

Quality Risk Management in the FDA-Regulated Industry

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José Rodríguez-Pérez

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Acronyms

API—active pharmaceutical ingredient
ART—assisted reproductive technology
BLA—Biologics License Application
CAPA—corrective and preventive action
CCP—critical control point
CDC—Centers for Disease Control and Prevention
CDER—Center for Drug Evaluation and Research
CDRH—Center for Devices and Radiological Health
CFR—Code of Federal Regulations
cGMP—current good manufacturing practice
CQA—critical quality attributes
EMA—European Medicines Agency
FDA—Food and Drug Administration
FDAAA—Food and Drug Administration Amendments Act
FMEA—failure mode and effects analysis
FTA—fault tree analysis
GHTF—Global Harmonization Task Force
HACCP—hazard analysis and critical control points
HAZOP—hazard and operability analysis

ICH—International Conference on Harmonization

IEC—International Electrotechnical Commission

ISO—International Organization for Standardization

NDA—New Drug Application

OOC—out of control

OOS—out of specification

OOT—out of trend

ORA—FDA’s Office of Regulatory Affairs

OTC—over the counter

PAT—process analytical technology

PDA—Parenteral Drug Association

PHA—preliminary hazard analysis

PPC—production and process control

QbD—quality by design

QMS—quality management system

QSIT—quality systems inspection technique

QSR—Quality System Regulation

QTPP—quality target product profile

RCA—root cause analysis

REMS—Risk Evaluation and Mitigation Strategy

RMP—risk management plan

SRP—site risk potential

USC—United States Code

Preface

Risk management principles are effectively utilized in many areas of business and government, including finance, insurance, occupational safety, and public health, and by agencies regulating these industries. The U.S. Food and Drug Administration (FDA) and its worldwide counterparts are responsible for protecting public health by ensuring the safety and effectiveness of drugs and medical devices. Regulators must decide whether the benefits of a specific product for patients and users outweigh its risk, while recognizing that “absolute safety” (or zero risk) is not achievable.

Every product and every process has an associated risk. Although there are some examples of the use of quality risk management in the FDA-regulated industry today, they are limited and do not represent the full contribution that risk management has to offer. The present FDA focus on risk-based determination requires that the regulated industries improve dramatically their understanding and capability of hazard control concepts. In addition, the importance of quality systems has been recognized in the life sciences industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

The purpose of this book is to offer a systematic and very comprehensive approach to quality risk management. It will assist medical and food product manufacturers with the integration of a risk management system or risk management principles and activities into their existing quality management system by providing practical explanations and examples. The appropriate use of quality risk management can facilitate compliance with regulatory requirements such as good manufacturing practice or good laboratory practice.

Quality risk management is a valuable component of an effective quality systems framework. It can, for example, help guide the setting of

specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions. An effective quality risk management approach can ensure the high quality of the product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve decision making if a quality problem arises.

Risk can be defined as the combination of the probability of occurrence of harm and the severity of that harm. However, each stakeholder might perceive different potential harms, place a different probability on each harm occurring, and attribute different severities to each harm. In relation to medical product, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a medical product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. Quality of the product must be maintained throughout the product life cycle such that the attributes that are important to the quality of the regulated product remain consistent.

Effective quality risk management can also facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight. Regulated product manufacturers are required to have a quality management system as well as processes for addressing product-related risks. These processes for managing risk can evolve into a stand-alone management system. While manufacturers may choose to maintain these two management systems separately, it may be advantageous to integrate them as it could reduce costs, eliminate redundancies, and lead to a more effective management system.

An effective and efficient quality management system is essential for ensuring the safety and performance of regulated products. A well-defined quality management system includes safety considerations in specific areas. Given the importance of safety, it is useful to identify some key activities that specifically address safety issues and ensure appropriate input and feedback from these activities into the quality management system. The degree to which safety considerations are addressed should be commensurate with the degree of the risk and the nature of the device. Some devices present relatively low risk or have well-understood risks with established methods of risk control, while others push the state of the art. Risk management principles should be applied throughout the life cycle of regulated

products and used to identify and address safety issues. In general, risk management can be characterized by phases of activities.

Quality risk management concepts deal with processes for managing risks, primarily to the patient of medical products and to the consumer of food, but also to the manufacturing plant operators, other persons, other equipment, and the environment. As a general concept, activities in which an individual, organization, or government is involved can expose those or other stakeholders to hazards that can cause loss of or damage to something they value. Risk management is a complex subject because each stakeholder places a different value on the probability of harm occurring and its severity. As one of the stakeholders, the manufacturer makes judgments relating to the safety of a medical product, including the acceptability of risks, taking into account the generally accepted state of the art, in order to determine the suitability of a medical product to be placed on the market for its intended use.

The content of this book will provide FDA-regulated manufacturers with a framework within which experience, insight, and judgment are applied systematically to manage the risks associated with their products. Manufacturers in other industries may use it as an informative guidance in developing and maintaining a risk management system and process.

The first chapter of the book presents the historical background of the risk-based concepts and how the initial safety-only focus moved to a wider scenario where several other elements need to be considered as well.

The second chapter presents what is currently being done in the different areas regulated by FDA. It describes the harmonization documents and international standards developed for different type of products such as medical devices, food, and drugs.

The third chapter describes the main principles of the quality risk management field, emphasizing the sound scientific basis of the quality risk management process and its close relationship with quality system elements.

The fourth chapter details the quality risk management process, defining responsibilities and then, sequentially, the whole process, starting with risk assessment, continuing with risk control and risk communication, and ending with review and evaluation of the effectiveness of the risk process.

The fifth chapter describes the integration between risk management and quality management, including three detailed examples of such integration. Process analytical technology (PAT) and quality system inspection technique (QSIT) are discussed as clear examples of this integration. The third example covers the prioritization of FDA inspection based on risk elements.

The sixth chapter presents a collection of the methodologies and tools more widely used during risk management processes. Each tool is explained

in great detail, including real examples from the FDA-regulated industry. These examples make this one of the most valuable sections of this book, along with the very detailed explanation and examples of practical applications that can be found in Chapter 7.

Finally, there are two appendixes. Appendix A contains general examples while Appendix B includes 10 case studies with the purpose of illustrating real examples of the quality risk management process (some of them refer more to the consequences of the lack of risk management processes) across the medical product arena.

Included at the end of this e-book is a 30-question exam (with answers) on the material discussed in the book.

Finally, I'd like to close this preface with a quote from FDA itself: *“one of the FDA’s most important initiatives is to continue the agency’s evolution of cutting-edge practices for risk management”* (FDA 2009a).

