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BACKGROUND AND INTRODUCTION

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Companies wishing to manufacture and distribute regulated health care products to the population of the United States must comply with the U.S. Food and Drug Administration (FDA) regulations, better known as *Current Good Manufacturing Practices* (CGMPs). 21 CFR 211.100 of U.S. CGMPs states "There shall be written procedures for product and process control designed to assure that drug products have identity, strength, quality, and purity they purport or are represented to possess ..."[1]. Regulations are a legal requirement and this CFR, among others, mandates that companies must take active steps to assure product quality.

Companies and individuals working for health care industries have an obligation to provide products that are safe and effective to their customers, users, and patients. The regulations codify this obligation, thus making it a legal requirement; but the obligation to provide safe and effective products is also a moral and ethical obligation that goes beyond the legal regulatory requirements. People working for pharmaceutical companies also have a duty of loyalty to operate for the welfare of the company. In other words, they have an additional obligation to operate efficiently and earn optimal profits within the framework of regulatory requirements and ethics. Companies and individuals must be able to align these legal requirements and business obligations.

The failure to provide safe and effective products will likely result in loss of business as well as other legal consequences. However, in recent years, it seems that the industry has faced pressure and challenges to balance these requirements and obligations. It has become more difficult to remain in compliance, serve

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customers, and be competitive. Companies have struggled with balancing regulatory requirements, scientific elements of product development and manufacture, and maintaining a productive business situation.

The pharmaceutical and biopharmaceutical industries are facing financial pressure because of the high cost of drug development and manufacturing as well as generic competition. There are business drivers and regulatory expectations for innovative approaches to speed up pharmaceutical product development and licensure, optimally use resources, and to assure continued product quality and patient safety. The industry must apply comprehensive risk management and innovative approaches to product life cycle not only to enhance patient safety but also to improve business outcomes. Hence, it is critical to understand appropriate risk management tools and approaches that would be acceptable to regulatory agencies. Other industries, including closely related ones such as the medical devices and food industries, have adopted a more structured approach to this subject than we have traditionally used. The application of risk management to medical devices is expected by medical device regulatory bodies [2–4]. Hazard analysis and critical control points (HACCP) is used in the food industry to identify potential food safety hazards, so that key actions, known as *critical control points* (CCPs), can be taken to reduce or eliminate the risk of the hazards being realized [5].

In the summer of 2002, the FDA announced an initiative to "enhance and modernize" pharmaceutical regulation. In the fall of 2004, it published the final report on *Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach*. This paper represented an attempt to "enhance and modernize" pharmaceutical regulation. It not only speaks of product quality and patient safety but also of the need for innovation and the cost of drug development and manufacture [6].

The paper offered initiatives and recommendations with the following objectives in mind:

1. Encourage the early adoption of new technological advances by the pharmaceutical industry.
2. Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance.
3. Encourage implementation of risk-based approaches that focus the attention of both industry and agency on critical areas.
4. Ensure that regulatory review, compliance, and inspection policies are based on the state-of-the-art pharmaceutical science.
5. Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the agency's business processes and regulatory policies concerning review and inspection activities.

The reference to risk-based approaches mentioned in (3) is of particular interest to the subject of this book. Facing limited resources, the agency recognized

that to best serve public interest, decisions on resource allocation, focus, and prioritization should be based on risk to patient safety and public safety. Those in the industry are impacted by the approach. For instance, a firm manufacturing over-the-counter (OTC) oral dosage products and having a relatively clean compliance record would likely be inspected less often or receive less attention than a firm aseptically manufacturing sterile injectables and having a more problematic compliance record.

The prioritization of resources based on risk to public safety make sense and it led to better productivity and effectiveness. It was logical that the agency would expect the industry to employ similar approach to make resource- and focus-related decisions. Firms are encouraged to use risk to product quality and patient safety as a criterion for decision making.

