Discussion of the importance of risk assessment and risk management in the biopharmaceutical sector.

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Introduction

The biopharmaceutical industry is a highly specialized field that involves the creation of pharmaceuticals through molecular biology techniques rather than traditional methods. These techniques involve the use of components from living organisms, such as DNA, to develop and manufacture products (Kesik-Brodacka, 2017). As a result, the industry is filled with many risks that need to be effectively managed to ensure patient safety and product quality (Reddy et al., 2014). Quality risk management is a critical process that focuses on identifying and controlling these risks, and it has proven to be a valuable tool to the biopharmaceutical sector (Ismael & Ahmed, 2020).

In recent years, risk assessment has emerged as a crucial step in quality risk management. It involves the identification of hazards and an analysis of the associated risks. The International Conference on Harmonisation (ICH) has developed a guideline, ICH Q9, which proposes a structured approach to risk management that can be applied to the biopharmaceutical industry. This guideline has become an essential tool for the industry, and its application has led to numerous benefits, including improved patient safety and product quality (International Conference on Harmonisation, 2023).

This essay will discuss the various risks associated with the biopharmaceutical industry and the importance of risk management and risk assessment. The applications of ICH Q9 to the biopharmaceutical sector will be explored, highlighting its significance in promoting patient safety and ensuring product quality.

History

Throughout history, several incidents have led to the development and implementation of risk management legislation, such as ICH Q9, which is used to prevent similar occurrences from happening again. These events have emphasized the crucial need for a robust quality management system that can be utilized to ensure the safety and efficacy of drugs while minimizing the risk of harm to patients. By analyzing and managing potential risks, a good quality management system can help to prevent events like these from happening in the future, ultimately improving the safety and effectiveness of drugs for patients.

The 1906 pure food and drug act was the first regulation enacted in the United States regarding pharmaceuticals. It came about due to a growing concern among the public regarding the purity and integrity of products. This concern was fuelled by the fierce competition between pharmaceutical companies, which was pushing them to develop innovative products that were both cheaper and more advantageous to their companies. This drive for innovation led to the development of medications that were not as efficient or pure as advertised. In order to combat this, the 1906 pure food and drug act was established (Law & Libecap, 2003). This act was aimed at ensuring that food and drug products met certain quality standards and were safe for consumption. It paved the way for the establishment of the Food and Drug Administration (FDA) in the United States in 1930, following a period of minor revisions and additions to the regulations (The Food and Drug Administration, 2018). The FDA was given the task of ensuring that food and drugs were safe, effective, and of high quality and that they met the standards set by the 1906 pure food and drug act.

The implementation of the Federal Food, Drug and Cosmetic Act in the United States in 1938 is a significant event in the history of risk management legislation. The Elixir Sulfanilamide Disaster was the catalyst for the enactment of this Act. The drug sulfanilamide, an antibacterial drug, was needed in a liquid form, and to produce this, diethylene glycol was used as a diluent of sulfanilamide. However, premarketing toxicity testing was not mandatory before the release of new drugs at that time, and this led to over a hundred deaths from diethylene glycol poisoning. The Federal Food,

Drug and Cosmetic Act aimed to prevent such incidents from happening again by requiring proof of safety before releasing new drugs (Wax, 1995). If the risks involved in releasing a new drug had been appropriately evaluated, then this event might have been averted. Therefore, this incident demonstrated the importance of risk management legislation and the need for a robust quality management system to ensure the safety of new drugs before they are released to the market.

During the late 1950s, an incident occurred that caused significant amendments to regulations in the pharmaceutical industry. At the time, the drug thalidomide was prescribed to treat nausea in pregnant women, but it led to a large increase in children being born with phocomelia and other deformities, such as congenital heart disease (Kim & Scialli, 2011). This event highlighted the significant gaps in the existing legislation, which failed to account for the potential risks of new drugs.

The thalidomide disaster demonstrated the consequences of inadequate analysis and management of risks associated with the pharmaceutical sector. As a result, there was a growing need for more stringent regulations to ensure that the safety and efficacy of new drugs were adequately assessed and that the potential risks were appropriately managed. In response, the Kefauver-Harris Amendments were passed in 1962, requiring developers to provide proof of both the safety and efficacy of their drugs before they were approved for release (Greene & Podolsky, 2012).

