White Paper: Pharmaceutical Industry

Webster's dictionary defines RISK as the "possibility of loss or injury: PERIL" and, "someone or something that creates or suggests a hazard." "At Risk" is defined as "exposed to a usually specified danger or loss (e.g. patients at risk of infection)".

Every product and every process has an associated risk. Every enterprise should have a methodology for identifying and evaluating the risks it faces and it should have a process for generating intervention plans to reduce the risks to an acceptable level. This process is generally referred to as a Risk Management Plan (RMP).

The paper presents a summary of Risk Management Programs in conjunction with the FDA's recently announced Risk Based Approach Initiative and compliance with FDA Guidelines.

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Risk Management Programs for the Pharmaceutical Industry

by Edward Griffith

The FDA's cGMPs for the 21st Century: A Risk-Based Approach Initiative

In early 2002, the Food and Drug Administration (FDA) announced their Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach initiative. According to the FDA position paper:

"The FDA oversees the quality of drug products using a two-pronged approach involving review of information submitted in applications as well as inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practice (cGMP). These two programs have served the country well by helping to ensure the quality of drug products available in the US. Now, as we approach the 25th anniversary of the last major revision to the drug cGMP regulations, it is time to step back and evaluate the currency of these programs so that:

- The most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality;
- The latest scientific advances in pharmaceutical manufacturing and technology are encouraged;
- The submission review program and the inspection program operate in a coordinated and synergistic manner;
- Regulation and manufacturing standards are applied consistently;
- Management of the program encourages innovation in the pharmaceutical manufacturing sector; and
- FDA resources are used most effectively and efficiently to address the most significant health risks.

The FDA defines a Risk Management Program (RMP) as, "a strategic safety program designed to decrease product risk by using one or more interventions or tools …". The FDA proposes that, "…the sponsor of every product submitted for approval consider how to minimize risks from the product's use. Risk management planning generally encompasses all efforts by a sponsor to minimize the risk from its product's use and may include product labeling, risk assessment, pharmacovigilance, and special studies or interventions. All products have some kind of risk management planning. For most products, traditional risk management planning consists of professional product labeling (i.e. the package insert or PI) and post market surveillance. However, the PI alone is not always sufficient to minimize a product's risk. In these cases, FDA proposes that sponsors submit a risk management program (RMP)…"

The FDA expects the RMP to follow a basic process of, "(1) learning about and interpreting a product's benefits and risks, (2) designing and implementing interventions to minimize a product's risks, (3) evaluating interventions in light of new knowledge that is acquired over time, and (4) revising interventions when appropriate".

Risk Management Programs (RMP)

A Risk Management Program starts with identifying the possible risks (and benefits) associated with a product or with the process used to develop, manufacture, and distribute the product. The following questions should be asked at each stage of the product's life cycle:

- What are the safety risks?
- Who is at the highest risk?
- What populations are at risk?
- Are the risks predictable?
- Are the risks preventable?

The last question, "are the risks preventable" is very important because it forms the basis of the intervention plan. In order to determine if the risk is preventable, the root cause of each risk has to be determined. Once the root cause is established, the probability of occurrence can be calculated and the risk interpreted for severity, frequency, or duration. Following interpretation, the next phase, Designing and Implementing Interventions (i.e. mitigation plans), can be started.

Risk Management Plans correlate the listing of risks with a listing of Risk Reduction Goals. The Risk Reduction Goals are the endpoint of the intervention plans. For example, if the severity of the risk has been evaluated as "Severe" with a frequency of "one per ten thousand", the Risk Reduction Goal could be to reduce the severity to "Moderate" and reduce the frequency to "one per five hundred thousand". Risk Reduction Goals must be measurable. That is, they must be written in a way that agreed upon metrics may be employed to measure the progress of the intervention plan and to ensure that the Risk Reduction Goals are being met. The intervention plan details the steps that will be taken to reduce the risk to the acceptable levels and includes the metrics that will be used to measure the progress against the stated risk reduction goals.

Two critical elements of the intervention plan are the criteria that will be used to evaluate the progress toward achieving the stated risk reduction goal and the metrics use to measure the results. According to the FDA, ideally, an overall approach to RMP evaluation would:

1. Select well-defined, validated metrics. A sample outcome metric for reducing the occurrence of an adverse event could be analysis of the number or rate of hospitalizations for that event in an administrative data system. A sample process metric would be to measure how many patients prescribed a product get lab monitoring to reduce their risk of serious sequelae.

