

Aditi Anand Apte

*Department of Pediatric Research,
KEM Hospital Research Centre, Pune,
Maharashtra, India*

Address for correspondence:

Dr. Aditi Anand Apte,
Department of Pediatric Research,
KEM Hospital Research Centre,
Rasta Peth, Pune - 411 011,
Maharashtra, India.
E-mail: dr.aditiapte@gmail.com

Abstract

Reporting of adverse events for marketed drugs: Need for strengthening safety database

Pharmacovigilance is an evolving discipline in the Indian context. However, there is limited regulatory guidance for adverse event reporting outside the purview of clinical trials. There are number of deficiencies in the framework for adverse event reporting from the perspective of pharma industry, health-care professional and general public due to which adverse events for marketed drugs are highly underreported. This article discusses the need to strengthen national safety database by promoting and mandating reporting of adverse events by all the stakeholders.

Key words: Adverse events, marketed drugs, pharmacovigilance

IMPORTANCE OF ADVERSE EVENT REPORTING

Adverse drug events are important causes of mortality and hospitalization worldwide.^[1] Adverse drug events decrease patients' quality of life^[2] and may reduce their confidence in the whole healthcare system. They also add to the total cost of health care and increase the number of undue investigations as they mimic a disease process.^[3] Collection of adverse events helps to generate a signal regarding any new adverse event associated with a drug and also judge the health risk associated with it depending on the severity and commonness of the adverse event.^[4] This may further lead to change in the reference safety information (contraindications, warnings, and precautions, use in special population) and depending upon its risk-benefit analysis, may also be responsible for withdrawal of a drug from the market. For example, withdrawal of rosiglitazone due to associated risk of hepatotoxicity.^[5] Thus, it is extremely important to increase awareness among

health-care professionals regarding diagnosis, prevention, and reporting of adverse drug events.

ADVERSE EVENTS AND DRUG DEVELOPMENT

Indian pharmaceutical industry is estimated to be worth \$4.5 billion and is growing at a rate of 8–9% annually.^[6] This includes the introduction of new chemical entities, biological products, vaccines, new dosage formulations, new routes of administration, and new uses of existing drugs. A drug during its evaluation in clinical trials is only exposed to few thousands of population excluding pregnant, lactating women, patients with hepatorenal dysfunction, patients with concomitant illnesses and medications. But once in the market, the drug is exposed to a large patient population with varied characteristics.^[7] Here, it becomes necessary to monitor the behavior of a

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Apte AA. Reporting of adverse events for marketed drugs: Need for strengthening safety database. *Perspect Clin Res* 2016;7:111-4.

Access this article online

Quick Response Code:



Website:

www.picronline.org

DOI:

10.4103/2229-3485.184781

new drug, as many uncommon and rare adverse drug events may come up in the postmarketing period.

PHARMACOVIGILANCE PROGRAMME OF INDIA

Although a formal adverse event monitoring system for reporting of adverse events was suggested for India in 1986, nothing much happened till 1997 when India joined World Health Organization adverse event monitoring program based in Uppsala, Sweden. A formal national pharmacovigilance program only started in India since January 2005 and was based on the hierarchy of peripheral, regional, and zonal centers for collection of adverse events that reported to Central Drug Standard Control Organization (CDSCO) and Uppsala Monitoring Centre. It was aimed to order to collect and analyze safety data regarding a drug, communicate associated risk to the practicing physicians and general public and arrive at regulatory intervention if necessary. Since 2010, the program has been reorganized as Pharmacovigilance Programme of India (PvPI) in collaboration with Indian Pharmacopoeia Commission, Gaziabad. The program directly subscribes to Vigibase database of the Uppsala Monitoring Centre, whereby every adverse event monitoring center can report an adverse event to the national coordinating center through Vigibase.^[8]

INDIAN REGULATIONS RELATING TO PHARMACOVIGILANCE

As per the recent amendments in Schedule Y, there is an obligation for expedited reporting of all serious and unexpected adverse events during a clinical trial to the regulatory authorities, sponsors, and ethics committees. As a part of postmarketing surveillance, all pharmaceutical companies are entitled to provide half yearly periodic safety update reports (PSURs) to Drug Controller General of India (DCGI) for initial 2 years after marketing of a new drug and thereafter yearly for another 2 years. Schedule Y also provides a structure for PSURs, which encompasses of line listing and narratives of adverse events reported to the manufacturer as well as from the published data. This also includes reports of postmarketing surveillance studies.^[8]

CHALLENGES FACED IN PHARMACOVIGILANCE OF MARKETED DRUGS

Underreporting of adverse events

The adverse events occurring for investigational new drugs are meticulously reported to regulatory bodies as per

Schedule Y^[8] and Indian good clinical practice guidelines.^[9] However, once marketed, pharmacovigilance for these drugs is dependent on the postmarketing surveillance studies carried out by the manufacturer and spontaneous reporting of adverse events by physicians.