Risk management and assessment are not new. People use risk assessment as a way to help make decisions every day. When you walk across the street, drive through a yellow light, or order a meal—you employ a level of risk assessment, weighing the impact of a hazard and the likelihood of the hazard happening against anticipated benefit. Companies do the same in many aspects of corporate functioning from financial decisions, to investments, to plant locations, and product development. If their objective is to serve their customer, then it makes sense that they would employ this type of decision making to manufacturing and response to patient needs and safety.

In 2005, the ICH (International Conference for Harmonization) issued Q9 Guidance on quality risk management. ICH Q9 was later issued in 2006 as Guidance for Industry by the FDA and adopted by the EU as Annex 20 of the European GMPs in 2011. The guidance remains optional for pharmaceutical product manufacturers in the United States and Europe [7]. However, references to risk assessments and criticism for not employing such measures have appeared in FDA warning letters dating back to 2006 [8]. Regulatory citations indicated that companies face questions on how decisions related to product quality were made, if assessments of the risk of process steps and changes to product quality were not employed. If a company's obligation is product quality and patient safety, it should take such risks into account when making manufacturing decisions. How else could it make these decisions?

In the spring of 2005, at the PDA (Parenteral Drug Association) annual meeting in Chicago, the leaders of the Process Validation Interest Group asked its members for their topic of most interest or concern. The overwhelming answer was risk management. The leaders then asked how many of those individuals were currently utilizing or were aware of efforts within their respective organizations to utilize risk management. Only a few raised their hands. This was not unexpected. ICH Q9 was being issued and reviewed. Papers presented at the PDA annual meeting spoke about the need for risk management.

One person in the meeting noted that their risk assessment efforts were unsuccessful, as they were subject to criticism from local regulators, because of the misuse of the risk management. The misuse apparently involved using risk assessment to identify process-related risk, but then failing to take steps to mitigate that

risk. The objective of risk management, as discussed later, is not just to identify risk, but to mitigate and reduce risk, thus improving the manufacturing process.

The outcome of the 2005 meeting was an initiative by the PDA Science Advisory Board to create a task force of industry professionals to investigate and develop a model for the use of risk management for aseptic processes. This would later become the basis of PDA *Technical Report No. 44 Quality Risk Management for Aseptic Processes*, as well as later efforts on companion documents and reports. The task force was made up of 15 individuals from sterile drug manufacturing within 15 different organizations and companies. Only a few had direct experience with formal risk management and that experience had largely come from the medical device industry. The use of formal risk assessment and management techniques for pharmaceutical and biopharmaceutical manufacturing appeared to be a work in progress at best.

In 2008, the PDA published Technical Report No. 44. The technical report presented concepts and a program for evaluating the risk of process failure in making decisions for the manufacture of sterile drug products using aseptic processing. One point presented in TR 44 was that aseptic processing was not necessarily risky. The hazards associated with aseptic processing were significant. However, if well controlled, the risk should not necessarily be high. In other words, determining the risk was the objective of risk management—rather, process improvement through control and mitigation were the key objectives [9].

Since 2004, more and more FDA guidance has included recommendations for risk management and assessments. In the 2008 draft version of the FDA Guidance for Industry on the General Principles of Process Validation, the FDA included a modest level of references to risk assessments in the text. Some industry comments questioned the apparent "lack" of focus on risk in the document. When asked, FDA representatives responded that they felt risk management principles and methodology were so prevalent in the fabric of industry operation that it was not necessary to emphasize it in the guidance. The number of references to risk management and assessment nearly doubled in the 2011 final version [10–12].

Throughout the next several years, industry standards, guidance, and technical reports were prepared to address risk-based decision-making. In 2001 through 2011, the ISPE (International Society of Pharmaceutical Engineering) published a series of industry guides, employing risk-based methods for design and qualification of pharmaceutical manufacturing facilities and processes, including Volume 5 of its *Facilities Baseline Guides: Commissioning and Qualification* (with revisions in progress) and the *ISPE Guide*: *Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*. These guides presented methods for qualifying pharmaceutical manufacturing facilities incorporating risk to product-quality-based decision criteria. The baseline guide introduced the concept of evaluating systems based on their relative impact to product quality [13].