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Introduction to Quality Risk Management

1.1 WHAT IS QUALITY RISK MANAGEMENT?

Organizations of all types and sizes face internal and external factors and influences that make it uncertain whether and when they will achieve their objectives. The effect this uncertainty has on an organization's objectives is "risk."

All activities of an organization involve risk. Organizations manage risk by identifying it, analyzing it, and then evaluating whether the risk should be modified by risk treatment in order to satisfy their risk criteria. Throughout this process, they communicate and consult with stakeholders and monitor and review the risk and the controls that are modifying the risk in order to ensure that no further risk treatment is required. All organizations manage risk to some degree, and the final goal is to integrate the process for managing risk into the organization's overall governance, strategy and planning, management, reporting processes, policies, values, and culture.

Risk management can be applied to an entire organization, at its many areas and levels, at any time, as well as to specific functions, projects, and activities. Although the practice of risk management has been developed over time and within many sectors in order to meet diverse needs, the adoption of consistent processes within a comprehensive framework can help to ensure that risk is managed effectively, efficiently, and coherently across an organization.

Each specific sector or application of risk management brings with it individual needs, audiences, perceptions, and criteria. When properly implemented and maintained, the management of risk enables an organization to:

- Foster proactive management
- Improve controls and operational effectiveness and efficiency
- Be aware of the need to identify and treat risk throughout the organization
- Improve the identification of opportunities and threats
- Comply with relevant legal and regulatory requirements
- Improve mandatory and voluntary reporting
- Improve governance and stakeholder confidence and trust
- Establish a reliable basis for decision making and planning
- Effectively allocate and use resources for risk treatment
- Improve loss prevention and minimize losses
- Improve organizational learning and flexibility

The current management practices and processes of many organizations include components of risk management, and many organizations have already adopted a formal risk management process for particular types of risk or circumstances. The terms “risk management” and “managing risk” are commonly used. In general terms, “risk management” refers to the architecture (principles, framework, and process) for managing risks effectively, while “managing risk” refers to applying that architecture to particular risks (International Organization for Standardization 2009a).

Risk management principles are effectively utilized in many areas of business and government, including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the biopharmaceutical industry today, they are limited and do not represent the full contribution that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring, and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the

protection of the patient by managing the risk to quality should be considered of prime importance.

In the case of medical devices, manufacturers are generally required to have a quality management system as well as processes for addressing device-related risks. These processes for managing risk can evolve into a stand-alone management system, or manufacturers may choose to maintain these two management systems separately, but it may be advantageous to integrate them as it could reduce costs, eliminate redundancies, and lead to a more effective management system.

ISO 13471 was developed to assist medical device manufacturers with the integration of a risk management system or risk management principles and activities into their existing quality management system by providing practical explanations and examples.

The scope of the medical device manufacturer's quality management system will define the applicability and extent of implementing risk management principles and activities.

Processes required by the quality management system and performed by suppliers to the manufacturer are the responsibility of the manufacturer. Risk management activities relating to any process within the quality management system are also ultimately the responsibility of the manufacturer.

An effective quality management system is essential for ensuring the safety and performance of medical devices. A well-defined quality management system includes safety considerations in specific areas. Given the importance of safety, it is useful to identify some key activities that specifically address safety issues and ensure appropriate input and feedback from these activities into the quality management system. The degree to which safety considerations are addressed should be commensurate with the degree of the risk and the nature of the device. Some devices present relatively low risk or have well-understood risks with established methods of risk control.

Risk management principles should be applied throughout the life cycle of medical devices and used to identify and address safety issues. In general, risk management can be characterized by phases of activities. The first phase can be the determination of levels of risk that would be acceptable in the device. Manufacturers should have a procedure or policy to determine risk acceptability criteria. These risk acceptability criteria may come from an analysis of the manufacturer's own experience with similar medical devices or research on what appears to be currently accepted risk levels by regulators, users, or patients, given the benefits derived from diagnosis or treatment with the device. Risk acceptability criteria generally should be reflective of the state of the art in controlling risks.

The second phase can be *risk analysis*. This phase starts with identifying hazards that may occur due to characteristics or properties of the device

during normal use or foreseeable misuse. After hazards are identified, risks are estimated for each of the identified hazards, using available information. In the third phase, the estimated risks are compared to the risk acceptability criteria.

This comparison will determine an appropriate level of risk reduction, if necessary. This is called *risk evaluation*. The combination of risk analysis and risk evaluation is called *risk assessment*. The fourth phase can be composed of risk control and monitoring activities. The manufacturer establishes actions (risk control measures) intended to eliminate or reduce each risk to meet the previously determined risk acceptability criteria. Within the limits of feasibility, one or more risk control measures may be incorporated in order to achieve this end. Risk control activities may begin as early as design input and continue through the design and development process, manufacturing, distribution, installation, servicing, and throughout the medical device life cycle. Some regulatory schemes prescribe a fixed hierarchy of risk control measures that should be examined in the following order:

- Inherent safety by design
- Protective measures in the device or its manufacture
- Information for safety, such as warnings

Throughout the life cycle of the device, the manufacturer monitors whether the risks continue to remain acceptable and whether any new hazards or risks are discovered. Information typically obtained from the quality management system—for example, production, complaints, customer feedback—should be used as part of this monitoring. If, at any time, a risk is determined to be unacceptable, the existing risk analysis should be reexamined and appropriate action taken to meet the risk acceptability criteria. If a new hazard is identified, four phases of risk management should be performed. These activities can be performed within the framework of the quality management system.

1.2 TASTE OF RASPBERRIES, TASTE OF DEATH: THE 1937 ELIXIR SULFANILAMIDE INCIDENT

Following is a reproduction of an article by FDA's Carol Ballentine published in the June 1981 issue of the now-extinct *FDA Consumer* magazine related to the 1937 Sulfanilamide disaster.

By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it. By 1937 most of the arguments had been resolved but Congressional action was stalled. Then came a shocking development—the deaths of more than 100 people after using a drug that was clearly unsafe. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products.

“Nobody but Almighty God and I can know what I have been through these past few days. I have been familiar with death in the years since I received my M.D. from Tulane University School of Medicine with the rest of my class of 1911. Covington County has been my home. I have practiced here for years. Any doctor who has practiced more than a quarter of a century has seen his share of death.

“But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony.” (Letter by Dr. A.S. Calhoun, October 22, 1937)

The medicine that killed Dr. Calhoun’s patients was Elixir Sulfanilamide. During September and October 1937 this drug was responsible for the deaths of more than 100 people in 15 states, as far east as Virginia and as far west as California. The drug and the deaths led to the passage of the 1938 Food, Drug, and Cosmetic Act, which increased FDA’s authority to regulate drugs.

Sulfanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. In June 1937, however, a salesman for the S.E. Massengill Co., in Bristol, Tenn., reported a demand in the southern states for the drug in liquid form. The company’s chief chemist and pharmacist, Harold Cole Watkins, experimented and found that sulfanilamide would dissolve in diethylene glycol. The company control lab tested the mixture for flavor, appearance, and fragrance and found it satisfactory.

Immediately, the company compounded a quantity of the elixir and sent shipments—633 of them—all over the country.

The new formulation had not been tested for toxicity. At the time the food and drugs law did not require that safety studies be done on new drugs. Selling toxic drugs was, undoubtedly, bad for business and could damage a firm's reputation, but it was not illegal.

Because no pharmacological studies had been done on the new sulfanilamide preparation, Watkins failed to note one characteristic of the solution. Diethylene glycol, a chemical normally used as antifreeze, is a deadly poison. The first shipments were sent out in early September. On October 11, the American Medical Association (AMA) received reports from physicians in Tulsa, Okla., that an unfamiliar sulfanilamide compound was responsible for a number of deaths. The AMA asked for samples of the drug and then wired the Massengill Co., requesting the composition of the compound. The AMA laboratory isolated diethylene glycol as the toxic ingredient and immediately issued a warning, through newspapers and radio, that Elixir Sulfanilamide was toxic and deadly.

A New York physician learned of the deaths on the 14th and promptly notified Food and Drug Administration headquarters. An inspector from the agency's Kansas City Station confirmed that eight children and one adult had died and that all had taken a product labeled "Elixir Sulfanilamide, the S.E. Massengill Co., Manufacturing Pharmacists, Bristol, Tenn.-Va."

Inspectors were immediately dispatched to the firm's headquarters in Bristol and to branch offices in Kansas City, New York, and San Francisco. They found that the firm had already learned of the poisonous effects of the liquid sulfanilamide and had sent telegrams to more than 1,000 salesmen, druggists, and doctors. However, the telegrams merely requested the return of the product and failed to indicate the urgency of the situation or say that the drug was lethal. At FDA's insistence, the firm sent out a second wave of messages, worded more strongly: "Imperative you take up immediately all elixir sulfanilamide dispensed. Product may be dangerous to life. Return all stocks, our expense."

FDA then set out to make sure all of the drug was retrieved. Practically the entire field force of 239 FDA inspectors and chemists was assigned to the task. State and local health officials joined the search. Newspapers and radio stations continued to issue warnings. The staff began by checking the company's shipping

records and the distribution lists in the four distributing houses and in a number of wholesale and retail drugstores. Thousands of order slips were examined one by one. In one establishment alone, 20,000 sales slips were checked.

FDA employees tracked down the firm's 200 salesmen and questioned them about the dispersion of shipments and physician samples. Finding the salesmen was the first problem. In one typical case, a salesman was reported to be in a hotel in Washington, D.C. He was not there but forwarding addresses had been left for him in Jackson, Mich., and in Baltimore. These turned out to be for another man with the same name. Four days of searching finally found the man in University Park, MD. Once the salesmen were found, there was still the problem of getting the distribution information. One man in Texas, for instance, revealed the necessary information only after being jailed by state authorities.

In many cases, locating the purchasers of the elixir required some real detective work. In some drugstores, the elixir had been sold without prescriptions to purchasers whose names the druggist didn't know. In other cases, doctors had incomplete records—or none at all—of the names and addresses of patients for whom they had prescribed. In East St. Louis, Ill., for instance, 49 prescriptions were filled and the only identification on some were such notations as “Betty Jane, 9 months old,” or “Mrs. Jackson (no address).”

Even when the purchaser was finally located, the inspectors frequently needed to do some ingenious questioning to determine what happened to the purchased elixir. One East St. Louis woman told an inspector she had destroyed the drug. The inspector persisted in his questions however. What did she mean “destroy”? Had she poured it down the sink? Had she buried it? No, the woman said, she had thrown the bottle out the window into an alley. The inspector found the bottle still unbroken, still containing enough elixir to kill any child intrigued enough to swallow its sweet, raspberry-flavored contents.

Many doctors and pharmacists did everything in their power to recover the elixir. One physician postponed his wedding to help an FDA chemist search for a three-year-old boy whose family had moved into mountain country after obtaining a prescription.

Other physicians apparently were reluctant to admit that they had prescribed the drug, perhaps fearing they would be held accountable for its consequences. One inspector, checking out a Georgia drugstore, was told that a shipment of one gallon of elixir

had been returned to the manufacturer after only 6 ounces had been dispensed. The patient who had taken the 6 ounces had suffered no ill effects, the druggist reported, and the inspector confirmed that this was true. But the inspector assigned to Bristol reported that 12 ounces was actually missing from the returned gallon, so the inspector in Georgia did some more questioning around town and tuned his ears to the local gossip. He learned that two other people had also bought the elixir. Both had died.

Similarly, a South Carolina doctor told an inspector that he had dispensed the medicine to only five people and none had died. But when the inspector began asking questions around town, someone told him of the death of a lumber mill employee. The inspector recognized the symptoms as those characteristic of Elixir Sulfanilamide poisoning. Through the mill superintendent, he located the employee's sister. Yes, she said, her brother had gone to the doctor and had been given some red medicine before he died. She told the inspector that, in accordance with custom, all medicines and sickroom utensils had been placed on the grave, about one and a half miles back in the fields. Accompanied by family and friends, the dead man's sister and the inspector walked to the wooded knoll. On the single mound of fresh earth were several bottles, dishes, spoons, and a 4-ounce bottle containing about 1 ounce of Elixir of Sulfanilamide. It bore the weathered but legible prescription label of the doctor. In fact, the inspector learned, four of the doctor's patients had died after taking the elixir.

Victims of Elixir Sulfanilamide poisoning—many of them children being treated for sore throats—were ill about 7 to 21 days. All exhibited similar symptoms, characteristic of kidney failure: stoppage of urine, severe abdominal pain, nausea, vomiting, stupor, and convulsions. They suffered intense and unrelenting pain. At the time there was no known antidote or treatment for diethylene glycol poisoning.

In a letter to President Franklin D. Roosevelt, a woman described the death of her child:

“The first time I ever had occasion to call in a doctor for [Joan] and she was given Elixir of Sulfanilamide. All that is left to us is the caring for her little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. . . . It is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight.”