2. Use at least two different evaluation methods for key RMP goals or objectives. Preferably, the different evaluation methods would be both quantitative and representative to offset the biases that are intrinsic to any single evaluation process. For example, hospitalization data on an adverse event would not capture deaths that occurred out of the hospital; in such an instance, death certificate surveillance would offer complementary and more complete ascertainment of mortality risks. If it is not possible to implement two complementary representative methods, FDA suggests using other quantitative methods such as multiple site sampling or audits.

3. Use qualitative data collected from a large and diverse group of patients when quantitative data are either not available or not applicable to the evaluation measurement. Qualitative data such as focus group testing may be useful in assessing the effectiveness of education and comprehension about safety and risk information.

4. Consider using evaluation methods to assess if each RMP tool is performing as intended.

The remaining element of a RMP is a process for continuous review and evaluation. There should be a methodology established that assures the RMP is regularly reviewed and updated as necessary depending upon the status against the stated Risk Reduction Goals. The frequency of review should be based on the evaluation of the risk. The RMP for moderate to severe risks should be reviewed and updated more frequently than less those that have a lower evaluation.

SEI Risk Management Paradigm

The Software Engineering Institute (SEI) has identified 6 elements of a Risk Management Paradigm. The six elements are: Identify, Analyze, Plan, Track, Control, and Communicate. Each phase is briefly described as follows:

- **Identify:** Search for and locate risks before they become problems
- **Analyze:** Transform risk data into decision-making information. Evaluate impact, probability, and timeframe, classify risks, and prioritize risks
- **Plan:** Translate risk information into decisions and mitigating actions (both present and future) and implement those actions
- **Track:** Monitor risk indicators and mitigation plans
- **Control:** Correct for deviations from the risk mitigation plans
- **Communicate:** Provide information and feedback internal and external to the project on the risk activities, current risks, and emerging risks.

Risk management is a key process area (KPA) in SEI's Systems Engineering CMM" and Software Acquisition CMM models and is a Process Area at Maturity Level 3 in the CMM Integration SM staged models. According to SEI, "Risk Management is a practice with processes, methods, and tools for managing risks in a project.

It provides a disciplined environment for proactive decision making to:

- Assess continuously what could go wrong (risks)
- Determine which risks are important to deal with
- Implement strategies to deal with those risks".

The SEI Risk Management Paradigm states that, "each risk nominally goes through these functions sequentially, but the activity occurs continuously, concurrently (e.g. risks are tracked in parallel while new risks are identified and analyzed), and iteratively (e.g. the mitigation plan for one risk may yield another risk) throughout the project life cycle".

Elements of a Risk Management Program

The elements of a Risk Management Program can be used as tools to help clients realize their business requirements. For example, the following table and checklists correlate Risk and Issue Management techniques and methodologies to the basic process described by the FDA:

FDA Guideline	RMP Elements
Learning about and interpreting a product's benefit's and risks	- Risk and Issue Management Strategy - Risk Identification Technique - Risk Evaluation Technique
Designing and Implementing Interventions	- Risk Response Planning - Risk and Issue Management Plan
Evaluating and Revising Interventions	- Risk and Issue Management Plan

Risk and Issue Management Strategy

The Risk and Issue Management Strategy defines the Approach, Responsibilities, and Activities (sometimes referred to as RACI) that should be done to effectively manage the risks and issues. The Risk and Issue Strategy contains a brief explanation on the manner in which risks and issues will be handled by responsible individual(s) and how risks and issues will be raised, analyzed, reviewed, communicated, and escalated.

Risk and Issue Management Plan

The Risk and Issue Management Plan documents the strategy for managing the risks and issues and describes the corresponding approach, responsibilities, activities, and tools.

The approach to risk and issue management specifies the manner in which risks and issues will be handled. The initial risk and issue identification approach is defined, the notification process and the way to document the risks and issues are determined, and the escalation process is established.

The Risk and Issue Management Plan identifies the managers who have primary responsibility for managing the risks and issues, and the domains for which they carry this responsibility. It identifies the domain experts who will lead the analysis for specific management domains. It outlines the risk and issue management activities to be performed throughout the project.

The Risk and Issue Management Plan also provides tables to be used when categorizing and evaluating the risks and problems.

Risk Identification Technique

The Risk Identification Technique provides methods to identify risks that could affect the safety, quality, reliability, or durability of a product, process, or program and organizes the risks in order to evaluate them and plan an appropriate response. Sometimes this is referred to as a "Hazards Analysis". A Hazard Analysis is often used in conjunction with a "Failure Modes and Effects Analysis (FMEA)."

