FDA Lifecycle Approach to Process Validation—What, Why, and How?

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“PQ Forum” provides a mechanism for validation practitioners to share information about Stage 2 process qualification in the validation lifecycle. Information about supporting activities such as equipment and analytical validation is shared. The information provided should be helpful and practical so as to enable application in actual work situations.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please contact column coordinator Paul Pluta at paul.pluta@comcast.net or managing editor Susan Haigney at shaigne@advanstar.com with comments, suggestions, or topics for discussion.

KEY POINTS
The following key points are discussed:

• The US Food and Drug Administration issued Process Validation: General Principles and Practices in January 2011, which has given widespread visibility to the lifecycle approach concept.
• The process validation guidance integrates strategy and approaches to provide a comprehensive approach to validation. Three stages in the lifecycle approach are identified. The lifecycle concept links development, validation performance, and product or process maintenance in a state of control during routine commercial production.
• Understanding the sources of variation and control of variation commensurate with risk is a key component of the lifecycle approach.
• FDA has provided recommendations for the general lifecycle and stages 1, 2, and 3. Specific expectations are discussed.
• Stage 1—Process Design may be generally described as “process understanding.” Stage 1 work is ultimately reflected in the master production record and control records.
• Stage 2—Process Qualification may be described as “validation performance.” This stage comprises demonstration of final process performance by means of conformance lots. Stage 2 confirms the development work of Stage 1 Process Design.
• Stage 2 specific recommendations are provided for design of a facility and qualification of utilities and equipment, process performance qualification (PPQ), PPQ protocol, and PPQ protocol execution and report.
• Stage 3—Continued Process Verification may be simply described as “maintaining validation.” This stage comprises the ongoing commercial manufacturing of the product under the same or equivalent conditions as demonstrated in Stage 2 Process Qualification.
• The integration of development work, process conformance, and continuing verification provides assurance the product or process will consistently remain in control throughout the entire product lifetime.
• The lifecycle approach integrates various strategies, approaches, and expectations that had been mentioned in multiple previously published docu-
ments, guidelines, and presentations for many years.
• The concepts identified in the respective stages of the FDA process validation guidance—understanding, performance, and maintenance—serve as a model for all areas of validation and qualification.
• The new guidance affects many areas of site validation programs including organizational aspects, validation performance specifics, risk analysis, training, and documentation.
• Senior and functional management support is needed to transition organizations to the lifecycle approach to validation. Risk analysis is key to development and prioritization of a suitable program that will be embraced and supported.

INTRODUCTION
The US Food and Drug Administration issued Process Validation: General Principles and Practices (1) in January 2011. This guidance has given widespread visibility to the lifecycle approach concept. Validation managers are now responding to questions and comments about the guidance from their colleagues. The following discusses these and other areas of concern raised by attendees at validation meetings in Montreal (2010), Philadelphia (2010), and Amsterdam (2011). These are relevant “hands-on” questions from people that face validation problems every day. Topics addressed in this discussion include the following:
• What is different about the lifecycle approach? What is its emphasis compared to the 1987 FDA process validation guidance (2)?
• Why the lifecycle approach? Is it really a new approach?
• Should the lifecycle approach be applied to other areas of validation and qualification? What about using the lifecycle approach to other processes and to equipment, HVAC, computer systems, and other qualifications?
• How does the guidance affect our current validation programs? What areas need to be modified to be compliant with the new guidance?

THE LIFECYCLE APPROACH
The January 2011 process validation guidance (1) has integrated information, strategy, and approaches discussed in various US and international documents to provide a comprehensive approach to validation (i.e., the lifecycle approach). The guidance provides specific and detailed recommendations for each stage of the lifecycle approach.

The definition of process validation stated in the 2011 guidance is as follows:
“Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.”

The guidance describes process validation activities in the following three stages:
• Stage 1—Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
• Stage 2—Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
• Stage 3—Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.”

