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FDA Lifecycle Approach to Process Validation

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ABSTRACT

FDA lifecycle approach 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.

Keywords: FDA lifecycle, Validation guidance, Organizational functions, Training Risk analysis, Documentation

I. INTRODUCTION

The January 2011 process validation guidance 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)[1]. 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[2]."

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 state, 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[3]."
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[4].

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 batches 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[5].

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, 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[6]. The 1997 FDA Medical Device Quality Systems Manual 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[7].

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 (24) 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[8].

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 productis 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[9]. 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[10].

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[11].

Training

The issuance of the 2011 FDA guidance requires appropriate training for all involved in validation-related activities[12–13]. 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[14-15].

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[16-18]. 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 mustin 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[19].

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[20].

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[21].

II. CONCLUSION

"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.

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