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A few simple tests on experimental animals would have demonstrated the lethal properties of the elixir. Even a review of the current existing scientific literature would have shown that other studies—such as those reported in several medical journals—had indicated that diethylene glycol was toxic and could cause kidney damage or failure. But in 1937 the law did not prohibit the sale of dangerous, untested, or poisonous drugs. Dr. Samuel Evans Massengill, the firm's owner, said: "My chemists and I deeply regret the fatal results, but there was no error in the manufacture of the product. We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part." The firm's chemist apparently did not share this feeling; Harold Watkins committed suicide after learning of the effects of his latest concoction.

Through the dogged persistence of federal, state, and local health agencies and the effects of the AMA and the news media, most of the elixir was recovered. Of 240 gallons manufactured and distributed, 234 gallons and 1 pint was retrieved; the remainder was consumed and caused the deaths of the victims.

Twenty-five seizures were made under federal law. The charge was misbranding. "Elixir," FDA said, implied the product was an alcoholic solution whereas it was, in fact, a diethylene glycol solution and contained no alcohol. If the product had been called a "solution" instead of an "elixir," no charge of violating the law could have been made. FDA would have had no legal authority to ensure the recovery of the drug, and many more people probably would have died.

FDA Commissioner Walter Campbell, who was then pressing for better federal regulation of drugs, pointed out how the inadequacy of the law had contributed to the disaster. "It is unfortunate that under the terms of our present inadequate Federal law, the Food and Drug Administration is obliged to proceed against this product on a technical and trivial charge of misbranding. . . . [The Elixir Sulfanilamide incident] emphasizes how essential it is to public welfare that the distribution of highly potent drugs should be controlled by an adequate Federal Food and Drug law. . . . We should not lose sight of the fact that we had many deaths and cases of blindness resulting from the use of another new drug, dinitrophenol, which was recklessly placed upon the market some years ago. Deaths and blindness from this [drug] are continuing today. We also should remember the deaths resulting from damage to the liver that have occurred from cinchophen poisoning, a drug

often recommended in such painful conditions as rheumatism. We also have unfortunate poisoning, acute and chronic, resulting from thyroid and radium preparations improperly administered to the public.

“These unfortunate occurrences may be expected to continue because new and relatively untried drug preparations are being manufactured almost daily at the whim of the individual manufacturer, and the damage to public health cannot accurately be estimated. The only remedy for such a situation is the enactment by Congress of an adequate and comprehensive national Food and Drugs Act which will require that all medicines placed upon the market shall be safe to use under the directions for use. . . .”

As it turned out, the Elixir experience did more than hasten enactment of the 1938 Federal Food, Drug, and Cosmetic Act. The New Drug section, added to prevent such tragedies, gave the United States a new system of drug control which provided superior protection while stimulating medical research and progress. And 25 years later, it saved the Nation from an even greater drug tragedy—a thalidomide disaster—like that in Germany and England. Here again, history repeated itself. A pending bill, the Drug Amendments of 1962, was finally enacted.

## 1.3 SEVENTY YEARS LATER

At the end of September 2006 several hospitals at Panama City (Panama) were getting full with patients with contradictory symptoms. The symptoms seemed to match with Guillain-Barré syndrome, but these patients were also losing their ability to urinate, a symptom not related to Guillain-Barré. The death rate of this mysterious illness was nearly 50% when hospital management decided to isolate all the patients with the illness in a large room so that doctors could compare notes and theories. Soon, patients from other parts of the country started to arrive at hospitals. Doctors had no idea what was happening: the mysterious illness was attacking elderly citizens with hypertension and diabetes history. About half were receiving a blood pressure medicine, and many did not remember clearly if they had been taking other drugs. Suspecting something wrong with the hypertension drug, the medicine was removed from the pharmacies while the U.S. FDA conducted laboratory analyses, revealing the blood pressure drug was safe.

Most of the patients taking the blood pressure medicine developed a cough (a common side effect) and they were prescribed an expectorant. Immediately, biological samples and the syrup were sent to the United States for analysis. When urine analyses for a series of metals, pesticides,

or their metabolites resulted negative, Centers for Disease Control (CDC) scientists recalled previous incidents in Nigeria and Haiti. The CDC analysis revealed that the samples contained approximately 8% v/v diethylene glycol (DEG). Later, raw glycerin was analyzed and results revealed 22.2% v/v DEG.

The Panamanian government implemented a nationwide campaign, collecting around 6000 bottles of cough syrup and three other products with the tainted glycerin manufactured by Social Security Laboratories. The 46 barrels of syrup were bought by Social Security Laboratories through a Panamanian middleman, Grupo Comercial Medicom, who bought the product from Rasfer Internacional, a Spanish company. In fact, Rasfer received the product from CNSC Fortune Way, which in turn bought it from the Taixing Glycerine Factory. At the request of the United States, the Chinese FDA investigated Taixing Glycerine Factory and CNSC Fortune Way, but the agency concluded that it is not under their jurisdiction because the factory is not certified to make medicine. Taixing sold the syrup as “TD glycerin,” wording that neither Chinese inspectors nor Spanish medical authorities comprehended. Unfortunately, Taixing used “TD” for the Chinese word *tidai*, meaning “substitute.”

The New York Times reported that Taixing was closed by the Chinese government and CNSC Fortune Way was never sanctioned (Bogdanich and Hooker 2007). In Spain, Rasfer Internacional declared bankruptcy after the lawyer of Medicom filed a lawsuit of \$400 million in July 2008. Spanish authorities are prosecuting the general manager of Rasfer Internacional. Meanwhile, in Panama, the legal representative of Medicom remains in jail pending trial. Seventeen other persons have also been charged in relation to this incident.

Panama’s case made CDC set standardized methodology for DEG identification, hoping to have more timely response in future events. After that incident, FDA also issued an Industry Guidance document “intended to alert pharmaceutical manufacturers, pharmacy compounders, repackers, and suppliers to the potential public health hazard of glycerin contaminated with DEG and recommended appropriate testing procedures for the use of glycerin.” As of June of 2011, the number of confirmed deaths according to the official Panama government list rose to 219 victims.

