Risk Assessment and Risk Management in the Pharmaceutical Industry

Clear and Simple

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To Gray Brown

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FOREWORD

Risk assessment and risk management have become increasingly important factors in the manufacture and quality control of pharmaceuticals and biopharmaceuticals, especially aseptically produced products.

For the last thirty years or so, pharmaceutical manufacturers have relied on process validation and on in-process and finished product testing to assure the quality of the drug products reaching the consumer. While this system generally has been effective in controlling quality, it can be resource intensive since it tends to deal with all potential process and product defects in the same manner. Thus a minor variation in tablet weight is considered with the same significance as a failed sterility test, even though the two situations are considerably different in terms of risk to the patient. Clearly, it is better for pharmaceutical manufacturers and regulators to focus their efforts on those process and product defects which can significantly or seriously affect the patient who uses the product. This need has formed the basis for the risk assessment and analysis initiatives which have been proposed and implemented globally in the pharmaceutical industry.

The U.S. Food and Drug Administration announced a new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, in August 2002. This initiative and the assessments of existing CGMP programs resulting from it inspired the FDA to implement a new science-based regulatory strategy emphasizing quality systems, risk assessment and risk management. Several compliance programs and guidance documents have been developed to support the initiative, including the draft guidance for industry on *Quality Systems Approach to Pharmaceutical Current*

Good Manufacturing Practice Regulations, Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, and *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites — A Pilot Risk Ranking Model,* all published in September 2004.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published Q9, Quality Risk Management. The document outlines a risk management strategy involving risk identification, assessment, control, communication and review.

This book defines risk, discusses hazards and risks, and provides tools to evaluate risk, while providing the background and context necessary to understand the concept of risk management detailed in the regulatory guidance documents and to develop effective strategies for dealing with risk in the pharmaceutical industry.

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PREFACE

Writing about risk assessment and risk management as it applies to the pharmaceutical industry connects the ends of an arc that, for me, began twenty-five years ago. My first professional job in the pharmaceutical industry was that of an industrial hygienist at Eli Lilly and Company. In that role, I was involved in reducing personnel exposure to potentially toxic materials such as research compounds, solvents, intermediates, and finished drug products that could adversely affect their health – immediately or at some future time. Those experiences shaped my next set of work activities in quality assurance where my colleagues and I focused on risks not to the operator or analyst or maintenance person but to the patients using the drug products. Since then, my work has focused on training and how it can be used as a tool to improve performance and reduce risks to patients and organizations resulting from quality, compliance, and GMP failures. If you have been in the industry for some time, you too can attest that the current emphasis on risk assessment and risk management by regulatory agencies and the industry isn't as much a new interest, but one that has evolved and is becoming more structured and formalized.

One of the paradoxes of our industry is that despite some of the amazing products we discover and the huge manufacturing facilities we construct, we in the pharmaceutical industry are reluctant to look beyond our boundaries to learn things from other industries and disciplines. Our insular point of view may be, in part, an outgrowth of the highly regulated nature of the industry and the influence of regulatory agencies, our long-held view of ourselves as "different," and the fact that – at least until recently – the economics guiding our industry weren't like those seen in bulk chemical, computer chip, or

food-processing industries. Although we have been able to satisfy our patients, our regulators, and ourselves with relatively informal risk assessment methods (for example, with "what if…" analyses), other industries like nuclear power, petrochemical, and aerospace – and their regulators – have been using much more formal, analytical, and statistics-driven risk tools to make decisions for many years.

As we broaden our perspective to look at how other industries and professions assess and manage risks, we can find a number of different tools implemented by the nuclear power, aerospace, food, and defense industries. This book is meant to give only an introduction to an incredibly wide, rich, and fascinating discipline that you may want to continue to explore in more depth with further reading and training.

In this book, we begin with the most general ideas – history, definitions, conceptualizations of risks and hazards – and proceed to overviews of the risk management process and some of the more commonly used risk assessment methods and tools. Later chapters explore in more detail the phases of the risk management process and examine how the various tools can be applied to identifying hazards and evaluating their potential impact and effects.

