Mintage Journal of Pharmaceutical & Medical Sciences
REVIEW ARTICLE
ISSN 2320 –3315

RISK MANAGEMENT IN PHARMACEUTICALS

V. SIVA RAMA KRISHNA*, PRIYANKA SRIVASTAVA

Department of Quality Assurance, SVKM'S NMIMS School of Pharmacy & Technology Management, Shirpur, Dist. Dhule, Pin-425405, M.H, India.
Email: pebelvsrk.chowdary@gmail.com

Received -15-02-14; Reviewed and accepted -28-02-14

ABSTRACT

Objective: To review the risk in pharmaceutical industries and the risk management process and tools. There is risk always in anything we do. All the industries on this globe perform actions that involve risks; risk is only dangerous when there is no anticipation to manage it. Risks if assessed and controlled properly will benefit the industries against the fall and makes stronger. Risk should not be assessed as bad, but should assess as an opportunity for making things resilient by proper management. Risk management can benefit industries from disasters either natural or human. The impact of the risk should be assessed in order to plan alternatives and minimize the effect of the impact. Risk in pharmaceutical industry is very high because it involves research, money and health. The impact is severe and the probability of the risk is more often in pharmaceutical industry. A risk management plans and control measures will help the companies to do better at the time of uncertainties and create positive opportunities to turn those risks into benefits which maximize quality. Materials and Methods: The information was collected and compiled from scientific literature present in different databases and articles, books. Results: The risk management process and tools helps to minimize the risk and its effects. Conclusion: The risk management is at the core of any organization. Risk management should be part of organization culture. The risk management is a wise investment if properly processed.

Key words: Risk, Management, ICH Q9, uncertainty, Pharmaceutical Risks.

INTRODUCTION

The word Risk has been used since 1621 as risqué and later it has been spelled as Risk since 1655. What is risk? Risk as various definitions, as per The ISO 31000 (2009) /ISO Guide 73:2002 definition of risk is the 'effect of uncertainty on objectives'.

Effect

An effect can change or alter the result, goal, objective we need or expected. It might be positive or negative.

Objective

An objective is varied or differed. It can be financially, health, environment, production, process, organization, profits and sales objectives etc.

Uncertainty

Uncertainty is the state at which there is a partial or complete absence of information related to knowledge or understanding an event, its consequence, or likelihood.

That means we do not have clue about an event (a particular happening, occasion, occurrence) and what will be the outcome of that, a positive or negative result. Risk is always associated with things that are uncertain. There can be lot of examples to understand uncertainty, a sudden fire broke out from an industry, or loss of valuable resources in an accident, a natural calamities. All these are uncertain things where we got no idea when it happens.

But most common definition of the word "risk" is possibility of loss or injury.

Risks can be positive too, positive risks are risks that result in good things happening; sometimes called opportunities.

An organization can be of any type large, medium, small, profit and non–profit organizations; they all have certain objectives and goals. There is no organization is devoid of goal. While every organization when striving to reach their goals there are lots of factors that cause the deviation, or delay in reaching the desired goals.

Risk management in Pharmaceuticals [2]

Risk is associated in every single aspect in pharmaceuticals from development of a molecule to its way to the customer. We should be aware of important risks associated in Pharma.

- Regulatory risks – The stringent laws and rules made by regulatory bodies which change often, are very hard to keep up by the companies, which involves a lot of efforts.
- Human risks - Human errors, risks involved in shortage of skills, l oss of personnel.
- Financial risk – These risks involve in financial transactions, loans, uncertainty of a return, interests rate etc...
- Foreign exchange risk – Risks of exchange rates, economic conflict between countries.
- Market risk – This might be due to risks from stock, interest rates, commodity rates, even foreign exchange rates also affect the market.
- Political risk – This risks associated are due to change of governments, leaders.
- Area risk – Location of the business running, support of the public nearby.
- Natural hazard risk – Risks because of natural calamities which is danger for every type of business.
- External threats – Risks like loss of value due to competitors, substitutes in the market.
- Security Risk of security breach, loss of documents, data or any other value information. It might be either due to external or internal persons.

These are the risks mostly associated with Pharma industry. But pharmaceutical industries involve in making a product which is used or consumed by living creatures which is called as drug. So making of a drug is a complex process from research & development to its way out into the market. It is a risky journey. The uncertainty of risk associated is very high. To understand the various risks involved primarily the drug life cycle should be understood.