These sections of the 2011 guidance clearly identify the key difference between the lifecycle approach compared to validation in the 1987 FDA guidance. The 2011 lifecycle approach to process validation encompasses product and process activities beginning in development and continuing throughout the commercial life of the product. The 1987 definition and subsequent discussion in the guidance placed major emphasis on the validation protocol, testing, results, and documentation—what is now considered to be Stage 2 in the lifecycle approach. Development work and post-validation monitoring were not emphasized in the 1987 guidance.

Approach to Process Validation—Stages 1, 2, and 3
The approach to process validation stated in the 2011 guidance clearly emphasizes contemporary concepts and expectations for pharmaceutical manufacturing. The manufacturer should have great confidence that the performance of manufacturing will consistently produce active pharmaceutical ingredients (APIs) and drug products meeting expected attributes. This confidence is obtained from objective information and data from laboratory, pilot, and commercial-scale studies (i.e., the work of Stage 1). After completion of Stage 1 development, Stage 2 Process Qualification confirms the work of Stage 1.
After successful Stage 2 performance, Stage 3 Continued Process Verification maintains the validated state. The guidance states:

“The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation through sound science.”

Successful validation depends on knowledge and understanding from product and process development. Specific key areas mentioned in the guidance include the following:

• “Understanding the sources of variation
• Detect the presence and degree of variation
• Understanding the impact of variation on the process and ultimately on product attributes
• Control the variation in a manner commensurate with the risk it represents to the process and product.”

FDA Recommendations

The 2011 guidance discusses several areas and provides specific details. These include recommendations for the general lifecycle and stages 1, 2, and 3. The entire recommendations section of the guidance is provided online at FDA.gov.

General considerations. These considerations are applicable to all stages in the lifecycle. For example, an integrated team approach that includes expertise from multiple disciplines and project plans is recommended. The support of senior management is termed “essential.” Other general topics discussed include the initiation of studies to further understand product and process during the lifecycle, attribute evaluation, and the need for higher levels of control for parameters associated with higher risk.

Stage 1—process design. This stage may be generally described as “process understanding.” Studies are conducted during this stage to develop and characterize product and process. The work of Stage 1 should be commensurate with the identified or expected risk for the product and process.

Stage 1 recommendations address development activities that will ultimately be reflected in the master production record and control records. The guidance clearly states the goal of stage 1: “To design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.” The following two topics are discussed:

• Building and capturing process knowledge and understanding. This section discusses the role of product development and uses terminology common to the quality-by-design (QbD) initiative—quality attributes, design of experiments (DOE) studies, and so on.
• Establishing a strategy for process control. This section addresses reducing input variation, adjustment for input variation during processing, and related topics.

Stage 2—process qualification. This stage may be simply described as “validation performance.” This stage is most similar to the traditional definition and performance of validation. The testing of Stage 2 should be commensurate with the risk identified for the product and process.

Stage 2 comprises demonstration of commercial process performance by means of conformance lots. This stage confirms the development work of Stage 1. Successful stage 2 performance demonstrates that the proposed manufacturing process is capable of reproducible commercial manufacture. Process performance qualification (PPQ) conformance lot manufacturing includes increased testing to demonstrate acceptability of the developed formulation and process.

The 2011 validation guidance provides several specific recommendations for the respective stages of process validation. Validation managers must become familiar with these requirements and incorporate them into their site training programs. The guidance discusses the following in Stage 2.

Facility, utilities, and equipment. The FDA 2011 guidance specifies the following regarding facility, equipment, and utilities:

• Utilities and equipment construction materials, operating principles, and performance characteristics must be appropriate for their specific use.
• Utilities systems and equipment must be built and correctly installed, according to manufacturer’s directions, and then properly maintained and calibrated.
• Utility system and equipment must be qualified to operate in the ranges required in processing. The equipment should have been qualified under production-level loads and for production-level durations. Testing should also include interventions, stoppage, and start-up as is expected during routine production.

The 2011 guidance provides specific expectations for a plan to qualify facility, equipment, and utilities, as follows:
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• The plan should include risk management to prioritize activities and documentation
• The plan should identify
  (1) Studies or tests to use
  (2) Criteria appropriate to assess outcomes
  (3) Timing of qualification activities
  (4) Responsibilities
  (5) The procedures for documenting and approving the qualification
• Change evaluation policy
• Documentation of qualification activities
• Quality assurance (QA) approval of the qualification plan.

