Implementing the ASTM standard for verification (commissioning and qualification)

Standard's key objective is to give industry-wide flexibility regarding implementation

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Regulations have long required pharmaceutical and biopharmaceutical manufacturers to validate manufacturing processes, demonstrate control of manufacturing environments, and control contamination. In the United States, this mandate falls under the Code of Federal Regulations (21 CFR Parts 210 and 211). In 1998, the International Society for Pharmaceutical Engineering (ISPE) initiated an effort to develop its Commissioning and Qualification Baseline Guide to help manufacturers focus and prioritize their qualification efforts using the risk assessment tool of impact assessment. More recently, a task team formed through ISPE worked with the American Society of Testing and Materials (ASTM) committee E55.03 on a new consensus-based standard, *Standard Guide for the Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*. The standard (ASTM E2500) was voted upon and approved at the end of May.

Although participation by the U.S. Food and Drug Administration (FDA) in ASTM Committee E55 and FDA's affirmative vote of the standard do not constitute adoption, it points toward the agency's support for the new standard, which aligns with FDA's published cGMPs. Furthermore, the National Technology Transfer and Advancement Act (NTTAA) and OMB Circular A-119 on Federal Participation in the Development of Voluntary Consensus Standards and in Conformity Assessment Activities both direct agencies such as the FDA to use voluntary consensus standards in lieu of government-unique standards whenever possible.

The standard provides high-level guidance—it explains what needs to be done but not how. The specifics of that will be addressed in an updated ISPE baseline guide. A task team is in place, and its goal is to have a revised draft of the guide available for ISPE membership review in time for ISPE's annual meeting in November. Although the process is generally the same for everyone, how organizations choose to implement the standard will vary depending on their quality goals, time and cost requirements, and even internal roles and responsibilities. Navigating the process can be complex from the perspective of both engineering and project management. It requires a bit of a paradigm shift in management philosophy. Most companies will have to expand their project teams in order to leverage the product knowledge obtained by applying ICH Q8 and implementing a science- and risk-based approach by applying ICH Q9. The additional effort and resources, however, can not only facilitate regulatory compliance but can deliver additional benefits for the facility owner.

Balancing cost, efficiency, quality, and safety

ISPE initially developed its C&Q baseline guide to lay out engineering approaches and practices that would help owners design and validate cost-effective manufacturing facilities that meet their intended purposes in a timely manner. Its goals are to bring common terminology and methodology to all involved in the C&Q process, to provide a system

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impact assessment process, foster an interdisciplinary team approach, and establish a basis for planning and execution. It aims to eliminate such costly practices as repeating verification steps during qualification, qualifying systems that only require commissioning, and optimizing documentation levels. The guidelines also are designed to help minimize the project schedule and eliminate costly delays.

Built on the key concepts of good engineering practice (GEP), impact assessment, and qualification practices, the baseline guide addresses the process of designing, constructing, commissioning, and qualifying facilities, utilities, and equipment regulated by the FDA or other health authorities. The document positions commissioning and qualification activities as the foundation for process validation. In fact, a well conceived and executed commissioning and qualification plan greatly facilitates a timely, cost-effective validation effort. The document also recognizes that taking a comprehensive approach to commissioning and qualification plays a critical role in delivering effective, safe, and efficient facilities, utilities, and equipment.

