Risk-Based Quality Management Systems

What Are We Waiting For?

by Carol DeSain

Let's skip over the next ten years, the changes in FDA policy, politics and leadership; the age-old excuses of industry; the overreactive institutionalization of risk by management consultants and QA professionals; and the inevitable loss of time, money, and experienced staff that comes from taking too long to do the obvious.

The Obvious

Adequate use of limited resources in the development, manufacturing, and distribution of medical products requires a triage of tasks. There is not enough time or money or personnel available to validate every process, investigate every procedural deviation, qualify every supplier, and perform clinical studies or stability studies on every design change with the same rigor of analysis.

Risk-based decisions are necessary to assure that limited resources are focused — first of all — on marketing practices, manufacturing operations, and product development studies that can have the greatest impact on product safety and performance.

A systematic, risk-based approach is necessary to assure that decision making is consistent throughout a product lifecycle, throughout a product family, throughout the company, and throughout the industry. Based on agreed-on definitions of *hazards* and *acceptable risk*, this approach also minimizes the bias of case-by-case decision-making.

Risks to patient safety should be the baseline risk managed by any risk-based quality management system (QMS). Despite the many types of hazards and associated risks in the development, manufacturing, and marketing of pharmaceutical and biotech products, the baseline hazards of concern — common across all product types and all regions of distribution — are clinical hazards. A *clinical hazard* is a clinical effect that is severe or life-threatening:

- Severe — would result in serious injury, permanent impairment, irreversible effects (**1**); requires unplanned medical intervention with hospitalization to prevent or mitigate serious permanent injury or death; presents a high patient safety concern
- Life Threatening — death or serious permanent injury is likely to occur (**1**); presents a catastrophic patient safety concern.

In QMS development, companies can choose to identify, assess, and control additional risks (e.g., product performance, business, and regulatory risks), but every company should be expected to develop a quality management system that effectively manages risks to patient safety.

Systematic product development supports risk-based decision making by assuring that information about clinical hazards and associated safety-critical product features, and manufacturing processes — identified during product development — are

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- used consistently during product development to eliminate or minimize risk and
- communicated consistently to commercial manufacturing and marketing for use in risk control programs.

Systematic integration of information from the market into the product development process increases the likelihood that a developed product will meet user needs.

Product risk profiles can change over time with information gained through increased use of a product, increased distribution, improvements in clinical practice, changes in a disease state, and changes in manufacturing technologies or source materials. Monitoring for new risks and the effectiveness of risk control programs should be established in operations, in the clinic, and in the market. Periodic and event-based review of this information (risk review) helps assure that product risks remain acceptable, providing better protection of the public and the company from new and/or unexpected risk.

QMS processes are those within an organization that help fulfill **QUALITY** objectives associated with a product development **LIFECYCLE,** a commercial supply chain, a marketed product study, and surveillance.

Quality Policy and Quality Objectives

Quality Policy

To establish a set of product requirements, operational processes and practices, and organizational communication tools that result in adequate, consistent, and improving

- public health
- product quality
- productivity
- employee satisfaction
- customer satisfaction
- regulatory compliance

Quality Management System Objectives

- to fulfill quality policy
- to protect and/or improve public health
- to maintain quality standards that are acceptable to all regulatory bodies in countries where products are distributed
- to communicate quality policy and QMS objectives throughout the organization to identify, assess, and control uncertainty in products, QMS processes, and their interrelationships, resulting in
  - no new or additional risks to patients or product users
  - increased product safety over time
  - consistent or improved product effectiveness over time
  - decreased variability in product quality characteristics over time
  - decreased variability in manufacturing and testing processes over time
  - decreased variability in quality of facilities, utility system performance, utility system outputs, environments, materials, equipment performance, etc. over time
  - decreased variability in employee performance over time
  - decrease in product complaints, product recall, and product returns, over time
  - increased responsiveness to market signals or variables associated with product safety and performance

Effective and efficient use of resources, provided in a well-designed quality management system, can assure

- identification and understanding of variables in the market, in clinical practice, and in product manufacturing that could affect product safety and performance
- quick and effective response to adverse clinical effects of product use, and
- continuous improvement of products during development and after commercialization.

Quality management system performance should be measurable. Performance metrics, designed to support quality objectives, should be reviewed routinely, judged for acceptability, and acted upon as appropriate.

QMS and GMPs

Although FDA regulations for the pharmaceutical and biotechnology industries have not changed significantly in 30 years, expectations for a quality management system approach have been clearly promoted by the FDA and others (**2–14**). In response, many companies have introduced quality management systems that incorporate the following differences from traditional GMPs.

