EXECUTIVE SUMMARY

Recent documents and discussions have emphasized a comprehensive and integrated approach to the validation of manufacturing processes—the lifecycle approach to process validation. This approach comprises process understanding derived from laboratory studies and process development history; commercial scale manufacturing operations at target process parameter values (conformance batches); and maintenance of the validated state through ongoing monitoring of process performance.

Process understanding includes all scientific and technical work conducted in support of validation conformance batches and subsequent routine manufacturing and monitoring. This work includes the lab-scale, pilot-scale, and commercial-scale studies conducted to establish the design space within which the process can successfully operate during routine commercial manufacturing. Process understanding must include an understanding and control of variable input factors (materials, people, etc.) affecting the process, as well as technology transfer from pilot scale to commercial scale processing. The control of critical variable input factors will result in predictable and acceptable outputs that define product quality and process acceptability.

When the process is understood and process parameters are optimized, validation performance is conducted. This phase includes the components of traditional validation performance: A validation plan, validation protocol, appropriate sampling, testing, and acceptance criteria. This phase of process validation also includes the qualification of associated equipment, facilities, and utilities.

After validation performance and release of the manufacturing process for commercial manufacturing, there must be appropriate systems to maintain the validated state of the manufacturing process. Qualification of associated equipment and systems must also be continually maintained.

All work associated with process validation must be documented.

The terminology associated with the various phases of validation has had minor variations over the years. Despite this variety, the intent of all process validation programs is the same: Process understanding, validation performance including conformance batches, and maintenance of the validated state.

INTRODUCTION

This first offering of the “Validation Learning Center” provides a summary of information about validated processes as expressed in various regulatory documents and recent presentations. This column should help to clarify current expectations for validated processes. Subsequent papers addressing the individual concepts of this column are planned for future issues of the Journal of Validation Technology.

Guidelines for process validation have remained essentially unchanged over the years—current expectations for validated processes have not changed from the concepts discussed in the 1980s and 1990s. More recent documents and discussions have emphasized a more comprehensive and integrated approach to the validation of manufacturing processes. This recent emphasis has specifically included development work conducted in advance of the conformance batches (previously referred to as the validation batches) and monitoring activities to assess the maintenance of the validated state and provide the data to implement continuous improvement. This approach has been de-
scribed as a lifecycle approach to process validation. In the lifecycle approach, validation is never completed—validation is always ongoing. The lifecycle approach extends far beyond a minimal "three-lot" approach to process validation. This approach is consistent with other recent discussions, (e.g., quality by design and quality systems).

Validated processes, to which the above is applicable, include manufacturing process validation of pharmaceutical and biotech products and medical devices; cleaning validation; as well as similar processes. Associated equipment, facilities, utilities, etc. supporting each respective process validation must also be qualified and maintained.

OVERVIEW OF EXPECTATIONS FOR VALIDATED PROCESSES

Product manufacturers are expected to have sufficient knowledge and experimental data to have confidence that the manufacturing process consistently delivers a high quality product. Research and development knowledge must yield manufacturing processes that are robust, are based on scientific and technical principles, and are appropriately well controlled. Manufacturing process performance must be demonstrated to confirm acceptability before product is released for commercial distribution. Thereafter, quality systems must maintain process controls and guarantee assurance of continuing high quality product manufacturing and product performance. This integrated and comprehensive approach to process validation characterizes a truly validated process.

The following three integrated and continuing phases thus characterize a validated process:

- **Process understanding.** Knowledge and understanding of relationships between process variables and quality attributes are determined during product and process development. Process understanding and establishment of process design space are fundamental to validated processes and are crucial to consistent manufacturing. Good understanding of the manufacturing process must be technically and scientifically based, and critical process parameters and quality attributes must be identified. Identification of critical variables and adequate control of these variables is necessary for validated processes. Without control of critical variables, relationships determined in experimental studies will not be meaningful. Effective transfer of this knowledge and understanding to commercial scale manufacturing is critical for both validation and successful routine manufacturing. Long term and ongoing manufacturing success must be the focus and the objective of the product and process development effort supporting process validation.