Finding the "best" way or the most accepted ways of using the analysis tools has been a challenge in preparing this book. Much of the published work on the topic either includes a great deal of detail and is highly technical and complex, or contains less detail and lacks much practical guidance. For most of the tools, there is no one standardized way of using them that has been accepted by all professions; rather, there are many variations of the tools. For example, you may use forms or data-recording documents such as the ones found shown in this book, find others that are shown in some of the references, or adapt any and all to better meet your needs. My intent was to present the methods in a consistent manner to illustrate the differences in how they function and in how they fit into the larger risk management process. For some of the tools, I based my description of the method on work done by the authors and organizations mentioned at the start of the corresponding chapter describing the tool in detail.

Some examples throughout the book illustrate how the tools can be applied in "real life." Limitations imposed by time and confidentiality prevented me from including more examples. The good news is that a growing number of risk assessment examples and cases are appearing in industry publications and are being presented at meetings and conferences.

As the pharmaceutical and biopharma product manufacturers and service providers begin to use risk management practices and risk assessment tools, our knowledge and understanding will shape "best practices" that will influence the broader industry. We in the industry see a door being opened by regulators and organizations such as the U.S. FDA and the International Conference on Harmonization (ICH) as they establish guidelines on using risk management for the pharma industry. In all these efforts, it is critical that regulatory agencies, particularly the reviewers of submissions and the inspectors and auditors of our facilities, processes, and systems gain a thorough and practical understanding of risk management concepts and risk assessment methods. We also need to keep in mind that both the industry and its regulators must maintain a focus on the people using the products we develop and manufacture as we work together in our different roles to ensure that end users worldwide have safe, pure, and effective drug products.

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Rochester, New York
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INTRODUCTION

Thinking About Risk Management

"Risk management" is an oxymoron. Although risk management is the term we use, what we are doing in fact is establishing a process for making decisions or choices that will, it is hoped, result in a decrease in risk level.

In the risk management process we identify hazards and determine the probability of their being expressed and the potential resulting impact; We find ways to control risks by trying to reduce the chances of exposure to hazards and through modifying the consequences should such an exposure occur. This is accomplished by making trade-offs.

Sometimes the trade-off involves time or people or money: We can improve the quality of a product by introducing automation, or we can take advantage of new opportunities by hiring more people. Exchanging one thing for another frequently can be very clear and simple.

At other times, it may *appear* there is no cost; that the trade-off works totally to our advantage. Sometimes, though, the trade-off's full impact is not readily apparent. At first things look great – we're achieving more than we had planned – but it isn't until years or generations later that the real effects of that trade-off become known. Our environment has the scars to show what can happen when, for example, seemingly innocent changes introduce a new species; when misunderstanding the long-term effects of a pesticide causes damage; or when diverting rivers to create dams affects ecosystems.

As a tool for making decisions, risk management doesn't deem choices as inherently bad or good. Those who use the risk management process correctly and with wisdom and integrity determine whether the outcome is the best possible scenario for all stakeholders or a Faustian deal.

ACKNOWLEDGEMENTS

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1

AN INCOMPLETE HISTORY OF RISK MANAGEMENT

If you went to work this morning, you took a risk. If you rode your bicycle, walked, or drove a car, you took a risk. If you put your money in a bank, or in stocks, or under a mattress, you took other types of risk. If you bought a lottery ticket at the newsstand or gambled at a casino over the weekend, you were engaging in activities that involve an element of chance – something intimately connected with risk. The work *risk* has its roots in the old French word *risqué,* which means "danger, in which there is an element of chance" (Littré, 1863). The word *hazard,* another term integral to discussions of risk management, comes from a game of chance invented at a castle named Hasart, in Palestine, while it was under siege (Oxford English Dictionary, 1989).