DRUG LIFE CYCLE

Discovery and Research [3]

The need to discover starts by understanding the basic of a disease, how it occurs and its effect on the body from cellular level to genetic level, every aspect should be clear. Then every known molecule or discovered molecule has been targeted to interact with the target and its effect of the molecule on the particular target will be known. The molecule may either work or may not on that particular target.

Drug Development

It involves developing the lead molecule or the most potent structure is constructed which is effective. After developing a lead molecule testing is done which is very much required by regulatory bodies in cellular level that is in cells (in vitro) and in animals (in vivo). By this the effects or the action of the drug is well known. A drug molecule is subjected to clinical trials which help to find out valuable information of the molecule or drug those are safety, efficacy, toxicity and various studies of pharmacodynamics and pharmacokinetic characteristics. These clinical trials involve testing drug on human volunteers.

Regulatory Review and Approval

After the clinical trials, the data or the results obtained in the clinical trials should be submitted to authorities e.g. FDA and national authorities. These authorities after a thorough inspection of the clinical data, safety, and efficacy of the drug molecule will then give approval to drug manufacturing.

Production and marketing

After the approval by the regulatory authorities the drug can be manufactured in large scale and marketed which involves time, money and efforts for developing the quality to the maximum. Later the post marketing surveillance is conducted which is called as phase 4 clinical trial. To know the effect of the drug after it has been marketed and used by the patients over large population and various regions.

Pharmaceutical world is growing rapidly and market is growing in terms of value and volume. The norms of the regulatory bodies make new challenges to the industry because laws in the pharma made by regulatory bodies are more stringent.

The uncertainty of risk levels in the research is high because we do not know whether the drug molecule is successful or not. It involves lot of time, money and has more prone to failure. The drug research is complex process and companies which are huge can face these problems than the small ones which are new and financially unstable with less experience in the research.

Patent is very much required for a drug in development and to get the rights to sell the developed drug for a time period. The company which has a patent on the drug molecule enjoys the monopoly pricing for a period of twenty years.

There is no need for a company to invent or formulate a new drug; it may also enter the generic market in which the drug prices of a generic drug are 30-90% less than the branded drugs. But the generic drugs can be manufactured only after a time period i.e. if a patent expires of the branded drug or filing an ANDA application which involves stringent regulations, and time driven actions to make and market the generic drugs.

After the research activities and developing a molecule which shows the sign of action are selected and its effect will be recorded or known by performing clinical trials. The trials involves on animals in laboratory and then on humans later. The clinical trial involves four phases.

Phase 1 It involves testing the drug on 20 – 80 volunteers to check the safety of the drug in the given dose level. If there are any abnormalities or unacceptable reactions that occur then the drug will be terminated. This means after the research of the drug for years investing time, money, and efforts if the drug molecule is working negatively than the required action it has been terminated, so the level of risk is high.

Phase 2 It involves testing the drug on more humans counting in hundreds (100 – 300). In this the drug efficacy along with effective dosage and administration frequency are analysed, if the results are not satisfactory, the drug is taken back to further development.

Phase 3 Thousands of patients are involved in phase 3, about 300 – 3000 patients are selected and testing is done. This phase is most expensive and time taking. Efficacy of the drug and drug-drug interactions, side effects, toxicity, plant design are also been studied, and every aspect should be documented and statistical data must be presented to regulatory bodies. At this phase of drug trials any unwanted action by the drug or any misrepresentation of data might put the company in trouble.

Phase 4 It is called as post marketing surveillance i.e. after approval of the drug to enter into the market. The safety surveillance is done that is called as pharmacovigilance. In which further drug – drug interactions, actions of drugs on pregnant women and long term adverse effects on large population and over the long time are collected. If there are any adverse reactions occurred over long time then the drug manufacturing is stopped and all the investment made is a loss.

The entire process from drug research to this point takes about 12 – 14 years and involves billions of us dollar. (Costing over 1 billion U.S $).

Out of approximately 5000 screened compounds only 250 goes for preclinical testing and 5 move to clinical testing and only one compound gets approval to manufacture and market.

The risk involved in clinical trials is the highest because humans are involved and lots of works (studies) are conducted and the probability of uncertainty is high. The molecule when shows undesired effect the whole project of drug development is terminated.

Then the manufacturing of the drug at industry scale is done, which involves the suppliers, raw materials, equipment - machines, technology, employees, teams, managers, shareholders and huge money investment. All these are called internal and external stake holders. External also involves consumers, public, political systems, etc...

