

# risk based approaches

## THE IMPACT ON QUALIFICATION

### Drivers for Change

Recent regulatory developments and industry trends are stimulating an increased focus on the application of science- and risk-based practices to qualification management. Total validation costs for projects are still reported to be as high as 20% of the total installed cost - industry continues to challenge these costs.

The development of the 21st Century Risk-Based Initiative by the US Federal Drug Administration (FDA) has opened the door for industry to work with the regulator and to seek cost reduction strategies that still meet regulatory expectations. Bob Adamson, Foster Wheeler's manager of pharmaceutical compliance, discusses the changes.



Bob Adamson

### What is Risk?

Is it risk assessment, or risk management? There are a variety of definitions and two are proposed:

- Risk management is a systematic process for the identification, assessment, control and communication of risks to life, property or valued objects.
- Risk assessment is not a single process but a systematic approach to organizing and analyzing scientific knowledge and information that supports a risk decision.

### Regulatory Expectations

There has been much regulatory activity in the past two or three years that has addressed the topic of risk. At the forefront has been the FDA with its new approach initiatives. These focus on understanding the process, identifying critical steps, improving consistency in regulatory activities, and bringing risk-based strategy into the inspection program. In promoting this program, the FDA has already implemented a number of activities or actions and issued various guidance documents.

### What are the Risks?

Risks in drug development, manufacture and use are inherent in:

- the drug itself and its known side-effects
- the delivery systems and method of delivery
- manufacturing defects; the area in which we, as engineers and designers, can have an impact

Risk management can be viewed as a tiered hierarchy of levels of risk methodologies for implementation. The higher levels are driven by principles and involve examining risk by ranking and filtering techniques. Lower down are quantitative methods such as failure modes effects analysis (FMEA), root cause analysis, event tree and fault tree analysis, which involve assessing the likelihood of the event occurring.

Sources of risk can be identified and associated with the product and can be examined and related to process activities, identifying critical steps, critical control points and associated parameters which can then be linked directly to activities in the manufacturing process that need to be controlled by the application of good engineering practice and good science.

### FMEA

FMEA is a systematic process for identifying potential design and process failures before they occur, with the intent to eliminate them or minimize the risk associated with them. The technique was used as early as 1949 in a military standard.

Many pharmaceutical companies are now using this approach for their computerized systems to determine where to focus their validation resource. It also provides a documented process for recording the decisions and so provides proof of review to offer to regulatory bodies. The GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture follows a simplified FMEA approach to assign a risk class.

### Impact Spectrum

The ISPE Commissioning and Qualification Guide introduces the concept of determining whether a system has an impact on product quality, illustrated by the 'Impact Spectrum'. The Guide follows a simple methodology that is familiar to engineers, dividing the facility into systems, assessed against a predetermined set of criteria in order to ascertain any effect on product quality. Further assessments at the component level in the system identify whether the component is critical. Systems are determined to be either direct impact, indirect impact or no impact, with direct impact systems being qualified and indirect or no impact systems executed to good engineering practice.

### Implications of Risk-Based Approaches

Risks can affect both the enterprise and the project. Risks to GAMP can occur at any stage, even as early as the bid proposal phase, or as late as the commissioning and qualification itself. Typical examples can occur in:

- Planning - where in the worst case there is none or too little
- Schedule - inadequate time is allowed for qualification; projects in the industry are often highly schedule-driven with a focus on mechanical completion rather than the actual qualified facility
- Design - poor specification of qualification requirements at the design stage
- Regulatory change - failure to plan for changes or unexpected change by the regulators
- Budgetary - failure to make adequate allowance for qualification expenditure

The Commissioning & Qualification Guide addresses some of these issues. It defines the extent of qualification through the impact assessment process, involves QA in the process and defines methodologies in SOPs, change control, protocols, etc. A common example in the design process is the timely delivery and quality of supplier documentation. The new approach to qualification places greater reliance on supporting documentation and avoiding testing repetition. Another example is well-defined user requirements, which form the basis of testing in the latter stages of qualification. Ill-defined user requirements lead to test acceptance criteria that are too often inappropriate for final qualification.

### Cost and Quality

Frequently, there's a failure to recognize the relationship between cost, quality and schedule. Taking account of the risks to quality and validation at the start of a project allows us to understand the impact of change. We can plan to mitigate or eliminate risk factors; failure to do so results in transfer of risk to the end of the project, where the cost of change and rectification may be an order of magnitude larger.

### Right First Time

In summary, we manage risk by understanding products and processes and using the tools available. Regulatory bodies are expecting science-based decisions using risk management approaches and the FDA has fully embraced risk. We need to be right first time - failure to manage risk to quality will lead to increased cost, schedule delays and poor quality.