In his 1998 book *Against the Odds*, Peter Bernstein describes how thinking about risk evolved in part because of changes in mathematical numbering systems, an understanding of the statistical basis of probability, and the rise in popularity of gambling. Although games of chance and gambling were depicted in Egyptian tomb paintings from 3500 B.C.E., it wasn't until the Renaissance that a "scientific" or statistical basis for gambling was presented. This was because the Hindu-Arabic numbering system (the numerals 1, 2, 3, and so forth) appeared in Europe between 1000–1200 C.E. allowing calculations beyond simple addition and subtraction to be performed. It wasn't until the Renaissance, however, that the ten

digits – 0 to 9 – that we take for granted fully replaced the more clumsy Roman numerals.

During the Renaissance, Girolamo Cardano, a sixteenth-century physician, gambler, and mathematician (though perhaps not in that order) wrote a book titled, *Liber de Ludo Aleae* ("Book on Games of Chance") that seems to have been the first study of probability in cards, dice throwing, and gambling. According to Bernstein, other great thinkers contributed to the growing body of literature on the subject: Galileo, in about 1630, wrote a brief essay, *Sopra le Scoperte dei Dadi* ("On Playing Dice"), in part to please Cosimo II, the Grand Duke of Tuscany. Other mathematicians and those organizing large bodies of data such as birth and death records established properties and rules concerning sampling, actuarial tables, and ways to predict behavior and events occurring in populations.

Money and financial interests drove early thinking on the topic of risk. Aristotle, in his treatise *Politics*, discusses the concept of *options* – a financial instrument that allows individuals to buy and sell goods from one another at pre-arranged prices. Options contributed to the dramatic "tulipomania" frenzy in Holland in the 1630s – people purchased and sold paper options instead of the actual tulip bulbs. Options were traded in the U.S. in the 1790s in what would later become the New York Stock Exchange.

Futures, in use in Europe since medieval times, were another type of financial instrument that helped reduce risk for farmers and commodity buyers. In 1865, futures on products such as grain, copper, and pork bellies were sold on the Chicago Board of Trade.

Insurance – a financial tool that reduces risk for a person or party by "sharing" potential financial burdens with others (who are compensated in some way for taking on the added risk) – has roots that reach back to 1800 B.C.E. when it was used to help finance voyages by ships. An early form of life insurance was provided by trade and craft guilds in Greece and Rome. As trade expanded in the Middle Ages, new forms of insurance were used to protect farmers and traders from droughts, floods, and other disasters.

Lloyds of London, probably the best-known insurance company in the world, was born in a coffee shop near the Tower of London in 1687, in part because the shop was a gathering place for ship captains who shared information about past and upcoming voyages, routes, weather, and hazards. Those who wanted to share in a risk

could sign their names on a board under the terms of a contract that all could see. From this practice arose the term "underwriters." Uses for insurance continue to expand, protecting individuals and groups from a variety of hazards. For example, a golf contest promoter could be insured against losses from a winning hole-in-one; musicians could be insured against lost income if they became unable to perform; a Hollywood screen actor could even insure her legs against injury.

Between the 1970s and 1990s, *derivatives*, complicated financial contracts so named because they derive their value from one or more assets, became popular, though highly risky, investments among individuals and organizations. Derivatives are used to hedge or protect against a financial loss and are particularly useful in conditions where there is significant volatility (i.e., financial risk); futures and options are two very simple forms of derivatives.

Concern Over Technological Risks

The Industrial Revolution sparked concern over risks that could be caused by technology. Specifically, it was the invention of steam-powered engines that changed how society and government viewed and controlled risks.

Steam engines, particularly those used on ships, had a potential to cause a greater number of casualties than other man-made inventions that had been devised until the late 1700s. In the 1800s, when high-pressure steam engines appeared, 2,563 people were killed, and nearly that number were injured in 233 steamboat accidents occurring between the years 1816 and 1848 (Burke, 1997).

