

Are You Ready for the Risk-Management Paradigm Shift?

By Susan M. Mondabaugh, PhD

The entire concept of risk management is undergoing a significant change as the result of several FDA initiatives. The question is, are we, as regulatory affairs professionals, keeping pace, adapting our work practices and providing guidance for corporate philosophies?

One of FDA's top initiatives is more efficient risk management, encompassing many facets of drug development and manufacturing. FDA recognizes that efficient risk management is essential to leveraging existing resources required by both industry and the agency in bringing new drugs to market and maintaining existing products.

Manufacturing

The US good manufacturing practice (GMP) regulations have not been updated in more than 20 years. In August 2002, FDA announced the Pharmaceutical cGMPs for the 21st Century Initiative. The intent of this initiative was to integrate quality systems and risk-management approaches into existing programs for the purpose of encouraging manufacturing and technological innovation. In September 2004, FDA released the Draft Guidance for Industry *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice [cGMP] Regulations*. This guidance proposes a quality systems model that complies with the cGMP regulations in 21 CFR Part 210 and 211. For medical devices, the quality system regulations

in 21 CFR Part 820, finalized in 1996, are equivalent to the pharmaceutical cGMPs.

The 2004 guidance defines risk assessment as "a systematic evaluation of the risk of a process by determining what can go wrong (risk identification), how likely is it to occur (risk estimation), and what the consequences are." In the context of the cGMP initiative, risk assessment is also used in determining the need for discrepancy investigations and corrective action, and risk management can guide the setting of specifications and process parameters.

Consistent with the Pharmaceutical cGMPs for the 21st Century Initiative, the PAT (Process Analytical Technology) initiative has been introduced by FDA and was published in the Guidance for Industry, *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, in September 2004. An important PAT component is a risk-based framework that uses the overall scientific understanding of how the formulation and manufacturing process affects product quality to control critical parameters. The objective is to minimize the risk of manufacturing a poor-quality product. The degree of process understanding is inversely proportional to the risk. The level of understanding of the critical process parameters in a quality systems environment determines the extent of documentation needed to support process and product changes. Simply stated, if the level of

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process understanding is high and the facility has a well-functioning quality system, the regulatory burden for making changes is lower.

The ICH Draft Guideline, *Q9 Quality Risk Management*, was released for consultation (ICH Step 2) in March 2005 and published in the *Federal Register* on 8 August 2005.¹ It contains quality risk-management principles that can be applied to all facets of pharmaceutical manufacturing to enhance risk-based decision-making by both industry and health authorities. The guideline proposes a quality risk-management process for assessing, controlling, communicating and reviewing risks (**Figure 1**).

The next ICH guideline, *Q10 Quality Systems*, is under development.

