equipment. The following items should be recorded:

Figure 3

Electrical (Utility Power)

Function/Application: Supply Power for the operation of the *(device/system name)*

Source:	**Unit ID No.**	**Unit ID No.**
Outlet ID:		
Panel ID:		
Breaker ID:		
Main Junction ID:		

Connected to Emergency/Backup Power Source (Yes/No): _____

Specified:	**Unit ID No.**	**Unit ID No.**
Volts:	208	115/120
Phase:	Three (3)	Single (1)
Hertz:	50/60	60
Amperes:	8A (max.)	Not Specified

Specification Source: (Equipment Nameplate/Instruction Manual)

As Found:	**Unit ID No.**	**Unit ID No.**
Volts:		
Within Spec.:	Yes/No:	Yes/No:
Phase:		
Hertz:		
Amperes:		(Not Measured)

As-Found Voltage will be ±10% (or 15%) of the specified value.
Insulation:_____ Type of Ground:_____
Conduit – Material: _____ Size: _____
Safety Cut-Off Location: _____
Safety Cut-Off Identification: _____

Component Specifications

This section verifies that all the major components purchased with or as options added to the system have been delivered and installed. The component lists should be able to be generated from the original purchase order specification sheet. Each component will have its own data collection page or section of a page (See *Figure 4*). It is a good idea to decide during the purchase/contract phase what system components are required for your target process. The purchase order specifications assumes that the responsible department heads actually went to the effort of specifying out the equipment before it arrived on the loading dock or shop floor. Don't be surprised that if this activity occurred, the information was not captured or maintained in an organized, written form.

Material compatibility may also be an issue. If it is for your particular process, this information line should be added to the section to confirm that the proper materials have been delivered. If there is not a product contact issue, then the consideration of materials is simply and primarily for longevity of your investment and ease of care and maintenance.

Figure 4

Component: (Chart Recorder)
Serial No.: _____ Location: _____
Manufacturer: _____ Model No.: _____
Chart No.: _____ Info. Reference: (Name Plate)
As Found:
Calibration Date: _____
Spare Parts List Available (Yes/No): _____
Certificate of Calibration Available (Yes/No): _____
Specified Information Confirmed (Yes/No): _____
(include copies in Final Report)
Additional Data:

Critical and Reference Instrumentation

The information collected is generally the same for either the Critical or Reference Instrumentation. The main difference between the data collected in these sections is that the Reference

Instrumentation usually is not calibrated and may or may not be verified for accuracy. The Reference Instrument read-out is usually for general information only and is not directly reflective of a crucial control parameter.

The equipment's calibration requirements should also be recorded either in this section or in a subsequent component section. It is important that the accuracy, precision, and resolution of the instrumentation be recorded for future reference. This information may come directly from the equipment or sensor manufacturer. This assures that this piece of equipment is actually capable of recording and/or controlling the process within the process design parameters.

See the following examples (*Figure 5*) of some of the key information to collect for this section of the qualification protocol.

Figure 5

Critical Instrumentation	Reference Instrumentation
ID No.: _____	ID No.: _____
Type: (Circular Chart Recorder)	Type: (Gauge)
Manufacturer: _____	Manufacturer: _____
Model No.: _____	Model No.: _____
Serial No.: _____	Serial No.: _____
Range: _____	Range: _____
Scale Division: _____	Scale Division: _____
Location: _____	Location: _____
Use: (Temperature Recorded)	Use: _____
Calibration due date: _____	**Verification date:** _____

A Note About Cleaning

There should be some recorded coverage of the state of cleanliness of the chamber in question. A determination that the chamber is "Fit For Use" should be the focus of this effort. There should be a fairly clear understanding of what may or may not be contaminating the interior surfaces of the chamber. The surface survey should provide detail on the possible range of contaminants that may have a deleterious effect on the product that will be exposed to the chamber environment when it becomes fully operational. A routine, post-construction cleaning for "heavy dirt" that may be conducted by the construction or installation contractor, may not bring the surface or internal environmental conditions to a state that supports its use in a particular process. Additional, focused cleaning may be required. A General Data gathering section may be useful for recording the various cleaning activities, as well as other miscellaneous information discovered during the IQ process. The cleaning and state of the chamber could also be recorded as part of the commissioning phase of the EQ.

Operational Qualification

The OQ is the documented verification that the equipment/system performs in accordance with the design criteria over the entire defined or anticipated operating ranges of the equipment. The OQ includes review and certification of operating and maintenance documents and records.

The OQ is the stage of validation which finds its base in a satisfactory process installation (IQ) and/or current operation (legacy process, current batch). For a legacy process, OQ is the stage where the current operation of the process is carefully reviewed and the validity of the variable targets, process controls, personnel, and outputs are verified and their adequacy, necessity, and sufficiency are established.

The OQ will contain, but not be limited to, this set of elements: Safety Features, Failure Modes, Safety and Environmental Health Review, confirmation of Standard Operating Procedures, and Temperature Distribution Studies of both the empty and loaded chambers.

General Operation

The general equipment control functions should be initially exercised at the beginning of the OQ. This basic step assures that the equipment is functional and that the more detailed and exhaustive tests that might follow can be accomplished. All the basic control functions should be tested at this time. i.e., power on/off, control parameter adjustment buttons, switches, indicators, lights, etc., both individually and collectively.

Safety and Alarm Features and Failure Modes

If there are any safety and alarm features, these should also be tested by inducing the condition that triggers them. It may be as simple as disconnecting a sensor lead or as complicated as actually providing an artificial/simulated condition. The purpose of this test section is to verify that if a failure mode is observed or a control parameter is exceeded, then the proper alarm event is triggered or safety system is activated.

If there are no safety or alarm features on a particular piece of equipment, this section may be omitted. It may be a good idea to include a notation at some point that states there are no safety or alarm features associated with this piece of equipment to close the loop for future reviewers.

