# PHARMACOVIGILANCE-AN EMERGENCE

**A Case Study By Dr Deven V Parmar[1] and Dr. Dharani Munirathinam[2], USA**
*([1]Faculty at Fellow American College Of Clinical Pharmacology*
*[2]Pharmacovigilance consultant, ACCP Member)*
*Email:- gokul.dharani@gmail.com*

## INTRODUCTION

Pharmacovigilance (PV), defined by the world health organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Emergence of PV activities and the awareness would play a vital role in ensuring that doctors, healthcare professional, together with the patient, have enough information to make an educated decision when it comes to choosing a drug for treatment and eventually achieving the patient safety in large.

## HISTORY OF PHARMACOVIGILANCE

In the early days of drug development there were no regulations monitoring the quality, efficacy and safety of drugs. In the late 1950 and early 1960it became evident that drugs were not only treating diseases but had a negative impact. Adverse drug reactions (ADRs) were acknowledged as a problem related to drug use, following the thalidomide disaster, authorities all over the world began to set up systems in order to monitor the safety of drugs. These spontaneous reporting systems were based on the collection of reports of ADRs from healthcare professionals. The WHO recognized the need for global drug monitoring, and in 1968 the WHO Pilot Research Project for International Drug Monitoring started its operation with 10 participating countries, to develop a system for the detection adverse effects of drugs.[1-4]

## PHARMACOVIGILANCE PROCESSES

The PV activities can be roughly divided into three groups: regulatory, industry, and academia. The PV process includes an ongoing continuous reporting process called as the Individual case safety reporting (ICSR) and Aggregate reporting.

In the ICSR process cases are reported from sources that include spontaneous, clinical trials and literature. However, spontaneous reporting of ADRs by physicians and pharmacists has been the backbone of data collection in PV and has proven its value in detecting relatively rare and serious ADRs. Within the new legislation, spontaneous reporting will continue to play an

important role and the range of possible reporters will be expanded by including patients. Spontaneous reporting systems focus on detecting signals of new ADRs and it has proven its strength in detecting previously unknown harm. It has also met criticism; under-reporting and its inability to quantify adverse drug reactions are most often mentioned. The field of drug safety has been receiving a great deal of attention lately.

Now with the new regulations the aggregate reporting structure is evolving from reactive mode to the pro active mode of ADRs reporting and analysis. The cases reported through the ICSR are further analyzed in depth and reported through many reports that include Periodic Safety Update Reports, Periodic Benefit Risk Evaluation Report, Safety Summary Report, and Clinical Overview for the initiation of any changes to the labels for the EU. PADER is the report predominantly submitted for the US FDA. A Developmental Safety Update Report is required to be submitted for the drugs in the late clinical trials and early post marketing phase. In the Aggregate reporting the newer regulation insists on Risk Management Plan by the EU and Risk Evaluation and Mitigation Strategy Report by the US FDA. [6-10]

## PHARMACOVIGILANCE EVOLUTION

The withdrawal of rofecoxib directed renewed attention to drug safety. The decision to withdraw rofecoxib was made after the safety monitoring board of the APPROVE trial found an increased risk of cardiovascular (CV) events in patients treated with rofecoxib compared to placebo. [5]

The events leading to the withdrawal of rofecoxib, and what have happened since the withdrawal, have been discussed in numerous papers. In the recent years after the withdrawal of rofecoxib in 2004, followed by the debate about the cardiovascular safety of rosiglitazone, which ultimately lead to the suspension of the marketing authorization of the drug in the European Union (EU). In the EU the evaluation of the PV system started in 2006, and lead to legislative changes, which were endorsed in September 2010 and has come into force in July 2012. To support the implementation of the new EU Pharmacovigilance legislation, the European Medicines Agency (EMA) is developing a new set of guidelines for the conduct of PV.