The introduction of the Kefauver-Harris Amendments marked a significant turning point in the pharmaceutical industry, as it emphasized the importance of thorough testing and evaluation of new drugs to ensure their safety and efficacy. The amendments established a comprehensive system for regulating new drugs, which included requirements for clinical testing, data analysis, and reporting of adverse reactions. By requiring proof of efficacy, the amendments aimed to ensure that new drugs were not only safe but also effective (Greene & Podolsky, 2012).

In 1990, a significant development in the pharmaceutical industry occurred during a World Health Organization meeting. A recommendation was made to establish a unified set of guidelines that could be used to ensure the safety and efficacy of pharmaceutical products while also reducing clinical trial redundancies. This recommendation led to the creation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which has since become an essential component of the industry (Singh, 2015).

In 2005, the ICH released a publication called the ICH Harmonized Tripartite Guideline: Quality Risk Management (Q9). ICH Q9 is a comprehensive guideline that focuses on a variety of potential approaches to a reliable quality management system. The guideline aims to provide a structured approach to managing risks associated with pharmaceutical production, ensuring that product quality is consistently maintained at a high level (Milá Cáceres et al., 2010).

This development demonstrates the continued evolution of the pharmaceutical industry and the importance of continuously improving regulations and guidelines to ensure product safety and efficacy.

Methods

The ICH Q9 guideline is a comprehensive framework for quality risk management in the pharmaceutical industry. The guideline provides a structured approach to identifying, assessing, and managing risks in order to ensure the safety, efficacy, and quality of pharmaceutical products (International Conference on Harmonisation, 2023).

The ICH Q9 guideline outlines a 4-step process for quality risk management in the pharmaceutical sector. The first step is risk assessment, which is further divided into three sub-steps: hazard identification, risk analysis, and risk evaluation. During hazard identification, potential hazards are identified and documented. Risk analysis involves

the determination of the likelihood and severity of the identified hazards. Finally, risk evaluation is performed to determine whether the risks are acceptable or not.

The second step in the risk management process is risk control, which aims to minimize the identified risks to a tolerable level. This involves selecting and implementing appropriate risk management measures, including preventative, corrective, and mitigation actions.

The third step in the process is risk review, which involves the implementation of procedures for the continuous review of risks and events to ensure that risk management measures remain effective over time. This step is crucial for ensuring that any changes or updates to the risk management plan are implemented in a timely manner.

Finally, communication is essential for ensuring that all stakeholders are aware of the identified risks and the measures in place to manage them. This involves sharing information about the risks and risk management strategies with all relevant parties, including regulators, healthcare providers, patients, and other stakeholders.

To assist with risk management, ICH Q9 provides a risk management control diagram, which is shown in Figure 1. This diagram outlines the various steps in the risk management process and can be used to guide risk management activities in the pharmaceutical sector.

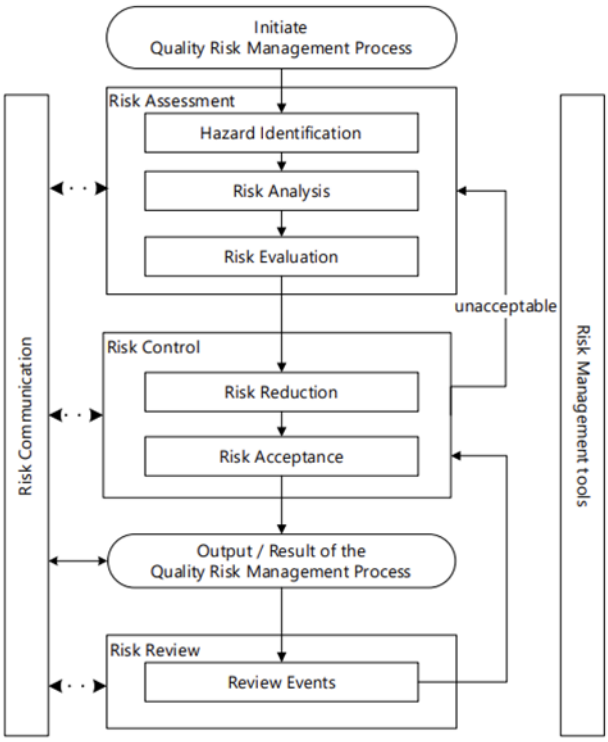

Figure 1: ICH Q9 Risk Management Tool (International Conference on Harmonisation, 2023).