The above is a clear directive to the site validation approval committee (VAC) as to FDA’s expectations for facilities, equipment, and utilities qualification. Process performance qualification. The PPQ is intended to confirm the process design and development work and demonstrate that the commercial manufacturing process performs as expected. This stage is an important milestone in the product lifecycle. The PPQ should be based on sound science and experience. The PPQ should have a higher level of testing and sampling. The goal of the PPQ is to demonstrate that the process is reproducible and will consistently deliver quality products.

PPQ protocol. A written protocol is essential and should discuss the following:
• Manufacturing conditions, process parameters, process limits, and raw material inputs
• How data are to be collected and evaluated
• Testing and acceptance criteria
• Sampling plan including sampling points and number of samples
• Number of samples should demonstrate statistical confidence
• Confidence level based on risk analysis
• Criteria for a rational conclusion of whether the process is acceptable
• Statistical methods used to analyze data
• Provision to address deviations and non-conformances
• Design of facilities, qualification of equipment and facilities
• Personnel training and qualification
• Verification of sources of materials and containers and closures
• Analytical method validation discussion
• Approval by appropriate departments and the quality unit.

PPQ protocol execution and report. Protocol execution should not start until the protocol has been approved. Changes to the approved protocol must be made according to established procedures. The routine manufacturing process and procedures must be followed (i.e., usual conditions, personnel, materials, environments, etc.). The PQ report should do the following:
• Discuss and cross-reference all aspects of the protocol
• Summarize and analyze data
• Evaluate unexpected observations and additional data not specified in the protocol
• Discuss deviations and non-conformances
• Describe corrective actions
• State a clear conclusion whether the process is validated or if not, what should be done to validate the process
• Be approved by appropriate departments and the quality unit.

Stage 3—Continued process verification. This stage may be simply described as “maintaining validation,” or “maintaining the validated state.” Maintenance activities of Stage 3 should be commensurate with the risk identified for the product and process.

Assuming good development of the process, identification of potential variation, and control of same, the manufacturer must maintain the process under control over the product lifetime (i.e., the work of Stage 3). This control must accommodate expected changes in materials, equipment, personnel, and other changes throughout the commercial life of the product based on risk analysis.

Stage 3 comprises the ongoing commercial manufacturing of the product under the same or equivalent conditions as demonstrated in Stage 2. This phase continues throughout the entire commercial life of the product or process. Specific topics discussed in this section include the following:
• Ongoing program to collect and analyze process data, including process trends, incoming materials, in-process material, and finished products
• Statistical analysis of data by trained personnel
• Procedures defining trending and calculations
• Evaluation of inter-batch and intra-batch variation
• Evaluation of parameters and attributes at PPQ levels until variability estimates can be established
• Adjustment of monitoring levels based on the above
• Timely assessment of defect complaints, out-of-specification (OOS) findings, deviations, yield
variations, and other information

- Periodic discussion with production and quality staff on process performance
- Process improvement changes
- Facilities, utilities, and equipment must be maintained to ensure process control.

WHY THE LIFECYCLE APPROACH?

For manufacturing processes to be truly validated, each of the stages must be addressed and integrated. This integration of development work, process conformance, and continuing verification provides assurance that the product or process will consistently remain in control throughout the entire product lifecycle. Process validation must not be considered a one-time event or a focused one-time task performed just prior to commercial launch that emphasizes only the manufacture of three conformance lots. Acceptable manufacture of three conformance lots must not be interpreted as completion of validation. These lots cannot truly represent the future manufacturing process with unexpected and unpredictable changes. Conformance lots are often inadvertently biased (i.e., they may utilize well-characterized and controlled API and excipients, be manufactured under well-controlled conditions, be monitored by expert individuals, and performed by most experienced or well-trained personnel—all “best-case” conditions). It is highly unrealistic to contend that the manufacture of three conformance lots under “best-case” conditions conclusively predicts successful manufacturing over the product lifetime. True process validation must be a process that is never completed and is always ongoing.