- **Validation performance (conformance batches) including associated qualifications.** The performance of multiple full-scale manufacturing lots confirms the acceptability of manufacturing processes as previously designed and developed. This activity includes the supporting qualification of associated process equipment and systems. Significant testing of ranges of critical input variables is not typically conducted at commercial scale for processes for which robust process understanding has been developed. Range data will have already been captured during process development. Processes controlled by process analytical technology (PAT) are desirable since these processes adjust to variation in process inputs and thereby minimize variation in the process output.

- **Maintenance of the validated state.** Validated processes must be continually maintained and monitored to guarantee process control. Qualification of associated equipment and systems must also be continually maintained. Ongoing process monitoring and review of performance data at appropriate frequency is necessary to assure continued acceptable performance and control of the validated process. Process monitoring should lead to enhanced process performance, process improvements, and further control of variation.

For manufacturing processes to be truly validated, each of the above must be addressed. The integration of development work, process conformance, and continuing monitoring and maintenance provides assurance that the product/process will consistently remain in control throughout the product lifecycle.

Process validation must not be considered a one-time event. Process validation must not be a focused one-time task performed just prior to commercial launch—with emphasis on the manufacture of three conformance lots. Acceptable manufacture of three conformance batches must not be interpreted as completion of validation. These lots cannot truly represent the future manufacturing process and all future predictable and unpredictable changes. These lots may be "biased," i.e., they may utilize well characterized and controlled active pharmaceutical ingredients (API) and excipients, be manufactured under exceptionally
well controlled conditions, and performed by most well-trained personnel. This is not a realistic representation of routine manufacturing conducted over the product life. It is not possible for the manufacture of three conformance lots to conclusively demonstrate that a manufacturing process is truly validated.

Supporting Presentations and Documents

Two recent separate presentations have discussed the lifecycle approach to process validation. In “Lifecycle Approach Process Validation” (1) and “Benefits of a Pharmaceutical Quality System” (2), the lifecycle approach is described as comprising a series of activities occurring over the entire life of the product/process (i.e., overall validation is continually ongoing). The lifecycle approach necessitates comprehensive design and development work on the product/process for comprehensive understanding and to identify potential sources of variation. Before commercial manufacturing and distribution is initiated, a manufacturer must have enough data and knowledge about the product and process to support product distribution. Therefore, more process knowledge will be gained during the commercial manufacturing phase of the lifecycle, potentially leading to process improvements. The 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’s commercial life. The 2004 FDA *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach Final Report* (3), developed by a cross-agency workgroup including FDA, CDER, CBER, ORA, and CVM, included the following statement: “… a focus on three full-scale production batches would fail to recognize the complete story on validation.” Additional commentary on the inadequacy of three commercial scale lots for the validation of a manufacturing process is captured in the following statement of Chris Joneckis, CBER, made during his presentation: “Changing the Paradigm of Process Validation” (4) “… while commercial scale production of conformance lots is an important component of process validation, ... it alone cannot achieve the stated goals of process validation.”

The International Conference on Harmonization (ICH) *Q8 Pharmaceutical Development* (5), *Q9 Quality Risk Management* (6), and *Q10 Pharmaceutical Quality Systems* (7) provide current global thinking on various aspects of the product lifecycle from development through commercialization. These documents 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. It describes a comprehensive understanding of the product and manufacturing process which is the basis for future commercial manufacturing. ICH Q9 provides a systematic approach to quality risk management through various risk assessment tools such as Failure Modes Effects Analysis (FMEA) and other methods. The application of these tools in pharmaceutical development, equipment, facilities, utilities, materials management, production, and other areas of pharmaceutical manufacturing is discussed. ICH Q10 complements Q8 and Q9 and discusses the application of the various quality system elements during the product lifecycle. Product/process knowledge management and risk management are enablers of the quality systems approach. Elements of the quality system include process performance monitoring, corrective action and preventive action (CAPA), change control, and management review. These quality system elements are applied throughout the various phases of the product lifecycle, and they are essential elements of effective process validation.