The identification and study of possible risks and adverse events caused by hazards are known as risk assessments. It also contains an assessment of the risk's severity and potential outcomes (Potter, 1996). ICH Q9 provides examples of various different methods that can be used to undertake risk assessments such as fault tree analysis and failure mode effects analysis (International Conference on Harmonisation, 2023). Xing & Amari (2008) explain the difference between different types of risk assessment methods. Inductive system analysis is a method in which risks are targeted and it is assessed as to how this risk can impact the system and cause an adverse event. An example of this is failure mode effects analysis (FMEA). Deductive system analysis is a method in which a possible adverse event is first targeted and potential risks and causes for this are deduced after. An example of this is fault tree analysis (FTA).

Fault tree analysis (FTA) is described by Kritzinger (2017) as a 'top-down analysis'. This is another way of describing it as deductive as it focuses on the main adverse event initially before working down to each individual risk. A potential process flow for fault tree analysis as created by Kritzinger (2017) is shown in Figure 2.

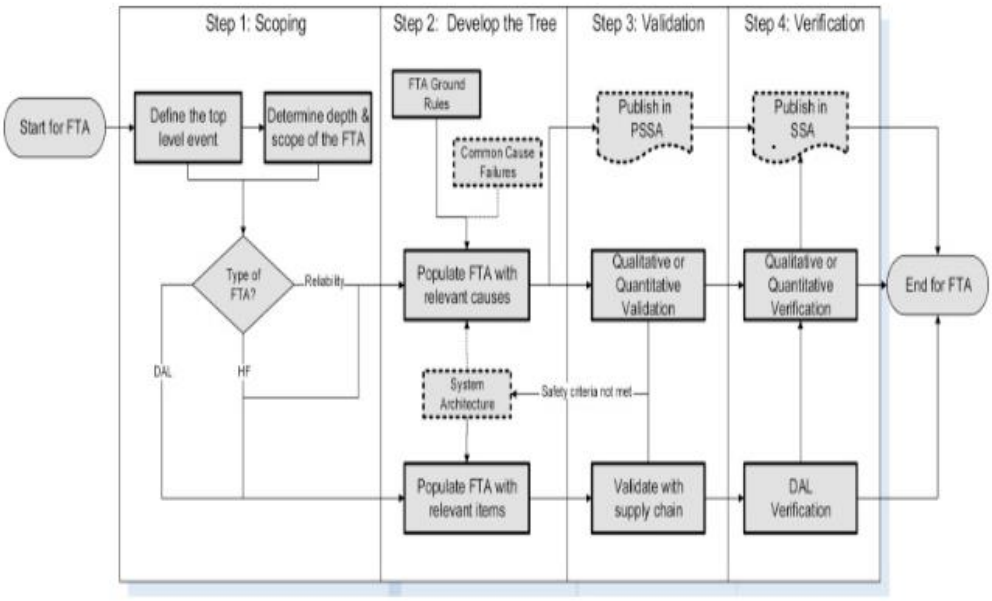

Figure 2: Process control for fault tree analysis (Kritzinger, 2017).

Failure mode effects analysis (FMEA) is defined by McDermott et al. (2017) as a system used to prevent issues with products and their product before they happen. They go on to explain that it is used to enhance the safety of consumers and prevent product defects. Although this method has been shown to be effective, it has also been shown to use a lot of resources (Chiozza & Ponzetti, 2009). Failure mode effects analysis starts with the selection of the process to be studied. It is then necessary to create a team of multidisciplined members as this method of risk assessment requires team input. All the information for this process must then be collected and hazard analysis can begin. The first stage in hazard analysis is to identify failure modes for each phase of the process and then evaluate the probability and the impact of these failure modes. Each failure mode should then be ranked according to the severity, and then ranked again according to the probability. It is then required to identify the failure modes that strike the biggest concern. Once hazard analysis is complete, action measures should be produced and implemented in order to avoid these risks (Chiozza & Ponzetti, 2009).

Patient Safety

Mollah et al. (2013) argue that the pharmaceutical sector requires a comprehensive risk management strategy to ensure patient safety. To support this claim, Kesik-Brodacka (2017) suggests that implementing risk management practices can significantly reduce product risks to the patient. Furthermore, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) emphasizes that the primary concern when managing product quality and availability risks is patient safety (International Conference on Harmonisation, 2023). It is crucial to note that availability and supply issues of a drug can have severe implications on patient care and safety, as pointed out by Phuong et al. (2019). When a drug is not readily available or is in short supply, patients may not receive treatment for their medical condition, or their treatment may be limited. In addition, Phuong et al. (2019) reveal that availability issues stem from a variety of factors, such as a shortage of raw materials, natural disasters, and regulatory compliance issues, among others. Therefore, a comprehensive risk management approach must be employed to ensure the continuity of patient care and safety in the pharmaceutical sector.