In 2007, the ASTM (American Society for Testing and Methodology) issued E2500-07, the *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*. E2500-07 discussed a risk- and science-based approach to the qualification or

verification of equipment used to manufacture and test pharmaceutical products. It was an effort to use risk to product quality and patient safety as important factors when deciding what to qualify, how to qualify, when to qualify, and who should be involved in the qualification and approval effort [14].

When the ASTM committee E55 was assembled to create and review what would become E2500-07, they discovered that while many, companies recognized that quality risk management was an important tool for making product manufacturing decisions, few, had real experience or input into practical means to accomplish this in an effective manner. As such, the committee was faced with creating desired state approaches rather than reflecting tried and true best practices. Throughout related meetings and discussions, it appeared that most companies had some appreciation for the need to manage risk to product quality and as a part of that to take steps to assess and document the assessment of that risk. However, it also appeared that companies did not always utilize risk management techniques optimally or effectively in making decisions. One is reminded of a company visited not long after the 2005 PDA meeting. The company had a vigorous risk management program, complete with corporate directives, policies, procedures, and a risk management department. They had volumes of carefully filled out risk assessments, which were placed in binders and displayed. When asked what these risk assessments were used for, the response was to assess risk. The assessment forms were meticulously filled in, reviewed, and approved. After that, they were placed in binders and placed on a shelf. Whether the information was used to help make any decisions was not apparent. This illustrates the misconception that the objective of risk management is to merely assess or categorize risk, rather than using it to provide information to help make informed decisions and improve the process.

The objective of risk management should be to improve the process by reducing or mitigating risks. There needs to be a clear link between risk management principles as described in guidances such as ICH Q9 and other guidances and practical manufacturing activities. The book offers the reader multiple perspectives and approaches to risk management and assessments. The chapters in this book emphasize that quality risk management of pharmaceutical manufacturing processes is an important topic because of the following:

1. It is a regulatory expectation, in that it helps to assure product quality and ensure patient safety. The FDA, European Medicines Agency (EMA), and many other regulatory agencies strongly recommend the use of risk assessment and the consideration of risk to patient safety and product quality in making decisions related to product development, manufacture, and distribution.
2. It is a good business practice. Properly used, risk management should help assure product quality as well as promote efficient utilization of resources and prioritization of efforts. It should help companies reduce redundant and non-value added efforts, while allowing them to focus on efforts that have optimal impact on product quality.

3. It is a logical and effective means of obtaining useful information needed to make sound quality and business decisions. Risk management represents an organized method for obtaining, analyzing, and communicating useful information.

The regulatory environment emphasizes the use of enhanced knowledge of product performance over a range of material attributes, manufacturing process options, and process parameters to identify risks to patient safety and product quality. Risk analysis and risk management are acceptable and effective ways to minimize patient risk and determine appropriate levels of validation and controls. The use of quality risk management does not obviate company obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of regulatory inspections. The effective and consistent analysis of risks associated with manufacturing processes and quality systems typically leads to more robust decisions and yields greater confidence in outcomes. The ultimate goal of the risk management process of an organization is to bring focus and effort to the issues that impart the highest risk to product quality and/or patient safety. Risk management outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

1.1 RISK MANAGEMENT OF PHARMACEUTICAL AND BIOPHARMACEUTICAL MANUFACTURE

The efficient manufacturing of quality pharmaceutical products presents a challenge in the present day business environment. If not properly controlled, these challenges can represent risk to product quality and in turn patient safety. There are several reasons why the business environment presents unique challenges, including the following:

1. *The need to understand and comply with evolving regulatory requirements and expectations*. In the past, the FDA represented the benchmark or standard source for drug product and manufacturing regulations. Most foreign regulators utilized the principles presented by the FDA in their own regulations. However, as European and other non-U.S. markets developed, companies faced unique interpretations and presentations of regulations and requirements from other regulatory bodies. At times, as one regulatory body would attempt to modernize its regulations or guidance, other countries would lag behind, creating the potential for misinterpretation and misalignment of regulatory expectations or focus.
2. *The use and integration of innovative technologies with existing manufacturing methodology*. New technologies such as automated processes, PAT

(process analytical technology), rapid microbiological analysis, and single-use manufacturing systems offer the potential for process improvement and risk reduction by eliminating process variation, human intervention, and more reliable product and process testing/monitoring. However, these technologies may bring with them new or additional risks associated with understanding the limitations of the technology.

