



REVIEW ARTICLE

Pharmacovigilance in generic Indian pharmaceutical industries - Need of the moment

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ARTICLE INFO ABSTRACT



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Introduction: The pharmacovigilance department is liable for monitoring the safety of medicines during clinical trials and normal clinical use. The necessity of the pharmacovigilance department is an utmost requirement for effective regulations of the drug approval process and conscious pre and post-approval vigilance of the undesired effects, especially in India.

Methods: In the light of the regulatory notification GSR 287(E) dated on 8th march 2016 by CDSCO, it has become clear that it is necessary to take measures to set up and improve the operation of the pharmacovigilance of medicinal products for human use in pharmaceutical companies.

Results: The regulators have also developed and posted Guidance document for marketing authorization holders (MAH) for Indian marketers and made clear that the MAH should be responsible for continuously monitoring the safety of its medicinal products for human use, for updating the health authorities of any changes related to the drug, and for ensuring that the product information is kept up-to-date. MAH should record all suspected adverse reactions occurring in the country, and which are brought to their attention spontaneously by the patients or their health care, or occurring in the context of the post-authorization study.

Conclusions: According to the Regulatory Guidance document, MAH is also responsible for the submission of the information on suspected adverse reactions of a newly approved drug or applicable product, in form of periodic safety update reports (PSURs), to the competent authorities.

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Introduction

The pharmacovigilance (PV) department is responsible for monitoring the safety of medicines in general clinical use and also during clinical trials, it is also known as the Drug

Safety department. The main aim of the pharmacovigilance department in the pharmaceutical industries to maintain the risk-benefit ratio of the drug and minimize the risk as much as possible (World Health



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Organization, 2002). According to the regulations of worldwide health agencies, pharmacovigilance units are meant to collect adverse events from all over the country or worldwide, that were caused or might have been caused by the use of company-specific drugs (World Health Organization, 2004). Definition of Adverse event (AE) is, any untoward medical occurrence in a patient or clinical investigation participant who was administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment, a serious adverse event (SAE) is an adverse event which results in any of the following

- Fatality
- Life-threatening
- Requires or prolongs hospitalization
- Permanent disability
- Congenital anomaly
- Birth defect

Medically serious condition (Indian Pharmacopoeia Commission, 2017).

An adverse drug reaction (ADR) is a noxious and unintended reaction to a medicinal product that will have a causal relationship with the drug. All ADR may be due to: Uses not complying with the wording marketing authorization: Unauthorized use of medication (off-label use), abuse, misuse, medication errors, overdose, and adverse reactions associated with occupational exposure (Indian Pharmacopoeia Commission, 2017). The PV Guidelines (Pharmacovigilance Guidance Document Module II) recommend tracking some "special situations": Pregnancy and breast-feeding (is necessary to follow the outcome of the pregnancy and the development of the new-born); pediatric population or older [(or populations provided for in Summary of Product Characteristics(SmPC))]; lack of therapeutic efficacy, a major failure of the product in the achievement of the pharmacological waiting for an approved indication (e.g., treatment failure, poor response, a patient does not respond to medication, no results with the drug, etc.) (Indian Pharmacopoeia Commission, 2017). A pharmaceutical company can achieve this either by in-house systems Pharmacovigilance system or can sign contractual arrangements with clinical research organizations specializing in pharmacovigilance function for meeting their pharmacovigilance obligations.

Relevant legislation

Many regulatory notifications have been published on the requirement of the Pharmacovigilance department-

Notifications

- GSR Notification no 287(E) dated 8th March 2016 emphasizes that all MAH shall have established PV System for ADR collections (Ministry of Health and Family Welfare, 2016).
- Section 28.2 of Schedule M, which mandate that the Companies holding manufacturing licenses supposed submit ADR reports
- Schedule D (II) section 2.18 mentions that the Importer of the drugs shall submit the detailed study reports
- GSR Notification no. 227 (E) – Fifth Schedule (New Drugs and Clinical Trial Rules)

Guidelines

- The Pharmacovigilance Guidance Document is placed on the regulatory website for the review of stakeholders and their comments (Basu et al., 2018).
- Draft Pharmacovigilance System Inspection, Guideline -2018

Components and capabilities of a complete Pharmacovigilance System

Based upon the aim and scope of pharmacovigilance, certain elements and capabilities are very essential to a fully functioning pharmacovigilance system as shown in **Figure 1.** (Gagnon et al., 2012). These include as follow:

