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Developing a Risk Management Strategy for Medical Devices in the US Market

– By Nancy Madison

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Risk management is an essential component of regulatory compliance for medical device companies marketing their products within the US. Yet, since risk management requirements have evolved over the course of more than a decade, it is not possible for a regulatory professional to rely upon just one source to determine exactly what type of risk management system should be implemented to comply with US regulations. The best approach is to become knowledgeable about the information provided in many US Food and Drug Administration (FDA) and international documents before determining how to develop and deploy a risk management system that is both compliant with the requirements and appropriate to the risk-level of the company's products and processes.

This article reviews the key regulations, standards and guidance documents that a regulatory professional should understand before mapping out a risk management strategy for the US market.

21 CFR Part 820 Quality System Regulation (Final Rule, 7 October 1996)

To understand FDA's risk management requirements for medical device companies it is necessary to start with the Quality System Regulation (QSR) as published in the final rule for 21 CFR Part 820, 7 October 1996. This regulation is still current. Only slight modifications have been made since its initial publication, none of which relate to risk management.

The term "risk" is mentioned only once in the body of the QSR, in Subpart C Design Controls, section 820.30(g)—Design Validation. This section of the regulation reads "Each manufacturer shall establish and maintain procedures for validating the device design...Design validation shall include software validation and risk analysis, where appropriate."¹

Although this is the singular reference to risk in the body of the QSR, the

preamble to 21 CFR Part 820 as published in the final rule on the same date provides substantially more references to and insight into FDA's risk management requirements for medical device companies. FDA states unequivocally that "Risk Analysis must be conducted for the majority of devices subject to design controls and is considered to be an essential requirement for medical devices under this regulation..."²

In the preamble, FDA introduces six key concepts that provide the framework for its risk management philosophy. Regulatory professionals in the medical device industry should be familiar with these key concepts in order to have an accurate lens for interpreting how and where to apply risk management strategies throughout their companies.

FDA uses the term "risk analysis" in place of the term "hazard analysis" for the first time in the preamble. The agency justifies this term replacement by comparing the narrow focus of hazard analysis to the comprehensive focus of risk analysis, explaining that hazard analysis is in fact embodied within risk analysis. Risk analysis, as defined in the preamble, includes not only identifying potential hazards but also determining the risks of those hazards and reducing those risks to an acceptable level while ensuring that any changes resulting from risk reduction efforts do not in fact introduce any new risks.

The second key concept the preamble introduces regarding risk analysis is the principle that risk analysis must be performed for both potential hazards that could result from device failure as well as for potential hazards that could result from user error. In other words, a medical device company is not exempted from responsibility for any harm that results from user error.

The preamble also establishes the principle that controls should be put in place that are commensurate with the risks involved, thus making it clear that risk management requirements are proscriptive rather than prescriptive. A medical device company, in fact, is given significant flexibility in implementing a risk management system as long as the system is commensurate with the risks inherent in the company's products and processes.

Although risk analysis is only mentioned once in the body of the QSR, the preamble makes it clear that risk controls apply to any phase of the product lifecycle that incorporates risk, including incoming component acceptance and manufacturing.

The preamble also explicitly states that the corrective and preventive action (CAPA) system should be commensurate with the risks associated with the devices being manufactured. FDA clearly expects that there will be procedures in place to assess the risk of nonconformities and to determine different corrective and preventive actions depending upon the level of risk involved.

Finally, in the preamble, the agency makes it clear that it considers international risk analysis standards to be sound and that it expects medical device companies to follow them. FDA explicitly states that it sees no need to develop its own risk management regulation. In the preamble, the agency references the risk analysis standards that were then in place or in development, namely EN 1441 and ISO 14971:2000, but states explicitly that international risk management standards will

continually evolve over time and that it is critical for medical device companies to stay current with the evolving standards.

Do it by Design

The second document with which regulatory professionals should acquaint themselves regarding risk management is the guidance document, *Do it by Design*, issued by FDA in December 1996. This was the first guidance document to be issued after the final rule for 21 CFR Part 820 was published in October of 1996 and reflects the fact that for the first time, the design phase was subject to the QSR. The inclusion of the design phase in the QSR was a reflection of the mounting evidence from adverse event reports that poor device design was often the cause of hazards.

User error had also been implicated in adverse event reports as a source of harm. This insight motivated FDA to focus on the importance of human factors engineering in device design. *Do it by Design* reflects that focus and the then current thinking about how to design and test medical device user interfaces to ensure devices' safety and effectiveness. This document provides the foundation for FDA's subsequent guidance documents on device usability issues.

Design Control Guidance for Medical Device Manufacturers

This guidance was issued 11 March 1997 to provide further elaboration on the role of risk management within the design phase. Although risk analysis is mentioned only in the design validation section of the QSR, this guidance emphasizes that risk management is an integral portion of the design process, beginning with developing design input requirements. It recommends deploying a systematic approach early in the design process to identify and evaluate risks, and reduce those considered unacceptable, since changes are easier and less expensive to make early in the process. It clearly states that the scope and complexity of both the design and development plan and the design input requirements should be commensurate with the inherent risks of the devices being produced. It also explicitly states that risk analysis results should be one of the design outputs.

The term "risk management" appears in place of "risk analysis" for the first time in this guidance. It is defined by FDA as "the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk."³

Guide to Inspections of Quality Systems

A regulatory professional can gain additional insight into FDA's risk management philosophy by becoming familiar with *A Guide to Inspections of Quality Systems*, issued in August 1999. The main purpose of this guidance is to describe how FDA personnel should conduct inspections using a then new, top-down approach, but it also provides interesting insight into FDA's philosophy about the key areas where risk management activities are essential.