3. *Adapting existing manufacturing methodology to new products and dosage forms*. Sometimes, tried and true approaches that have worked for older technologies will not work as well for newer technologies. An example may be the use of aseptic process simulations or media fill tests designed to demonstrate aseptic technique proficiency, used to assure aseptic processing control in relatively intervention-free automated or isolator systems.
4. *The retooling of facilities and the transfer of products and technology as a result of consolidation of plants and assets*. There are likely to be physical, procedural, and cultural differences between facilities that need to be considered in order to effectively manufacture products.
5. *The loss of knowledgeable staff through attrition and reorganization*. Even the best controlled processes, with the most well-written procedures, are subject to a certain level of "tribal knowledge." Efficient and effective manufacturing depends in part on the dissemination of information, much of which is learned from experience. However, if that experience or the people who have it are no longer with the company, then what will replace that experience-based knowledge?
6. *The need to better understand the interdependencies and variability of materials, technology, and product on more complex processes*. More complex products and dosage forms, as well as combination products, present new process development and manufacturing challenges.
7. *The need to maximize productivity and minimize cost*. Quality may be the number one factor in pharmaceutical manufacturing, but controlling cost and resources has taken on a major level of importance in most modern manufacturing operations. This often leads to LEAN manufacturing methods, doing more with less, automation, and streamlined operations and workforces. All are for the good, but established methods of quality assurance may also need to adapt to this new business environment.
8. *The need to control processes to achieve consistent quality and maintain product supply from and across multiple plants and locations*. As seen in the 2009 heparin issue, where products and supplies originated in emerging growth countries, there may be a need to examine the effectiveness of existing methods and procedures for quality control and quality assurance including audit, training, monitoring, and testing regiments [15]. In addition, more complex products and inspection techniques may result in or uncover quality issues with critical supplies, such as glassware and product contact containers. Improved methods of identifying and addressing these issues may be necessary. Where inspection is not enough, quality by design

(QbD) and other ways to identify and mitigate risk may be one answer to supplier and supply-related quality issues.

1.2 A PRACTICAL GUIDE TO RISK MANAGEMENT

It is important to have a clear concept on various terms used in risk management. The concept of risk has two components: (i) probability of occurrence of harm and (ii) the consequence of that harm (i.e., severity). A hazardous situation is a circumstance in which people, property, or environment is exposed to one or more harm(s)[16] [ISO 14971]. Risk analysis involves the estimation of risk(s) for each hazardous situation or failure mode. Harm, in the context of this book, is damage to health, including the damage that can occur from loss of product quality or availability. Severity is a measure of the possible consequences of a hazard. Hazard is a potential source of harm (i.e., an immediate output from the product/process/system that directly causes harm). Risk is the possibility of suffering harm or loss. More specifically, risk is the relationship between impact of a hazard and the probability of that hazard occurring to such an extent as to result in harm. Risk to product quality is the combination of the severity or the impact of an unwanted event and the likelihood that event will occur to a degree which will adversely affect product quality. Some examples of hazards, harm, and risk are listed here:

1. Hazards
   - Product not sterile or impure
   - Product subpotent or superpotent
   - Product contaminated
   - Product mislabeled
   - Product unsealed or improperly sealed
   - Product missing or unusable product
   - Ineffective product
   - Lack of product supply
   - Noncompliance
   - Product rejection
   - Inefficient process
   - Misuse of product
   - Poor process yield
   - Failure to receive product approval
2. Harm
   - Injury to patient
   - Disruption of product supply

ICH Q9 explains what quality risk management is, how it can be applied to pharmaceuticals, and how it can provide a common language with an agreed process for the pharmaceutical industry and regulators. In ICH Q9 risk management models, "risk" is defined as "the combination of the probability of occurrence of harm and the severity of that harm." While the combination of probability and severity is helpful in reflecting the level of risk importance, detectability often influences the decision-making process in manufacturing risk management.