So the personnel involved in pharma drug manufacturing should be skilled and qualified. The equipment should have required standards so that the quality of the product is never reduced. The quality is one of the most important assets and it is very much required because the drug designed has been administered by a human and any deteriorated quality will affect the people's health. **[4]**

Even the large companies may have lot of rigorous research going but will have very few products in the market which should cover the expenses of the research going and manufacturing of the current products.

Fraud is the most dangerous risk, which involves either own personnel or external person involving in stealing the data or the formulae and other important information which makes huge loss of efforts made and time spent.

The marketing and sales is a high priority in Pharma, which involves post surveillance and making sales effective by sales force, who focus on primarily the doctor and the pharmacists.

These sales people who are known as Pharma marketers require scientific knowledge about the product with more of communication and interpersonal skills because they need to sell the product or should make a doctor to prescribe it to a patient. Risk involved here is skilled and proper knowledgeable personnel should be employed and trained well, if not competitors product might be prescribed by the doctor and loss of sales may occur, a proper relationship should be maintained with doctor.

As in every industry the risk of natural calamities is often, the Pharma industry is also prone to it when proper measures are not taken against fire, earthquake, floods, rains, etc...

Always a contingency plan should be present and made with past experiences and expert references.

Risk management plan

A risk management plan helps to find out the possible risks involved in every aspect of research, development, manufacture and marketing.

- What are the risks?
- When might they occur at which phase?

- Who is at risk?
- What might be the loss due to the risk?
- Are they avoidable?

So first the root cause of the risk should be known, then the probability of occurrence and its impact is figured and this helps to reduce the loss level to acceptable level.

The Risk Management Strategy gives an idea in which risks and issues will be figured. How risks and issues will be raised, analysed, reviewed, communicated, and escalated.

Risk management process: [5, 6]

The process of Risk management involves four phases.

- Mitigation
- Preparedness
- Response
- Recovery

Mitigation

Mitigation efforts attempt to prevent hazards from developing into disasters, or to reduce the adverse impact of disasters when they occur. The mitigation phase differs from the other phases because it focuses on the long-term measures for reducing or eliminating risk. The implementation of mitigation strategies can also be considered a part of the recovery process if applied after a disaster occurs. However, even if applied as part of recovery efforts, actions that reduce or eliminate risk over time are considered mitigation efforts.

A fore running activity to the mitigation is the better identification of risks. Identifying and evaluating hazard is a physical process. In risk assessment, various hazards within a given area are identified. Mitigation measures can be any kind structural or nonstructural. Structural measures use technological solutions while non-structural measures include legislation, land use planning and insurance. Mitigation is the most cost efficient process to reduce the impact or of hazards. However, mitigation is not always suitable and structural mitigation in particular may have adverse effects on ecosystem. Mitigation provides the regulations regarding evacuations and sanctions against those who break the rules. If there is higher risk, then mitigation should be higher to slow down the severity, seriousness or painfulness.

Preparedness

An efficient preparedness measure is to create an Emergency Operations Center (EOC).

Common preparedness measures include the following:

- Communication plans having terminology and methods that can be understood easily.
- Development and practice of multi-agency coordination and incident command.
- Proper maintenance and training of emergency services, including mass human resources such as community emergency response teams.
- Development and exercise of emergency population warning methods combined with emergency shelters and evacuation plans.
- Inventory, stockpiling and maintenance of supplies and equipment.
- Developing organizations of trained volunteers from amongst civilian populations. Professional emergency workers are immediately overwhelmed in mass emergencies, trained, organized and responsible volunteers can be extremely valuable. Another is the Red Cross. If volunteers are organized, trained in the incident command system, and agree to mobilize, it may go a long way in the mitigating hazards as has been demonstrated by experience of Emergency Response Teams such as in the Red Cross etc,
- Casualty prediction to forecast casualties and injuries or deaths arising out of a given kind of event. This gives planners and administrators an idea of size and package of resources needed to be made available to respond to a particular kind of event.

Response & Recovery

In the recovery phase, an attempt is made to restore the affected area to its original state. It differs from the response phase in its focus; recovery should be started as soon as possible after the emergency needs have been addressed. Recovery efforts are primarily concerned with actions that involve reconstruction of destroyed property may be some reemployment and bring purchase of infrastructure. An important aspect of effective recovery efforts is taking advantage of a 'window of opportunity' to take measures that might be otherwise unpopular. The citizens or public who has affected from the disaster are likely to accept the mitigation changes if the wound of disaster is still ripe.