Is This Really a New Approach?

The lifecycle approach to process validation is not really a new approach or a new concept (3). In an interview with FDA investigator Kristen Evans published in the Journal of Validation Technology in February 2000, the investigator commented on the failure of manufacturers to recognize a lifecycle approach to validation (see Sidebar).

The three-stage lifecycle description of process validation as discussed in the FDA process validation guidance integrates various strategies, approaches, and expectations that had been mentioned in several published documents, guidelines, and presentations. FDA representatives have openly discussed the lifecycle approach to process validation for several years (4,5,6). The draft process validation guidance that formally introduced the lifecycle approach for industry comment was published in 2008 (7). The


Q. What are some of the major process validation problems you have seen during your inspections of manufacturing facilities in the United States?

A. I think, as a whole, the failure to recognize the lifecycle approach to validation. We see many firms, for whatever reason, thinking that once they complete their prospective three-batch validation, that’s the end and they’re on their way. I like to say that prospective validation is not the end. It’s not the beginning of the end; it is hopefully the end of the beginning. But, clearly, it’s an ongoing process. It requires a concerted effort to really maintain confidence in the process and to be able to demonstrate that at any given time. So, when we conduct our inspections, we want to know how the firm gives itself, and therefore us, the confidence that a given process on that day is under control. And you’re not simply saying, “Well, we validated it a few years ago,” or “We’re going to do our annual review in a couple of months, and that will show us,” but rather, systems are in place at any given time to show from a big picture that it’s validated. As opposed to general problems discussed in the previous paragraph, a more specific problem that we see is a lack of scientific rationale in the protocols and acceptance criteria. At least there is a lack of documentation of such rationale, which is what we’re expecting to see. We want the process to be there, that you’ve come up with a scientific study, a protocol—this is what you’re attempting to show, and this is why, and this is how it’s going to be evaluated, and then just simply executing that. That’s documentation of the scientific rationale.

Note: The above comments are the personal opinions of Mr. Evans and are not FDA policy.
lifecycle approach overcomes the “checklist” approach to process validation, whereby, process validation is considered to be a “one-time event.” Encouraging comprehensive process understanding improves root cause analysis when manufacturing problems occur. Successfully manufacturing three validation lots without sufficient process understanding does not provide good assurance that the manufacturing process will consistently yield an acceptable product throughout the product commercial life.

The September 2006 FDA Quality Systems Approach to Pharmaceutical CGMP Regulations (8) clearly discusses expectations for maintenance of the validated state. In discussing performance and monitoring of operations, the regulations state, “An important purpose of implementing a quality systems approach is to enable a manufacturer to more efficiently and effectively validate, perform, and monitor operations and ensure that the controls are scientifically sound and appropriate.” Furthermore, “Although initial commercial batches can provide evidence to support the validity and consistency of the process, the entire product lifecycle should be addressed by the establishment of continual improvement mechanisms in the quality system. Thus, in accordance with the quality systems approach, process validation is not a one-time event, but an activity that continues through a product’s life.” This document also discusses trend analysis, corrective action and preventive action (CAPA), change control, and other quality systems programs.

The FDA Pharmaceutical cGMPs for the 21st Century—a Risk-Based Approach (9), states the following:

“We have begun updating our current thinking on validation under a Cross-Agency Process Validation workgroup led by CDER’s Office of Compliance Coordinating Committee with participation from CDER, CBER, ORA, and CVM. In March of this year, FDA began this process issuing a compliance policy guide (CPG) entitled Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08, Sec 490.100) (10). The CPG stresses the importance of rational experimental design and ongoing evaluation of data. The document also notes that achieving and maintaining a state of control for a process begins at the process development phase and continues throughout the commercial phase of a product’s lifecycle. The CPG incorporates risk-based approaches with respect to inspectional scrutiny; use of advanced technologies, and by articulating more clearly the role of conformance batches in the product lifecycle. The document clearly signals that a focus on three full-scale production batches would fail to recognize the complete story on validation.”