ICH Q9 places focus on risk to patient safety due to a product defect or loss of quality along the supply chain. ICH Q9 defines risk management as *a systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk*. Risk management is then a process by which sources of risk are recognized and steps taken to mitigate, reduce, or eliminate the chance of harm. If the objective of risk management is to avoid harm, then one way to meet this objective is to provide a means to make decisions based on relative risk [17].

Figure 1.1 of ICH Q9 presents a logical flow for managing risk [17]. The flow can be broken down into distinct steps and substeps.

1. *Risk assessment* —understand the process.
   - *Risk identification—identify process/quality hazards and potential harm it might cause*.
   - *Risk analysis—determine what event or condition could cause the hazard*.
   - *Risk evaluation—rank or score the relative risk of the hazard, in an effort to recognize when improvement has occurred*.
2. *Risk control* —react to the outcome.
   - *Risk reduction—improve the process through mitigation of the risk*.
   - *Risk acceptance—decide if the process risk has been reduced to an acceptable level or if further mitigation or evaluation is necessary*.
3. *Risk communication* —interact with interested parties to relay risk-related information in order to implement mitigation-related changes or communicate residual or remaining risk.
4. *Risk review* —follow up and periodically reassess to determine if changes have been implemented and if changes are effective.

Risk management is a method to

- recognize and address potential weakness in the process, in an effort to assure objectives are met
- identify potential hazards
- assess likelihood of occurrence
- decide if process risk is acceptable
- communicate risk
- reduce risk

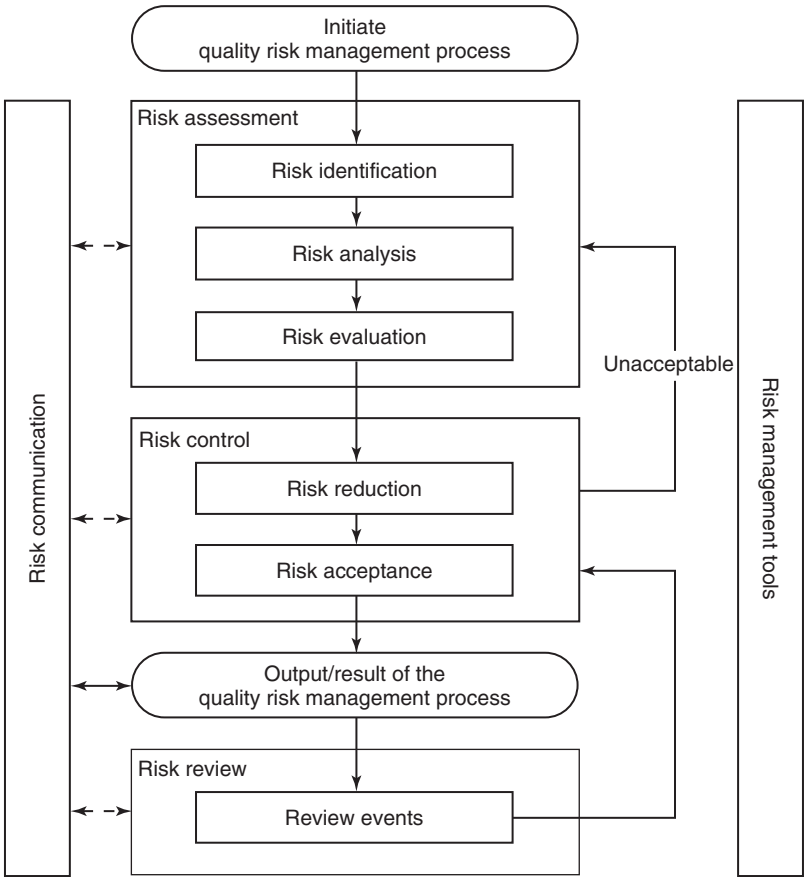

Figure 1.1 Overview of a typical quality risk management process.