**PROCESS UNDERSTANDING**

The basis for process validation is the scientific and technical work conducted in advance of validation performance (conformance batches) and subsequent routine manufacturing. This work includes the lab-scale, pilot-scale, and commercial-scale studies conducted to establish the routine commercial manufacturing process.

Process understanding is basic to validation. For processes to be understood, they must be based on scientific and technical principles. The process must be designed to consistently meet the product quality attributes. Relationships between process parameters and quality attributes must be known. Ranges of process parameters that yield (and do not yield) acceptable quality attributes must be known. These activities are often referred to as the establishment of design space and operating space for the process.

The routine commercial scale process should be based on lab-scale and pilot-scale work. Parameters
in the various unit operations are studied to determine those that are most significant. The relative control of these parameters within their acceptable range is a critical determination. This is a departure from prior practice where control ranges for critical parameters may have been tested during the manufacture of conformance batches.

The documented results of work conducted to understand the manufacturing process include final master manufacturing production and control documents, containing operational ranges and limits; control mechanisms, including in-process sampling and testing; and final product specifications, for important product quality attributes.

Control of Input Variables

Process understanding must necessarily include an understanding and control of factors affecting the process including the characteristics of the inputs and the effects of critical process variables. Process inputs with important sources of variation may include materials, equipment, processes, measurement systems, manufacturing staff, and the manufacturing environment. A robust process will yield acceptable product despite reasonable variation in process inputs. No process can be robust without appropriate control of input variables. Material inputs, including the characteristics of active drug and inactive excipients, may be difficult to control. Physical attributes are typically less controlled than their chemical composition and impurity levels, but may have great influence on the manufacturing process. For example, the particle size of the active drug may need to be modified or controlled to assure dissolution and bioavailability. Either the supplier can meet a pre-defined particle size or we must address this need within the process itself by including a step for particle size processing and verification. However, if the active drug is quantitatively a minor part of the formulation, it may be more important to control the particle size of the major inactive excipient to assure a repeatable process. Storage and handling of input materials may affect a process. For example, crystallization of drug by addition of solvent stored outside in winter will likely be different than drug crystallized in summer due to temperature variation in the crystallization solvent. Each of these examples demonstrates the value of good process input control with respect to effective process validation.

Personnel who influence process parameters/variables and operate equipment may be another source of process variation depending on the level of automation in the process. For example, an operator whose judgment influences the particle size of a tablet granulation has great effect on the process quality attributes and all downstream processes. Ongoing training of personnel is critical to minimize human effects on processes.

Other less direct process-related variables that may affect the process, and thus require control, include process equipment and associated process control measurement instrumentation. The installation qualification (IQ) of process equipment should specify periodic preventive maintenance requirements and calibration requirements for the equipment.

Control of input variables is critically important for cleaning processes. Variables associated with cleaning include material inputs, process parameters, and environmental conditions. Control of personnel variability in manual cleaning processes is especially critical. The 1990’s cholesteryamine resin incident involved inadequate control of drums containing insecticide residue. The 2007 Viracept incident, in which product containing high levels of genotoxic substance, involved control of equipment cleaning processes.

Product and Process Technology Transfer

Once adequate product and process knowledge and understanding are compiled, the next step is to effectively transfer this knowledge and understanding to the personnel performing the manufacturing process. Product and process understanding at laboratory scale and pilot scale manufacturing is fundamental. However, manufacturing at commercial scale can be significantly different than smaller scale processing, and some aspects of commercial processes may only be studied at commercial scale. Accordingly, knowledge management from technology transfer activities can be extremely important for conformance batches and subsequent commercial manufacturing.