In the 2004 revision of FDA Compliance Policy Guide Sec. 490.100, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08), expectations for validated processes are clearly stated. “Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of the initial conformance batches. Conformance batches (sometimes referred to as validation batches and demonstration batches) are prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. Prior to the manufacture of the conformance batches the manufacturer should have identified and controlled all critical sources of variability.” FDA has removed reference to manufacture of three lots as a requirement for validation in this document.

The process validation guidance is consistent with FDA QbD principles. The various QbD presentations and publications strongly encourage demonstrations of process understanding for both API and drug product (11,12,13,14). In the 2006 FDA Perspective on the Implementation of Quality by Design (QbD), a QbD system is defined as follows:

• The API or drug product is designed to meet patient needs and performance requirements
• The process is designed to consistently meet critical quality attributes
• The impact of starting raw materials and process parameters on quality is well understood
• The process is evaluated and updated to allow for consistent quality over time
• Critical sources of process variability are identified and controlled
• Appropriate control strategies are developed.

The various FDA guides to inspections (15,16,17), all issued during the 1990s, emphasized the development phase of the validated process and associated documentation. This included documented experiments, data, results, control of the physical characteristics of the excipients, particle size testing of multi-source excipients and determination of critical process parameters. Development data serves as the founda-
tion for the manufacturing procedures, and variables should be identified in the development phase. Raw materials were identified as a source of lot-to-lot variation, as were equipment or processes that could impact product effectiveness or product characteristics (i.e., the validated state must be maintained).

Some of the key concepts in the 2011 process validation guidance were originally mentioned in the FDA 1987 guidance. For example, the 1987 guidance states, “...adequate product and process design...quality, safety, and effectiveness must be designed and built into the product...” and “During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, electrical, and performance characteristics.” In addition to discussing actual validation protocols, the document mentions several post-validation considerations, as follows: “...quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact product effectiveness or product characteristics, and whenever there are changes in product characteristics. The quality assurance procedures should establish the circumstances under which revalidation is required.”

The 2011 process validation guidance clearly states its consistency with International Conference on Harmonisation (ICH) Q8, Q9, and Q10 documents (18). These documents provide current global thinking on various aspects of the product lifecycle from development through commercialization. They provide a comprehensive and integrated approach to product development and manufacturing to be conducted over the lifecycle of the product. ICH Q8 discusses information for regulatory submission in the ICH M4 Common Technical Document format (19). ICH Q8 describes a comprehensive understanding of the product and manufacturing process that is the basis for future commercial manufacturing including QbD concepts. ICH Q9 provides a systematic approach to quality risk management through various risk assessment tools. ICH Q9 also suggests application of risk management methods to specific functions and business processes in the organization. ICH Q10 complements Q8 and Q9, and discusses the application of the various quality system elements during the product lifecycle. Elements of the quality system include process performance monitoring, CAPA, change control, and management review. These quality system elements are applied throughout the various phases of the product lifecycle.

The 2000 ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (20) discusses activities conducted prior to and post validation. For example, ICH Q7 states that critical parameters or attributes should be identified during development, and these critical process parameters should be controlled and monitored. Non-critical parameters should not be included in validation. Regarding post validation, there should be periodic review of validated systems.

**Medical Device Validation Guidance**

Although the 2011 process validation guidance does not apply to medical devices, medical device documents espouse an equivalent comprehensive approach to process validation. In the January 2004 Global Harmonization Task Force (GHTF) Study Group 3, Quality Management Systems—Process Validation Guidance (21), activities conducted during product or process development to understand the process are described. For example, “The use of statistically valid techniques such as screening experiments to establish key process parameters and statistically designed experiments to optimize the process can be used during this phase.” This document also describes activities conducted post-validation to maintain the product or process. For example, “Maintaining a state of validation” by monitoring and control including trend analysis, changes in processes or product, and continued state of control of potential input variation such as raw materials. Tools including statistical methods, process capability, control charts, design of experiments, risk analysis, and other concepts are described.