The Natpara parathyroid hormone injection is a current example of a drug with a supply issue that has shown the need for effective risk management strategies in the pharmaceutical industry. The Food and Drug Administration (FDA) has reported an availability issue with this injection due to recalls caused by errors with the packaging. The FDA website reveals that the rubber septum on the cartridge can cause the needle to become clogged. This causes concerns regarding the possibility of underdosing of the hormone, leading to hypocalcaemia (The Food and Drug Administration, 2019). It is apparent from this case that availability and supply issues of a drug can heavily impact patient care and safety.

To manage the risks associated with product availability concerns, Appendix II of ICH Q9 recommends utilizing product quality risk management tools to analyze the impact of these concerns and establish the relevant steps to be taken in such an event (International Conference on Harmonisation, 2023). The Natpara injection recalls have resulted in the FDA implementing a ‘Special Use Program,' which restricts the supply

of Natpara injection cartridges to only those patients facing severe consequences due to the shortage. Additionally, each cartridge must be used only once to avoid underdosing, as stated on the FDA website (The Food and Drug Administration, 2019). The development of this program may have been influenced by the guidelines provided in ICH Q9, which emphasize the need for effective risk management procedures to ensure the quality of packaging and reduce defects (International Conference on Harmonisation, 2023).

The ICH guidelines are now adopted as regulations by many regulatory bodies, including the FDA (The Food and Drug Administration, 2020). This regulation has ensured that a plan is in place for the occurrence of issues such as the Natpara injection recalls. Without proper risk management procedures in place, such a plan may not have been possible. Therefore, it is essential to understand the importance of implementing risk management strategies to mitigate the impact of potential supply issues in the pharmaceutical sector, as patient safety is a main concern when managing product quality and availability risks.

Ensuring patient safety in the pharmaceutical industry involves not only managing the availability of drugs, but also ensuring their quality throughout their entire lifecycle. As emphasized by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), managing product quality is a crucial element of patient safety (International Conference on Harmonisation, 2023). A recent example that highlights the importance of quality risk management is the recall of Teligent Pharma, Inc.'s lidocaine HCl topical solution (4%). This product failed quality testing due to its super potency, which could have potentially led to local anaesthetic systemic toxicity and cardiovascular toxicity symptoms such as bradycardia and cardiovascular collapse (The Food and Drug Administration, 2021).

The recall of Teligent Pharma's product demonstrates the possible impact of ICH Q9 on a company's quality risk management processes. According to the guidelines, quality risk management should be implemented throughout the entire lifecycle of a

product to ensure its quality (International Conference on Harmonisation, 2023). In this scenario, the company's post-distribution stability testing played a critical role in identifying the super potency issue and voluntarily recalling the product, thus mitigating the potential risks to patient safety.

The FDA's regulations on quality risk management have been essential in ensuring patient safety in the pharmaceutical industry. The adoption of ICH Q9 guidelines as regulations by many regulatory bodies, including the FDA, has provided a framework for pharmaceutical companies to manage risks associated with their products (The Food and Drug Administration, 2020). Without these regulations, companies may not have implemented risk management procedures or carried out stability testing, putting patient safety at risk. Therefore, the recall of Teligent Pharma's lidocaine HCl topical solution serves as a reminder of the importance of quality risk management in ensuring patient safety in the pharmaceutical industry.

Financial Benefits

Mollah et al. (2013) propose that risk management can be utilized as a means to enhance business performance within the pharmaceutical sector. It has been observed that pharmaceutical corporations face mounting financial pressures, stemming from the escalating expenses associated with drug development and production, as well as the challenges of maintaining product quality and keeping pace with rival companies. To address these challenges, many companies have implemented new, automated technologies to streamline their operations and improve process efficiency. However, this investment, combined with heightened competition within the industry and surging raw material prices, has resulted in reduced profit margins for pharmaceutical firms (Ilarraza Marzán, 2021). Thus, risk management may serve as a valuable tool for companies to optimize their business strategies and sustain long-term success within the pharmaceutical sector.