- A qualified person for pharmacovigilance – Officer In-charge (PvOI) (India)
- Safety system (database) support
- Safety case processing and review
- Medical writing and aggregate reporting
- A sound quality management system including standard operating procedures (SOPs)
- Quality standards, metrics, and training
- Signal detection and risk analysis
- Global safety reporting

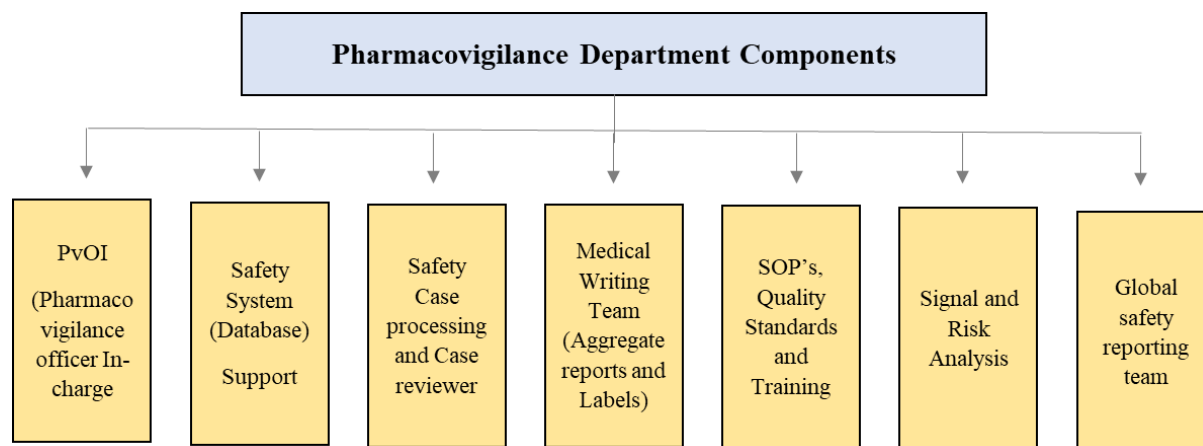


Figure 1: Schematic diagram of complete Pharmacovigilance system components

Pharmacovigilance Activities for the Generic Drugs in India

To meet the PV requirements in the country for its marketed products, as per regulations, a generic company in India is mainly required to carry out the following activities: Collection, monitoring, and reporting of spontaneous adverse event reports, including expedited reporting of serious unexpected adverse reactions and preparation of the PSURs if applicable (Arora *et al.*, 2008).

Pharmacovigilance officer-in charge (PvOI)

In compliance with Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules, 1945, and to ensure smooth functioning of pharmacovigilance activities to establish PV Department in the company, two qualified and trained persons should be authorized by the company management as PvOI and duty-in-charge with responsibilities for dealing Pharmacovigilance (PV) activities at the organization. Both can be either a medical officer or a pharmacist trained in the collection and analysis of ADR (Adverse Drug reactions) and also a duty-in-charge to work in the absence of PvOI (Singh GN, 2017).

Roles and responsibility of PvOI

PvOI should be responsible for the following –

- Development of the training modules in the departments.
- Identification of the PV activities and framing the SOP and the revision of the SOP.
- Establishment and maintenance of QMS of PV departments.
- PvOI should be available 24*7.
- PvOI should respond to the regulatory queries.

Sources of Adverse Event for a pharmaceutical company

Adverse event from the Business executives/Medical Representatives

Medical representatives are the link between the company and the HCPs. HCPs are the primary source for adverse events detection and through Medical representatives, they report AEs to the company. Hence medical representatives should be trained on the AE reporting process. They must know the importance of the PV in an organization. Also as per the regulatory authorities, their job description should include the collections of adverse events related to company products.

Robust adverse event and product quality complaint intake

As per the pharmacovigilance guidance document, the company must have a PV dedicated toll-free number and Email ID mention on the company website. These will help patients to directly report the adverse events and product quality complaints to the company. The intake of adverse events requires strict adherence to internal procedures, careful patient and HCP interaction. In medical information services, only a highly skilled and trained specialist would have the ability to discover and collect adverse events and product quality complaints.

Monitoring Social Media for Adverse Events

Social media has become a big platform for marketing and promoting platform. A new study shows that- More people report adverse events on Twitter than to FDA (Freifeld *et al.*, 2014). To monitor the direct reviews and comments on the products, social media accounts are very beneficial. Hence it's a company's responsibility to monitor social media platforms to collect adverse event data.