The 1997 FDA Medical Device Quality Systems Manual (22) further emphasizes activities to be conducted post validation. It states, “Process and product data should be analyzed to determine what the normal range of variation is for the process output. Knowing what is the normal variation of the output is crucial in determining whether a process is operating in a state of control and is capable of consistently producing the specified output. Process and product data should also be analyzed to identify any variation due to controllable causes. Appropriate measures should be taken to eliminate controllable causes of variation... Whether the process is operating in a state of control is determined by analyzing day-to-day process control data and finished device test data for conformance with specifications and for variability.”

The 1997 Guide to Inspections of Medical Device Manufacturers (23) states, “It is important to remember that the manufacturer needs to maintain a validated state. Any change to the process, including changes
in procedures, equipment, personal, etc. needs to be evaluated to determine the extent of revalidation necessary to assure the manufacturer that they still have a validated process.

**APPLYING THE LIFECYCLE APPROACH**
The concepts identified in the respective stages of the FDA process validation guidance—process design (understanding), process qualification (performance), and continued process verification (maintaining validation)—serve as a model for all areas of validation and qualification. Although not specifically mentioned in the FDA guidance, the sequence of understanding, performance, and maintaining the validated state is certainly applicable and desirable for other processes in pharmaceutical manufacturing including packaging, cleaning, analytical, and so on. Further applying this sequence to equipment qualification, HVAC, computer systems, and other areas is also appropriate and desirable. Presentations on these associated topics at validation meetings have already been structured according to this model. The installation qualification-operational qualification-performance qualification (IQ/OQ/PQ) model and the ASTM E2500 (25) model are consistent with understanding, qualifying, and maintaining qualification through calibration, preventive maintenance, change control, and associated activities. Applying the stages 1, 2, and 3 sequence of activities to all validation and qualification unifies the site approach to project management activities, standardizes expectations, facilitates training, and generally simplifies organizational thinking.

**THE AFFECT ON CURRENT VALIDATION PROGRAMS**
A major concern of validation practitioners gets to the “bottom line”—How does the 2011 guidance affect current validation programs, and how can the new guidance be implemented?

**Organizational Aspects**
The lifecycle approach to process validation requires commitment from many areas in the organization. The lifecycle approach must become part of organizational strategy. This will require a comprehensive and continuing view of validation rather than focus on the performance of the usual three conformance lots—and “job done.” Many firms organize their operations in distinct silos (e.g., R&D, manufacturing, and quality). The silos create barriers to communication and cooperation. The R&D organization develops the product. After development is completed, the product is transferred to manufacturing. Commercial operations personnel “adjust” the process and make it ready for validation and routine production. The validation function coordinates process validation. After the conformance lots are successfully completed, the validation effort is finished. Manufacturing then continues routine commercial production with oversight by the quality unit or the qualified person (QP). Often there is minimal ongoing constructive interaction between R&D, validation, manufacturing, and quality during the product lifetime.

The lifecycle approach to validation is clearly different than the above described situation. Product R&D and technical support should approach their work as supporting the entire product lifecycle including commercial manufacturing. They must be involved in monitoring and maintenance of the validated state. Their work should provide the technical basis or justification for all aspects of manufacturing including any changes and necessary improvements. The validation group should coordinate the process qualification stage of manufacturing based on technical development work, and should participate in determining the ongoing control strategy. The validated state must be maintained through process monitoring, technical data evaluation, and change control. Manufacturing “fixes” or “tweaks” should be evaluated by technical people, and should ideally be supported by data or sound technical judgment whenever possible. R&D should be involved in process improvements and provide the technical justification for these improvements. Organizations should foster development of a continuous business process beginning in R&D and continuing throughout the entire product lifecycle with ongoing collaboration and communication among all relevant organizational areas. The lifecycle approach to process validation must become a comprehensive organizational effort.