## 1.4 RISK-BASED APPROACH

Developing a risk culture is one of the most important tasks a regulated firm can do to manage the risk. All medical products carry some degree of risk (from design and manufacturing errors to use errors), and even the safer, over-the-counter medicines and devices are highly regulated. Regulators,

by definition, are inherently risk averse, and FDA is not an exception, but finally, during 2002, it announced a significant new initiative, “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach,” to enhance and modernize the regulation of pharmaceutical manufacturing and product quality—to bring a 21st century focus to this critical FDA responsibility. The initiative was intended to modernize FDA’s regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. As part of this initiative, both the pharmaceutical and the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated with the following objectives in mind:

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- 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

Early in the initiative, a number of multidisciplinary working groups were formed, comprising FDA experts from various areas of scientific and regulatory practice within FDA. As a result of this work, FDA completed its assessment of the existing cGMP programs and began to develop the product quality regulatory system of the future following these guiding principles in order to minimize the risks to the public health associated with pharmaceutical product manufacturing:

- Risk-based orientation
- Science-based policies and standards
- Integrated quality systems orientation
- International cooperation
- Strong public health protection

FDA identified a risk-based orientation as one of the driving principles of the cGMP initiative. The progress outlined below reflects FDA's commitment to the adoption of risk management principles that will enhance the Agency's inspection and enforcement program, which is focused on protecting the public health.

## FDA's Strategic Action Plan

The Agency's strategic plan identified efficient risk management as a key element. Efficient risk management requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry. FDA identified efficient risk management as the primary way to make the most effective use of Agency resources and address these challenges. This approach incorporates rigorous analysis to consistently identify the most important risks, and the use of a quality systems approach to designing, conducting, and evaluating FDA core business processes.

## Risk-Based Model for Inspectional Oversight

The Agency also developed a risk-based model for prioritizing sites for manufacturing inspections, which is discussed under Chapter 5.3.2.

## Part 11 Guidance

With the issuance in 2003 of the guidance for industry Part 11, Electronic Records, Electronic Signatures—Scope and Application, many barriers to scientific and technological advances were removed, and the use of risk-based approaches to managing computer systems is encouraged.

## Aseptic Processing Guidance

The final guidance for industry on Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process advocates a risk-based framework, underscoring the value of proactive approaches to ensuring sterility. Among the sections of the guidance that address risk-based approaches are those relating to key roles played by personnel, design, environmental control, and media fills in an aseptic processing operation. This guidance states that “nearly all drugs recalled due to non-sterility or lack of sterility assurance in the period spanning 1980–2000 were produced via aseptic processing.”

## 1.5 MORE THAN SAFETY RISKS: FROM SAFETY RISKS TO QUALITY BY DESIGN (QBD)

An effective risk management process involves many complex and interrelated activities whose final goal is *to protect the patient* and users of medical products, which is exactly the mission of FDA.

When properly managed, the risk management process will help regulated companies to ensure customers' and users' safety, and to protect the company value and reputation. On the other hand, when ineffective risk management processes are in place, some consequences can be:

- Injuries and even deaths related to unsafe medical products
- Regulatory actions, including costly product recalls, warning letters, and even injunctions
- Tarnished corporate image
- Decreased value for stakeholders and stockholders

Better design of medical products, including the design of their manufacturing and quality control processes, is a critical element of the risk management process. However, there is another crucial step, which is during the use of the product. To minimize this type of risk (for example, an error when using a medical device or taking a drug), FDA developed specific guidances, among them:

- *Risk Evaluation and Mitigation Strategies* (REMS), which require Medication Guides for some drug and biological products
- *Quality by Design*, which aims to design safer and better drugs and biotechnology products
- *Design control for medical devices* focused on meeting user needs
- *Do It by Design: An Introduction to Human Factors in Medical Devices*

### Medication Guides

Medication Guides were introduced in the late 1990s for products perceived to pose “serious and significant public health concerns.” It was mandatory for pharmacists to distribute them at the time of drug dispensing. For some medical products (mainly drug and biological products) that FDA

determines pose a serious and significant public health concern, distribution of FDA-approved patient medication information that is necessary to patients' safe and effective use of the drug products is required. It is called a Medication Guide and it applies to products used primarily on an outpatient basis without direct supervision by a healthcare professional. These regulations are codified in 21 CFR part 208.

## Quality by Design

*Quality by design (QbD)* is a concept first outlined by well-known quality expert Joseph M. Juran in various publications, most notably *Juran on Quality by Design*. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned in the first place. QbD is a systematic approach to development of new products and processes and it begins with predefined objectives, emphasizes product and process understanding and process control, and is based on sound science and quality risk management. The concept promotes industry's understanding of the product and manufacturing process starting with product development, basically building quality in, not testing it. Under this concept, when designing and developing a product, a company needs to define desired product performance and identify its critical quality attributes (CQAs). On the basis of this information, the company then designs the product formulation and process to meet those product attributes. This leads to understanding the impact of raw material attributes and process parameters on the CQAs, and identification and control of sources of variability. As a result of all this knowledge, a company can continually monitor and update its manufacturing process to assure consistent product quality. This systematic approach to product development and manufacturing varies a great deal from the traditional approach, which was extremely empirical.

While QbD principles have been used to advance product and process quality in every industry, and particularly the automotive industry, they have most recently been adopted by FDA as a vehicle for the transformation of how drugs are discovered, developed, and commercially manufactured. During an FDA presentation at 2007 PDA/FDA Joint Conference (Winkle 2007) the agency presented the following benefits from the adequate implementation of QbD.

Benefits for FDA include:

- Enhances scientific foundation for review
- Provides for better coordination across review, compliance, and inspection

- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of preapproval review
- Provides for more flexibility in decision making
- Ensures that decisions are made on science and not on empirical information
- Involves various disciplines in decision making
- Uses resources to address higher risks

Benefits for the industry include:

- Ensures better design of products with fewer problems in manufacturing
- Reduces number of manufacturing supplements required for post-market changes—reliance on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing—less waste
- Ensures less hassle during review—fewer deficiencies, quicker approvals
- Improves interaction with FDA—deal on a science level instead of on a process level
- Allows for continuous improvements in products and manufacturing process
- Allows for better understanding of how active pharmaceutical ingredients (APIs) and excipients affect manufacturing
- Relates manufacturing to clinical considerations during design
- Provides a better overall business model

## Design Controls for Medical Devices

Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk. It is intended to be a framework within which

experience, insight, and judgment are applied to successfully manage risk. It is included in this guidance because of its effect on the design process.

Risk management begins with the development of the design input requirements. As the design evolves, new risks may become evident. To systematically identify and, when necessary, reduce these risks, the risk management process is integrated into the design process. In this way, unacceptable risks can be identified and managed earlier in the design process, when changes are easier to make and less costly.

An example of this is an exposure control system for a general purpose X-ray system. The control function was allocated to software. Late in the development process, risk analysis of the system uncovered several failure modes that could result in overexposure to the patient. Because the problem was not identified until the design was near completion, an expensive, independent backup timer had to be added to monitor exposure times.