This new guidance on good pharmacovigilance practices (GVP) is organized in 16 different modules. With the new legislation a strengthening of post-authorisation regulation of medicines will be implemented, which has 2 key elements: one related to the process, where it is important that there are clear roles, responsibilities and obligations for the key responsible parties and the other related to the collection of high-quality data relevant to the safety of medicines and patient safety, which is a requirement for the prompt identification of potential risks. [6-9]

The FDA and the current system of post marketing surveillance were criticized. Firstly, the FDA uses only a limited number of data sources (clinical trials and spontaneous reporting) when it comes to assembling information on the safety of a drug. Secondly, the FDA has no control over the performance of post-marketing safety studies. The majority of post-marketing study commitments is never initiated, and the proportion of post-marketing safety studies (phase 4

studies) that were completed declined from 62% between 1970 and 1984 to 24% between 1998 and 2003.

Thirdly, the FDA has no authority to take direct legal action against companies that do not fulfill their post-marketing commitments. In response to the criticism, the Centre for Drug Administration (CDER) at the FDA asked the Institute of Medicine (IOM) to assess the US drug safety system. In September 2006, the IOM released the committee's findings and recommendations in a report 'The future of drug safety: promoting and protecting the health of the public'. The main message in this report is that the FDA needs to follow the safety of a drug during its whole life cycle. This life-cycle approach includes identifying safety signals, designing studies to confirm them, evaluating benefits as well as risks, using risk-benefit assessments to integrate study results and communicating key findings to patients and physicians.[6-10]

## DEVELOPMENTS

Pharmacovigilance and the methods used need to continue to develop in order to keep up with the demands of society. The Erice Declaration on transparency, which was published in 1997. In this declaration, PV experts from all over the world, representing different sectors, emphasize the role of communication in drug safety with the following statements:

• Drug safety information must serve the health of the public

• Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for health care providers

• All the evidence needed to assess and understand risks and benefits must be openly available

• Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all

• Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated.

It is believed that these factors will help risks and benefits to be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust. This declaration was followed in 2007 by the Erice Manifesto for global reform of the safety of medicines in patient care. The Erice Manifesto specifies the challenges which must be addressed to ensure the continuing development and usefulness of the science, in particular:

• The active involvement of patients and the public in the core debate about the risks and benefits of medicines, and in decisions about their own treatment and health

• The development of new ways of collecting, analyzing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it

• The pursuit of learning from other disciplines about how PV methods can be improved, alongside wide-ranging professional, official and public collaboration

• The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clinicians, patients and the general public, based on the demonstrable benefits of PV to public.[10,11]

In the past, PV has been most concerned with finding new ADRs, but *Waller and Evans* suggest that PV should be less focused on finding harm and more focused on extending knowledge of safety. In recent years, regulatory agencies have been reforming their systems in order to keep pace with the developments in PV, with the focus on being more pro-active. [17]

*EUROPE*

In 2005, a document was drafted by the Heads of the Medicines Agencies called 'Implementation of the Action Plan to Further Progress the European Risk Management Strategy'. In July 2007, the EMEA published a document in which they discussed the achievements booked to date. These achievements included the implementation of legal tools for monitoring the safety of medicines and for regulatory actions. Particular emphasis was placed on:

• Systematic implementation of risk management plans

• Strengthening the spontaneous reporting scheme through improvements of the Eudra-Vigilance database

•Launching the European Network of Centre's for Pharmacoepidemiology and Pharmacovigilance(ENCePP) project to strengthen the monitoring of medicinal products

• The conduct of multi-center post authorization safety studies

• Strengthening the organization and the operation of the EU PV system

In the course of the next 2 years, two main areas will be covered by the European Risk Management Strategy: further improving of the operation of the EU PV system and strengthening the science that underpins the safety monitoring for medicines for human use.

## METHODOLOGICAL DEVELOPMENTS

*TRANSPARENCY*

The Erice Declaration, as well as *Waller and Evans*, stated that transparency is important for the future of pharmacovigilance. In the last few years transparency around ADRS has increased. The registration of clinical trials will allow the necessary tracking of trials to ensure full and unbiased reporting for public benefit. A number of countries, including Canada (http://www.hc-sc.gc.ca), the Netherlands (http://www.lareb.nl) and the UK (http://www.mhra.gov.uk), have made their databases containing the data from the spontaneous reporting system freely available to the public. [10]

