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PHARMACEUTICAL RISK MANAGEMENT PLAN: A TOOL FOR PHARMACEUTICAL INDUSTRY

Ravindra Trivedi, Darshil Shah*, Dilip Maheshwari

Department of Quality Assurance and Pharm Regulatory Affairs, L.J Institute of Pharmacy, Ahmedabad

A Risk management plan is documented plan that describe adverse reaction and potential adverse reaction associated with the use of a drug and how they are being handled. The Risk management plan has to submit as part of core dossier with the application to regulatory authorities in the common technical modules by regulatory personnel of industry. Plan is handled differently from country to country. Regulated countries like United States, Japan and Australia have established risk management system as well which illustrates the increasing importance of introduction of risk management and specially risk minimization activities.

Key words: Pharmaceutical, Risk management plan, Pharmacovigilance, Risk management

INTRODUCTION [1][2]

Pharmacovigilance is the pharmacological science relating to collection, detection, assessment, monitoring and prevention of adverse effects with pharmaceutical products. Pharmacovigilance is derived from Greek word "Pharmakon" means Drug and "Vigilare" means to keep watch. Pharmacovigilance is mainly focuses on the adverse reaction of drug which are defined as any unintended or noxious response is occurring during the treatment.

HISTORY OF PHARMACOVIGILANCE [3]

In 1961 due to thalidomide disaster the first systematic efforts were initiated to address drug safety issue. At that time many thousands of congenitally deformed infants were born as the result of exposure in uterus to unsafe medicine promoted for use of pregnant mothers, after that in sixteenth world health assembly adopted resolution that reaffirmed the need of early action in regard to rapid dissemination of information on adverse drug reaction and led, later to creation of world health organization research project for international drug monitoring in 1968.

Address for correspondence

Mr. Darshil B. Shah
Assistant Professor,
Department of Quality Assurance and Pharm Regulatory Affairs, L.J Institute of Pharmacy, Ahmedabad
Email: darshilshah89@yahoo.com

From these beginning of emerged practice of Pharmacovigilance. Pharmacovigilance includes different types of adverse reaction reporting system such as spontaneous reporting, clinical trial reporting as well as expedited reporting, risk management, Medication errors, signal management, post authorization safety studies, Periodic safety update reports and incident management plan.

RISK MANAGEMENT [4]

Management is set of Pharmacovigilance activities and intervention designed to identify, characterize, prevent or minimize risk relating to medicinal products including the assessment of effectiveness of the effectiveness of those activities and intervention. Risk assessment means identifying and characterization the nature, frequency, and severity of the risk associated with the use of product. Risk minimization means minimizing product's risk while preserving its benefits. Risk management is discipline within Pharmacovigilance that is responsible for signal detection and the monitoring of risk benefit profile of drugs. A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the risk-benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial authorization is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole. The management of a single risk can be considered as

having four steps, risk detection, risk assessment, risk minimisation and risk communication which are summarized in table 1.

RISK MANAGEMENT PLAN [7] [8]

A Risk management plan is documented plan that describe adverse reaction and potential adverse reaction associated with the use of a drug and how they are being handled.

The document is required to submitted, in specific format, with all new market authorization requests.

In particular, pharmaceutical companies as well as regulatory authorities have placed increasing emphasis on how to detect, manage and communicate risk, as not everything is known about the safety of newly approved medicinal products because clinical trials are not able to detect rare drug induced adverse event at the time of approval.

As medicinal products are subject strict regulation throughout the product lifecycle, pharmaceutical companies have to provide evidence that their product is effective and safe.

So, during the past years, risk management plan has become an important tool for industry as well as for regulators.

The risk described in a risk management plan fall into one of three categories:

- Identified Risk
- Potential Risk
- Unknown Risk

Risk management plan represents a summary of safety profile, important identified risks, and important missing information concerning a medicinal product for human use and constitutes a regulatory instrument for dealing with anticipate risks of human medicinal products.

The Risk management plan has to submit as part of core dossier with the application to regulatory authorities in the common technical modules by regulatory personnel of industry.

A Risk management plan can be submitted as a stand-alone document with annexes at any time of the product life-cycle e.g. during pre-clinical testing, pre-approval clinical development or post approval, but specifically:

- For marketing Authorization for new chemical entity
- For marketing authorization for Biosimiliar
- For marketing authorization for a generic/ hybrid product
- For Marketing authorization paediatric
- For marketing authorization for new dosage form, indication or manufacturing change of a biological product
- At the request of regulatory authorities
- At the initiative of the marketing authorization holder
- On the demand during a scientific advice or pre submission meeting.

The main function of risk management plan is to improve Pharmacovigilance by identifying potential safety issue of human medicinal products, presenting how to reduce risk and consequently to increase the knowledge about human medicinal product concerned.

