Managing Product Risk from Cradle to Grave; Application of Risk Management in the Development of Medical Devices

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Summary

A Risk Management strategy was developed for a DuPont business dedicated to the development of medical devices. This strategy took into consideration five different forms of risk: Risk associated with product development, risk associated with the manufacturing process, risk associated with business scenarios, risk associated with stewardship of the product and risk associated with post-market surveillance.

Keywords

Risk management; Product development; ISO 14971:2007; ISO 13485:2003; Medical devices

Introduction

"If anything can go wrong, it will", said Captain Edward A. Murphy in 1949 [1]. What has famously become known as "Murphy's Law" is something anyone involved with product development, manufacturing and commercialization activities grapples with throughout the life of a product. The "if" in Murphy's Law implies probability of occurrence, that is, the likelihood that an unintended event will take place. The "anything" in Murphy's Law refers to potential hazards which can result in harm. Our responsibility, as quality professionals, is to work with our teams and business leaders to effectively integrate robust risk management processes into our management systems to identify the "anythings", quantify the "ifs", and establish effective controls to prevent, if possible, or to reduce the probability of occurrence of the "anythings" to a tolerable level.

Over the past 30 years, I have been involved with the design, development, manufacturing and quality support of medical devices, mostly with the DuPont Company. In a regulated environment, such as medical devices, having regulations, standards and guidance documents available facilitates the implementation of risk management practices [2, 3]. They tell you what the expectations and requirements are, but do not tell you how to implement them. It is up to you, the quality professional, to provide guidance to your management teams, to effectively implement into your systems what is appropriate for your business. In this paper, I will present examples of risk management practices we have integrated into our management system.

Classically, risk management practices for medical devices focus on product safety and efficacy. Standards such as ISO 14971:2012, Medical devices – Application of risk management to medical devices, focus on the product. But what about business risk? Risk to the environment? There are other risks that need to be taken into consideration as part of the overall risk management process. In our business, we have developed a risk management strategy that includes analyzing and evaluating business risk, cradle-to-grave risk (also known as product stewardship), supplier process risk, risk associated with a commercialized product, as well as product risk.

Some Background

While this paper is intended to be a sharing of experiences, and not a primer on risk management, I feel it is necessary to review a few important terms. The definitions are from the 2012 version of ISO 14971. I tend to look at hazard and harm in a broad sense, in terms of cause and effect, where a hazard is a condition or conditions (a cause) which could result in a harm, and a harm as the resulting outcome (or effect) of the hazard.

Term	Definition (Reference: ISO 14971:2012)
Risk	Combination of the probability of occurrence of harm and the severity of that harm
Hazard	Potential source of harm (Author's Note: This can also be thought of as a potential failure mode)
Harm	Physical Injury or damage to the health of people, or damage to property or the environment
Risk Analysis	Systematic use of available information to identify hazards and to estimate the risk
Risk Assessment	Overall process comprising a risk analysis and a risk evaluation
Risk Control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.
Risk Evaluation	Process of comparing the estimated risk against given criteria to determine the acceptability of the risk
Risk Management	Systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk.

Table 1. Basic risk management terms

A Risk Management Strategy

In this paper we examine the following five elements that comprise our risk management strategy.

Risk Management Elements	Description
Product Risk	The management of product risk as a work stream across the product lifecycle, utilizing a stage/phase-gated product development and commercialization framework.
Process Risk	The management of process risk by contract manufacturing organizations (CMOs).
Business Risk	The management of various scenarios that could negatively impact business goals and objectives.
Product Stewardship	The management of how the DuPont Company views and values every aspect of a product, its components and by-products, throughout its life cycle, with emphasis on health, safety and environmental concerns.
Post Market Surveillance	The management of how we look at various performance indicators after the product has been commercialized with respect to risk management.

Table 2. Risk management elements

Figure 1. Risk management strategy comprised of five elements

Product Risk Management

The basis of our product development efforts for medical devices centers on our product development and commercialization framework (PD&CF). The essence of this framework is a stage (phase) gated process, with a set of required deliverables assigned to each stage/phase. The project team is accountable to a management oversight team, which, in our case, is made up of a board of directors. This oversight team has the authority to approve or reject the team's request to move into the next stage of development.

