EBOOK

HOW TO UNDERSTAND ASTM E2500

AN ARTICLE BY
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Reviewing history of qualification practices in the biopharmaceutical industry, there has been constant tension between perceptions of regulatory requirements, application of good engineering practice, project delivery constraints (cost and schedule), and successful technology transfer resulting in high levels of process performance and reliability. In the late 1980's and early 1990's regulators stepped in with expectations of formal installation, operational and performance qualification prior to manufacture. Quality assurance, having little background in the realities of design, fabrication, and commissioning, invented qualification practices that matched the expectations for a licensed manufacturing process and batch record documentation. Projects quickly became bogged down with protocol deviations and premature implementation of Quality Assurance (QA) pre-approved change control.

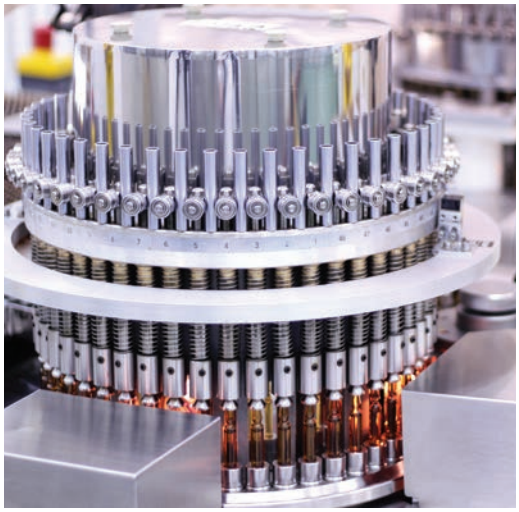
The first attempts at qualification resulted in protocols that added little value: collecting purchase orders, drawings, cut sheets etc. Lots of money was spent but qualified equipment and systems did not work to meet operational needs, and production spent months making it work right. Meanwhile, companies undertook efforts to reduce costs by writing prescriptive Installation Qualification/Operational Qualification (IQ/OQ) procedures. These procedures mandated content which, along with templates and model protocols, constituted an attempt to standardize, streamline and reduce cost and time. Yet equipment and systems still failed to perform under operational conditions – inspections and tests mandated by procedures were disconnected from process requirements and quality risk management. Regulatory fear drove companies to apply very tight controls to any and all systems within the scope of a project.

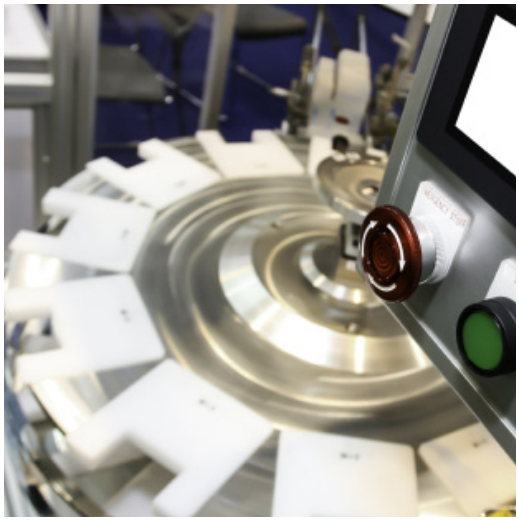
Typically, the industry has taken a black vs. white approach to quality systems: everything is classified as either "Good Manufacturing Practice (GMP)" with a plethora of documentation, procedures and other controls, or it is "non-GMP" and little is done or documented. Rather than fixing the core issues causing the problems, industry instead sought to draw a smaller fence around what was GMP.

This was reflected in the 2001 ISPE Commissioning and Qualification Baseline Guide: Direct Impact systems, and Critical Components, were subject to "qualification practices" which included "additional testing and enhanced documentation…" The guide was unclear about when QA pre-approved change control needed to be implemented, and certain illustrative figures blurred the lines between commissioning and qualification. The guide overall contained the promise of cost reduction, schedule reduction, and quality improvement through the use of good engineering practice. However, the aforementioned "qualification practices" and the segregation of systems into black, white, and in-between (indirect impact) prevented the Baseline Guide from achieving its full potential.