QMSs apply to a greater scope of operations than GMPs: Product development operations and some marketing activities should be within the QMS. Research operations should not be managed by the QMS. This change in scope requires that an organization

- define when research ends and product development begins
- assure that product development activities proceed according to an established product development process to assure adequate and timely flow of information within a quality management system.
- assure that marketing information can be used to establish market and user requirements based on market studies, monitor the market after a product is in distribution, and review market advertising and promotion material.

System-Level Documents: The quality management system approach requires system-level documents. Documentation of the QMS and associated QMS processes in a QMS manual should establish an organization-specific approach to quality. A quality manual is more than a well-organized list of existing plans and procedures. It is expected to establish the design of a quality system, identify its functional components (QMS processes), define a process approach to management, and provide a link between quality policy, quality objectives, and routine practices (see "Quality Policy" and "Quality Management System" boxes). A QMS manual should facilitate review of the system by regulators, auditors, and QA staff.

A QMS manual should identify all QMS processes; define the contribution of each process to the organization; establish responsibilities,

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process inputs, outputs, controls, interrelationships with other processes, links to quality objectives, and links to the routine practices and procedures of the organization. Note: QMS processes are those within an organization that help fulfill quality objectives associated with a product development lifecycle, a commercial supply chain, a marketed product study, and surveillance.

Measurable Objectives: The QMS approach expects that the performance of a QMS and its processes are measured, monitored, and judged routinely for their effectiveness. Quality objectives of an organization should be measurable. QMS processes should establish process metrics that align with an organization's quality objectives. Periodic process and system reviews judge the effectiveness of quality management.

Management Responsibilities: A QMS differs from GMPs in that management effectiveness in fulfilling its responsibilities is monitored and judged routinely. Management is generally responsible for

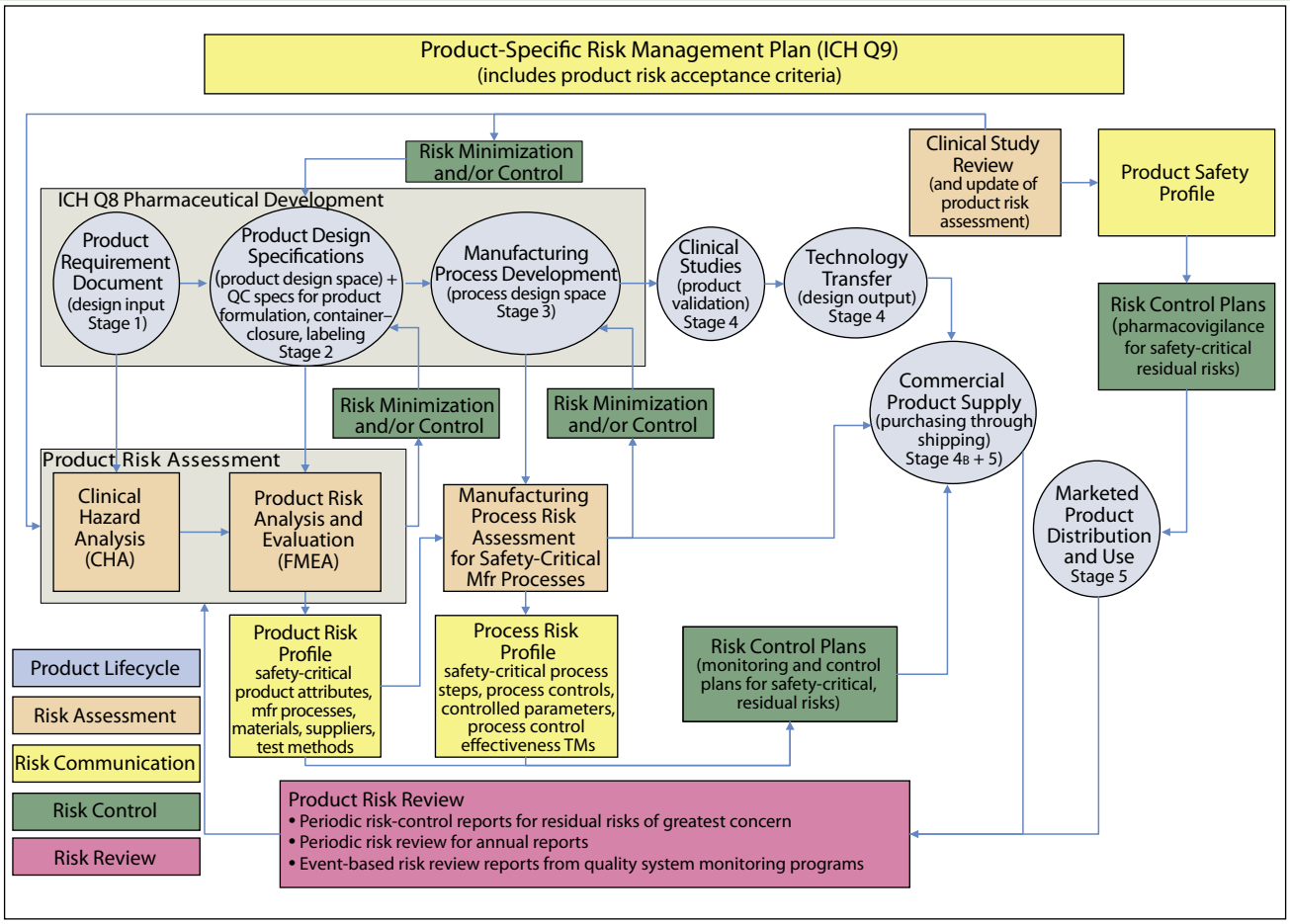
- establishing the QMS and associated quality policy and objectives
- effectively communicating quality objectives throughout the organization
- providing adequate resources to the organization
- periodically reviewing the effectiveness of the QMS and its processes, and
- changing the quality policy, objectives, or system.