Risk management practices are integrated into this framework, so that specific risk management deliverables are satisfied at predetermined stages. You will notice that there is much planning, analysis and evaluation occurring in the early stages of development to ensure that we are as thorough as possible identifying potential hazards and failure modes. The table below summarizes these activities, and indicates the appropriate design control elements that are addressed concurrently.

Product Development & Commercialization Phase/Stage	Risk Management (RM) Activity	Design Control Element
Concept / Feasibility	• RM Plan & Strategy developed • Potential Design Risks identified • Initial Risk Analysis performed • Preliminary Hazard Analysis performed • Risk Management File initiated • RM Report generated	• Customer Requirements identified • Design Inputs drafted based on Customer Requirements • System Functional Specifications developed
Development	• Risks are evaluated • Risk Control Measures identified • Risk Control Measures implemented and Residual Risk assessed • Risk Control Measures implemented until the Residual Risk is acceptable and/or the medical benefits outweigh the Risk. • RM Plan updated & Report generated	• Design Verifications conducted • Design Reviews completed • Design Transfer planning initiated • Design Outputs constructed
Validation / Regulatory	• Implemented Risk Control Measures are evaluated for effectiveness and corrected as necessary. • Residual Risk Risk/Benefit analysis performed • RM Plan Updated & RM Report generated	• Product Validation completed • Design Reviews completed
Commercialization	• Post Market Surveillance activities initiated	• Product Surveillance and Management Reviews

Table 3. Risk management activities performed and design control elements addressed during product development and commercialization.

The project team dedicates a significant amount of energy early in the project, identifying potential hazards and failure modes and determining if they are applicable to the device. They are analyzed in terms of their impact on the system and then evaluated to determine the likelihood of occurrence and probability of harm.

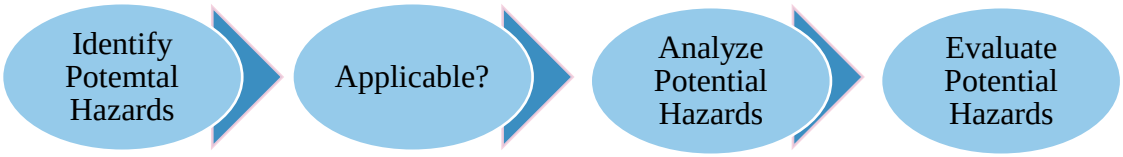

Figure 2. Potential hazards and failure modes processing sequence

An example of potential hazards and failure modes considered:

- User requirements (what is the intended use)
- Is it used to sustain or support life
- Is special intervention required in case of device failure
- Is it intended to contact the patient or other persons
- Is energy delivered to or from the patient
- Are substances delivered to or extracted from the patient

RM Tool	Description
Potential Hazards Checklist	• Asks thought provoking questions to aid the team in the identification of device characteristics that could impact safety. • Used to identify Potential Design Risks
Preliminary Hazard Analysis Checklist	• Lists Potential Hazards, such as energy hazards, biological hazards, environmental hazards, hazards resulting from incorrect output of energy or material, hazards related to the use of the medical device, and hazards arising from functional failure, maintenance, and aging • Assists in the determination of the applicability of potential hazards • Used to perform Initial Risk Analysis
Preliminary Hazard Analysis Worksheet	Provides a more in depth analysis of the hazard: • Where is the hazard likely to appear, e.g. component, subsystem, system? • What is the potential mode of failure? • What is the likely cause of the hazard or failure? • What are the system level effects of the hazard? • What are the potential risk control measures?
Failure Modes and Effects Analysis	Provides the structure to perform an evaluation of the potential hazards. • Calculation of the Severity Probability Number (SPN), based on probability of occurrence and the severity of harm, used to determine risk reduction and mitigation activities. • Calculation of the Risk Priority Number (RPN), based on the SPN and probability of detection, used as a relative measure of risk (it is not used to determine risk reduction and mitigation activities).