- improve the process
- provide information needed to help make decisions

Risk management approaches should

- focus on risk to patient safety
- result in improved process understanding
- result in improved process
- be planned, logical, and documented
- add value
- avoid "checklist" approach
- should support and be consistent with the validation program
- should be documented

1.2.1 Additional Points to Consider

People who are designing manufacturing processes and respective control strategies need to realize the relative risk inherent in these process steps. In this case, it is the relative risk of process failure that could adversely affect product quality and patient safety. The unwanted effect on product quality is the loss of quality attributes. Quality attributes are those elements or functions of the product that define it.

For pharmaceutical products, these attributes include the following:

Strength—potency, efficacy, effectiveness
Safety—does not cause harm, contamination, loss of sterility
Purity—free of foreign substances, contamination
Identity—what it purports to be, lot number, expiry date

In the pharmaceutical industry, we are primarily concerned with risk to patient safety or public welfare. Loss of product quality leads to loss of patient safety. If the failure or unwanted event is found and removed before it can affect the patient, then there is no harm. If there is no harm, then there is no risk. Therefore, detection becomes an important element in determining relative risk.

Risk assessments and management techniques should be used to provide the information needed to make sound decisions, but they should not be used to make the decision itself. In other words, setting a predetermined decision based on a numeric scoring from a risk assessment model and then blindly following that outcome without further analysis and thought can lead to problems and biased assessments.

For risk management to be useful, risk assessments must be as accurate as possible. Therefore, objectiveness and unbiased assessment and analysis are key. It is essential that companies take care of the following:

1. Avoid preconceived decisions or results.
2. Do not use risk assessment to *validate* a position or to justify a questionable process.
3. Use diverse assessment team(s) to assure objectivity.
   - Use experienced facilitator if necessary.
   - Allow for adequate time, but do not overdo it.
4. Pay attention to the outcome.
   - Aseptic process is an example.
5. Document for future reference.
6. Pay attention to results.
7. Plan for follow through and feedback.
8. Plan for communication.

Mitigation of risk involves taking action and making changes. These changes may not mitigate all risk and may add other risks—or residual risks. Residual risks are risks that remain after mitigation changes are made. It is important to recognize and address these residual risks. This does not mean avoiding mitigation changes because of residual risk.

Choose the risk assessment method that best fits the complexity and impact of the decision to be made. One method may not fit all applications. Avoid unnecessarily complex or burdensome methods when simple ones will accomplish the same result. However, choose a method that will provide enough information and is as objective as possible.

1.3 OVERVIEW OF THE BOOK

Companies have struggled with the best way to effectively use and demonstrate the use of risk-based information gathering, evaluation of information, and decision-making processes, often doing too little or too much. In an effort to assist the reader with the development and use of effective risk-based approaches for pharmaceutical and biopharmaceutical product manufacturing, this book will provide guidance, including some divergent views on practical and pragmatic ways to incorporate risk into their operations. While the contents of this book are not meant to include all of the methods and areas where QRM can and should be incorporated, it provides several approaches and examples that can be used as a framework for developing and implementing risk-based decision-making methods for other processes and process steps.

The first chapters are designed to familiarize the reader with the subject of risk management in the context of pharmaceutical and biopharmaceutical manufacturing and present basic concepts and ideas for developing and utilizing an effective risk management program. To that end, Chapter 1 provides an introduction and background to risk management for pharmaceutical and biopharmaceutical products and processes. Chapter 2 introduces the reader to general information on the development and use of a risk management program. It shows widely used risk assessment tools and methods, many of which are used in subsequent chapters. Chapter 3 provides additional insight into the nuances of the risk management program, including regulatory expectations, a high level overview of the cognitive and social aspects of risk, as well as thoughts on developing an objective risk management program and an effective organizational culture. Chapter 4 presents views and a commentary on the use of statistical analysis to assist with the planning of risk-based approaches and with useful analysis of the resulting information.