Supporting Documents

The utilization of process understanding as the basis for validation is not a new concept. Documents discussing expectations for validated processes, with respect to the role of process knowledge, have been published for more than 20 years. It is noteworthy that several documents issued before 2000 discussed the importance of product development activities in support of process validation.

In “Lifecycle Approach Process Validation” and “Benefits of a Pharmaceutical Quality System,” expectations for process understanding in advance of process vali-
process understanding for both API and drug product. The various Quality by Design (QbD) presentations and publications strongly encourage demonstrations of process understanding for both API and drug product. In 2006 FDA Perspective on the Implementation of Quality by Design (QbD) (8), A QbD system is defined as:

- The API/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.

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 7132c08)” (9), 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."

Recent medical device documents are consistent with a comprehensive approach to process validation. In the Global Harmonization Task Force (GHTF) Study Group 3, “Quality Management Systems—Process Validation Guidance” (10), activities conducted during product/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."

The November 2000 ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (11) also discussed activities conducted prior to and after validation. Specifically, the ICH Q7 stated that critical parameters/attributes should be identified during development, and that these critical process parameters should be controlled and monitored. Non-critical parameters should not be included in validation. There should be a periodic review of the performance of validated systems.

An example of work conducted to understand the process is presented in the 2006 “Process Robustness—A PQRI White Paper” (12). A robust process is able to tolerate expected variability of raw materials, operating conditions, process equipment, environmental conditions, and human factors. Process understanding is key to developing a robust process. Steps for developing a robust process are described as follow:

- Form the team, including experts from research and development (R&D), technology transfer, manufacturing, statistical sciences, and others
- Define the process unit operations, including parameters and attributes. Fishbone (Ishikawa) diagrams are demonstrated.
- Prioritize experiments to focus on most critical parameters. Use statistical designs.
- Analyze measurement capability. Accurate and precise measurement systems are needed.
- Identify functions relationships. Multivariate designed experiments are recommended.
- Confirm critical process parameters and critical quality attributes by analysis of experimental data.

The 1987 FDA Guideline on General Principles of Process Validation (13) is widely referenced as the basis for process validation. The 1987 document included mention of the following, all of which describe activities to be conducted prior to validation: 

- "To provide 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."

The various 1994 FDA Guides to Inspections, "Oral
Solid Dosage Forms” (14), “Topical Drug Products” (15), and “Oral Solutions and Suspensions” (16), reiterated and furthered the concepts of the 1987 Process Validation Guidance. These documents emphasized the development phase of the validated process including documented experiments, data and 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 foundation for the manufacturing procedures. Variables are identified in the development phase, and raw materials may vary lot to lot.

VALIDATION PERFORMANCE (CONFORMANCE BATCHES) INCLUDING ASSOCIATED QUALIFICATIONS

When the process is understood and process parameters are optimized, the validation performance phase is conducted. Validation should confirm the information and process operating parameters determined in process development. Validation further confirms the effectiveness of technology transfer activities that transition manufacturing from pilot scale to large scale manufacturing. Validation is not the final step in development, is not process optimization, and is not final debugging. There is an expectation of a highly developed and well understood process when the final conformance lots (also called validation lots or demonstration lots) are manufactured.

This phase of the validation continuum includes the components of traditional validation performance: A validation plan; validation protocol; appropriate sampling; testing; and acceptance criteria, all of which are approved prior to manufacture of the validation lots. Sampling and testing exceeds that which will be conducted for future routine manufacturing after the validation lots. All equipment used in the process is qualified, calibrated, and maintained. All personnel are adequately trained. All documentation has been approved. The validation lots are manufactured; testing and results are acceptable; and the validation report is written and approved.