Table 4. Risk management tools used to evaluate potential hazards and failure modes and evaluate risk

Process Risk Management

Prior to understanding what, where and when something can go wrong in manufacturing processes, we need to understand its capability. Taking the time to identify Critical Control Points (CCPs) and Critical Process Parameters (CPPs), understanding the normal (common cause) variation, and determining process capability are fundamental in order to determine potential process weaknesses and hazards. This activity takes on a new dimension when all of the manufacturing is performed by contract manufacturing operations. In our business, it is our responsibility, as the owner of the design, to ensure that all contract manufacturing operations (CMOs) are qualified per the requirements in our quality management system. They, in fact, are included within the scope of our ISO 13485:2003 based quality system certification. We, as the owner of the product design, are responsible for controlling the inputs, i.e. product requirements to each CMO, as well as reviewing and approving their outputs, e.g. batch review and product approval.

Performance of Process Risk Assessment by the CMO: The Failure Mode and Effects Analysis (FMEA) tool is typically used by each CMO. The initial analysis begins with the identification of key process steps which are noted in a flow chart or diagram. Process inputs are identified and Potential Failure Modes, Potential Causes and Potential Failure Effects are identified for each process input. Current controls for each process input are noted. A Risk Priority Number (RPN) is then calculated for each potential failure mode, based on probability of occurrence, severity of harm, and detectability. Recommended actions, as well as actions already taken, are identified for each.

For a medical device such as ours, a two syringe delivery device designed to deliver two polymer solutions to prevent the formation of adhesions following surgery, the following processes are reviewed at one or more CMO:

- Raw Materials: Acceptance, Storage, Handling and Preparation
- Equipment Calibration and Maintenance
- Delivery Device Manufacturing
- Formulation Processes
- Sterilization Processes
- Packaging Processes
- Storage Conditions
- Handling Processes

As is the case with product risk management, risk control measures are identified, implemented and reviewed.

Business Risk Management

Business risk management practices consist of the identification and assessment of various scenarios by the management and project teams, a qualitative evaluation of these scenarios with respect to likelihood of occurrence, the degree of potential impact of these risks on strategic objectives, and the identification of actions to deal with these risks. This practice allows the management team to be aware of the risks it is facing and provides a useful tool to identify and prioritize necessary mitigating measures.

This practice helps management to:

- Identify major risks related to its unit
- Agree on exposure and necessary responses
- Provide guidance for repair/mitigation activities

The final deliverable is:

- A categorized overview of significant business risks
- An action list of relevant control improvements

Risk Category	Business Risk Description Scenarios
Development (R&D)	• Product unable to meet requirements • Product unable to pass pre-clinical safety requirements • Final design too expensive vs. business plan
Sourcing (Purchasing)	• Raw materials too expensive • Single source raw materials
Production (Supply Chain)	• Primary supply chain: Cannot or will not produce • Product stewardship or sustainability requirements cannot be achieved • Out of specification product not detected by QA • Improper waste disposal along supply chain • Use of hazardous materials will cause potential safety and environmental liabilities
Protection (Intellectual Property)	• IP protection unachievable • Validity of IP challenged
Registration & Compliance	• Clinical trials demonstrate that product is not safe • Clinical trials take longer and cost more than planned • Delays in country specific registration • Unable to obtain quality system certifications
Marketing and Sales	• Increased competition impacts product commercialization • Unable to obtain strong marketing partner • Product liability claims requiring costly litigation • Off-label use & product recalls • International market risks
Distribution	• Supply chain failure: No product available to supply customers • Product damaged or not maintained at proper conditions

Table 5. Business risk scenarios

For each scenario, Exposure is calculated from the product of Impact and Likelihood of Occurrence. Priority Risk and Response is determined by the management and project teams for each scenario.

All scenarios are reexamined throughout the product development and commercialization process.