Quality risk management is widely considered as a crucial tool for businesses, offering a preventative approach rather than a reactive one (Milá Cáceres et al., 2010). This

approach has several advantages, including the efficient use of resources with less waste, reducing costs, and maximizing profits. The benefits of quality risk management can be applied to physical resources, such as reducing waste from products that fail to meet quality standards by identifying issues before manufacture, as well as other resources, such as employee time.

One of the key advantages of ICH Q9 is its ability to aid businesses in understanding the formality required for different risks and making decisions based on this information, as highlighted in Annex II (International Conference on Harmonisation, 2023). This knowledge enables businesses to allocate their resources more efficiently by focusing on high-risk concerns that require extensive intervention while avoiding investing in areas of low risk. This not only saves resources but also ensures that they are used more effectively.

In addition to resource efficiency, ICH Q9 Annex II emphasizes the role of quality risk management in increasing the flow of materials and personnel, which can further improve the effectiveness of the business processes (International Conference on Harmonisation, 2023). By increasing efficiency, companies can achieve a competitive advantage by producing high-quality products and delivering them in a timely and cost-effective manner. Therefore, the implementation of quality risk management can be regarded as a strategic decision that not only enhances product quality but also positively affects the company's overall performance.

Gustafsson (2000) has emphasized the importance of quality risk management in the decision-making process for research and development (R&D) projects, stating that early recognition and termination of initiatives likely to fail could result in significant cost savings for organizations. The International Conference on Harmonisation (ICH) Q9 guidelines can play a vital role in this regard, as they aim to enhance risk-based decision-making in various aspects of pharmaceutical manufacturing, including R&D (International Conference on Harmonisation, 2023). By utilizing ICH Q9's principles, businesses can evaluate the risks associated with R&D projects and determine

whether it is worthwhile to invest further resources into the project, thereby minimizing the risk of financial loss and potential harm to trial participants.

According to a study by DiMasi (2002), the economic benefits of early project termination cannot be overstated. The study showed that most clinical trials are terminated in phase III, but if only 5% of these trials were terminated earlier in phase I, clinical costs could be reduced by over $19 million. Hence, the application of ICH bQ9 guidelines in risk assessment and decision-making can lead to significant cost savings and resource optimization in the R&D phase of pharmaceutical manufacturing.

Conclusion

In conclusion, the significance of risk management and risk assessment in the biopharmaceutical sector cannot be overstated. Historical incidents such as the elixir sulfanilamide disaster of 1937 (Wax, 1995) and the thalidomide tragedy of the late 1950s (Kim & Scalli, 2011) have demonstrated the crucial role of risk assessment and risk management in protecting public health and safety. Furthermore, modern examples, such as the recall of the Natpara parathyroid injection (The Food and Drug Administration, 2019), have highlighted the need for ongoing and thorough risk assessments throughout the product life cycle.

To ensure that biopharmaceutical products meet the highest standards of quality, safety, and efficacy, the principles of risk management and risk assessment are embedded in regulatory guidance, such as ICH Q9 (International Conference on Harmonisation, 2023). The guidelines provide a systematic and proactive approach to identifying, evaluating, and mitigating risks throughout the product life cycle. Risk assessment tools such as FMEA and FTA to identify and mitigate potential risks are explained in the guidelines. FMEA is a systematic process for identifying, analyzing, and prioritizing potential failures and their effects, while FTA is a top-down approach for identifying the causes of a failure and its potential consequences (Xing & Amari, 2008). By applying ICH Q9 principles, biopharmaceutical companies can take a risk-

based approach to decision-making, allocate resources more effectively, and continually improve the quality of their products.

ICH guidelines have been implemented by regulatory bodies around the world due to their recognized potential in improving pharmaceutical quality and safety. This ensures that regulatory bodies can guarantee that pharmaceutical products are developed and manufactured, focusing on patient safety and efficacy. The FDA is one regulatory body that has implemented the ICH guidelines and encourages other countries to do so (The Food and Drug Administration, 2020).

In summary, the effective implementation of risk management and risk assessment in the biopharmaceutical sector is essential for maintaining public health and safety and ensuring the development of high-quality and effective products. Through the application of regulatory guidance such as ICH Q9, biopharmaceutical companies can establish a risk-based approach that prioritizes patient safety, promotes continuous improvement, and also maintain positive business outcomes in the highly competitive biopharmaceutical sector.

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