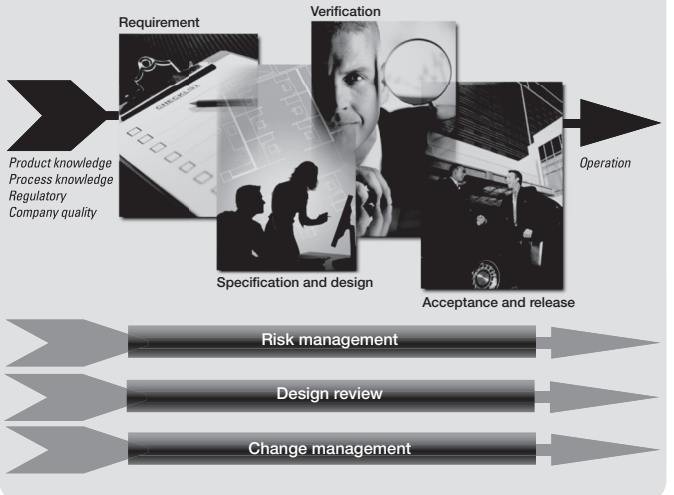
A comprehensive approach requires assessing each system for its potential impact on the product quality and patient safety. At one end of the spectrum, parking facilities have no impact; at the other, the water for injection (WFI) or U.S. Pharmacopeia (USP) water system clearly has a direct impact. The gray areas are systems such as air conditioning, chilled water, or building management, which may have an indirect impact, depending on how they are designed and used. If the systems have no impact or only indirect impact, following GEPs should be sufficient. For systems with direct impact, it is necessary to make impact assessments at the component level to determine which components are critical. For example, if the HVAC system will have a direct impact, a component assessment might determine that only specific elements—the main and terminal HEPA filters and the sensors for temperature, differential pressure, and humidity—are likely to have an impact and are therefore critical. Components identified as critical will require qualification. The quality assurance unit must endorse the rationales to support these assessments.

ASTM verification: A risk- and science-based approach

The ASTM verification standard takes the ISPE baseline to the next level. The standard describes a risk- and science-based based approach to specifying, designing, and verifying elements of a manufacturing capability to ensure that those systems and equipment are fit for intended use, and that product quality risks related to those manufacturing elements are managed effectively. Ultimately, the manufacturing capability should be able to support defined and controlled processes that consistently produce a product that meets defined quality requirements. The standard applies a number of key concepts including a risk-based approach as provided by ICH Q9, Quality Risk Management; and a science-based approach and quality by design, as provided by ICH Q8. It applies the concept of critical quality attributes and calls for the use of subject matter experts (SMEs) to make critical determinations. Like the ISPE guidance, it acknowledges that GEPs may be sufficient for certain systems. It also seeks to minimize the paperwork burden by allowing for the use of vendor documentation.

The standard applies to all elements of pharmaceutical and biopharmaceutical manufacturing capability, from the actual manufacturing systems, equipment, and automation systems; it can also be applied to laboratory and information systems. It applies to new manufacturing systems and may be used when implementing changes and improvements to existing systems and equipment. Finally, the standard is applicable throughout the product life cycle, from concept to retirement.

Figure 1: Good engineering practice



In effect, this is the same basic scope of activities that compliance professionals in the industry have addressed for the past 30 years but in a new, more flexible package that allows the pharmaceutical company to determine the methodology. The standard uses new terminology and better defines current terminology, reflecting the science- and risk-based approach, and it puts the quality team and technical experts in new roles.

One of the major differences is the concept of verification. Under the ASTM standard, the company should define a systematic approach to verify that the manufacturing elements—individually and in combination—are fit for intended use, have been properly installed, and operate correctly. The company must document the verification approaches used, providing a level of detail appropriate to the level of risk to product quality and patient safety, as well as the complexity and novelty of the approach. Traditional installation and operational qualification protocols can be set aside in favor of documented confirmation by SMEs that all acceptance criteria have been met. This documentation should include a review or overview of results, as well as a review of any nonconformance to acceptance criteria and corrective actions taken. The documentation should clearly state whether the manufacturing system or equipment is fit for intended use.

In contrast to the traditional qualification process, the verification approach requires that the quality unit shift its emphasis from quality control to quality assurance. Where previously the quality unit was involved in every protocol test case, every minor discrepancy, and endless wordsmithing to justify minor departures from engineering

specifications, under the ASTM standard, the responsibility for engineering quality control falls on the technical experts with appropriate oversight by quality assurance. Non-critical discrepancies are addressed through GEPs. Instead of an obsessive focus on documenting every minor detail, the team can now focus its documentation practices on technical content—a far more efficient approach.

A new process paradigm

The move to the ASTM verification standard requires a new approach to the specification, design, and verification process, moving away from the "V Model" of commissioning and qualification. The new paradigm demands that the principles of good engineering practice, risk management, design review, and change management are applied at each stage of the process, from compiling design requirements to acceptance and release and beyond.