Safety and Environmental Health Review

This section should support the idea that the piece of equipment or system and the manufacturing process is in full compliance with the policies, goals, and objectives of the Safety & Environmental Health Department (if your organization has one). It should also be noted that any inherent risk to the health and welfare of the employees of your organization have been accounted for, and adequate personal protective equipment and training have been provided for the safe and effective operation of this piece of equipment.

Review of Standard Operating Procedures

The purpose of this test section is to verify that the procedures that apply to this system in the areas of operation, cleaning, calibration, and maintenance are on file and will be reviewed for compliance.

Record the title, control number, revision number, and revision date for each applicable procedure currently in place for equipment that is the subject of the protocol.

Review each document for compliance to actual operating procedure. There may be an SOP in place, but to actually follow the SOP and operate the equipment may not function as it was first intended. In the review of our SOPs, we occasionally run into an odd document that does not accurately represent the way the piece of equipment is used in day-to-day production.

“It is also a good idea to make sure that the time and date marks on all associated data is in agreement.”

A document in at least draft form must be in place for the operation, cleaning, calibration, and maintenance of the equipment or system and its components. Part of the overall validation effort is the review and approval of documents discovered during the execution of the protocol to assure compliance to either the corporate quality system or other regulatory guidelines.

Temperature Distribution – Empty Chamber

Should the monitoring occur in the air medium within the chamber or should the thermocouples (TC’s) be bathed in a container that will buffer the volatility of the medium? If you choose to monitor the chamber environment using the air medium only, do not be surprised if you are unable to meet your control specification. Generally, it is a good practice to put the tips of your TCs in some kind of fluid. This more closely emulates the effect on product but

in an empty chamber condition. In most cases, particularly lab-sized refrigerators, the control sensors for the unit are bathed in a fluid medium. No other containers should be in the chamber at the time of this study.

The intent of the empty chamber temperature distribution (ECTD) study is to establish a baseline performance for the particular piece of equipment. It is generally for information purposes only. (See discussion on "worst case" conditions.) The ECTD may be compared to the loaded chamber temperature distribution (LCTD) study, but no conclusions or inferences about performance variabilities should be made. The ECTD is not necessarily indicative of the true nature of the performance of the unit in a loaded condition, but it does give you a good ballpark idea what the chamber temperature distribution might be like once the load is in place and has equilibrated.

The length of time to conduct the temperature distributions is determined by the individual organization. Generally they are monitored continuously from 12 to 24 hours. It is manageable for me to specify "at least 12 hours" and collect 20-24 hours, simply because I do not always have the luxury of remaining in one location for an extended period of time and need to shuttle between far-flung facility locations to keep a number of different activities going at the same time. The sample rate is usually every 10 to 20 minutes. I have found 15 minutes to be a very solid rate of sampling for my system to record during a temperature distribution.

Some data acquisition systems have the capability of taking samples more frequently but report at the extended or less frequent rate that has been selected by the operator. This advanced capability is very handy if you see a transient fluctuation and you want to analyze the occurrence at a higher sample rate.

In the case of large spaces, like walk-in coldrooms, I have found it best if the ECTD is done in sectors or quadrants. This concentrates the number of sensors available into a smaller area. It also provides a more useful profile for later examination. Depending upon the capabilities of the multichannel data acquisition device I am using, I may be able to do up to two sections at a time. This is usually 16 monitoring points per section, including the process control/recording sensor location.

Temperature Distribution – Loaded Chamber

The objective of the LCTD study is to map the contents of the chamber. You want to see if there are any places within the load where the chamber is not providing storage at the proper conditions. It may also be important to your individual process to know how long it takes for a newly introduced load to reach process temperature stability.

Should the chamber be filled to capacity or merely a representative, simulated load used? Particularly with a new piece of equipment, it is a good practice to challenge the device in a "Worst Case" load configuration, if at all possible. The load should, of course, be reasonable and prudent for the unit's intended use. Sometimes it is neither practical nor possible to fill the chamber to capacity due to the size of the chamber or the type of materials to be simulated for the load because of cost and/or availability.

For example, we have a number of moderately sized (≈30,000 ft^3) 2 – 8ºC Coldrooms and (≈5,000 ft^3) -20ºC Freezer Rooms. There is no possibility for us to challenge areas that large in a worst case, loaded condition until we transfer actual product into the chambers. We are limited to conducting ECTDs only. Because of this limitation, it is also a good idea, if you have the capacity, to occasionally monitor the loads with remote sensors. You will then be more able to assure that the load is coming to equilibrium within an amount of time that does not risk the potential for product degradation. This evaluation is dependent on the ruggedness and robustness that has been designed into that particular product.

The size and volume of container(s) used in the challenge load should reflect the average container size that will be contained in the proposed actual loads. The material or medium in the containers should emulate the materials to be actually used whenever possible.

What is "Worst Case?"

In the previous section, the use of the term "worst case" was a specific descriptor for the type of load used to challenge the chamber and system capabili-

ty. Some loads, by their physical makeup, are more or less thermally stable once they have achieved equilibrium with the chamber environment.

In comments received as part of the peer review of this article, an interesting point of view was forwarded. I felt this an important enough concept to include a brief discussion. I have taken the liberty of paraphrasing it for the sake of clarity.

Is a loaded chamber or an empty chamber the "Worst Case" condition? In many cases, a full chamber is easier to keep at operational conditions, because there is more mass present and less air. Opening the door changes out air easily (in smaller volume chambers), but product in the chamber will maintain its temperature much longer (than the surrounding thermal transfer medium). Recovery of a full chamber can be much quicker than an empty chamber (because there is a lot less air volume to bring back to the controlled/equilibrated state). The best answer to this situation is to have a specific performance criterion for both the empty and the loaded chambers.

The explanation presented by the editorial reviewer is particularly applicable whenever one is considering the performance of a chamber environment separately from the chamber load, whether it is an incubation chamber, a refrigeration chamber, or an autoclave chamber. When conducting the temperature mapping of the chamber and the load within the chamber, one should ask a number of key questions to bring a tighter focus to your efforts, i.e., How much influence does the load have on the stability of the chamber environment? How much effect does the chamber environment have on the load? What is my focus for this particular test section, and have I stated the intent clearly?