In 1838, the U.S. Congress, after years of debating the role the federal government should have in regulating steam engines, took steps to protect the public by passing the first law regulating an industry. The Steamboat Inspection Service was established by federal authorities. It was not sufficiently effective, however, and accidents continued, killing 685 people from 1850–1851. In 1852, Congress passed another version of the Steamboat Inspection Act, which among other things established higher safety standards and moved the Inspection Service from the oversight of the Department of Justice to that of the Department of Treasury (U.S. Coast Guard, 1974).

Since the Industrial Revolution, the nature of hazards and risks has changed. Hazardous agents have grown both larger – bridges, airplanes, oil tankers, skyscrapers, for example – and smaller – pesticides, biologically active agents made through recombinant technology, subatomic particles, and electrons moving through integrated circuits, for instance.

Responses to Risks

In response to threats to individuals, society, and the environment, regulators, industry, and others involved in managing and controlling risks have taken a variety of approaches. One approach in the U.S. – situated at one extreme of the risk management spectrum – was the "Delaney Clause" that was added to three places in the Federal Food, Drug, and Cosmetic Act and which prohibited the addition to foods of any pesticide, additive, or coloring agents (in 1954, 1958, and 1960, respectively) shown to be carcinogenic in humans or animals. Underlying this clause was the belief that no threshold existed below which a given chemical could not provoke a carcinogenic response. This rationale also was referred to as the "one-hit" model: One contact between a carcinogenic substance and a cell was enough to cause cancer. Under the Delaney Clause, it didn't matter if the animal with cancer had been exposed to hundreds of times the amount of the substance in question that a person might consume normally over a lifetime, or that the animal species had a metabolic pathway very different from that of humans. Under Delaney, the goal was absolute safety.

In contrast to this approach is the one used by industrial hygienists to protect workers from chemical and hazardous agents that could cause immediate or long-term negative health consequences. Threshold Limit Values®, or TLVs®, are guidelines that are established, interpreted, and applied by professionals to prevent "an unreasonable risk of disease or injury" (ACGIH, 2005). For example, methylene chloride, a chemical known to cause cancer in animals, has an eight-hour time-weighted average limit of 50 parts per million (ppm), meaning that a normal, otherwise healthy worker exposed to this level over a forty-hour work week would not be expected to develop any type of health injury.

TLVs® are regularly evaluated and, when warranted by human exposure information or animal test data, changed to better protect workers who may be exposed.

Industrial hygienists frequently use risk management practices to identify, control, and monitor potentially hazardous agents. To comply with the Occupational Safety and Health Act (OSHAct), firms need to perform process hazards analysis (Code of Federal Regulations, 1992). The regulation requires the use of the methods discussed in this book.

The U.S. Environmental Protection Agency (EPA) is another agency that mandates hazard assessments. The EPA's regulation on Chemical Accident Prevention Provisions (Code of Federal Regulations, 2005a) requires that the "owner or operator…shall prepare a worst-case release scenario analysis…" and at least one "alternative release scenario for each regulated toxic substance in a covered process(es) and at least one alternative release scenario to represent all flammable substances held in covered processes." These alternative scenarios would be based on those with the highest probability of occurring as well as other considerations listed in the regulation.

In 1975, the U.S. Nuclear Regulatory Commission, in its WASH–1400 Report (U.S. Nuclear Regulatory Commission, 1975), required the use of probabilistic risk analysis (sometimes written as PRA, which can cause it to be confused with the acronym for preliminary risk analysis). While similar to risk assessment techniques such a failure mode effects analysis (FMEA) and other methods (including those described in this book), PRA uses experimental and actual data of failures to calculate, quantitatively, risks in a system.

In the 1990s, the U.S. Food and Drug Administration (FDA) began requiring manufacturers of certain types of foods to use a risk management method called hazard analysis and critical control points (HACCP) to identify, control, and monitor risks. The program first began with low-acid canned foods, expanded to include seafood, and then, in 2001, juices. The U.S. Department of Agriculture also requires that meat and poultry processing plants use HACCP as a risk management process. The FDA is considering mandating that HACCP be used in most all food processing and firms (CFSAN, 2001).