Likelihood of Occurrence (Remote → Probable)	Impact ($) → ($$$$$)	Exposure	Priority Risk	Response	Risk Response Details
Very Low Low Medium High Very High	Very Low Low Medium High Very High	Low Medium High	No Yes	Reduce Accept	Description of risk response actions indicated for each scenario.

Table 6. Business risk evaluation criteria

Product Stewardship Risk Management

At DuPont, Product Stewardship is the business process responsible for the management of a product throughout its existing life cycle, focusing on the health, safety and environmental issues at each phase [4]. Product Stewardship requires good communication among business and project team members along the product life cycle to assess the needs of all stakeholders involved. This includes working with customers to develop appropriate risk management measures and addressing their emerging needs for the products and services supplied to them. These activities may include the development of safety data sheets and labels (indicating hazard and use information), training, facilitating product stewardship reviews and the publication of various forms of information.

The product life cycle begins at the start of the development stage and continues along the product trail from raw materials to ultimate fate (e.g., recycling, reuse, refurbish, or environmental impact) with suppliers, manufacturers, distributors, customers, and consumer impacts identified.

Chemicals and chemical products provide many benefits to society, and are managed in a responsible way to minimize the potential for adverse effects on humans and the environment. DuPont is committed to ensuring that public health and the environment are protected from unreasonable risk resulting from exposure to chemicals, and applies appropriate risk management measures to achieve this objective. DuPont manufactures, stores, transports, uses, disposes, and recycles its products in a manner that protects human health and the environment.

Integration of Product Stewardship Risk Management: Product stewardship protocols are developed for different product types. Subject matter experts from the product team are assigned to respond to appropriate sections. The completed protocols are reviewed during each phase of development. Each item on the protocol is analyzed for potential hazards. A risk assessment is performed by examining the likelihood of occurrence and probability of harm. Mitigation actions are then determined based on the outcome of the assessment.

Product Stewardship Protocol Elements for a Medical Device: The manufacturer of a medical device must show that their product is safe and effective. To accomplish this, there are many elements and requirements that must be considered throughout the product life cycle, from cradle to grave. The table below, consisting of 28 sections, illustrates the many factors that are analyzed for potential risk, as a part of the product stewardship process. Each section contains many considerations, which are too numerous to include in this paper. For a typical protocol, it is not unusual to have upwards of 200 individual considerations.

Section No.	Section Title	Section No.	Section Title
1	Scope of the Product Stewardship Review	15	New Hazard Information
2	Product Description and Product Trail: For New & Modified Products & New Applications for Existing Products.	16	Supplier Concerns
3	Hazard Characterization and Risk Assessment	17	Contract Manufacturer Concerns
4	Product Composition	18	Distribution
5	Physical Hazards	19	Review of Customer's Use & Experience
6	Human Toxicity Hazards & Effects	20	Customer Risk Management Techniques
7	Environmental Risks, Effects & Impact	21	Feedback Systems (Post Market Surveillance)
8	Regulatory Assessment	22	Product Recall Planning
9	Inventory Compliance	23	Efficacy
10	Import & Export Controls	24	Legal Risk Management
11	Packaging and Labeling Concerns	25	Issues with Potential Impact on Customers
12	Shipping & Storage Information & Requirements	26	Personnel Training
13	Risk Assessment Summary	27	Competition
14	Product Risk Management	28	Final Report & Approval

Table 7. Product stewardship protocol review elements for a medical device

Post Market Surveillance

Post Market Surveillance is a process we have integrated into our quality management system to examine multiple performance indicators once the product has been commercialized. It is a regulatory requirement for medical devices, and a key element of the continual improvement practices integrated into our quality system.

Post Market Surveillance activities include:

- Follow-up actions from earlier Post Marketing Surveillance reviews
- Known manufacturing problems
- Product quality improvements
- Changes to risk analysis
- Knowledge of long-term performance/reliability and/or chronic complications
- Knowledge of changing performance trends
- Knowledge of performance in different user populations
- Feedback on indications of use
- Feedback on instructions for use
- Feedback on user training
- Feedback on use with other devices
- Feedback on customer satisfaction
- Vigilance reports
- Knowledge of ways in which the device is misused
- Feedback on continuing market viability

The output of this assessment is compared against previous risk assessment work in two ways:

1. To determine if mitigation actions have been effective.
2. To determine if new potential or known hazards have been identified and need to be analyzed and evaluated.