This guidance breaks a quality system down into four major subsystems: management controls, design controls, corrective and preventive action and production and process controls. As described below, risk management requirements

are directly mentioned in the inspection techniques for three of these major subsystems and indirectly mentioned in the fourth.

Design Controls Subsystem

In the section devoted to investigational techniques for the design controls subsystem, investigators are advised to ensure that risk analysis was performed, that it was addressed in the design plan, that it continued throughout the design process, and that it was completed by design validation. Investigators are reminded that risk analysis complexity should be commensurate with the degree of risk.

The Quality Systems Inspection Technique (QSIT) guidance also reminds the investigator that potential hazards from both device failure and user error must be identified and evaluated in terms of risk. Any risks that are deemed unacceptable must be reduced through either redesign or labeling, ensuring that any changes do not introduce new hazards.

Investigators are advised to review records to ensure that risk was analyzed in determining both design input and output requirements, that the degree of design change control correlates to the degree of device risk, and that the design review process incorporates risk analysis.

Corrective and Preventive Actions Subsystem

The QSIT guidance stresses the importance of verifying the appropriate use of risk analysis within the CAPA subsystem through the review of both procedures and records.

FDA investigators are advised to review CAPA procedures to ensure that risk analysis techniques are used appropriately in the following areas:

- scaling nonconformity investigations to the risk of the nonconformity
- determining the root cause of a failure
- determining the significance of a failure
- determining if a nonconformity requires a corrective or preventive action

Guidance for reviewing specific CAPA records also highlights the need to verify the appropriate use of risk analysis in the following areas:

- incomplete failure investigations records for potential unresolved nonconformities to ensure there are no high risk unresolved problems
- nonconforming product records where it was determined that corrective or preventive actions were not necessary to ensure that these decisions were appropriate to the product risk
- product and quality concession records to ensure that they were appropriate to the product risk

Production and Process Controls Subsystem

Risk management factors into both the selection of the process to review in this subsystem and how the process is reviewed. The QSIT guidance advises FDA investigators, when selecting a process to review, to consider both the degree of device risk the process is being used for and the degree of risk of the process for causing device failures. While conducting the review, FDA investigators are advised to verify that

the firm has a solid understanding of when deviations from device specifications could occur during manufacturing. The guidance suggests that documented product and process risk analysis procedure records would be good proof of this.

Management Controls Subsystem

Although risk analysis is not mentioned directly in the management controls section of the QSIT guidance, it is indirectly referenced as an area for investigators to focus on if the lack of risk analysis is found in either the CAPA or production and process controls subsystems. Clearly, FDA places the burden on management to ensure that risk analysis is used appropriately throughout the company.

Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management

FDA's goal in providing this guidance, issued in July 2000, is "to minimize use-related hazards, assure that intended users are able to use medical devices safely and effectively throughout the product life cycle, and to facilitate review of new device submissions and design control documentation."⁴ In this guidance, the agency focuses on methods to decrease use-related failures by integrating human factors engineering into all stages of risk management. It delineates empirical techniques to identify use-related hazards, discusses the challenges involved in evaluating the risks associated with use-related hazards, and provides examples of ways to mitigate and control user-related failures. Finally, it emphasizes the importance of documenting all of these efforts as proof of their occurrence.

Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff (February 2003)

Issued in February 2003, this FDA guidance explicitly states which risk management components need to be included in certain premarket submissions including: Premarket Approval applications, Premarket Approval Supplements, Product Development Protocol submissions, Humanitarian Device Exemption applications and Modular Review submissions. It reaffirms that the design and development plan should include risk management activities and, while acknowledging that all risk management activities might not be complete, requires that an explanation of how future risk management activities will be incorporated into the design and development plan be included. It also requires an explanation of how risk management was utilized to establish receiving acceptance activities procedures, as well as an explanation of how the CAPA system is integrated with the risk management program.

ISO 14971:2007 Application of Risk Management to Medical Devices

ISO 14971 is the international standard for risk management for medical device companies. The second edition was issued in March of 2007 and FDA recognized it as a consensus standard in September 2007.



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ISO 14971:2007 is divided into two major sections: the body of the standard and 10 informative appendices. From the body of the standard, a regulatory professional can learn all of the essentials about the key concepts, processes and documentation requirements for a risk management system. The appendices provide useful insights and examples of the rationale behind the requirements, how to apply risk concepts to medical devices, and how to develop a risk management plan.

A key differentiating point between ISO 14971:2000 and ISO 14971:2007 is the emphasis placed on collecting and reviewing production and postproduction information through postmarket surveillance of both the company's products and similar products from competitors. Although the emphasis on postmarket surveillance has yet to make it into any FDA guidance documents, it undoubtedly will.

Conclusion

ISO 14971:2007 should be used to develop a robust, global risk management strategy for medical devices. For the US market, it should be interpreted from the perspectives provided in FDA guidance documents. In particular, specific attention should be paid to identifying potential use-related hazards and to applying risk management to design controls, CAPA and manufacturing controls.

REFERENCES

1. 21 CFR Part 820, Quality System Regulation, Subpart C—Design Controls, Section 820.30(g)—Design Validation, Revised 1 April 2007.
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3. FDA Design Control Guidance for Medical Device Manufacturers. 11 March 1997; page 5.
4. Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management. 18 July 2000; p 5.

ABOUT THE AUTHOR

Nancy Madison is president of Compliance Express. She founded the company in 2004 to provide regulatory compliance software and services to medical device companies. She holds an MSEECS from UC Berkeley, an MA from Harvard University and a BA from George Washington University. She can be reached via email at nmadison@complianceexpress.com.

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