This line of reasoning is similar in nature to the "Small Load Effect" discussed in a Short Course by Richard T. Wood, Ph.D.; *Design and Validation of Terminal Sterilization Processes* (Parenteral Drug Association, Inc.; 1990), where the small or minimum load configuration may actually present a greater challenge to the process than the larger/maximum load configuration. There is a great deal of interplay between the load and the chamber environment. It is important to view these conditions from as many perspectives as feasible for the type of project in which you are involved. Further development of the concept for employing worst case scenarios can be found in the PDA/PhMRA Task Force Technical Report No. 28: *Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals*; (Parenteral Drug Association, Inc., August 1998; Vol. 52, No.5, Supplement S3, Sept./Oct. 1998). Various forms of risk assessment can be used to determine the most effective challenge for the equipment being qualified.

Tips When Monitoring the Temperature Distribution Studies

TIP #1 – Make sure you begin each section of the testing with a fresh chart in the circular chart recorder or enough paper in the strip chart recorder. The same goes for the instrument you are using to monitor and/or map the process in question.

TIP #2 – Remember to record the pertinent information (Type, ID#, Calibration Due Date, etc.) about the data acquisition device(s) you are using to conduct the temperature distribution studies.

TIP #3 – If the sensors for the process recorder and system controller are not in the same location within the chamber, make sure that at least one TC is placed with each sensor. This does not usually occur in new pieces of equipment. One might encounter this situation in either very large chambers or older pieces that have been reconditioned or repaired and returned to the shop floor from some other area in the plant. If the control and monitoring sensors are separated, it may be advisable to have the two sensors relocated to the same location in the chamber. This may or may not be possible but should be explored in any case. It causes far fewer headaches in the long run if everything is consolidated as much as possible.

TIP #4 – It is also a good idea to make sure that the time and date marks on all associated data is in agreement. First, this makes it easier for you to compile and summarize all data for the final report. Second, it causes less stress and anxiety for any reviewers and respondents that may be involved in the auditing of the reports in the future. ❑

Terms and Definitions

Refer to the **Institute of Validation Technology's** *The Validation Dictionary* for sources of most terminology used in this article and for the specific terms that follow.

Calibration – Documented comparison, by written and approved procedures, of a traceable measurement standard of a known accuracy with another measuring device to respond, detect, correlate, report, or eliminate any variation in the accuracy of the item/device being compared over an appropriate range of measurements. This process results in documented adjustments, or corrections that can be made, or the development of a deviation chart so that an instrument's reading can be correlated to the actual value being measured if maximum accuracy is required.

Calibration Verification – (a.k.a. – **Verification of Accuracy**) The assaying of calibration material and information to confirm that the calibration of the instrument, kit, or test system has remained stable throughout the reportable range for test results. Performance and documentation of calibration verification is required to substantiate the continued accuracy of a quantitative test method for the reportable range of test results.

Control Number – A unique or distinctive combination of letters or numbers, or both, assigned to a document that can be used to determine a complete history of the purchasing, manufacture, control, packaging, labeling, servicing, maintenance, installation procedures, and distribution of a production run, lot, or batch of a finished device or product.

Critical Device – A device intended for surgical implant into the body or to support or sustain life, and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in significant injury to the user.

Critical Instrumentation – Those instruments which are pertinent to the proper operation, control, and recording of critical process parameters (i.e., temperature and/or pressure controllers and/or recorders utilized for the documentation of process release parameters) to assure the quality, safety, identity, strength, and purity of the product.

Device – An instrument that will give analytical answers as a result of electrical or mechanical measurements on an element, compound, solution, instrument, system, etc. Devices can be broken into three categories: utensils, instruments, and equipment, of which only equipment needs to be validated.

Equipment – 1] An item which has an individual function and precise physical limits within the structure. An item of equipment is made up of several components in accordance with a physical configuration.

2] A device or collection of components that performs a process or analysis to produce a specific result. Equipment must be validated.

Noncritical Instrumentation (**Reference Instrumentation**) – Any instrument that is used primarily for convenience, operator ease, or maintenance. These instruments do not directly control or monitor process parameters or impact documentation of process control (e.g., use-point gauges).

Process Control Parameter (**Process Variable**) – 1] Those measurements and conditions associated with the manufacturing process that have a potential impact on the identity, strength, quality, and purity of a product. Examples of parameters of concern are process rates of flow, weights, volumes, temperature, and pressure.

2] Those process operating variables that can be assigned values to be used as control levels or operating limits.

Qualification, Validation and Certification – One qualifies facilities and utilities; one doesn't validate them. One qualifies and validates equipment, processes, and procedures. The act of qualification is more of an audit, performed to determine if something is built, installed, or operates correctly. To validate is to test by use of challenges, either under normal production or worst-case conditions. Certification is a documented statement by an authorized and qualified individual(s) that an equipment/system validation, revalidation, qualification, requalification, or calibration has been performed appropriately and that the results are acceptable. Certification may also be used to denote the overall acceptance of a newly validated manufacturing facility. ❑

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1. Lopéz, O., "Process Control Hardware Installation Qualification Protocol;" Vol. 5, No. 1, November 1998.
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6. Stromp, J., "Reflections on Writing IQ, OQ, and PQ Protocols;" Vol. 1, No. 2, February 1995.

Suggested Reading

1. BioPharm Magazine; Advanstar Publications, Inc., 131 West First Street, Duluth, MN 55802-2065; Reprints Phone: 800-822-6678.
2. Parenteral Drug Association (PDA); 7500 Old Georgetown Road, Suite 620, Bethesda, MD 20814; Phone: 301-986-0293.
3. International Society for Pharmaceutical Engineering (ISPE); 3816 West Linebaugh Avenue, Suite 412, Tampa, FL 33624; Phone: 813-960-2105.

Facility Validation

Validating USP Purified Water, Compressed Air and HVAC Systems

By Jean-Pierre Thiesset
Alcon Laboratories, Inc.

Facility validation is a tremendous task in which many different processes and pieces of equipment must be considered.