Preventing chemical disasters [7]

In 1987 the global chemical industry launched a voluntary initiative, Responsible Care, committing chemical companies to achieve frequent improvements in environmental, health and safety performance beyond or more levels of regulations required by the local or international regulations.

The chemical industry, in countries such as Japan, Mexico, Canada, China and Thailand has also set up emergency networks. Every major region and country has developed and adapted its own system, following ICE and CHEMTREC guidelines.

Chemical companies are complementing emergency networks with their own schemes and systems. Most chemical companies provide their deliveries with safety data sheets, emergency procedures and emergency labels, under the supervision of technical agencies.

Companies may also offer direct assistance and support to disaster victims, by funding recovery activities, helping implement conservation and emergency preparedness plans, and offering medical care to victims and their families. Experience at the organization and association has made us to formulate our own references on how great we can use international resources in the disaster prevention and how public-private partnerships may reduce impacts over the hazards. We must create a case or brief bag of disaster reduction actions compiling best practice and lessons learned from previous disasters, and an archive or classification of technologies for disaster reduction. The chemical industry should have well developed codes, translated into several other languages and adapt to the different environments in which we operate the organization.

After all we must enroot, establish and enhance early warning systems still the most severe aspect of risk reduction or attrition. We need to create suitable technical instruments, constantly monitored and improved by network of professionals. The lack of suitable early-warning systems is the key obstacle to prevention, allowing accidents to develop into fully-fledged disasters.

Risk management methods and tools are very important to find the risk and minimize its impact: [8, 9, 10]

Basic risk management methods

These methods involve flowcharts, previous data, cause and effects diagrams.

FMEA (Failure Mode Effect Analysis) – Potential tool for evaluation of processes failures and its impact on the product. It helps to find out important failures and its impact. It can be used for analysing the equipment or machines involved in process of manufacturing the product.

FMECA (failure modes, effects, and critical analysis) – This model is helpful to find out the occurrence; degree of severity can be measured. It is helpful in finding out the risks and their impact in manufacturing process.

Fault tree analysis This model shares the idea of tree or a chain which shows the failure (single failure) and reason for the failure

with one or more reasons involved for the cause of failure. It is helpful to find out the root cause of the failure.

HACCP (Hazard analysis critical control point) – This is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a framed approach that employs technical and scientific principles to analyze, evaluate, prevent, and control the risks and cause of risks from manufacturing process, product and marketing. HACCP consists of the following seven steps: Determine the critical control points

- Inculcate the critical limits
- Authorize a team to monitor the critical control points.
- Monitor and control is required when there is deviation.
- Set up system to verify that the HACCP system is working effectively.
- A record-keeping system to note down the process in employed.

CONCLUSION

Risk is present at every level in the industry and any type of the industry is associated with risk. The probability of uncertainty are may be high or low. Risks may be negative or positive (which are assumed as opportunities). Proper approach to manage the risk is very important and it cannot be done alone by a single individual. This is a team approach and followed by every individual. Everyone has a part to play and which involves assessing, evaluating, and implementing the strategies. The risk management is at the core of any organization. Risk management should be part of organization culture. Risk cannot be avoided but it can be turned to our advantage and make organization more resilient in coming future. As Pharma sector or industry is involved more in innovation, research and development the probability of uncertainty is very high and risk involved can cause huge loss of time, money, and efforts. Proper risk management methods and tools are required to assess and evaluate the risks. By evaluation, serious risks with severe impact can be found and solutions or measures are implemented to reduce the impact of risks. The risks measures implemented are properly monitored and controlled so that to assure all things are going according to the plan. The risk management is a wise investment if properly processed.

REFERENCES

1. Brooks. S, Creek More .R, Definitions of Risk. December, 2008.
2. Edward Griffith, Risk Management for the Pharmaceutical Industry. March 2004.
3. Risk management in pharmaceuticals and life sciences industry. KMPG. The Economist. June 2009.
4. Risk management in drug development projects. Helsinki University of technology laboratory of industrial management, report 2004.
5. http://www.theirm.org/ (Accessed on 25-08-2013).
6. Heinz-Peter Berg, Risk Management: Procedures, Methods and Experiences. (1) 2010.
7. Frank, Quality Risk Management Principles and Industry Case Studies.
8. Guidance for industry. Quality risk management. Q 9. ICH. June 2006.
9. Pharmaceutical R&D: Costs, Risks, and Rewards, February 1993.
10. Guidance for industry. Pharmaceutical quality system Q 10. ICH. April 2010.
11. Simon Mills, WHO Guideline on quality risk management. United Kingdom, August 2010.