**Validation Performance Specifics**
The 2011 guidance describes many specific details and expectations for Stage 2 and Stage 3. Validation and quality managers should evaluate their practices and procedures regarding these specifics. FDA recommendations for Stage 2 PPQ protocol-related activities are substantial. FDA recommendations for Stage 3 post-validation monitoring are significantly different from a traditional “Annual Product Review” approach. Deficiencies in site programs should be identified and corrective actions or improvements prioritized. Risk to the patient and to the organization should be considered in prioritization.
Risk Analysis
Risk assessment has a critical role in all of the activities described herein. All activities conducted in the organization should be conducted with risk in mind. ICH Q9 describes various risk assessment methods and potential applications of risk assessment. There are numerous applications of risk management used during the entire process validation lifecycle. Examples cited in ICH Q9 relevant to process validation include product and process development, facilities and equipment design, hygiene aspects in facilities, qualification of equipment, facility, or utilities, cleaning of equipment and environmental control, calibration and preventive maintenance, computer systems and computer controlled equipment, and so on. In brief, risk assessment helps to identify the most important potential problems in all three stages of process validation, and then addresses these problems appropriately. There should be consistency between the risk-based activities in all three stages of process validation. Risk management must become pervasive in the organization.

Training
The issuance of the 2011 FDA guidance requires appropriate training for all involved in validation-related activities. All involved in validation and validation-related activities must be aware of the 2011 process validation guidance and concepts therein. Personnel who previously considered themselves to be apart or distant from commercial product validation (e.g., development scientists) must now be included in validation training.

Especially important are personnel who write validation plans, protocols, results, and associated documents. These writers must think comprehensively, incorporating pre-validation development information as well as considerations for post-validation maintenance of the validated state into their validation documentation.

Also critically important for training are the site VAC members. There must be a clear understanding and agreement among VAC members and the validation group as to their functions and responsibilities. Clearly stating the responsibilities of the VAC provides focus and expectations for the VAC. Clearly stating the responsibilities of the VAC provides clear expectations for those submitting protocols, validation plans, and other documents for VAC review and approval. VAC members must maintain awareness and compliance with the 2011 process validation guidance. The VAC members should consider themselves to be a surrogate FDA (or other regulatory agency) auditor. The VAC should assume responsibility for site preparedness for future regulatory audits of the validation function. Future audits will certainly include concepts and recommendations stated in the 2011 process validation guidance.

Terminology
The terminology associated with the various phases of validation has had minor variations over the years. The 2011 process validation guidance describes process design, process qualification, and continued process verification stages in the validation lifecycle. Stage 2 Process Qualification includes PPQ manufacturing of commercial lots. The 1987 FDA validation guidance describes installation and operational qualification, process performance qualification, and product performance qualification. Products lots manufactured in the process qualification phase were termed “conformance lots.” PPQ batches have also been named “demonstration lots,” “qualification lots,” “PQ lots,” and “validation lots,” in past years. Stage 2 process qualification phase also includes equipment, facilities, and utilities qualification.

While the variety of terminology used may cause difficulties in communicating, the intent of all validation programs is the same: Sequential process understanding, validation performance, and maintaining the validated state as described herein comprise the validation lifecycle continuum. Validation programs addressing these phases of the product or process lifecycle, no matter what specific terminology is used or how categorized in documentation, will meet the expectations robustness, repeatability, and reliability for validated process. Regulatory investigators are knowledgeable and able to interpret different organizational terminology as long as the sequence of process understanding, validation performance, and maintaining the validated state are demonstrated.

Documentation
All work associated with process validation in all stages of the validation lifecycle must be documented. This includes product and process design, experimental and development studies for process understanding, risk analysis in development, designed experiments, process parameter optimization, validation and qualification protocols, and process monitoring to maintain the validated state. Development scientists must understand that their work is integral to the validation lifecycle. Development reports may be requested in regulatory audits. Summary documents are recommended, especially when multiple documents must be integrated by the reader. All work associated with equipment, facilities, and utilities qualification and analytical validation must
also be documented. Document quality is important; in many cases, documents are reviewed literally years after they are written and long after authors have moved on to new careers inside or outside of the company. All associated documents must be readily available. Documents are often required to be quickly retrieved in regulatory audits. Document storage in an easily accessible centralized location is recommended.