Adverse drug events are estimated to be the fourth to sixth largest cause of death in the USA.^[1] As against this, in India, drug adverse effects are responsible for only 3.4% of the hospital admissions and 1.8% of deaths.^[10] These figures are disproportionate with the country's populations and indicate high underreporting of adverse events from all stakeholders. The possible underlying factors are a lack of knowledge and awareness about PvPI, lethargy, indifference, insecurity, complacency, workload, unwillingness to engage due to little personal benefit and lack of training and awareness.^[11]

Lack of clear regulatory guidance

In India, there are no obligations for expedited reporting of serious and unexpected adverse events of all marketed products to the regulatory authorities. Although CDSCO has provided a format for spontaneous adverse event reporting, there are no regulatory guidelines regarding aggregate reporting of spontaneous adverse events for all marketed products. Furthermore, Schedule Y does not specify rules for reporting of foreign adverse events from multinational clinical trials and adverse events from published data. Amendments in Schedule Y addressing the above issues are long awaited.

Challenges for marketing authorization holders

Due to the limited guidance provided by Schedule Y on continued pharmacovigilance of marketed drugs, marketing authorization holders in India comply with guidance documents from United States Food and Drug Agency, International Conference on Harmonisation and European Medicines Agency for pharmacovigilance-related responsibilities. This is also because many Indian multinational companies have their subsidiaries located in Europe and USA where there are clear regulatory requirements for reporting of foreign adverse events and adverse events from published literature. With increasing number of contract research organizations (CROs) in the field of pharmacovigilance having the licensed pharmacovigilance databases and call centers for reporting of adverse events, companies find it more convenient to delegate their pharmacovigilance responsibilities to these CROs. However, there is a lack of clear safety surveillance system by drug companies by which they can monitor all adverse events for their marketed drug products.

Pharmacovigilance infrastructure and quality of adverse events

The numbers of centers for collection of adverse events are inadequate in comparison with the large geographical

area and enormous patient population. There is no well-defined system (like yellow card system in the UK) for collection of adverse events by health care professionals and patients. Many of the adverse events reports may not provide adequate information about the adverse event (patient initials, age at onset of the reaction, reaction terms, date of onset of reactions, suspended medications, reporter information).^[12] Thus, many events may not qualify as adverse events and the data are lost unless extensive follow-up is done.

Lack of awareness amongst stakeholders

There is no conventional training on pharmacovigilance for medical or paramedical students. Health care professionals including doctors, nurses as well as pharmacists, especially from peripheral areas of India need to be educated as well as motivated regarding the importance of adverse event reporting and the process of adverse event reporting.^[11] This will increase the number of adverse event reports and the quality of adverse event reporting.

There is poor awareness in the general public regarding the adverse event reporting system and patients who actually experience the adverse events do not have access for reporting any adverse event.

Pharmacovigilance for alternative medicines

A large patient population in India is catered by alternative disciplines of medicines such as Ayurveda, Siddha, Unani, and Homeopathy. There is a wide misconception that medicines from these disciplines are without any adverse effects. There have been cases of serious drug interactions due to herbal and herbo-mineral medicines reported in the literature.^[13] Furthermore, there are reported instances, where the herbal medicines used for certain illness were intentionally adulterated with modern medicines such as steroids or oral hypoglycemic agents.^[14] It is important to extend the pharmacovigilance activities for monitoring of these alternative medicines so as to promote only safe and rational use of these drugs. Pharmacovigilance centers in major teaching hospitals should be equipped with facilities such as high-performance liquid chromatography and high-performance thin layer chromatography which can help in detection of any adulterants.

PROBABLE STRATEGIES FOR IMPROVEMENT

A good pharmacovigilance practice guideline should be developed in consultation with national as well as international expert bodies in pharmacovigilance. Risk management plans for important molecules should be

initiated by pharmaceutical companies in consultation with DCGI. Passive reporting of adverse events should be made mandatory not only for the pharma sector but also for all public as well as private hospitals, although this has been debatable as it may decrease the quality of reports.^[11] Extensive training of health care professionals and the inclusion of basic pharmacovigilance in all medical, as well as paramedical curriculums, will help in effective capturing of maximum adverse events. Apart from spontaneous reporting of adverse events, other active surveillance methods such as prescription event monitoring and maintenance of disease registries should be promoted and monitored by regulatory bodies. Pharmacovigilance inspections similar to regulatory inspections in clinical trials by regulatory bodies can help to keep a check on the pharmacovigilance activities.