The processes addressed within this article include:

- A United States Pharmacopoeia (USP) purified water system that produces USP purified water for use in component and final product cleaning. This water is not used as a constituent of the product itself.
- A compressed air system, which generates oil free air, used in manufacturing processes to blow off components and final products. This system also supplies compressed air to manufacturing equipment.
- A heating, ventilation and air conditioning (HVAC) system that controls temperature, humidity and differential pressure for a class 100,000 controlled manufacturing environment (CME).

"A validation plan does not necessarily need to be an all-encompassing 100-page document."

Successful facility validation requires organization, attention to the different systems and processes one-at-a-time, and patience. It is important not to try to complete the validation before it starts.

The first step is forming a validation team. The importance of assembling a team that includes all interested parties at the beginning of the project is obvious. At a minimum, this team should include, representatives from facilities, manufacturing, quality, validation engineering and information technology. The next important step is developing a validation project plan. This will not decrease the amount of work to perform, but it will significantly contribute to successful validation.

Validation Project Plan

A validation plan does not necessarily need to be an all-encompassing 100-page document. A more concise document, which clearly states the project's purpose, the validation approach, and the overall acceptance criteria may be more useful. A validation project plan should be developed so that it serves as a road map. It ensures that each required task has been executed as planned. Specific qualification protocols, which contain the detailed testing, can be developed separately for each piece of equipment.

An effective validation project plan must contain:

1. Validation project plan number, subject and approval blocks.
2. Project purpose.
3. Project scope.
4. Facility and system: Define what the system does (system description and intended use) and how the system does what it is required to do (design description).
5. Project responsibilities: Define project manager/leader, team members and their respective responsibilities.

6. Planning and organization: project goals, objectives and expected benefits, project organization, constraints, impact on existing systems and operations, proposed time line and major milestones.
7. Validation methodology: broad overview of the validation approach to be taken.
8. Validation responsibilities: consider the supplier's responsibilities as well as those of the validation team.
9. Validation procedure. Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) requirements. List the specific protocols which must be implemented, (usually one per system, or one for each specific IQ, OQ and PQ). Note: List only major tests that must be included in each qualification. It is not necessary to provide explicit detail within the scope of this document. (The detailed procedure for executing a qualification of a particular system will be specified within a specific protocol for that qualification).
10. Validation deliverables. These might include supplier qualification, operational procedures, process documents, preventive maintenance schedules for each piece of equipment, training plans, and other documentation.
11. Acceptance criteria. List the acceptance criteria for the validation project plan.
12. Attachments. It may be helpful to use a "check sheet" format that contains the list of specific protocols to implement. This section should refer to supporting documentation, such as drawings, flowcharts, and Gantt charts.

After the project plan is approved, the team can begin executing the plan.

USP Purified Water System Validation

This system is described as two stainless steel piping distribution loops which provide continuously recirculating, ambient temperature, USP purified water to manufacturing areas. This system consists of:

■ A supply water (city water) pretreatment system. A multi media depth filter which filters the city water with an automatic backwash system when pressure drop exceeds a predefined value. This filter removes particulate matter greater than 10 microns. A carbon filter removes organic contaminants and chlorine from the water by absorption.

■ A deionized (DI) water production system. A cation/anion unit removes dissolved ions in the water by ion exchange. First, the water passes through a strong acid cation exchanger, (cation exchange resin regenerated with acid HCl). Then, the water flows through a strong base anion exchanger, (anion exchange resin regenerated with caustic soda NaOH). When the resistivity of the water after the cation/anion unit is lower than a predefined value, a regeneration cycle is triggered. A one micron filter completes this DI water production system.

■ A water temperature maintenance and distribution system. This system includes: a sanitary pump, a hot water generator for sanitizing, an ultra violet (UV) disinfecting lamp, a 0.1 micron filter, a bank of three parallel mixed polishing beds, a one micron filter, a second UV disinfecting lamp, a second 0.1 micron filter, and two distribution loops which are connected back to the sanitary pump.

■ A monitoring system. The resistivity of the water is monitored at several points in the system ensuring that the water delivered by the system is greater than a predefined value, and a system of yellow and red indicators alerts maintenance technicians and users if resistivity goes below this predefined value.

USP Purified Water System Installation Qualification (IQ)

The most difficult part of a USP purified water system validation is not the OQ, but the IQ. An important part of a quality USP purified water system resides in its architecture, piping, valves characteristics, and installation method. Knowing that, it becomes evident that the validation must start even before the first pipe is installed by the choice of the right company to perform the soldering, installation and verification.

It is recommended that vendor selection criteria include a requirement for the vendor to provide a quality assurance plan for the project. Their plan should address the following:

Figure 1

Classic Installation Qualification (IQ) Testing

Test #	Test Designation	Test Description
1	Drawings and schematics review.	Verify that drawings and schematics are available for the following when applicable: major components, connections, wiring, inter-connections, piping.
2	Manuals review.	Verify that a manual is available for each major component.
3	Major components identification.	Record the following for each major component: designation, brand, model, serial number.
4	Major components installation.	Verify that each major component is correctly installed.
5	Connections verification.	Verify that connections conform to drawings and schematics.
6	Wiring verification.	Verify that wiring conforms to drawings and schematics, and wires and cables are identified at both ends.
7	Tagging verification.	Verify that valves, gauges, relays, contractors and fuses are identified and tagged according to drawings and schematics.
8	Utilities verification.	Verify that the following utilities conform to manufacturer specifications when applicable: power supply (voltage), air pressure and quality, water pressure and quality.
9	Plant capacity.	Verify that the plant has the capacity to produce the required utilities without impacting the existing processes.
10	Personal computer software installation (if applicable).	Verify that the computer is in compliance with the minimum software requirements, that the software is available on appropriate medium (e.g., CD-ROM, diskette), that no error message is displayed during the software installation, and the software main menu can be displayed after installation. Verify that the software is compatible Year 2000 (i.e., will continue to operate correctly on January 01, 2000 and the years after).
11	Program review (if applicable).	Verify that program listing (source code) and functional flowchart are available for review, that the program is correctly commented and contains no dead code, and the program has been saved for backup (current and previous versions saved on separate directories or drives).
12	Supplier validation questionnaire review.	This is a questionnaire sent to the supplier of pieces of equipment which contain hardware or software ensuring that the supplier has a software quality assurance system in place. It is used to evaluate the extent of validation testing required.
13	Equipment verification by a safety officer.	A safety officer must verify that the equipment is safe for use in a manufacturing environment.
14	Calibration verification.	A representative from the metrology department must verify that pieces of equipment which required calibration have been calibrated, and that a rationale has been written for the pieces of equipment which do not require calibration.