Analytical
The guidance briefly discusses expectations for analytical methodology in process validation. It states that process knowledge depends on accurate and precise measuring techniques. Analytical areas supporting early Stage 1 R&D work must be aware that their methods and data may be subject to inspection in validation audits. Test methods must be scientifically sound (e.g., specific, sensitive, accurate), suitable, and reliable. Analytical instruments must function reliably. Analytical method development reports must be available for auditor review. Procedures for analytical methods, equipment maintenance, documentation practices, and calibration practices should be documented or described. Current good manufacturing practice CFR 210 and 211 must be followed as appropriate for batch release of commercial lots.

Management Support
The support of senior management and the respective functional management of affected areas in the organization is critical to implementing the lifecycle approach. Management in the organization must become familiar with the 2011 validation guidance and its ramifications. Transitioning organizations to the lifecycle approach to validation cannot be completed without management support. Employees provide what management expects. Validation and quality professionals should help their management to assess the status of their organizations. Deficiencies must be corrected and enhancements implemented. Validation and quality professionals should prioritize activities based on risk to patient and organization. Economic impact must also be considered. A balance of risk, cost, and compliance considerations is key to development of a suitable validation program that will be embraced and supported.

CONCLUSIONS
FDA issued Process Validation: General Principles and Practices in January 2011, which has given widespread visibility to the lifecycle approach concept. This comprehensive approach to validation has significant and far-reaching ramifications. Three stages in the lifecycle approach have been identified. The lifecycle concept links development, validation performance, and maintenance of the process in a state of control during routine commercial production.

FDA has provided recommendations for the general lifecycle and stages 1, 2, and 3 including specific details for each of the stages. Stage 1—Process Design may be generally described as “process understanding.” Stage 1 work will ultimately be reflected in the master production record and control records. Stage 2—Process Qualification may be described as “validation performance.” This stage comprises demonstration of commercial process performance by means of conformance lots and confirms the development work of Stage 1. Stage 2 details are also provided for design of a facility and qualification of utilities and equipment, PPQ, PPQ protocol, and PPQ protocol execution and report. Stage 3—Continued Process Verification may be simply described as “maintaining validation.” This stage comprises the ongoing commercial manufacturing of the product under the same or equivalent conditions as demonstrated in Stage 2. Stage 3 continues throughout the entire commercial life of the product or process. Understanding the sources of variation and control of variation commensurate with risk should be applied during all stages of validation. The integration of development work, process conformance, and continuing verification provides assurance the product or process will consistently remain in control throughout the entire product lifetime.

The lifecycle approach is not a new concept. This approach as described in the guidance integrates various strategies, approaches, and expectations that had been mentioned in several previously published documents, guidelines, and presentations. The concepts identified in the respective stages of the FDA process validation guidance—understanding, performance, and maintenance—serve as a model for all areas of validation.

Implementation of the lifecycle approach in site validation programs has significant ramifications for the organization. Organizational functions previously “distant” from commercial processes are now integral to ongoing performance. Post-validation monitoring of process performance including timely responsiveness to data trends is an expectation. The lifecycle approach affects many areas of validation programs including organizational aspects, validation performance guidance specifics, risk analysis, training, and documentation. Senior and functional management support is needed to transition organizations to the lifecycle approach to validation. Risk analysis is key to development and prioritization of a suitable validation program that will be embraced and supported.
REFERENCES
10. FDA, Compliance Policy Guide 7132c.08. Section 490.100. Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval.
18. www.ICH.org

ARTICLE ACRONYM LISTING
API Active Pharmaceutical Ingredient
CAPA Corrective Action and Preventive Action
DOE Design of Experiments
FDA US Food and Drug Administration
ICH International Conference on Harmonisation
IQ Installation Qualification
OOS Out of Specification
OQ Operational Qualification
PPQ Process Performance Qualification
PQ Performance Qualification
QbD Quality by Design
QP Quality Person
R&D Research and Development
VAC Validation Approval Committee