

## Risk Management Plan Its Importance and Emphasys on Pharmacovigilance Activities

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### Introduction

Risk is probability of harm being caused. Risks related to the medicinal products may be any risk relating to quality, safety or efficacy of medicinal product as regards to patient's health or public health and any risk of undesirable effect on environment. Risk management system is a series of pharmacological activities for identification of risk, its assessment, minimization or prevention and its communication [1,2]. Risk management plan (RMP) is the complete description of risk management system. Main aim of RMP is to ensure safety of the patient using the drug. RMP's are required to be submitted during the authorization of a drug. An updated RMP should now be submitted at the request of the national competent authority, whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the risk-benefit balance or as a result of an important pharmacovigilance or risk minimization milestone being reached.

### Risk management plan: steps involved

Risk management plan includes following steps:

**Safety Specifications:** It summarizes on important identified risks, important potential risks, and missing information due to limitations of clinical trials. It helps to identify needs for data collection and helps in the construction of pharmacovigilance plan [3].

**Pharmacovigilance plan:** It describes about routine and additional pharmacovigilance activities and action plan for each safety concern. Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety Specification whether the studies are intended to identify and characterise risks, or to assess the effectiveness of risk minimization activities.

**Evaluation of need for risk minimization activities:** This is to evaluate whether risk minimization strategies are needed beyond the pharmacovigilance action plans.

**Risk minimization plans:** It lists safety concerns for which risk minimization activities are proposed. These may include either routine risk minimization measures or additional risk minimization measures and assessment of their effectiveness. Routine risk minimization methods include summary of product characteristics (SmPC), labeling, restricted and special medical prescriptions. Additional risk minimization methods include education training material or training programs for medical practitioners, pharmacists and patients and restricted access. This could at least theoretically help to improve risk communication [4-6] and consequently could reduce harm caused by new drugs. It is important that intended safety information should reach health care practitioners, pharmacists and consumers with in adequate time frame if it is not so then the whole risk management system and pharmacovigilance are at vain. These additional risk minimization measures should be performed or implemented only when they are essential for safe and effective use of medicines but not to be combined with marketing programs.

### Role of risk management plan for drug safety in actual world:

Medicinal products are given authorization on the basis that, the risk-benefit balance is judged to be positive for the target population at the time of authorization. They appear to be safe and well tolerated but safety in actual world is unclear as there are many limitations [7] during clinical trials as medicinal products are studied in homogeneous population in limited number in ideal conditions and with limitations in terms of age, sex, race and ethnicity; co-morbidity, restricted co-medication, relatively short duration of study and follow up and the marketed drug addresses huge population and relatively longtime exposure. Thus risk management plan plays a vital role in both pre and post approval of drug [2].

Risk Management Plan (RMP), Risk Evaluation and Mitigation Strategy (REMS) are now a standard part of planning pharmacovigilance in EU and USA respectively [5]. The concept of both the RMP and the REMS is to minimize risks related to a medicinal product through interventions and to communicate those risks to patients and healthcare providers.

Risk management plan addresses routine pharmacovigilance activities and also additional pharmacovigilance activities to reinforce routine pharmacovigilance activities if necessary.

### Importance of additional pharmacovigilance activities

It is the responsibility of market authorization holders to consider the situations when additional pharmacovigilance activities are needed. These additional Pharmacovigilance activities may be either non-clinical studies, clinical trials or non-interventional studies. For example, a medicinal product which is intended for long term use may only have relatively short term follow up data at the time of authorization. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is ambiguous preclinical data, e.g. carcinogenicity in only one species, may also require long term follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another criteria when additional pharmacovigilance activities should be considered, is when a potential risk with an individual medicinal product has a significant background incidence in the target

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population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the normal incidence. Whenever doubt exists for requirement of additional pharmacovigilance activity then competent authority should be considered.

Adverse reactions need not present immediately after the release of a new drug onto the market there is every possibility that they might occur even decades after the drug was first prescribed. Although it is expected that through combination of premarketing clinical trials and post marketing spontaneous reporting, safety concerns could be expected to be resolved within several years of a new drug being placed onto the market, it is not so.

There have been several well established drugs which have provoked reactions following a latency period of years or even decades. Due to time elapse and many devious issues such reactions are more difficult to detect, whereas those with a short latency period are likely to detect easily. However, this does not mean that detecting those reactions with a longer latency period is impossible. There have been some such cases where drug safety conclusions have been reached even though the adverse reactions rather than affecting patients, have affected their children and grandchildren.

Epidemiologic studies may prove to be very important in detecting drug safety problems even many years after the medicinal products have been launched. **Diethylstilbestrol (DES)** is a synthetic non-steroidal estrogen that was first synthesized in 1938. It was prescribed to women as an estrogen intended to prevent pregnancy related risks and miscarriage in USA. It was not until 1970 that suspicions were raised over a series of cases of a rare vaginal cancer (clear cell adenocarcinoma). This disease is associated with patients in their seventies but was being diagnosed in patients aged between 14 and 22 years old. A case control study finally confirmed the suspicion in 1971, some thirty years after the drug was placed onto the market that the cancer was associated with exposure of the embryo to stilbestrol taken by the mother. It was also later found that there were other serious problems associated with intake of the drug, including malformations of the cervix and uterus; decreased fertility; ectopic pregnancies; and higher incidences of spontaneous abortions and preterm births.

It is difficult to detect adverse reactions that just represent an increase in frequency over the "normal" incidence of a disease. For

example, if a medicine's side effect is that it causes heart attacks but is used mostly in an elderly population for example for treating arthritis, it could be difficult to distinguish what is caused by the drug from what would be expected to occur anyway in these patients without the drug. This is the situation with rofecoxib (Vioxx) [4] -a Nonsteroidal Anti-Inflammatory Drug (NSAID) that has now been withdrawn over safety concerns. It was marketed to treat osteoarthritis, acute pain conditions, and dysmenorrhea. Rofecoxib was approved by the Food and Drug Administration (FDA) on May 20, 1999. It gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. On September 30, 2004, it was withdrawn from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. Thus pharmacovigilance activities play a vital role in drug safety.

## Conclusion

Pharmacovigilance and Risk management plan are life time processes they do not stop once a drug released or well established in the market for any number of years, nor when a patent simply dies. Every medicine available needs to be constantly monitored by drug safety systems supported by services that are comprehensive, legally compliant and effective at every stage of the drug's life cycle.

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