❶ Material and equipment receipt and acceptance procedures ensuring that materials conform to their specifications. The program should include methods for lot number tracking, review of certificates of conformance and material test reports.

❷ Inspection procedures. These must be detailed, referencing the equipment to use, the technician certification and/or training required, the methods, the sampling plans, and the acceptance criteria for each test. For example, stainless steel welded pipe tests are done in accordance with the appropriate American Society for Testing and Materials (ASTM) specification. The inspections may include verification of outside diameter and wall thickness, inspection of inner diameter surface anomalies (minor pits only, no porosity, no inclusions), cleanliness (e.g., no dirt, grease, grit, oil), and chemistry. Most of these tests require the use of sophisticated instrumentation by certified technicians. Examples of water system tests include: slope verification and pressure testing.

❸ Welders performance qualification proce-

dures and records.

❹ Welding procedures. These may include, but are not limited to, cutting, facing, deburring, cleaning, pipe fitting, purging, and alignment.

❺ Weld documentation. May include a weld numbering system, welder identification, time and date.

Choosing the right company ensures that the water system IQ will be completed practically at the same time of the installation itself. The only part that will be left to organize is a classic IQ (see *Figure 1* Installation Qualification (IQ) testing). During a review of drawings, make sure to verify that your installation has no dead legs. It is not as easy as it seems, because dead legs can be hidden everywhere. (For example, a dead leg can be created when a valve is closed.) Verification that the system has been correctly pasteurized will complete the IQ testing portion of the water system qualification.

USP Purified Water System Operational Qualification (OQ)

The OQ of a USP purified water system is time consuming, but not really complicated, due to the fact that this type of system does not contain a lot of complex pieces of equipment.

Start by checking each component separately to ensure that it functions as it is supposed to operate:

❶ Verify pump is capable of producing the specified flow rate.
❷ Verify on/off sequence of the UV lights.
❸ Verify the hot water generator is capable of producing the required temperature for the sanitizing cycle.
❹ Verify valves open and close as intended.
❺ Verify alarms are activated as intended.

Once every component has been checked and deemed acceptable, the water system OQ can begin. The system tests consist of the sanitizing cycle test, chemical tests, microbial tests and documentation and training verification. Before conducting any other tests, it is important to check the sanitizing cycle ensuring that the system maintains circulating water at a minimum temperature of 85ºC (185ºF) for 30 minutes. It is critical to ensure that the power supply to the UV lights is shut off during the sanitizing cycle preventing a deterioration of the UV lights. Ideally, the system is designed to automatically cut the power supply to the UV lights when the temperature reaches 50ºC, (122ºF), and turns it back on when the temperature comes back under 40ºC (104ºF). For safety, it is important to install a pressure release valve in order to allow the release of the excess pressure generated during the sanitizing cycle when the temperature increases. This valve must be checked ensuring it is working properly.

The next step is verifying that the control system is operating as necessary. The control of the resistivity, temperature and other parameters are performed by a computerized system. First, it is necessary to verify that the values recorded by the control system conform to the actual values. One method to do this is measuring all the parameters with calibrated instruments. Record the date and time the measurements are taken, along with the values obtained. Compare these manually obtained values to those recorded and saved by the control system during the same period. During the OQ, it is necessary to verify that the control system acts and reacts as it is intended. For example, the system must maintain temperature at an acceptable range, activate correct indicator lights based resistivity readings. The system may also generate customized special reports or exception reports. An important fact to remember is that all computerized systems, including most of today's USP purified water systems, contain software programs which need to be validated.

During the operational qualification, chemical and microbial tests will be performed. It is important to define the testing frequency conducted at each point-of-use. At a minimum, chemical tests consist of the following:

- Description
- Resistivity
- pH
- Total solids
- Chloride
- Sulfate
- Ammonia
- Calcium
- Carbon dioxide
- Heavy metals
- Oxidizable substances

Figure 2

Chemical and Microbial Test Matrix

			Operational Qualification				Performance Qualification Phase 1									
Test	**Loop**	**Days**	**1**	**2**	**3**		**4**	**5**	**6**		**7**	**8**	**9**	**10**	**11**	**12**
C	N/A	Ctrl	X	X	X		X	X	X		X	X	X	X	X	X
H	A	Begin	X	X	X		X	X	X		X	X	X	X	X	X
E	A	End	X	X	X		X	X	X		X	X	X	X	X	X
M	B	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	B	End	X	X	X		X	X	X		X	X	X	X	X	X
	A	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	A	End	X	X	X		X	X	X		X	X	X	X	X	X
	B	Begin	X	X	X		X	X	X		X	X	X	X	X	X
	B	End	X	X	X		X	X	X		X	X	X	X	X	X
	A	POU-A1	X				X				X			X		
	A	POU-A2		X				X				X			X	
	A	POU-A3			X				X				X			X
M	A	POU-A4	X				X				X			X		
I	A	POU-A5		X				X				X			X	
C	A	POU-A6			X				X				X			X
R	A	POU-A7	X				X				X			X		
O	A	POU-A8		X				X				X			X	
B	A	POU-A9			X				X				X			X
I	A	POU-A10	X				X				X			X		
A	B	POU-B1	X				X				X			X		
L	B	POU-B2		X				X				X			X	
	B	POU-B3			X				X				X			X
	B	POU-B4	X				X				X			X		
	B	POU-B5		X				X				X			X	
	B	POU-B6			X				X				X			X
	B	POU-B7	X				X				X			X		
	B	POU-B8		X				X				X			X	
	B	POU-B9			X				X				X			X
	B	POU-B10	X				X				X			X		