Supporting Documents

In “Lifecycle Approach Process Validation” and “Benefits of a Pharmaceutical Quality System,” expectations for process validation performance are described. This phase addresses facilities/equipment/utilities qualification and performance qualification of the process to be validated. Equipment/facilities/utilities must be appropriately designed and qualified to support the manufacturing process. Protocol considerations must go beyond the three lots manufactured and must lead to the conclusion that the process will consistently yield a quality product in future product manufacturing. The validation lots are manufactured at commercial scale with qualified equipment/facilities/utilities, approved materials and components, master production and control documents, and trained personnel. Processes are run at nominal operating parameters within the acceptable range or design space. Lots are extensively tested with increased process control monitoring beyond typical Quality Control (QC) levels of testing. The net results of the Performance Qualification (PQ) is that the process is acceptable for routine commercial manufacturing based on the supporting process understanding work and the demonstrated validation performance.

MAINTENANCE OF THE VALIDATED STATE

After validation performance and release of the manufacturing process for commercial manufacturing, there must be appropriate systems to maintain the validated state. Maintenance of validation comprises the continuing demonstration of ongoing validation—after traditional validation has been completed, validation is not finished but is continually ongoing. Validation of processes must be continually maintained through ongoing monitoring and control. Programs and activities involved in maintenance of the validated state include timely process data monitoring and review, statistical process control, timely test data monitoring and review, trend analysis, study of out-of-trend (OOT) and out-of-specification (OOS) data, CAPA, change control, appropriate validation of changes, revalidation, management review, and other associated activities.

Process monitoring will reveal opportunities for improving the process, improving control strategy, and reduction of variation.

Qualification of associated equipment and systems must in turn be continually maintained. Activities associated with maintaining the qualified status of equipment include preventive maintenance programs, calibration programs, monitoring, review, and evaluation based on risk analysis, periodic revalidation of critical equipment, and associated activities.

Supporting Documents

In “Lifecycle Approach Process Validation” and “Ben-
efits of a Pharmaceutical Quality System,” expectations for maintenance of the validated state and activities to assure that the process remains in a state of control are clearly expressed. Activities described include trending and assessment of data; monitoring critical operating and performance parameters; product performance characteristics; personnel training; and problem investigations. Establishing process history over time should suggest process improvements and enhanced control strategies. Change control and periodic assessment of process and test data should be used to decide if and when new validation or other development work needs to be initiated. This is in contrast to prior approaches which may have specified re-validation activities on time rather than event based premises.

The September 2006 FDA Quality Systems Approach to Pharmaceutical CGMP Regulations (17) clearly discusses expectations for maintenance of the validated state. In discussing performance and monitoring of operations: "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 insure that the controls are scientifically sound and appropriate." Further, "Although initial commercial batches can provide evidence to support the validity and consistency of the process, the entire product life cycle 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 discusses trend analysis, CAPA, change control, and other quality systems programs.

ICH Q10 Pharmaceutical Quality System similarly discusses continual improvements of process performance and product quality. Four elements discussed include:
- Process performance and product quality monitoring system
- CAPA system
- Change management system

These activities should be conducted during all life-cycle stages. In the manufacturing stage, these activities maintain a state of control, facilitate continual improvement, and expand the body of product/process knowledge.

Recent medical device documents are consistent with a comprehensive approach to process validation. In the GHTF Study Group 3, Quality Management Systems—Process Validation Guidance (January 2004), activities conducted post validation to maintain the product/process are described. For example, "maintaining a state of validation" by monitoring and control including trend analysis, changes in processes and/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 ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November, 2000) also discusses activities conducted post validation. Specifically, it stated that critical parameters/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. There should be periodic review of validated systems.

The 1997 FDA Medical Device Quality Systems Manual (18) further emphasizes the activities that should be conducted post validation. It mentions as follows: "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 (19) states the following: "It is important to remember that the manufacturer needs to maintain a validated state. Any change to the process, including changes in procedures, equipment, personnel, etc. needs to be evaluated to determine the extent of revalidation necessary to assure the manufacturer that they still have a validated process."