Risk Evaluation Technique

The Risk Evaluation Technique evaluates the priority and severity of an identified risk that threatens the safety, quality, reliability, or durability of a product, process, or program. The Risk Evaluation Technique allows the project team to assess the risk relatively quickly and to organize them for subsequent action.

Impact Criteria Determination Technique

The Impact Criteria Determination Technique helps to identify the project areas or product attributes that might be impacted by a risk or a problem, and establishes the criteria used to evaluate the impact of problems or the potential impact of risks.

Each project risk and problem will have an impact assigned to it in order to determine its severity and priority.

Risk Response Planning Technique

The Risk Response Planning Technique allows the project team to determine how it will react to the risks or problems. The response can vary from accepting the risk as it is, changing the product, process, or program, to avoid the risk altogether, or to actively pursue ways to reduce the risk's threat to the product, process, or program.

Checklists

The following checklists are used to assure that all of the necessary Risk Management Procedures have been identified and completed. Depending on the circumstances of the project, this checklist should be reviewed at key milestones throughout the project.

Define Risk and Issue Management Strategy

- Review the project description and project profile from the Project Statement and any contractual information for information about risk and issue management.
- Establish the approach to effectively manage the risks and issues (what, who, when, how).
- Define the approach that will be used for the initial identification of the risks and issues.
- Determine the notification process and the way to document the risks and issues.
- Establish the escalation process that will be used to obtain decisions on major risk or issue situations.
- Identify the management areas under which risks and issues can be raised. These management areas can be internal or external but they all have a relationship with the product, process, or program (e.g., relationship with the end user, third party contract organizations, product pre / post market surveillance, internal Corrective and Preventive Actions (CAPA), etc.).
- Identify the manager who will have the primary responsibility for managing the risks and the issues for each management area. This means the manager will be responsible for risk evaluation, defining possible risk response, and making a recommendation for each risk and/or issue identified as part of his/her management area.
- Identify the domain experts who will be in charge of the analysis of the risks and issues for each management area.
- Identify the risk and issue management activities (including the initial identification and evaluation of risks done at the beginning of the project) and determine which individuals are responsible, who participates, and when the activities should be performed or at what frequency.

Build Risk and Issue Analysis Tables

- Define the criteria that will be used to classify each risk and issue.
- Identify the product, process, or program areas that might be impacted by a risk or a problem.
- Define the criteria that will be used to evaluate the impact of a risk or a problem. These criteria are defined for each project area that can be impacted by a risk or a problem and for each level of impact (low to high).
- Create the Risk and Problem Impact Evaluation Table that will be used to determine the potential impact of a risk or a problem.
- Define the Risk Severity Matrix that will be used to determine how much a risk can threaten the product, process, or program.
- Review the Risk and Issue Management Plan and obtain approval from the stakeholders. Make any necessary corrections to the plan, according to comments received.
- Communicate the project's Risk and Issue Management Plan to all interested parties.

Summary

All products and all processes have an inherent element of risk. The questions are “What risks are involved”, “What impacts do the risks have”, and “How do we manage the risks to keep them within acceptable levels”? A Risk Management Plan is required to be able to answer these questions.

Risk Management Plans have been used as best business practices for many years. RMPs are being used more often in business environments that are experiencing reduced resources with increased liabilities. One such organization is the Food and Drug Administration. The FDA recognizes that it needs to reorganize its procedures and processes to incorporate the use of Risk Management Programs within the agency and within the industries it regulates. Consequently, the FDA has started issuing position papers and guidelines on what it expects to see in an RMP.

This paper reviewed the current thinking of the FDA regarding Risk Management Plans, presented a summary of the SEI outline for an RMP, and described RMP elements that can be used for establishing, conducting, and communicating an effective Risk Management Plan that will comply with the FDA guidelines.

Headquarters & United States
FUJITSU CONSULTING
333 Thornall Street, Edison, NJ 08837, United States
Tel: +1 732 549 4100 Fax: +1 732 549 2375

Canada
FUJITSU CONSULTING
200 Front Street West, Simcoe Place Suite 2300, Toronto, Ontario, Canada M5V 3K2
Tel: +1 416 363 8661 Fax: +1 416 363 4739

Quebec
DMR CONSEIL
1000 Sherbrooke Street West, Suite 1600, Montreal, Quebec, Canada H3A 3R2
Tel: +1 514 877 3301 Fax: +1 514 877 3351

us.fujitsu.com