The Safe Medical Devices Act of 1990 added design validation requirements to the cGMP requirements in section 520(f) of the Act. Section 820.30 of the Quality System Regulation (QSR) lists the design control requirements that manufacturers should satisfy to be in compliance.

*Design Control Guidance for Medical Device Manufacturers* is another document that may assist manufacturers in understanding the intent of the design control requirements. This manual interprets the language of the QSR and explains the underlying concepts in practical terms.

*Do It by Design: An Introduction to Human Factors in Medical Devices* is a document that contains background information about human factors as a discipline, describes and illustrates device problems, and discusses human factors principles and methods as a part of the design control system. Both of these manuals are possible resources for manufacturers who are either developing or improving their design control system.

The design controls section 820.30 of the QSR applies to the design of products and processes, and changes to existing designs and processes. Changes to existing designs should be made in accordance with design control requirements even if the original design was not subject to these requirements. Each manufacturer of any class III or class II device, class I devices automated with computer software, and a few more exceptions included in the regulation, shall establish and maintain procedures to control the design of the device in order to make certain that specified design requirements are met.

## 1.6 ISO 31000

The international standard ISO 31000 is intended to be a family of standards relating to risk management codified by the International Organization

for Standardization (ISO). The purpose of ISO 31000:2009 (published November 2009) is to provide principles and generic guidelines on risk management. ISO 31000 seeks to provide a universally recognized paradigm for practitioners and companies employing risk management processes to replace the myriad of existing standards, methodologies, and paradigms that differ between industries, subject matters, and regions.

The purpose of ISO 31000:2009 is to be applicable and adaptable for “any public, private or community enterprise, association, group or individual.” Accordingly, the general scope of ISO 31000—as a family of risk management standards—is not developed with a particular industry group, management system, or subject matter field in mind, but rather to provide best practice structure and guidance to all operations concerned with risk management.

ISO 31000:2009 provides principles and generic guidelines on risk management, and it can be applied throughout the life of an organization, and to a wide range of activities, including strategies and decisions, operations, processes, functions, projects, products, services, and assets. ISO 31000:2009 can be applied to any type of risk, whatever its nature, whether having positive or negative consequences.

Although ISO 31000:2009 provides generic guidelines, it is not intended to promote uniformity of risk management across organizations. The design and implementation of risk management plans and frameworks will need to take into account the varying needs of a specific organization, its particular objectives, context, structure, operations, processes, functions, projects, products, services, or assets, and specific practices employed. It is intended that ISO 31000:2009 be utilized to harmonize risk management processes in existing and future standards. It provides a common approach in support of standards dealing with specific risks and/or sectors, but does not replace those standards. ISO 31000:2009 is not intended for the purpose of certification.

Currently, the ISO 31000 family includes:

- ISO 31000:2009 *Principles and guidelines on implementation*, adopted in the United States as ANSI/ASSE Z690.2-2011 *Risk Management Principles and Guidelines*
- ISO/IEC 31010:2009 *Risk management—Risk assessment techniques*, adopted in the United States as ANSI/ASSE Z690.3-2011 *Risk Assessment Techniques*

This standard is a supporting standard for ANSI/ASSE Z690.1, *Vocabulary for Risk Management* (ISO Guide 73:2009) and provides guidance on selection and application of systematic techniques for risk assessment.

Risk assessment carried out in accordance with this standard contributes to other risk management activities. The application of a range of techniques is introduced, with specific references to other national and international standards where the concept and application of techniques are described in greater detail. This standard is not intended for certification, regulatory, or contractual use:

- ISO Guide 73:2009 *Risk management—vocabulary*, adopted in the United States as ANSI/ASSE Z690.1-2011 *Vocabulary for Risk Management*

Scope: This standard provides the definitions of generic terms related to risk management. It aims to encourage a mutual and consistent understanding of, and a coherent approach to, the description of activities relating to the management of risk and the use of uniform risk management terminology in processes and frameworks dealing with the management of risk. This standard is intended to be used by:

- Those engaged in managing risks
- Those who are involved in activities of ISO and IEC
- Developers of national or sector-specific standards, guides, procedures, and codes of practice relating to the management of risk
- Those seeking principles and guidelines on risk management

## 1.7 HISTORICAL PERSPECTIVE AND CURRENT SITUATION

The roots of modern risk management can be tied to a cohort of regulatory initiatives in the latter part of the past century. The decision to approve a drug or any medical product (and its classification as prescription or non-prescription) is highly dependent on the answer to the following question: “Do the benefits of the medical product outweigh the risks?” Both manufacturers and FDA continually evaluate the potential benefits of a medical product versus its potential risks. Many factors are taken into consideration, some of which include:

- Seriousness of the disease or condition to be treated
- Size of the patient population
- Expected benefit of the medical product

- Expected duration of treatment
- Seriousness of the known or potential adverse events

These evaluations are performed not only prior to the approval of a new medical product, but also throughout the entire life cycle of the product. This serves as a means to continuously assess the safety and efficacy of existing product based on adverse event reports and results from post-marketing clinical studies.

In 1960, FDA instituted a policy of full disclosure. Manufacturers were required (and still are) to provide complete information about the product's indication, dosing, side effects, and so on, to healthcare professionals. This information is included in the product labeling.

The Controlled Substances Act (CSA) of 1970 is another early example of risk management. The CSA regulates manufacturers, prescribers, and dispensers as well as the label and warning, providing additional indicators of risk and tools to manage those risks beyond those established under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Common tools included boxed warnings and "Dear Healthcare Provider" letters.

The safe and effective use of drugs was the reason that FDA endorsed the requirement in the late 1970s to distribute patient package inserts (PPIs) with oral contraceptives and estrogen replacements to patients. Prior safety communications were geared toward healthcare professionals. Since oral contraceptives and estrogens were considered elective medications, FDA insisted that patients (consumers) be provided with written information about the benefits and risks of taking these products to assist in their decision about birth control methods.