In 1997, with the transformation of the medical device good manufacturing practices (GMP) into the Quality System Regulation (QSR) (which is much more aligned with the international quality standard ISO 9000), the FDA required risk analysis under the auspices of "design validation": "Design validation shall include software validation and risk analysis, where appropriate." (FDA, 21 CFR 820.30(g)). Although risk assessment is not specifically mentioned in the regulation's text in regards to corrective action and preventive action (CAPA), it is discussed in the regulation's preamble (FDA, 1996):

> 159. Other comments stated that the degree of remedial action should be commensurate with the risk associated with a product failure. FDA agrees that the degree of corrective and preventive action taken to eliminate or minimize actual or potential nonconformities must be appropriate to the magnitude of the problem and commensurate with the risks encountered. FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, *but FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment.* (Emphasis added.)

How risk assessment and risk management can be applied to medical devices is defined more clearly in the internationally adopted ISO Standard 14971, first published in 1998.

These measures led to the FDA's expanding use of risk assessment and risk management within the pharmaceutical industry in the first decade of the twenty-first century. In the FDA's report, *Pharmaceutical CGMPs in the 21st Century – A Risk-Based Approach* (FDA, 2004), the drug agency describes how it will internally use risk management in making decisions (i.e., setting inspection priorities, analyzing mounds of inspection and regulatory-action data, preparing new guidances and regulations). The agency "has identified efficient risk management as the primary way to make the most effective use of agency resources and address these challenges", which they face

today. In regulations and guidelines that the FDA has proposed or finalized, the risk management concepts appear throughout. Risk-based phrases such as, "when appropriate," "when necessary," and "critical" all attempt to compel the industry to carefully identify measures that are and are not appropriate, necessary, or critical.

Through the efforts of the International Conference on Harmonization (ICH) involving the drug regulatory bodies and industry groups from the European Union, Japan, and the U.S., guidelines concerning risk management are being created. Quality by Design (also known as "Q8") and Quality Risk Management ("Q9") are expected to have a major impact on both the industry and regulatory agencies.

Conclusion

As we have seen in this abbreviated history, the evolution of risk management has been influenced by expanding knowledge and tools as well as by the hazards that need to be addressed. Regulatory bodies, which tend to react in response to incidents, over time enacted measures to prevent recurrences. These bodies also have shaped how hazards are identified and controlled.

For the pharmaceutical industry, risk management is forcing us to scrutinize our processes, products, materials, vendors, equipment, facilities, distribution systems – the list can include many other aspects of what we do – better than we have in the past. The FDA has offered "regulatory flexibility" to industry as an inducement to move to more risk-based thinking, but what this really means is still being determined and will undoubtedly continue to evolve in the coming years.

Integrating formal risk management approaches into quality systems – and the decisions that are made as a consequence – involve their own kind of risk because they demand that regulatory agencies and the industry conduct business in new ways. Current thinking regarding risk management is moving away from strict rules that are determined for and applied to each member of industry and toward a paradigm that carefully considers, manages, communicates, and controls the risks associated with the routine and unique opportunities, problems, and crises we face (Coburn, *et al*,

2005). This undoubtedly will be uncomfortable at first for industry and regulatory bodies, but this different way of doing business has significant potential benefits for all involved.

"Managing risk is one of the things that bosses are paid for," yet "most companies still don't have any idea what is required of risk management," stated *The Economist* (2004). In the pharmaceutical industry there are few quality professionals, production managers, or engineers who can look at an existing process and identify the potential risks, state how those risks are controlled, and assess the success of those controls. If our regulatory agencies continue to move towards a goal of a more scientific basis for regulation, firms will need to formally elucidate and document process risks, controls, and monitoring practices. At the same time, regulatory agencies like the FDA will need to significantly change the way they perform inspections to enable its investigators to evaluate properly the firm's risk assessment and risk management practices.