*CONDITIONAL APPROVAL*

Both the FDA report and the report from the EU described earlier emphasize that compliance by marketing authorization holders needs to be improved when it comes to additional post-marketing studies. A possible solution to this problem would be a time-limited conditional approval, which would place pressure on the manufacturers to conduct and report additional safety studies. Within the EU, the EMEA has introduced a conditional marketing authorization. The Committee for Medicinal Products for Human Use(CHMP) delivers a conditional marketing authorization for products where there is a specific patient need. Examples include products for seriously debilitating or life-threatening diseases, medicinal products to be used in emergency situations in response to public threats and products designated as orphan medicinal products. A conditional marketing authorization is granted in the absence of comprehensive clinical data referring to the safety and efficacy of the medicinal product. However, a number of criteria have to be met including:

1. A positive risk-benefit balance of the product

2. Likeliness that the applicant will be in a position to provide the comprehensive clinical data

3. Unmet medical needs being fulfilled

4. The benefit of the immediate availability of the medicinal product to public health outweighing the risk inherent in the absence of additional data.

Conditional marketing authorizations are valid for 1 year, on a renewable basis. The holder is required to complete ongoing studies or to conduct new studies with the objective of confirming that the risk-benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of PV data.

The authorization is not intended to remain conditional indefinitely. Rather, once the missing data are provided, it should be possible to replace it with a formal marketing authorization. The granting of a conditional marketing authorization will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product are generated, submitted, assessed and acted upon. [13-16]

*RISK MANAGEMENT PLANS*

Another step in a more pro-active post-marketing surveillance is the introduction of risk management plans (RMPs). Such RMPs are being set up in order to identify, characterize, prevent or minimize risk relating to medicinal products, including the assessment of the effectiveness of those interventions. A RMP may need to be submitted at any time in a product's life cycle, for example, during both the pre-authorization and post-authorization phases. A RMP is required for all new active substances, significant changes in established products (e.g. new form/route of administration), established products introduced to new populations, significant new indications or when an unexpected hazard is identified.

The EU RMP consists of 2 parts: the first part contains a 'safety specification and a PV plan' and the second part contains an evaluation of the need for risk minimization activities and, if necessary, a risk minimization plan. The safety specification contains a summary of what is known and what is not known about the safety of the product. This specification encompasses the important identified risk and any information and outstanding safety questions which warrant further investigation in order to refine the understanding of benefit-risk during the post-authorization period.

A risk minimization plan is only required in circumstances where the standard information provision, by means of a medicine's summary of product characteristics, is considered inadequate. Insufficient patient information leaflets or inadequate labeling of the medicine are additional reasons for drawing up a risk minimization plan. Where a risk minimization plan is considered necessary, both routine and additional activities are to be included. Some safety concerns may have more than one risk minimization activity, each of which should be evaluated for effectiveness.

Many RMPs have already been established; however, to date, no quantitative or qualitative reports have been released by the EMEA. Information to the public about RMPs has also been scarce. If RMPs are to take an important place in PV, they need to be made public and easily accessible to scientists, professionals and patients. [17-19]

## UPDATE: CHANGES TO RMPS

In August 2013, there were two important changes to RMPs in the EU.

## UPDATES TO RMPS

There is no longer an automatic requirement to update RMPs on a fixed-time basis. The Agency and the NCAs are now adopting a **risk-based approach** to RMP updates.

An updated RMP should now be submitted:

- at the request of the Agency or an NCA;
- 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 benefit-risk profile or as a result of an important PV or risk-minimization milestone being reached.

When justified by risk, the competent authority may still specify a date for submission of the next RMP as a condition of the marketing authorization in exceptional cases.

If the date for the submission of a periodic safety update report (PSUR) and the need to update a RMP coincide, both can be submitted at the same time.

## CHANGES TO 'IMPORTANT MISSING INFORMATION'

The word 'important' has been removed from the phrase **'important missing information'** within risk-management documents defining what constitutes a safety concern in an RMP.

Safety concerns are now classified as:

- important identified risks;
- important potential risks;
- missing information.