POU	= Point of Use
X	= Test to be performed
	= Sanitizing Cycle to be Performed

As the system is stated to be a USP purified water system, the acceptance criteria for these chemical tests must comply with the USP purified water specifications. The chemical tests must be performed at points located as close as possible to the beginning and end of each loop, and at a control point located before the purification system. (This control point should fail the test, as it is located before the purification system). The microbial tests must be performed at each point of use. The validation acceptance level for Colony Forming Units (CFUs) per ml should be below the alert level. For example, action levels may be established at 50 CFUs/ml, and

alert levels may be 40 CFUs/ml. The acceptance level would then be < 40 CFUs/ml. It may be useful to use a matrix such as the one shown in *Figure 2* to define testing frequency. In the example shown in *Figure 2*, each point of use is tested at least once during the three days of the OQ/chemical and microbial testing and a sanitizing cycle is performed after day three.

The OQ phase will be concluded by verification that appropriate procedures and training are in place. It is important to verify that all required procedures for water system operation, monitoring, and maintenance are applicable and approved (see *Figure 3*, procedures required during facility validation). It is also important that individuals who utilize, and/or maintain the system have been trained appropriately and that this training is documented.

USP Purified Water System Performance Qualification (PQ)

The PQ of a USP purified water system could be conducted in two phases. The first phase consists of an intensive chemical and microbial testing during nine days with a sanitizing cycle between day three and day four. In the example shown in *Figure 2* (chemical and microbial tests matrix) each point of use is tested at least three times during the PQ phase. (Once before the sanitizing cycle and twice after the sanitizing cycle). A recalibration of each piece of equipment calibrated at the end of the IQ must be performed ensuring that the measurement performed during the validation test was valid. If some devices are found to be out of calibration, an investigation of the impact on the validity of the tests performed must be conducted, and a few or all OQ and PQ tests may have to be performed again.

The second phase of the PQ consists of a less intensive, (but more than routine monitoring) of the chemical and microbial conditions during three months to ensure that the system continues to produce the required water quality. Once the second phase of the PQ is completed, routine monitoring starts. Routine monitoring consists of the control of each critical point of use once a week and is used to ensure that the system continues to produce the required water quality. It also allows the assessment of the effect of seasonal changes on source water routinely recommended by industry experts.

Compressed Air System Validation

The compressed air system consists of the following:

Figure 3

Procedures Required During Facility Validation

Procedures	USP Purified Water System	Compressed Air System	Air Handling System
Water Sampling Method	Yes	No	No
Air Sampling Method	No	Yes	Yes
Chemical Test Method	Yes	No	No
Microbial Test Method	Yes	No	No
Hydrocarbon Test Method	No	Yes	No
Viable Particulate Test Method	No	Yes	Yes
Non-Viable Particular Test Method	No	Yes	Yes
Monitoring Procedures	Yes	Yes	Yes
Sanitizing Procedures	Yes	No	No
Excursion Reporting & Investigation	Yes	Yes	Yes
Calibration Procedures	Yes	Yes	Yes
Training Procedures	Yes	Yes	Yes
Standard Operating Procedures	Yes	Yes	Yes
Change Control Procedures	Yes	Yes	Yes
Preventive Maintenance Procedures	Yes	Yes	Yes

■ Oil free air compressor unit. This eliminates hydrocarbon content in the compressed air and eliminates or reduces the need for coalescing type filters.

■ Closed loop cooling system. In order to avoid contamination, the cooling system does not have contact with the compressed air.

■ A dryer. Serves to remove as much water as possible, decreasing the dew point.

■ A copper piping network. This network is oil free and has been cleaned with alcohol. (*Note that the use of galvanized piping, which is porous, is avoided. Such pipe materials will retain moisture.)*

■ Several 0.5 micron Millipore filters at each potential product-contact point of use.

■ A few coalescing type filters may be installed before the Millipore filters at any point of use where particularly high levels of cleanliness may be required due to the nature of product contact at that point.

Compressed Air System Installation Qualification (IQ)

The IQ of a compressed air system is much easier than the IQ of a USP purified water system. It consists of the Installation Qualification (IQ) testing described in Figure 1. The first step is verifying that all components and materials received conform to what was specified. One thing to consider is the installation of "quick disconnects" at each point of use or each monitoring point. This facilitates sample collection that will be necessary during the validation and any future monitoring. It is important to have appropriate instruction manuals and maintenance manuals with a spare parts list for each major component of the system (such as the compressor).

Correct installation of the piping, according to the compressed air network drawings must be verified. During verification, assure that the piping has been efficiently cleaned (flushed) with alcohol to removed any trace of oil, and/or other materials used during manufacturing and installation.

It is also necessary to consider utilities for each piece of equipment. Verify that the utilities comply with manufacturer's requirements. The overall plant capacity must be verified to ensure that it can safely provide the power supply required for each piece of equipment without affecting the functioning of the new and/or existing systems. Compressed air system leak testing followed by verification that all equipment and measurement tools were appropriately calibrated will conclude the IQ.

Compressed Air System Operational Qualification (OQ)

The OQ of a compressed air system consists of two phases:

■ Functional qualification at component and systems-levels.
■ Air quality testing.

During the first phase, each component and each specific piece of equipment must be checked to verify functional operation. Accordingly, it is necessary to design tests that challenge each major function. The ultimate test is one that verifies all functions of a piece of equipment in one unique operation. Unfortunately, this is difficult, and realistically, it will probably be necessary to perform many specific tests to thoroughly challenge each function.

The classic functional tests of compressed air system components might include, but are not limited to, the following:

■ Verification that mechanical moving parts move freely.
■ Verification that all necessary adjustments can be performed.
■ Verification that normal operating adjustments are not at the minimum or the maximum of the range.
■ Low and high alarm testing.
■ On/off sequences testing.
■ Simulation of a power supply shut down and recovery.