The next chapters present specific, yet not exclusive, areas of pharmaceutical and biopharmaceutical product development and validation where risk management techniques can be used, along with programs and approaches for doing so. As such, Chapter 5 discusses the use of QRM in QbD aspects of product and process development. The QbD approach is where quality is designed from the

outset, using a science and risk basis, as opposed to a traditional approach, where normally end-product testing used to check quality requirements have been met. Chapter 5 shows key steps for QbD and how to apply them.

Chapter 6 presents approaches to use and disseminate risk-based information in making decisions related to early product development and clinical product manufacture. It shows the integration of science and risk management to allow for successful product development, such as basis for design and product control strategy. It uses a block diagram for tablet manufacture, and an Ishikawa (fishbone) diagram, breaking the process into the 6Ms to identify risk factors that need to be considered and possibly controlled in designing the manufacturing and control process.

Chapter 7 discusses methods for using QRM to commission and qualify equipment and facilities utilized in the manufacture of products, including the evaluation and leveraging of information. It presents important considerations for the use of QRM in making decisions needed to plan, develop, and conduct more effective commissioning and qualification efforts. It shows some of the areas where risk assessment can effectively be used to help develop and implement a sound, efficient qualification program using simple but effective tools.

Chapter 8 then picks up the use of risk in developing and implementing a sound and effective process validation life cycle. It shows how risk-based approaches can be applied during process characterization and validation, for the identification of CPPs for new and existing processes, risk prioritization, technology transfer, process changes, and in defining review schedule. Cleaning validation and cross-contamination risks are also discussed in this chapter.

The next chapters present several specific areas of product manufacture where risk assessment can be used. Chapters 9 and 10 provide two views on the use of risk assessment for the evaluation and improvement of one of the most challenging and complex manufacturing processes—aseptic processes. Risk assessment in the context of aseptic pharmaceutical manufacture is the principal focus in Chapter 9, with particular description and explanation of a quantitative, statistical tool of risk analysis permitting a more exacting evaluation of risk. It describes aseptic processing hazards, such as intrinsic hazards, extrinsic hazards, risk of endotoxin, and models for microbial ingress. Chapter 10 reviews contemporary thinking relative to aseptic processing risk assessment and mitigation. Formalized risk assessment described in this chapter and its essential counterpart risk mitigation will play an increasing role in the design, operation, and maintenance of aseptic operations.

Chapters 11 and 12 present views on the use of risk for better understanding and operation of drug and biopharmaceutical manufacture. Chapter 11 focuses on the areas of risk that a drug company may encounter in pharmaceutical manufacturing, specifically addressing oral solid and liquid formulations. Common risks associated with the manufacturing process for a solid tablet outlined in a fishbone diagram are identified. A case study illustrates how to apply risk management principles to identify and mitigate risks that could affect product quality and patient safety using the HACCP process. Chapter 12 discusses applications

of risk management in critical areas of biopharmaceutical production, such as raw material supply, cell banking, fermentation, cell culture, purification, scale-up of production process, and distribution issues associated with cold chain.

Finally, Chapter 13 provides a risk-based approach to controlling processes and process-related changes. Integrating QRM into the change control system is essential to maintain risk management as a "living" process, but it can be especially challenging because change control covers many areas in manufacturing and most of the product life cycle. Chapter 13 provides some practical methods and tools that can be used to integrate QRM into an existing change control system.

1.4 FINAL THOUGHTS

Risk management can be a useful tool in controlling processes, assuring product quality, prioritizing resources, and understanding processes. Risk assessment can be helpful for obtaining the information needed to make manufacturing decisions in a challenging business environment. The consideration of risk in making product-quality-related decisions is not only a logical business practice but also a regulatory expectation.

Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. Proper documentation is important to achieve this goal. However, the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk. The application of risk management practices enables manufacturers to design processes that proactively identify, mitigate, and/or control risks. Risk management practices may be implemented via a well-designed risk assessment plan and activities.

The use of risk management, when properly planned and implemented, can provide valuable information. That information, when properly considered, can then lead to better product quality-related decisions. Those decisions, if properly implemented, can assure product quality and improved processes. Process improvement can better ensure patient safety, which is the objective of quality risk management.

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