Creating a risk management plan is complex, challenging and cross functional process that focuses on evaluating safety issue identified during product development.

Objective of Risk management plan:

- Identify or characterize the safety profile of the medicinal products concerned;
- Indicate how to characterize further the safety profile of the medicinal product concerned;
- Document measure to prevent or minimize the risk associated with the medicinal product including an assessment of the effectiveness of those intervention;
- Document post authorization obligation that have been imposed as a condition of the marketing authorization.

Need of Risk management plan:

At the time of authorization, information on the safety of medicine is relatively limited. This is due to the limitation of clinical trials, including:

- Relatively small number of subject in clinical trials compared with intended treatment population
- Restricted population in terms of age, gender or ethnicity
- Restricted to co morbidity
- Restricted co medication
- Restricted condition of use
- Relatively short duration of exposure and follow up
- Statistical problem associated with assessing many different outcomes.

Development of Risk management plan includes following:

1. Safety Specification: It Includes the summary of Important identified risks, and important missing information, and addresses populations potentially at risk and outstanding safety questions.
   It also helps to identify needs for specific data collection and facilities construction of Pharmacovigilance plan.
2. Pharmacovigilance Plan: It includes Pharmacovigilance activities and action plans for each safety concerns.
   It proposes action to address identified safety concerns, complementing the procedure in place to detect safety signals.

Table1. Risk management Steps

DIFFERENT STEPS OF RISK MANAGEMENT		
Risk detection and Risk Assessment	Identify the risk	Preclinical Studies
		Harms identified in clinical trials and meta analysis
		Formal mortality and morbidity studies
	Understand the risk	Rigorous case identification
		Case series analysis
		Clear description in label
	Monitor the risk	Post Marketing Surveillance
		Database analysis
		Prospective cohort studies and registries
Risk minimization and communication	Communicate the risk	Limited Distribution
		Limited Prescribing list
		Contradiction for certain groups, indications, Route of administration
		Advice for high risk group
	Measure outcomes for intervention	

REGULATION OF RISK MANAGEMENT PLAN IN REGULATED COUNTRIES:

Risk management plan is handled differently from country to country. Not every authority requires formal Risk management plan. Other regulated countries like United States, Japan and Australia have established risk management system as well which illustrates the increasing importance of introduction of risk management and specially risk minimization activities.

Europe: [12] [14]

In the Europe, the concept of a risk management plan was formally crystallized in an amendment to Directive 2001/83/EC on the Community code relating to medicinal products for human use by Directive 2004/27/EC on the Community code relating to medicinal products for human use. The format of risk evaluation and mitigation strategy is mentioned in the Guideline on risk management systems for medicinal products for human use in 2005 and Guideline on good Pharmacovigilance practices Module V in 2014 with revise Addition.

United States [14] [15]

In the United states food and drug administration act was come in 2007.This act improve the safety of drug by providing FDA with post approval authority over medicinal products and biopharmaceuticals through new risk identification and communication strategies. The format of risk evaluation and mitigation strategy is mentioned in the "Guidance for industry format and content of proposed risk evaluation and mitigation strategies, REMS assessment and proposed REMS modification" dated on September 2009. This act gives authority to FDA to decide that REMS is necessary, as part of approval process.

Japan [16]

In Japan, a regulation under the Ministry of Health, Labour and Welfare ordinance introduced on 1stOctober 2007 as " Early Phase Post marketing vigilance (EPPV)" and it is serve as an example of an early post marketing risk management plan. Early Phase post marketing vigilance constitute one type of post marketing condition for new medicinal product and provides a strong basis for better risk and life cycle management. To prevent serious adverse reactions from occurring just after start of marketing, it is obligatory to conduct EPPV, Which is part of the conditional authorization, six month after launch of new medicinal product.

Australia [17]

Australian authority Therapeutic goods administration has formally adopted Europe guideline volume 9A. The requirement for a risk management plan begins on 1st April 2009.

Canada [18]

Health Canada appreciates the submission of a Europe Risk management plan as a proactive approach outlining action to prevent risks. Risk management activities include the creation of product label and monographs, and package inserts; establishing education for health care professionals and

patient and communicating new risks to health care professional and patients.

India [19]

In India Risk associated with pharmaceuticals is measured under the Pharmacovigilance programme.

Brazil [20]

In Brazil Risk management and Pharmacovigilance plan is passed in accordance with RESOLUTION – RDC no. 4, dated 10/Feb/09 (DOU 11/Feb/09): Provides for Pharmacovigilance norms for the holders of marketing authorization for medical drugs for human use under regulatory guideline of Pharmacovigilance Plan and Risk Minimization Plan PVP/RMP in 2009.

CONCLUSION:

Risk management plan is now a day important tool throughout the life cycle of product to minimize the risk during the manufacturing. So, in regulated countries, regulatory authorities mandate to submit risk management plan.

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