Systems-level testing consists of verifying that the compressed air system delivers the required cubic feet per minute (cfm) at the specified working pressure, and is capable of achieving and maintaining the specified dew point.

The air quality testing phase can be planned in the same manner as the water quality testing by generating a matrix of tests to perform. The following tests should be performed on samples taken immediately after the dryer, and at each product-contact point of use:

■ Viable particulates. A typical acceptance level could be less than 0.1 colony forming units per cubic feet (CFUs/ft^3) if the alert level is equal to or greater than 0.1 CFUs/ft^3, and the action level exceeds 0.15 CFUs/ft^3.

■ Non-viable particulates. A typical acceptance level could be less than 9,000 parts per cubic feet (ppcf) for 0.5 micron particulates if the alert level is equal to or greater than 9,000 ppcf for 0.5 micron particulates, and the action level exceeds 10,000 ppcf for 0.5 micron particulates.

■ Hydrocarbon content.

As with any OQ, conclude by verifying that all required operational and maintenance procedures are in place, applicable and approved (see *Figure 3*, procedures required during facility validation). Verify that training of personnel who utilizes, and/or maintain the system has been documented.

Compressed Air System Performance Qualification (PQ)

As with the compressed air system OQ, the PQ is conducted in two phases. The first phase consists of performing the following tests at least one week after the OQ on samples taken just after the dryer, and at each product-contact point of use:

■ Viable particulates.
■ Non-viable particulates.
■ Hydrocarbons content.

The system components should be recalibrated as appropriate in order to ensure that the measurements performed during the validation tests are valid. If some devices are found out of calibration, an investigation of the impact on the validity of the tests performed must be conducted, and a few or all of the OQ and PQ tests may have to be performed again. The second phase of the PQ consists of a less intensive, (but more than routine) monitoring of viable and non-viable particulate levels over at least a three month period ensuring that the system continues to produce the compressed air meeting documented specifications.

HVAC System Validation

The HVAC system considered as part of this validation project supplies conditioned air to a Class 100,000 controlled manufacturing environment (CME) by way of a duct network. Areas are pressurized to achieve the required differential pressures between manufacturing rooms, corridors and gowning rooms.

The system consists of:

■ An air handling unit (AHU). This provides filtered air, and consists of fans and their motors, high efficiency particulate air (HEPA) filters, dampers, a condenser unit with its refrigerant piping, an indirect fired gas heating unit with its gas piping, and an electric panel.

■ A temperature and humidification system. Primary humidifiers inject low pressure steam into the main branches of the duct network in quantities sufficient to produce slightly less than the nominal percent of relative humidity (%RH) required when the air stream temperature is raised to the room's nominal temperatures. Electric duct heaters and terminal trim humidifiers respectively reheat and rehumidify the air prior to being distributed into each area in order to maintain each room's specified temperature and %RH.

■ HEPA filters at the end of the ducts just before the distribution of the air into the room.

■ A sensor system. This consists of temperature and humidity sensors located down-stream from the main stream distributors. Temperature and humidity sensors are located in each room. Differential pressure sensors are located between adjacent manufacturing rooms, between manufacturing rooms and adjacent gowning rooms, between manufacturing rooms and adjacent corridors, and between gowning rooms and adjacent corridors. All these sensors are connected to a computerized control unit.

■ A computerized control unit. This serves to monitor temperature, the %RH and the differential pressure. It also controls the AHU, the primary humidifiers, the trim humidifiers and the heaters. This system is built within a computer-type environment with a lot of hardware components (electronics and printed circuit boards). A complex interconnection network between the unit and the sensors and between the unit and the AHU, the humidifiers and the heaters allows the monitoring and control by this computerized control unit. Of course, the computerized control unit contains several software components which must be validated.

HVAC System Installation Qualification (IQ)

The IQ of a HVAC System may take more than a week, since it involves many different pieces of equipment. However, this does not necessarily mean that the IQ will be difficult to execute. As in any installation qualification, begin by addressing the tests and tasks defined in the installation qualification (IQ) testing described in *Figure 1*. Customize the IQ protocols as necessary for the unique system. It will usually be necessary to add a few tests that are specific for the type of system that has been installed. In the case of the HVAC system described in this article, the system-specific tests consists of, but are not limited to, the following:

■ Duct network verification. Assures the correct duct sections are installed according to drawings and cleaned as defined in cleaning procedure.

■ Room verification. Requires checking that the rooms have been prepared correctly, so that no air leak can compromise the differential pressure that is established by the system.

■ Filter performance. Challenges for leaks and filter integrity. A certified company that is familiar with the appropriate standards, and utilizes only calibrated test equipment must perform testing on all filters. It is critical to use a non-cancerous aerosol agent for HEPA filters integrity testing, Dioctylphthalate (DOP) is questionable, and should not be used.

The validation of a HVAC system, as with any system, could be compromised if scientifically sound measurement principles are not followed. Basic measurement principles require verification and documentation that all measurement instruments utilized have been calibrated, and that the calibration is traceable to National Institute of Standards and Technology (NIST). The calibration must be within the due date. The accuracy of the instrument must be sufficient given the characteristic being measured. The rule of thumb is that the tolerance accuracy ratio (TAR) should ideally be equal to ten. The TAR is the ratio between the total tolerance of the characteristic measured, divided by the accuracy of the instrument utilized. Calibration is a critical part of the IQ, which includes verification that calibration of all components and equipment within the system is calibrated appropriately.

HVAC System Operational Qualification (OQ)

The OQ of a HVAC system will also be very time consuming as it requires that several pieces of equipment be functionally challenged. The OQ of this HVAC System will be conducted in six phases:

❶ Functional challenge of the components and pieces of equipment.
❷ Room balancing.
❸ Testing temperature and %RH monitoring and control systems
❹ Temperature and %RH mapping.
❺ Testing differential pressure monitoring system.
❻ Testing air quality.