Special programs that extended beyond labeling and PPIs to restrict access to certain risky products were instituted between 1988 and 1998. Some products (Accutane, Clozaril, and thalidomide, for example) had specifically designed programs to detect or prevent serious adverse events. In the case of thalidomide, used for the treatment of complications of leprosy, it was approved in the United States (1998) with The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). The program required that all patients, pharmacists, and physicians be registered, and that patients be tested for pregnancy to avoid the potential for birth defects.<sup>1</sup>

In the late 1990s, after the removal of a number of high-profile drugs from the market due to emergent safety concerns (for example,

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1. Celgene Corporation. "Risk Evaluation and Mitigation Strategies (REMS) System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)." Accessed 3/13/12. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222649.pdf>.

fenfluramine), FDA's efforts with respect to drug safety, both pre- and post-marketing, came under scrutiny. Questions arose about the premarket and post-market assessments of safety and drug risks and whether the shorter review time frames specified by the Prescription Drug User Fee Act of 1992 (PDUFA) were resulting in the approval of more-dangerous drugs. As one of her first initiatives after being sworn in as FDA Commissioner in 1998, Dr. Jane Henney established a task force to evaluate the system for managing the risks of FDA-approved medical products, focusing particularly on FDA's part in the system. The result of that review was published in May 1999 (*Managing the Risks from Medical Product Use: Creating a Risk Management Framework*, report to the FDA commissioner from the task force on risk management). This report heralded the modern risk management era.<sup>2</sup>

The task force assessed risk management practices within the overall healthcare delivery system, focusing on the roles and responsibilities of each participant. The task force applied a risk management model used in other federal sectors. They also examined the various risks from medical products and their sources. The task force then evaluated FDA's role in the current system. First, they reviewed the Agency's *premarketing* risk assessment and approval processes to determine if serious adverse events were occurring at a higher rate than they had in the past. Next, the task force evaluated FDA's *post-marketing* surveillance and risk assessment programs to see if they were doing the job they were intended to do. Finally, the task force analyzed all of FDA's risk management activities to evaluate the Agency's role in the overall system for managing medical product risks. Medical products provide great benefit to the public, but they can also cause injury.

FDA and the many other participants in healthcare delivery act to maximize the benefits and minimize the risks associated with using medical products, but often the actions of the participants are insufficiently integrated. The task force believed that the common goal of maximizing benefits and minimizing risks could be greatly advanced if the participants in the system worked together to gain an understanding of these activities within a systems framework. To achieve such a framework, it is necessary to gain a better understanding of the risks involved and their sources, and it is also necessary to clarify the role of each stakeholder and ensure that these individual roles are well integrated. Only then can effective risk management strategies be planned.

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2. Accessed 3/13/12. Available at <http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm182957.htm>.

In July 2006 the Parenteral Drug Association's (PDA) Risk Management Task Force for Aseptic Processes conducted an electronic survey among its members to determine current industry practices regarding implementation of quality risk management in their organizations. This electronic survey was open and publicly available via the PDA website and targeted professionals in the regulated industry (pharmaceutical, medical devices, and biotechnology manufacturers) who are involved in initiating, implementing, or reviewing risk management programs or decisions in their organizations. One hundred twenty-nine members participated (Ahmed et al. 2008).

Among the major findings were:

- The “aseptic processing/filling” operation is the functional area identified as having the greatest need for risk assessment and quality risk management.
- The most widely used methodology in industry to identify risk is failure mode and effects analysis (FMEA). This tool is most widely applied in assessing change control and for adverse event, complaint, or failure investigations.
- Despite the fact that personnel training was identified as the strategy most used for controlling/minimizing risk, the largest contributors to sterility failure in operations are still “personnel.”
- Most companies still rely on “manufacturing controls” to mitigate risk and deem the utilization of process analytical technology (PAT) least important in this aspect.
- A majority of correspondents verified that they did not periodically assess their risk management programs.
- A majority of the correspondents desired to see case studies or examples of risk analysis implementation (as applicable to aseptic processing) in future PDA technical reports on risk management.

# 2

## Current Initiatives

### 2.1 FDA-WIDE

FDA oversees the public health standards of an industry that produces trillions of dollars worth of regulated products. The products include the entire food supply, except for meat and poultry, over-the-counter and prescription medications, blood products, vaccines, tissues for transplantation, medical equipment and implantable devices, devices that emit radiation, animal drugs and feeds, and cosmetics. FDA faces two challenges in assuring that U.S. citizens fully reap the health benefits of modern medical technology, and enjoy a safe and nutritious food supply:

1) *FDA must assure the safety and effectiveness of drugs, biologics, food additives, medicated animal feeds, and medical devices before they are allowed on the market.* This challenge means keeping pace with the increasing scientific complexity of products. FDA scientists must accurately judge the readiness of these products to be marketed, and help these innovative products reach the market as quickly as possible.

There must also be a sufficient number of reviewers to handle the product review workload in order to provide timely feedback to application sponsors to identify and address deficiencies. Any delays might:

- Postpone critically needed disease prevention and treatment, especially for a growing population of elderly and immune-compromised patients
- Increase the cost of bringing a new product to market by lengthening the time a product is in development
- Result in fewer low-cost alternatives for patients (including children and the elderly)

2) *FDA must also monitor the safety of products once they are on the market.* U.S. consumers use products that are manufactured worldwide and make their way to the market throughout a wide variety of distribution channels. To ensure that these products are safe, the Agency must oversee their entire life cycle—from production through distribution, and use/consumption.

On August 21, 2002, FDA announced a major new initiative pertaining to drug quality regulation, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach. In the initial concept paper issued on the initiative, FDA identified “a risk-based orientation” as one of the guiding principles that would drive the initiative. The concept paper stated that “resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production” and that “to provide the most effective public health protection, FDA must match its level of effort against the magnitude of the risk.”

The concept paper noted that in the short term, FDA intended to place more emphasis on risk-based allocation of resources for the oversight of drug quality. However, the concept paper also acknowledged that developing more systematic and risk-based approaches would be a long-term effort and that an intermediate step is to “use emerging science and data analysis to enhance compliance programs to target the highest risk areas.”

On August 20, 2003, FDA released its strategic action plan, *Protecting and Advancing America's Health*. This strategic plan reflects the Agency's continuing support and priority for the risk management goals of the Pharmaceutical cGMPs for the 21st Century initiative. The first core goal identified in the plan is “efficient risk management,” directed toward “ensuring that the Agency's limited resources can provide the most health promotion and protection at the least cost for the public.” The discussion of this goal specifically highlights the efforts of the Pharmaceutical cGMPs for the 21st Century initiative as central to the Agency's risk management program. One of the objectives under this goal is to “provide high quality, cost-effective oversight of industry manufacturing, processing and distribution to reduce risk.” Specifically identified under this objective is developing “new inspection approaches to more effectively utilize . . . resources.” Also highlighted is the need to “use emerging science and data analysis to *target the highest risk areas*.”

## 2.2 DRUGS AND BIOTECHNOLOGY PRODUCTS

### 2.2.1 ICH Q9

In September 2006 FDA adopted the International Conference on Harmonization (ICH) Q9 document entitled “Quality Risk Management.” This guidance provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, inspection, and submission/review processes throughout the life cycle of drug substances, drug products, and biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug products, and biological and biotechnological products).