Previously, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E2E and all EU risk-management documents

used the terms 'important identified risks', 'important potential risks' and' important missing information' to define safety concerns in RMPs. [17-19]

## RISK EVALUATION AND MITIGATION STRATEGY

The US FDA requests for a report similar to the EU RMP called the Risk Evaluation and Mitigation Strategy (REMS). In 2007, a new law that gave FDA many new authorities and responsibilities to enhance drug safety was enacted. It's called the Food and Drug Administration Amendments Act- sometimes called "FDAAA"- and one of its provisions gave FDA the authority to require a Risk Evaluation and Mitigation Strategy-(REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

A REMs may be required by the FDA as part of the approval of a new product, or for an approved product when new safety information arises. Essentially, a REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use.

Since medicines are very different from each other, each REMS for each medicine is also different.

This presentation discussed REMS and how they are used to help ensure that the benefits of certain medicines continue to outweigh their risks. [20]

## FUTURE PERSPECTIVES

On a regulatory level, progress has been made during the past few years. However, the results of these changes have yet to become apparent and, therefore, it has not yet been proven if these developments have contributed to better PV conduct. In order to further prove PV as a science, it is essential that academia develops new methods which can strengthen the current system.

Pharmacovigilance as we know it today has been about detecting new ADRs and, if necessary, taking regulatory actions needed to protect public health, for example, by changing the summary of product characteristics (SPCs) or withdrawing the drug from the market. Little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process of whether of not to use a drug. The gathering and communication of this information is an important goal of PV. [21]

## PHARMACOVIGILANCE AWARENESS

*Involvement of patients*

Another important development is the recognition of the patient as an important player in PV. Patients are the users of drugs, and it is their use of a drug in a safe manner that is the ultimate goal of PV activities. In an increasing number of countries patients are now allowed to report ADRs to the spontaneous reporting system. The EU and US FDA acknowledge the role of the patient in spontaneous reporting. [21]

## PHARMACOVIGILANCE IN INDIA

In India there was never a compulsion to have a strong PV system to detect adverse reactions of the marketed drugs. However, the increased interest of Indian regulatory authority in PV is clearly reflected by several instances including the amendment of Schedule Y, organizing several seminars, and training programs with WHO and several press releases from DCGI from time to time stressing the importance of a strong PV system in India, including the recent press release announcing the setting up of an independent PV team to review the safety of the anti-diabetic drug rosiglitazone.

Thus, the pharmaceutical companies who have been marketing generic drugs in India are now faced with greater regulatory reinforcement and increased accountability demands for ensuring a favorable benefit-risk balance of their products are required to take a more active approach to PV. This includes monitoring and reporting of spontaneous adverse reactions, submission of PSURs, conducting the risk-benefit analysis of new drugs, and relevant communications. For the companies conducting clinical trials in India, the regulatory timelines for reporting and the conditions for expedited reporting have been clearly defined.

## SCHEDULE Y

The legislative requirements of PV in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945. The Schedule Y also deals with regulations relating to pre-clinical and clinical studies for development of a new drug as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in India.

Schedule Y was thoroughly reviewed and its latest amendment, dated 20$^{th}$January 2005, indicates the continued commitment of DCGI to ensure adequate compliance of PV obligations of the pharmaceutical companies. In the amended Schedule Y, an attempt has been made to

better define the responsibilities of pharmaceutical companies for their marketed products as well as relating to the reporting of adverse events from clinical trials. The section entitled post-marketing surveillance includes the requirement for submission of periodic safety update reports (PSURs), PSUR cycle, template for PSUR, and the timelines and conditions for expedited reporting.

## NATIONAL PHARMACOVIGILANCE PROGRAM

This is a nation-wide program, sponsored and coordinated by the country′s Central Drugs Standards Control Organization (CDSCO) to established and manage a database of adverse drug reactions (ADRs) for making informed regulatory decisions regarding marketing authorization of drugs in India for ensuring safety of drugs. NPP sponsored by WHO and funded by World Bank became operational since January 2005.

The details of this program are beyond the scope of this article. Some of the major functions of this program include the monitoring of spontaneous ADRs, review of the PSURs submitted by the pharmaceutical companies and assessing the safety information so as to make appropriate recommendations on product label amendments, product withdrawals and suspension. NPP has its own form for spontaneous ADR reporting. The data elements of this form are almost similar to that of CIOMS form or MedWatch Form 3500A. The protocol of NPP provides guidance to healthcare professionals on completion of the spontaneous adverse event reporting form and describes the activities at various centers of PV.