Differences Between a Risk-Based QMS and a Traditional QMS

In 10 years all quality management systems are likely to be designed as risk-based. At the moment, however, some quality management systems do not use risk assessment systematically to inform decision making across a product lifecycle or within a manufacturing environment. Additional features of a risk-based QMS designed to identify, assess, and control uncertainty, should include the following.

Risk-Based Product Development: Product hazards should be defined, and product risk evaluation criteria and product risk acceptability values should be established at the beginning of

Figure 1: Risk based quality management system



product development. As product development proceeds, risk assessments should identify risks to be minimized and/or controlled through product design. At the end of product and process development, companies should have a documented understanding of product risks and their associated controls. This information should be communicated during technology transfer to the commercial manufacturing operation or contractor.

Risk-Based Commercial Manufacturing: Large-scale manufacturing can introduce new risks to manufacturing processes and products. Risk profiles provided from product development should be reviewed and updated during technology transfer to assure that no new risks have been introduced and that existing risk control measures are appropriate and effective. Interactions between a new product and an existing manufacturing facility should be assessed for risk from two perspectives:

- the new or increased risks to the product resulting from the manufacturing environment (mentioned above), and
- the new or increased risks to existing products in the manufacturing facility with the introduction of the new product.

Risk-Based Postmarket Surveillance: In a risk-based approach to development and manufacturing, probabilities are established in risk assessments about the likelihood of failures occurring. Once a product is in commercial distribution and its use increases from a few hundred patients supporting a clinical study to thousands of uses in the market, the validity of its probability-of-failure values is tested. When this information is collected and systematically integrated into existing risk profiles and risk assessments, patient safety can be rigorously monitored (as new risks are identified and existing risks are judged for adverse trends), and opportunities for product improvements can be identified.

Risk-Based Regulatory Oversight: With agreed-on definitions of hazard and risk acceptability, risk-based product development, commercial manufacturing, and market surveillance, regulatory decision making can be informed by science and knowledge. When a QMS has been established to assure consistent decision making and there is evidence of effective QMS controls, risk-based regulatory oversight should follow.

Risk-Based Quality Management System: A QMS should assure the integration and control of risk

- across a product lifecycle (development to market)
- throughout the manufacturing process chain (purchasing to distribution)
- throughout the regulatory lifecycle (IND submission, NDA/BLA/CTD submission, inspection, annual reporting,

postmarket surveillance studies, adverse experience reporting, and change submissions).

Risk Management for a Global Marketplace

Effective and consistent risk-based decision making relies on the implementation of systematic product development, risk management implementation over a product lifecycle, and a quality management system. None of these initiatives is effective without the other two components. In support of this, ICH issued a trio of guidelines to promote international harmonization: *Pharmaceutical Development* (ICH Q8), *Risk Management* (ICH Q9), and *Quality Systems* (ICH Q10). They provide a common approach to product development, market authorization, and risk management for a global marketplace.

Only a risk-based quality management system will prepare an organization for potential product opportunities. And only a risk-based quality management system will protect an organization from the risk that comes with the increasing complexity of innovative technologies, new emerging diseases, and a global definition of risk acceptability.

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