Post Market Surveillance outputs are discussed at the Management Review.

Inputs, or sources to a Post Market Surveillance review, include:

- Expert user groups
- Customer surveys
- Customer complaints and warranty claims
- Post CE-market clinical trials
- Literature reviews
- User feedback other than complaints
- User reaction during training programs
- Experience with similar devices made by the same or different manufacturer
- In-house testing
- Failure analysis of returned products

Conclusion

Managing risk is a continuous process. It begins at the early concept stages of a new product design and continues until the product and its by-products have been safely removed from the market place. While there are many different forms of managing risk, as shown in this paper, they all have several aspects in common, such as identifying potential hazards that could lead to unintended consequences, estimation of the probability of that occurrence, and the measure of the impact of risk reduction actions on the product. Have potential risks been reduces as low as possible? Have risk reduction actions introduced other potential hazards? These are questions that the project team is continually asking.

Risk management and quality management are closely aligned [5]. In fact, if you take a good look at all of the elements of a typical quality management system, you will find that most of them are subject to some degree of risk, that is, something can go wrong, if left uncontrolled.

In our applications of risk management practices and principles, we have integrated into a single system the identification, analysis and evaluation of the five areas noted. We have attempted to put as much thought as reasonably possible into the early stages of development, in order to identify the high priority risks up front.

So what have we learned and where can we improve this process? Using the Deming Cycle (Plan-Do-Check-Act), we are at the "check" portion of the cycle:

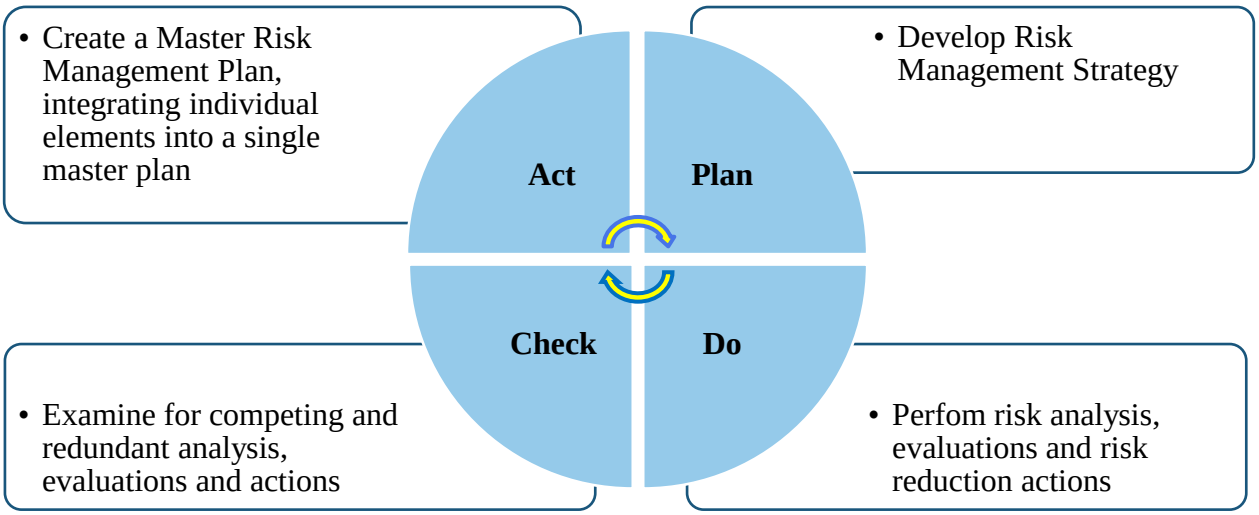

Figure 3. Risk management strategy plan-do-check-act analysis

We have found that there are potential overlapping and sometimes redundant potential hazards identified among the five elements. For example, cost, availability and quality of raw materials have a shared interest at the business level, at the CMO (supplier) level, and at the product level.