As there is limited guidance available in Schedule Y as well as the protocol published by the NPP, it becomes imperative for the Indian pharmaceutical companies to consult the guidance documents available from International Conference of Harmonization, US FDA, and European Agency for the Evaluation of Medicinal Products (EMEA) so as to develop well laid down procedures for optimally meeting their PV obligations for NCEs as well as for the generic drugs [22-26].

## REFERENCES

1) Adis International. The Erice Manifesto: for global reform of the safety of medicines in patient care. Drug Saf 2007; 30:187-90.

2) Assessment of the European Community System of Pharmacovigilance. European Medicines Agency 2006. Available via http://www.cbg-meb.nl/NL/docs/nieuws/rapp-fraunhofer.pdf Accessed March 1, 2012.

3) Biswas P, Biswas AK. Setting standards for proactive pharmacovigilance in India. Indian J Pharmacol. 2007;39:124–8.

4) Chapter 6 of The SAFETY of MEDICINES IN PUBLIC HEALTH PROGRAMMES: Pharmacovigilance an essential tool. WHO book.

5) Coombes R. FDA tightens its grip on drug regulation. BMJ 2007; 334:290-1.

6) Directive 2010/84/EU. Official Journal of the European Union 2010, Dec 31,L. 348/74-99.

7) European Medicine Agency Updates on RMP: EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp

8) European Risk management Strategy: Achievements to date. European Medicines Agency 2007. Available via http://www.emea.europa.eu/pdfs/human/phv/30816707en.pdf Accessed Dec 18 2007.

9) Good Pharmacovigilance Practices. European medicines Agency 2012. Available via http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=#section1 Accessed March 1, 2012.

10) Heath G, Colburn WA. An evolution of drug development and clinical pharmacology during the 20th century. J ClinPharmacol 2000; 40:918-29.

11) Hugman B. The Ericedeclaration : the critical role of communication in drug safety. Drug Saf 2006; 29:91-3.

12) McBride WG. Thalidomide and congenital malformations. Lancet 1961; 2:1358.

13) McClellan M. Drug safety reform at the FDA-pendulum swing or systematic improvement? N EnglJ Med 2007; 356:1700-2.

14) Merck Announces Voluntary Worldwide Withdrawal of VIOXX. Merck & Co. 2004. Available via http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf Accessed March 1, 2012.

15) Nair MD. Pharmacovigilance: the need for a formal system in India. 2001. Available at the site of Pharmabiz www.pharmabiz.com http://www.pharmabiz.com/article/detnews.asp?articleid = 11329&sectionid = 46 .

16) Protocol for National Pharmacovigilance Program. 2004 Nov; CDSCO, Ministry of Health and Family Welfare, Government of India.

17) Raine JM. Risk management - a European Regulatory View. In: Mann R, Andrews E (eds) Pharmacovigilance.2nd edn 2007. Wiley, Chichester.

18) Regulation 1235/2010. Official Journal of the European Union 2010, Dec 31,L. 348/1-16.

19) REMS update and guidelines by FDA: Website http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf

20) Schedule Y. 2005 Jan; CDSCO, Ministry of Health and Family Welfare, Government of India.

21) Status Report on the Implementation of the European Risk management Strategy. European Medicines Agency 2007. Available via http://www.emea.europa.eu/pdfs/human/phv/16895407en.pdf Accessed Dec 18, 2007.

22) The Importance of Pharmacovigilance. WHO 2002. Available via http://apps.who.int/medicinedocs/en/d/Js4893e/1.html Accessed Jan 20, 2012.

23) VanGrootheest K. The dawn of pharmacovigilance: an historical perspective. Int J Pharm Med 2003; 17:195-200.

24) Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003; 12:17-29.

25) Whitworth DR. India's pharmacovigilance system to monitor adverse reactions of drugs. Available at the site of Regulatory Affairs Focus Magazine www.raps.org http://www.raps.org/s_raps/rafocus_article.asp?TRACKID = &CID = 61&DID = 26350 .

26) Zwillich T. US lawmakers tackle safety reforms at the FDA. Lancet 2007; 369:1989-90.