NEW REFORMS IN THE FIELD OF PHARMACOVIGILANCE

Recent initiative by PvPI in organizing countrywide continued medical education and workshops in pharmacovigilance is a promising step ahead.^[15] Increasing number of medical colleges and public as well as private hospitals were expected to submit “Letter of Intent” to enroll in this program till the year 2015. The national coordinating center at Gaziabad also plans to provide training to all the enrolled centers and also publish medicines safety newsletters.^[16] A mobile app for adverse drug reaction reporting by health care professionals has been developed by National Co-ordinating Centre for PvPI in technical collaboration with NSCB Medical College, Jabalpur, which may significantly facilitate reporting of adverse events. In addition, provision of the PvPI – helpline number on the patient prescriptions is a useful model initiated by Indira Gandhi Institute of Medical Sciences, Patna which can be followed by others. Use of individual case study report completeness score and mandate for submission of adverse events in XML are few other developments.^[17]

CONCLUSION

Thus, it needs to be reinforced that pharmacovigilance is a responsibility of all including physician, nurse, pharmacist, drug company, and the regulator. Development of more solid programs, collaboration with private sector and increased awareness among all stakeholders can help us achieve a better pharmacovigilance system. Recently, there are promising new reforms in the field of pharmacovigilance which may improve the performance of passive adverse event reporting in near future.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
2. Sloat S, Boland J, Snowden JA, Ezaydi Y, Foster A, Gethin A, *et al.* Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: A cross-sectional prevalence study. *Support Care Cancer* 2015;23:671-8.
3. Kaushal R, Bates DW, Franz C, Soukup JR, Rothschild JM. Costs of adverse events in intensive care units. *Crit Care Med* 2007;35:2479-83.
4. Suke SG, Kosta P, Negi H. Role of pharmacovigilance in India: An overview. *Online J Public Health Inform* 2015;7:e223.
5. Cohen D. Rosiglitazone: What went wrong? *BMJ* 2010;341:c4848.
6. A Brief Report on Pharmaceutical Industry in India; March, 2012. Corporate Catalyst in India. Available from: http://www.cci.in/pdf/surveys_reports/Pharmaceutical-Industry-in-India.pdf. [Last accessed on 2016 Feb 27].
7. Suvama V. Phase IV of drug development. *Perspect Clin Res* 2010;1:57-60.
8. Schedule Y. Available from: http://www.cdsc.nic.in/html/D%26C_Rules_Schedule_Y.pdf. [Last accessed on 2016 Apr 26].
9. Indian Good Clinical Practice Guidelines. Available from: <http://www.cdsc.nic.in/html/GCP1.html>. [Last accessed on 2016 Apr 26].
10. Ahmad A, Patel I, Sanyal S, Balkrishnan R, Mohanta GP. A study on drug safety monitoring program in India. *Indian J Pharm Sci* 2014;76:379-86.
11. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India. *Indian J Pharmacol* 2015;47:65-71.
12. Suspected Adverse Drug Reaction Reporting Form. Available from: <http://www.ipc.nic.in/writereaddata/mainlinkFile/File416.pdf>. [Last accessed on 2016 Apr 27].
13. Cupp MJ. Herbal remedies: Adverse effects and drug interactions. *Am Fam Physician* 1999;59:1239-45.
14. Poornima B. Adulteration and substitution in herbal drugs: A critical analysis. *Int J Res Ayurveda Pharm* 2010;1:8-12.
15. Nationwide Training and Education Programmes/Conferences with PvPI Interest for the Year; 2016. Available from: <http://www.ipc.nic.in/showfile.asp?lid=483&EncHid>. [Last accessed on 2016 Apr 27].
16. Annual Achievements for the Year 2015-16 in Respect of Indian Pharmacopoeia Commission. Available from: <http://www.ipc.nic.in/showfile.asp?EncHid=&lid=518>. [Last dated on 2016 Apr 12].
17. Newsletter – Pharmacovigilance Programme of India. Available from: <http://www.ipc.nic.in/showfile.asp?lid=453&EncHid>. [Last accessed on 2016 Apr 27].