The first phase, the functional challenges of components and equipment is unique and specific for each system. The following will outline only a few of the functional tests that are required. As stated in previous sections, each specific function of each component or piece of equipment needs to be challenged. As a guideline, ask the following question: do the tests performed establish confidence that this piece of equipment operates as it is intended to function? It may be very useful to generate a table with two columns. The first column contains the list of all major functions of the system, and the second specifies which test is performed to challenge the function. Special attention must be given to the safety checks, and the alarm's verifications. These aspects must be thoroughly tested ensuring a safe working environment, and establishing confidence that abnormal or unsafe conditions will be detected before they reach critical levels.

Room balancing, the second phase, must be done by specialists. As with HEPA filter performance testing mentioned above, a certified company familiar with the appropriate standards must conduct these tasks, and utilize only traceable calibrated test equipment. Differential pressure specifications depend on the room's usage and the type of product manufac-

tured. The purpose of the operational qualification is not determining whether or not the specifications are correct, but in establishing confidence that the system conforms to the specifications. The PQ demonstrates that there is a high probability that the system will continue to conform to these specifications.

The third phase, testing the temperature and %RH monitoring and control system, consists of a verification that the values of the actual temperature, and %RH in the rooms are:

- Correctly measured.
- Correctly sent to and received by the control system.
- Correctly interpreted by the control system (i.e., control system sent back the appropriate control signal to AHU, humidifiers and heaters.)

The easiest method of verifying that the values are correctly sent and received by the control systems is for one person to record the actual value within the room being tested and another person to record the value registered by the control station at the exact same time. It is helpful if these two persons maintain communication through portable receivers and transmitters or other similar wireless devices. It is extremely important that they record the values at precisely the same time in order to obtain meaningful data. Remember to repeat this procedure for each instrument, and/or sensor that transmits data to the system. Never assume that if the value measured by one temperature sensor, for example, is correctly transmitted, the values measured by the other temperature sensors will also be correctly transmitted. There are many potential causes for a single sensor to fail, thus preventing accurate data transmission (for example, an improper connection, defective output in the transmitting unit, or defective input in the receiving unit).

Verifying that the values are correctly interpreted by the control system can be performed by testing whether the control system responds as defined by the specifications. Events for which a response can be evaluated might include: decrease or increase in the ambient room temperature, change in ambient room %RH; decrease or increase in the room temperature set points, and temperature or %RH reaching predefined alarm limits. It is important to test each room, and verify that each humidifier and heater is turned on and off, when (and only when) it is expected.

The fourth phase, temperature and %RH mapping, requires verifying that the entire room is in compliance with its specifications, not only the specific area where the sensor is physically located. This is performed by measuring the temperature and %RH in various locations throughout the room; for example, the middle of the room, each corner, and at three feet and eight feet points within each location. A data sheet like the one shown in *Figure 4* (temperature and %RH mapping) could be used to record the values measured.

The fifth phase, testing the differential pressure monitoring system, consists of a verification that the differential pressure values are:

- Correctly measured.
- Correctly sent to and received by the control system.
- Correctly interpreted by the control system.

Verifications of correct measurement and receipt by the control system can be performed in a manner similar to that described previously for the temperature and %RH verifications. In order to verify the interpretation of the data received, it is necessary to check that the system generates an exception report. Such reports must correctly document any instance where differential pressure goes above or below the predefined alarm levels, identify the fault, identify the location, and the time of the event (date, time).

In the final phase, air quality testing will be conducted in each room and consists of measuring: viable particulates and non-viable particulates. Typical acceptable parameters for viable particulate might be < 0.1 CFUs/ft^3 if the alert level is equal to or greater than 0.1 CFUs/ft^3, and the action level exceeds 0.15 CFUs/ft^3. Typical acceptable parameters for non-viable particulates might be an acceptance level < 9,000 ppcf for 0.5 micron particulates, if the alert level is equal to or greater than 9,000 ppcf for 0.5 micron particulates, and the action level exceeds 10,000 ppcf for 0.5 micron particulates.

The OQ will conclude, as described in the other OQ sections of this article, with verification that appropriate procedures are in place, applicable,

Figure 4

Temperature and %RH Mapping

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

Room #:_____.
Date: _____.
Performed by:_____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

East
North South
West

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

Instrument ID #: _____.
Calibration Date:_____.
Calibration Due Date:_____.

%RH at 3': _____.
Temp at 3': _____.
%RH at 8': _____.
Temp at 8': _____.

approved, and personnel who utilize, and/or maintain the system, have been trained appropriately.

HVAC System Performance Qualification (PQ)

The PQ of the HVAC system consists of the monitoring of the following parameters every hour over at least thirty consecutive days:

■ Temperature. A typical acceptance criteria could be > 20ºC (68ºF) and < 25ºC (77ºF).
■ %RH. A typical acceptance criteria could be > 30 %RH, and < 65 %RH.
■ Differential pressures. Acceptance criteria is very specific and based on use and product requirements.

Always assure that all acceptance criteria is consistent with those defined in the approved system specification for each particular case

A temperature and %RH Mapping might be performed for each room at the end of the thirty day testing period to confirm that the entire room is still in compliance with its specifications.

The PQ concludes with verification of calibration status of all equipment, and assuring that all measurements made during the testing phase are acceptable.

Validation of New Systems vs. Existing Systems

The validations described are pertinent to the qualification of new systems; however, the approach to qualifying existing systems will not be significantly different. It is still necessary to form a multidisciplinary team, develop and document validation project plans, and perform IQ, OQ & PQ. The IQ phase will be modified because the systems are already installed. For example, during an IQ of an existing system, it is necessary to verify that the original architectural drawings are consistent with the equipment, as it is currently installed. This is in contrast to an IQ of a newly installed system, in which the equipment is compared to approved drawings.

The OQ and PQ phases will be approached in the same manner for a newly installed system or an existing system. Do not make the mistake of assuming that a review of historical data is a sufficient method of meeting OQ and PQ requirements for an existing system. The only means to competently perform an OQ and a PQ is thoroughly establishing documented evidence that the system operates in accordance with approved specifications and that it will reliably continue to do so. ❑

References

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