The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. Product *quality* must be maintained throughout the *product life cycle* such that the attributes that are important to the quality of the drug product remain consistent with those used in preproduction and clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. In addition, use of quality risk management can improve decision making if a quality problem arises. 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 can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of other ICH quality documents, but it supports and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment.

ICH Q9 provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product life cycle. It is not intended to create any new expectations beyond the current regulatory requirements. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, for example, standard operating procedures). The use of

informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

## 2.2.2 QbD Guidances

*Quality by design* means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process. It means building quality into the process and product in a systematic, science- and risk-based manner. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from product development to the commercial manufacturing processes and for post-development changes and optimization. This concept is not new. In fact, the 1976 cGMP regulations, when viewed in their entirety, incorporate the concept of quality by design.

The QbD concepts were outlined in the ICH Q8(R2), Q9, and Q10 guidelines. These documents, already adopted by FDA, provide the foundation for implementing QbD during specific stages of product development. Putting the QbD process into place requires several steps. First, you want to define the desired product performance up front and identify product critical quality attributes (CQAs). Next, you design formulation and process to meet product CQAs. A critical component of QbD is understanding the needs of the patient and the specific quality attributes of the product that are linked to safety and efficacy. Thus, to implement QbD it is fundamental to understand the functional relationships between patient needs, product quality attributes, analytical capabilities, and the manufacturing process.

Pharmaceutical companies begin by identifying product requirements to meet patient needs and then determine the quality target product profile (QTPP) and the CQAs required to meet those patient needs. Based on this information, the company then designs the molecule, the manufacturing process, and the control strategy to ensure that the desired product quality is met consistently. The QbD approach can be maintained throughout the life cycle of the product to facilitate innovation and continuous improvement based on expanded knowledge and new technologies. This knowledge is gained during development and grows with more manufacturing experience through process characterization, scale-up, technology transfer, and manufacture, as well as through increased patient exposure to the

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product. This approach encourages incorporating prior process and product knowledge and experience-based methodologies into manufacturing throughout the life of the product.

When a product is developed using a QbD approach, the impact of raw and starting materials and process parameters on product quality are well understood, and the sources of process and product variability are well known and controlled. In contrast, traditional pharmaceutical manufacturing relies heavily on end product testing, and the process typically lacks the flexibility needed to respond to variables encountered during manufacturing. The outcome is often “quality by conformance” and a rigid, static manufacturing operation that is more susceptible to multiple manufacturing changes post licensure, thus requiring continuous updating of the application through burdensome global regulatory supplements, variations, or amendments.

QbD is a systematic approach to product and process design and development, and it includes the following key elements:

- Target the product profile
- Determine critical quality attributes
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product life cycle, including continual improvement

### ***Critical Quality Attributes***

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release, and stability. CQAs for other delivery systems can additionally include more product-specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials, and intermediates, the CQAs can additionally include those properties (for example, particle size distribution, bulk density) that affect drug product CQAs.

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing processes are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product:

- Definition of “critical” varied.
- Most of the applications related CQAs to those attributes that have a direct impact on product quality, safety, and efficacy.
- Most applications included CQAs for the drug product, but only some applications included CQAs for the drug substance.
- Some applications considered the drug substance’s property affecting downstream manufacturing as a CQA.
- Most applications related critical process parameters to CQAs.
- Most applications considered a process parameter noncritical if well controlled or well within the design space.

### **Risk Assessments**

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Risk assessment tools can be used to identify and rank parameters (for example, process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. The initial list of potential parameters can be quite extensive but can be modified and prioritized by further studies. The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further analyzed to achieve a higher level of process understanding.

With FDA moving forward with the QbD concept, risk management has become a priority process in the manufacture of pharmaceuticals. QbD, according to ICH Q8(R) is based on sound science and quality risk

management. It's a systematic approach to development that begins with predefined objectives and an emphasis on product process understanding and process control. In order to achieve this, a risk management process has to be a priority.

Tools used in the risk assessment included the fishbone diagram, FMEA, and Pareto analysis, among other tools. A fishbone diagram is used to identify all potential variables, such as raw materials, compression parameters, and environmental factors, that can have an impact on a particular CQA, such as tablet hardness. An FMEA can then be used to rank the variables based on risk (a combination of probability, severity, and detectability) and to select the process parameters with higher risks for further studies to gain greater understanding of their effects on CQAs. The risk assessment is prepared by a multidisciplinary team based on prior knowledge and experiments.

Through the process of risk assessment and risk control, you want to understand the impact of material attributes and process parameters on product CQAs and then identify and control sources of variability in material and the process.

The use of risk management in QbD will help to identify and link material attributes and process parameters to CQAs, enable early identification of risk to guide developmental efforts, and quantify the severity of harm and likelihood of occurrence. The benefits of risk assessment are numerous. It can be used as a systematic approach to identifying and classifying parameters in the design space, useful in process development, monitoring, improvement, and troubleshooting, and it's used to increase the assurance of quality.

It is important to provide a systematic risk analysis of how raw materials, process steps, and process parameters affect product quality. The risk assessment that leads to the development of a comprehensive control strategy to reduce risk to product quality should be described, and the risk reduction and control should be discussed for changes that occur inside or outside the design space. Risk assessment can provide increased assurance to quality because when process variability is identified and its linkage to product CQAs is understood, process and product controls reduce the impact of variability, and quality product will continue to be made when movement within the design space occurs in the future.

A risk assessment also is important for effective communication between FDA and industry and for intracompany communication (such as between research/development and manufacturing and between multiple manufacturing sites), and within FDA, risk assessment allows for a dialogue between pre- and post-marketing review functions and between review, compliance, and field inspection staffs.

## Design Space

FDA defines *design space* in its Guidance for Industry Q8 (2): Pharmaceutical Development as “The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.”

The idea behind design space is that process variability leads to product variability. Monitoring the parameters of drug attributes results in less process and, ultimately, less product variability. The advantage of the design space is that it provides a wider range within which material attributes can vary in the future without supplemental regulatory approval.

In establishing and presenting a design space, some key points to consider are:

- Effect of formulation-component properties on process performance and product quality
- Multivariate interactions
- Scale-up and equipment issues
- Effect of operation or site change
- Uncertainty addressed with risk management

A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure systems, and drug products contribute to the final product quality. These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the *critical process parameters* and material attributes.

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (for example, drug substance, excipients, primary packaging materials) based on an understanding of their impact on manufacturability or product quality
- Product specifications
- Controls for unit operations that have an impact on downstream processing or product quality (for example, the impact of drying