

Considerations in Effectively Applying Risk-Based Validation

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Introduction

The last three years have brought a seismic upheaval in the pharmaceutical and biotechnology regulatory landscape. The FDA's shift to a risk-based approach to product development has changed the rules and expectations for regulatory agencies and industry alike. Both manufacturers and regulatory authorities must now demonstrate that their processes are grounded in appropriate methodology. In issuing its Pharmaceutical cGMPs for the 21st century guidance in 2004, the FDA's objective was to propose a more scientifically rigorous quality system integrating quality, safety and risk-management considerations. The new paradigm has far-reaching implications for validation, which has always been perceived as a compliance exercise with its major emphasis upon documentation.

Historically, validation within the pharmaceutical industry has been an afterthought with respect to time and expended effort. It is usually the last step before a facility, system, or process is brought on-line and is deemed usable in a cGMP environment. We make the assumption our processes are controlled and predictable. The fact of the matter is we still fail within the validation exercise. This reality is the driving force behind the FDA's recent shift to a scientifically-driven risk-based quality argument.

Can industry leverage this new thinking? And if so, how? We've seen validation evolve into a costly and time-consuming exercise. At its best it is a focused confirmation of a well-defined design and development process; at its worst it is a profit center for large consulting firms to recoup lost profits.

For industry, Risk-Based Validation (RBV) represents the most efficient and effective combination of scientific rigor, quality assurance and business pragmatism. This article describes some of the considerations to effectively apply RBV methodology when approaching projects.

Classic Validation

The classic approach to validation is based on meeting corporate and market demand—regardless of the cost to the stakeholders of the company. The old adage “validate anything that moves but don't move anything that's already validated” sums up the traditional view of validation. This mindset essentially discourages innovation and continuous improvement and is partly why validation is perceived as a necessary evil rather than a value-added activity. Despite extensive sampling and testing, companies are often unable to achieve process stability. Processes fail because the drivers for stability have not been properly identified and eliminated or controlled. The cost of qualifying a process, which is not fully understood, continues to escalate. Without understanding the parameters that affect the process, there is no confidence that the process will behave predictably. In the end companies remain unable to characterize their process and the validation data compiled is not usable for troubleshooting and/or improving their processes or systems.

Risk-Based Validation

In the pharmaceutical and biotech industries, risk can be defined as the combination of the probability of occurrence of harm and the severity of that harm to all stakeholders in the drug development process. (Let's define

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stakeholders as the pharmaceutical company and its shareholders, its employees, country-specific regulatory bodies, the medical community, and the consumer.)

The FDA has taken landmark strides with respect to modernizing the techniques and methods to evaluate the safety, efficacy, and quality of medical products as they move from candidate selection and design to mass manufacturing. In September 2003, the FDA released “The Final Report Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach” signaling a change in regulatory philosophy from a uniform application of regulations to regulatory oversight based on the level of risk to the public. The FDA defined risk such that it can be mitigated through 1) the level of scientific understanding of how the formulation and manufacturing process factors affect safety, efficacy, and product quality; and 2) the capability of process control strategies to prevent or mitigate the risk of producing a poor-quality product. Risk-Based Validation (RBV) uses the new approach initiated by the FDA when validating facilities, systems, or processes. RBV approaches validation by reducing risk to acceptable limits in order to provide confidence the process will satisfy its specified requirements. In a nutshell, you only test and measure those parameters that matter.

The FDA was not the only health agency to recognize this need. At the center of this global mindset shift are several key guidance documents from The International Conference on Harmonization (ICH), ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management) and the forthcoming ICH Q10 (Quality Management). ICH Q8 articulates a more scientific framework for process and product development—termed Quality by Design (QbD)—which focuses upon understanding which key drivers affect process stability and ultimately product performance, rather than quality oversight. This document defines the essential precursors to RBV. ICH Q9 defines a methodology for assessing, mitigating and controlling risk that presents the industry with the opportunity of concentrating quality efforts on only those elements that matter. Such a framework can easily be tailored to fit an organization’s RBV methodology. ICH Q10, still under review, attempts to describe a method for integrating ICHQ8 and Q9 requirements into our quality management systems. Together these form the foundation for a new methodology aligning drug development and quality.

RBV Considerations

RBV is predicated upon understanding what does and does not drive the variability of the process, equipment or facility you are qualifying. Without this understanding it is impossible to effectively apply the risk-management tools necessary to refine the validation exercise. Leveraging the process development and product development information created for the CMC section of your product’s NDA is one avenue for gaining insight into what drives your process variation. This assumes the development work was performed in a manner which identifies the key parameters that ensure process stability. Another line of attack is to leverage your organization’s operation excellence program. The DMAIC (Define, Measure, Analyze, Improve and Control) roadmap is designed to identify the key variables, which steer the process and identify the error associated with the measurement tools that control the process. Integrating software quality control procedures, the organization’s position on CFR210 Part 11 compliance, and process scale-up/technology transfer procedures will provide the opportunity to assign risk and justify the appropriate qualification activity within the RBV framework. Incorporating these elements into an effective validation master plan (VMP), which specifies the characterization, sampling and measurement element arguments, will provide a single cohesive document to defend the qualification activity.

Conclusion

The regulatory shift in mindset to a more scientifically driven, risk-based framework has transformed the expectations for system validation. The ability to leverage the benefits of RBV is predicated on the assumption that key parameters, which drive process variation, have been identified and controlled. Through the incorporation of classic risk-management tools along with well-engineered process and product-development studies, it is possible to focus and defend the validation effort on those parameters, which affect the product’s process predictability, driving value into the validation exercise and removing waste from the validation effort.