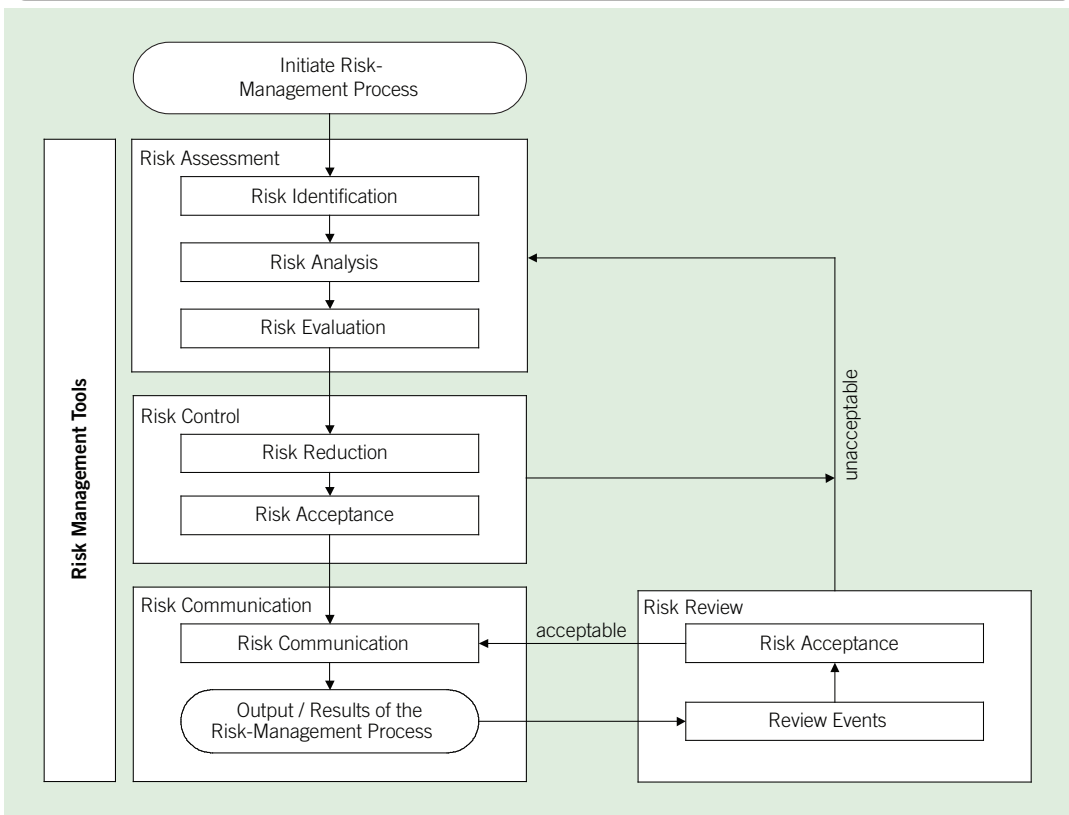
Drug Safety

Drug and biologic product risk management was captured in three guidances to industry released in March 2005:

- *Premarketing Risk Assessment*
- *Development and Use of Risk Minimization Action Plans*
- *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*

These documents are intended to complement

Figure 1: Quality Risk Management Process



one another; they provide tools to assess risks throughout the product lifecycle and methods to reduce risks to patients through routine risk-management and risk-minimization action plans (RiskMAPs).

FDA has defined risk management as an iterative process consisting of the following steps:

1. assessing product benefit-risk balance
2. developing and implementing tools to minimize product risk while maintaining benefits
3. evaluating tool effectiveness and reassessing benefit-risk balance
4. making necessary adjustments to risk-minimization plans to improve the benefit-risk balance

Risk minimization is intended to reduce potential patient dangers that are considered preventable. For most products, routine minimization consists of approved product labeling, updated periodically with new information from postmarketing surveillance activities, and postmarketing surveillance with periodic safety reports. For products with clinically important or unusual potential dangers, RiskMAPs must be developed and implemented. The need for a RiskMAP may be identified during the nonclinical or clinical phase or from safety signals detected during postmarketing surveillance when a larger patient population is exposed to the product. Drugs with known teratogenic or carcinogenic potential are examples of those well-suited to RiskMAPs. Most recently, FDA approved a strengthened RiskMAP, called iPLEDGE, intended to reduce the risk of fetal exposure to isotretinoin, a known teratogenic drug.

Challenges

The paradigm shift for drugs and biologics is to a quality systems environment in which risk assessment and management will be the driving forces for decision-making, whether on the manufacturing and process side or during the development and postmarketing periods. Regulatory affairs professionals unfamiliar with quality systems will need to learn them to keep pace with FDA's initiatives and better advise company management and other stakeholders. The regulatory professional's role is to interpret the new guidance documents from FDA and ICH, and effectively partner with counterparts in manufacturing, QA/QC, clinical, drug safety and other areas.

FDA compliance and enforcement activities can be expected to take a more risk-based focus as the agency applies its resources to maintain high-quality products to protect the public health. Postapproval manufacturing changes also will be more risk-based, and understanding and controlling critical process parameters will be essential in reducing the regulatory burden of implementing these changes. To minimize patient risks and maximize drug benefits, risk assessment, postmarketing pharmacovigilance and risk-minimization plans will assume greater importance throughout a product's lifecycle.

Table 1 lists guidance documents issued by FDA and ICH cited in this article. ■

REFERENCES

1. *Federal Register*, 70:151, 45722-4572.

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Table 1: Manufacturing and Safety Guidance Documents

Title	FDA	ICH
<i>Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations</i>	X	
<i>PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance</i>	X	
<i>Q9 Quality Risk Management</i>		X
<i>Premarketing Risk Assessment</i>	X	
<i>Development and Use of Risk Minimization Action Plans</i>	X	
<i>Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment</i>	X	