The 1987 FDA Guideline on General Principles of Process Validation includes mention of the following post validation considerations: "...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. These may be based upon equipment, process, and product performance observed during the initial validation challenge studies.*

DOCUMENTATION
All work associated with process validation must be documented. This includes risk analysis; development studies to demonstrate process understanding; design of experiments to determine critical process parameters, design space, and normal operating ranges; process parameter optimization; validation and qualification protocols; and process monitoring. Summary documents are recommended when multiple documents must be integrated by the reader. Documentation must be written for the reader. Clarity is much preferred over brevity. Documentation must stand alone (i.e., be understandable without additional explanation). 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 retrievable. Document storage in an easily accessible centralized location is recommended. Copies of experimental studies conducted by R&D personnel should be stored with validation documents so as to be readily available for validation audits (20, 21, 22).

TERMINOLOGY
The terminology associated with the various phases of validation has had minor variations over the years and will likely continue to evolve. The 1987 FDA Validation Guidance describes "Installation and Operational Qualification," "Process Performance Qualification," and "Product Performance Qualification." Product lots manufactured in validation have been termed "demonstration lots," "conformance lots," and "validation lots" in various documents over the years. The most recent FDA presentations addressing the lifecycle approach to validation uses the terms "Process Design," "Process Qualification," and "Commercialization" for the three phases of validation. The actual performance of validation within the Process Qualification phase is termed "Performance Qualification," and the lots manufactured are called "conformance batches." The Process Qualification phase also includes Equipment/Facilities/Utilities Qualification. The GHTF Process Validation Guidance for medical de-

CONCLUSIONS
Validated processes are expected to be robust technical processes—controlled, confirmed, maintained, and documented.

• Robust technical processes
  ~ Validated processes must be based on scientific and technical principles.
  ~ Criticality of validated processes is evaluated based on risk analysis.
  ~ Validated processes must be well understood based on data from designed experiments. Design space and optimized operating ranges should be determined by designed experimental testing.
  ~ Validated processes must be tolerant of expected input variation and process variability.

• Controlled
  ~ Input materials to validated processes must be well controlled.
  ~ Critical process parameters must be controlled within normal operating ranges.
  ~ Process equipment and associated measurement systems must be continually maintained.
  ~ Personnel must have ongoing training.

• Confirmed
  ~ Validation protocols including testing and results must demonstrate repeatability of the designed process.
  ~ Ongoing confirmation of the validated process must be supported by a maintenance and monitoring program.
• Maintained
  ~ Validated processes must be monitored by statistical process control and trending.
  ~ Change control programs determine the impact of changes to materials, process, and associated systems.
  ~ New validation and qualification is conducted as necessary.
  ~ Equipment, facilities, and utilities used in processing must be qualified. The qualified state must be continually maintained.
• Documented
  ~ Thorough, clear, and understandable documents demonstrating all of the above must be prepared.
  ~ Documents must be readily available.

Commentary on expectations for validated processes has been published for more than 20 years. The various activities and expectations discussed in published documents have not been well integrated. More recent guidelines and presentations have indicated that process validation must comprise activities beginning in product/process development and continue throughout the product lifecycle. These activities should be comprehensive, integrated, and ongoing throughout the entire product/process lifecycle. Process validation is a “process” that is never completed and is always ongoing.

REFERENCES
6. ICH Q9, Quality Risk Management, November 9, 2005.
9. FDA, “Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval Compliance,” Policy Guide 7132c.08, Section 490.100.

ARTICLE ACRONYM LISTING
API Active Pharmaceutical Ingredients
CAPA Corrective Action and Preventive Action
DQ Design Qualification
FDA United States Food and Drug Administration
FMEA Failure Modes Effects Analysis
GHTF Global Harmonization Task Force
IQ Installation Qualification
OOS Out-of-Specification
OOT Out-of-Trend
PAT Process Analytical Technology
PQ Performance Qualification
QbD Quality by Design
QC Quality Control
RD Research and Development