A potentially more effective way to examine risk is along the supplier → producer → customer interface. In this rather simplified diagram, all elements are examined together, at the various common points along the product development process. Within each there are several processes in which the individual elements should be examined together.

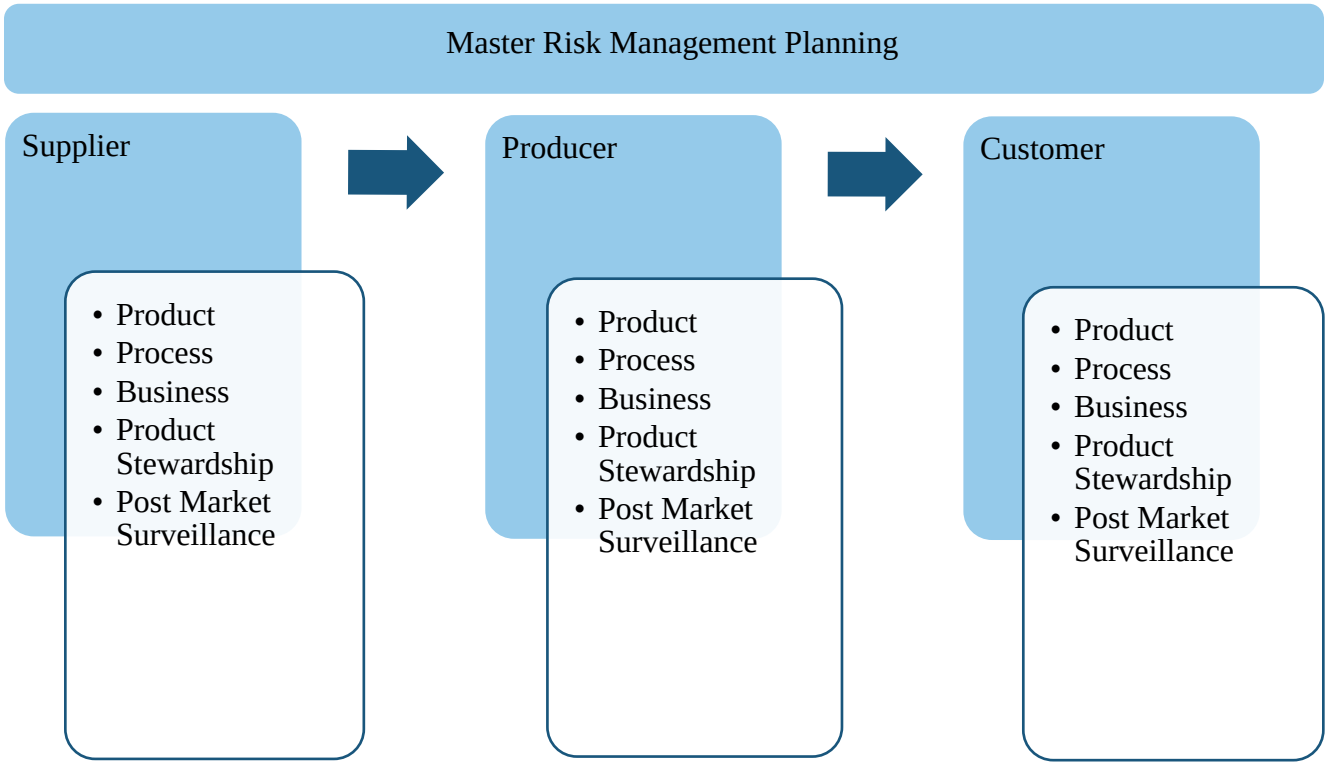

Figure 4. Examination of how individual risk management strategies should be evaluated, together, at discrete steps in the Supplier → Producer → Customer product development cycle

Risk management practices, like most other practices, tools and techniques used by quality management professionals, evolve, based on experience. In the development of medical devices, there is no room for error, so we must constantly look for ways to increase the efficacy in which we approach this critical aspect of product development and commercialization.

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