Instead, industry continued to struggle with legacy practices: "If we are going to 'leverage' a Factory Acceptance Testing (FAT), doesn't that FAT protocol have to be pre-approved by QA?" An audit of 400 IQ deviations performed in 2004 yielded the fact that 396 of those deviations were resolved by clever wordsmithing the deviation form – a pure paperwork exercise, with the remaining four requiring a field change to valves in a chill-water system. Hardly the stuff of value-enhancing efforts. Industry continued to spend vast sums of money and receive substandard value from those expenditures – compared to say Intel, who implements strict clean-build protocols, rigorously tests all equipment and systems using documentation that is reviewed afterwards, and can deliver ISO Class 3 cleanrooms on schedule. Why? Because the manufacturing process depends on such conditions. Companies that operate data centers require complex, planned, and documented testing of electrical supply continuity and HVAC performance. Why? To assure operational reliability. These are examples of good engineering practice in action!

By 2004, it was clear that the 2001 Baseline Guide had achieved moderate success but many battles continued to be waged across industry. Surprisingly, it was US FDA that came to ISPE in June 2004 to suggest the creation of an ASTM consensus standard for qualification. A committee was formed to write what eventually became ASTM E2500, "Standard Guide for Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment." This standard was released in 2007. The standard basically took the ISPE Baseline Guide to its next level.





It replaced the black and white impact assessment questions from the ISPE Baseline Guide1 with knowledge of the product and process and control of risks to product quality as the primary determinant of criticality. It provided clear guidance regarding how to resolve many deviations (use a subject matter expert), and when QA pre-approved change control was required (only when placing system into production).

Industry continued to struggle. ASTM E2500 introduced the term "verification" but was essentially silent on the idea of "commissioning" and the term "qualification." The team who wrote the standard had avoided "qualification" because it is not found in the US GMPs and therefore is not a regulatory requirement, at least in the US. For other regions such as the European Union where IQ/OQ/PQ* is explicitly mentioned, there was nothing in the standard prohibiting labeling documents as such instead of "verification". But industry got wrapped around such terminology, and teams that created IQ/OQ/PQ protocols were said to be using a "hybrid" ASTM approach. Not so – ASTM is a minimum standard, and teams are free to go beyond this minimum as long as the basic provisions are met: basing what is critical (critical aspects) on process science, quality risk control; using subject matter experts and involvement of QA as specified in the standard, etc.

We see four basic approaches in the industry currently:

On the first front, we have organizations that have yet to field a team that competently implements good engineering practice: requirements are ill-defined, design changes are not managed, commissioning is non-existent or minimal, and turnover packages are not accurate. The validation group is applying "old school" constricting practices of rigid protocols based on templates and procedures, onerous deviation processing, premature implementation of change control, and constant QA oversight. Schedules and budgets are routinely blown, and operations are not happy with what is delivered.

On the second front, the validation group has a bit more engineering "savvy" and essentially performs both commissioning and final verification inspections and tests to at least deliver what operations needs, albeit at excessive cost and time.

**Performance qualification*

On the third front, the project team is competent at the application of good engineering practice, but the validation effort has not yet grown confident enough to take advantage of the fact that equipment and systems have been delivered suitable for their intended use. Risk assessments are performed solely to achieve the old "GMP/non-GMP" segregation (as opposed to design and operational improvement). Driven largely by legacy practices, organizational sclerosis, or regulatory fear, qualification teams repeat what was done.

On the fourth front, full implementation has technology transfer teams providing product and process understanding. Risk assessments are performed not to achieve a "validation segregation" outcome but to inform designs, improve risk controls, and are done iteratively. Project teams apply good engineering practice to competently deliver fully commissioned and documented equipment and systems, QA focuses on product and process understanding and quality risk control, oversight of the quality system and final acceptance and release. Subject matter experts are free to adjudicate departures from specification, with quality involvement only when a critical aspect cannot be brought into conformance with specification necessary to achieve a process or risk control requirement. Equipment, automation and systems have been rigorously inspected and tested, and complex cycles for cleaning, sterilization, and operations have been developed. Production is provided with extensive training opportunities during project delivery, and receives a comprehensive turnover package to support operations, maintenance and future changes. The equipment and systems, including automation, work as production needs them to work in order to make product, right first time.

Strategy for success: competent application of good engineering practice, and a total team that is more concerned about getting the requirements, design and verification done properly as a cost, schedule, and quality enabler, vs. worrying about perceived regulatory expectations for this or that piece of paper. And doing what is necessary, whether GMP or not.