The keys to success under the ASTM standard are in upfront planning and interdisciplinary communication. Goals and objectives must be clearly defined, because they will drive the process and impact everything downstream. Accurate, well thought-out input into the requirements is critical. The requirements should be based on knowledge of the product and its manufacturing process, as well as regulatory requirements and the company's own quality requirements. Available product and process knowledge can be determined by reviewing the scientific data gathered during experimental and development work. This information can provide the basis for specific product/process requirements relevant to product quality and patient safety. Specification and design activities should focus on those aspects that have been identified as critical to product quality and patient safety. Subject matter experts should be the ones to identify and document these critical quality attributes—functions, features, abilities, and performance or quality characteristics—that are necessary to consistently produce products of the required quality. The company should have a systematic means of conveying these specifications to those responsible for design so that manufacturing systems and equipment are properly designed to meet relevant requirements.

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Subject matter experts also should define the acceptance criteria that must be satisfied in order to demonstrate that manufacturing systems and equipment meet the critical quality attributes. The quality unit should approve the acceptance criteria. The SMEs also should develop and approve the verification plan and specifications, including the method of verification and test strategy. Finally, the SMEs should perform the verification activities as defined, document the results, and document that verification activities have been completed. The ASTM standard allows for the use of vendor verification documentation.

An independent technical reviewer with the appropriate background, knowledge, and familiarity with the technical aspects of the manufacturing elements should review all completed verification documentation, ensuring that all tests have been completed and appropriately documented. The technical reviewer and SMEs should work together to address and resolve any departures from the verification plans and specifications.

From impact assessment to risk assessment

Another paradigm shift that the ASTM standard brings about is the approach to risk assessment. Since the ISPE baseline guide was introduced, companies have relied primarily on impact assessment—that is, evaluating the impact of the operating, controlling, alarming, and failure conditions of a system on the quality of the product. Impact assessment is a labor-intensive process that focuses on systems and components and usually is conducted after design development. Under the ASTM standard, impact assessment is just one of many tools, including hazard operability analysis (HAZOP), failure mode effects analysis (FMEA), and fault tree analysis (FTA) that can be applied to the process.

Risk assessment is performed throughout the design development to ensure that the systems and other facets of the design and operating philosophy can effectively monitor and control risks to the manufacturing process, such as process variability and contamination. Each selected process is assessed against a set of product and process user requirements. The risk management requirements include all components, functions, and features that serve, collectively or individually, to control risk. These are designated as critical elements. The risk assessment should determine the probability that any specific risk could impact process variation and the degree to which that impact could affect product quality and safety. Risks that are deemed unacceptable are to be eliminated by design, automated control, or procedural controls. Companies will find more specific details on risk management in ICH Q9.

When verifying manufacturing systems and equipment, the procedure should be documented in sufficient detail that trained individuals can repeat the test in the same manner and obtain the same results. Similarly, the observed results should be documented adequately, so that a technically competent person can verify that the inspection or test was performed properly and that the acceptance criteria were met. An independent SME should review the results to ensure that all tests were completed, acceptance criteria met, and all appropriately documented. Documentation should also include confirmation that any departures from specification have been addressed through GEPs or change control for nonconformance. Depending on the circumstances, the process of verification may or may not include performance testing. At the conclusion of verification, the subject matter expert will document the results of the verification effort in a verification report. The quality

unit, and possibly other technical experts, will approve the verification summary report.

Conclusion

Pharmaceutical and biopharmaceutical companies are challenged to develop manufacturing capability quickly and cost effectively while safeguarding product quality and patient safety. To date, approaches to meeting that challenge have run the gamut from equating commissioning with qualification—a costly, laborious, and time-consuming tactic—to eliminating any commissioning and going right to validation—a course of action that is often fraught with failure.

This phased approach can help the company obtain the desired outcomes from its chosen approach to verification/ qualification under the ASTM standard.

To determine the best approach for implementing the ASTM verification standard, the company will need to explore its goals for the process. Does the system need to improve compliance? Enhance product quality? Provide greater contamination control? Minimize capital costs? Initially, it may be helpful to find an expert who is experienced with this verification process to create an approach plan and preliminary schedule and then develop a detailed list of activities to determine the project scope. Once that detailed foundation has been laid, the request for proposal can include a list of expected deliverables to ensure that potential vendors are bidding "apples to apples." This phased approach can help save time and money and help the company obtain the desired outcomes from its chosen approach to verification/qualification under the ASTM standard.

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