Solicited Reports

Solicited reports can be derived from the organized data collection system. Which include clinical trials, non-international study, registries, patient support program, etc.

Literature Reports

MAH should perform a literature review for their marketed products from the Electronic literature database. If any adverse event is found, should be reported.

Reporting of Adverse Events

Analyzed reports of adverse events should be submitted to the regulatory authority within the specific timeline. There are different timelines set by the Regulatory agency (Venkatraman *et al.*, 2017).

Serious unexpected – 15 Calendar days,

Non-serious Cases – 30 Calendar days,

PSUR - Every 6 months for the first two years, annually for the subsequent 2 years (Venkatraman *et al.*, 2017).

The report should be submitted to PvPI in XML file by Email or Mobile App and for CDSCO the report should be submitted in CIOMS form on a specific Email ID (Nautiyal *et al.*, 2017).

Agencies Involved in Pharmacovigilance & Clinical Research Regulation in India

Various Indian regulatory agencies and their roles in overseeing Pharmacovigilance & clinical trial along with the Ethics committee are shown in Table 1 (Suke *et al.*, 2015).

Table. 1. Various Indian regulatory agencies

Agencies	Roles of various Regulatory Agencies
Drug Controller General of India (DCGI)	Implementation of the National Pharmacovigilance
Central Drugs Standard Control Organization (CDSCO)	Operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend.
Department of Biotechnology (DBT)	Provides product evaluation and validation through support for limited and large-scale field trials for agriculture products and clinical trials for health care products.
Ministry of Environment & Forests (MOEF)	An autonomous body for the setting of standards for drugs, pharmaceuticals, and healthcare devices and technologies in India.
National Pharmacovigilance Advisory (NPAC)	Collates, analyses, and archives adverse drug Committee reaction data for creating a healthy environment for the regulatory authorities to analyze the drug to be marketed in India.
Indian Council of Medical Research (ICMR)	Brought out the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000 as the 'Ethical Guidelines for Biomedical Research on Human Subjects.
Ministry of Health and Family Welfare (MHFW)	An autonomous body for the setting of standards for drugs, pharmaceuticals, and healthcare devices and technologies in India.

The challenges of PV in India

One of the biggest challenges facing by the regulatory agencies is the gross underreporting of adverse events. There are many reasons for this, including, inadequate skilled resources in PV, lack of medical expertise in drug administration, and inadequate awareness of adverse event reporting. There are some other challenges as well, such as, infrastructure which is still conservative, the wide time interval between guidelines and laws, the orthodox attitude towards the new drug research, and Pharmacovigilance and regulatory inspections are almost non-existent. The system needs to be refined with the collaboration of PV Expert and IT. Since PV deals with

large numbers of adverse event reports, it would be wise for PV experts to collaborate with IT professionals to develop and build a robust system. Software programs and databases should be developed and they can be used for collection and analyzing the set of data, calculate trends of drug usage in various diseases, drug compliance, medication errors, and drug interactions. Since there is more clinical research and Pharmacovigilance outsourcing work now being conducted in India, it has been worthwhile for the Regulatory agencies to invest in a robust PV system (Khattri *et al.*, 2012). However, sometimes adverse events are not recognized by the HCP's on admission and it may be responsible for the death of patients. Furthermore, the financial cost of ADRs

to the healthcare system is also huge. (Kalantri *et al.*, 2003) When new medicines are launched in the market, without long-term safety studies, patients self-medication and switch from prescription-only medicines (POM) to over-the-counter (OTC) more widely these are the main reason for exposing themselves to Adverse events. In the earlier stage, India's regulatory agencies and drug companies based their safety assessments on experiences derived from long-term use (Grady *et al.*, 2005). In recent years, many Indian companies are increasing their investment in research and development and also enhancing the capacity to develop new drugs. Once a product is being marketed, new information will be generated, which may have an impact on the benefit-risk profile of the product. The detailed evaluation and analysis of the new information generated through Pharmacovigilance activities are important to ensure the safe use of the medicine. Hence, the Regulatory agency should take some tough decisions and make commitments to make PV mandatory and start the culture of PV inspections (Singh GN, 2017).

Good pharmacovigilance practice: Need of the hour

For a successful pharmacovigilance program, all the stakeholders e.g. doctors, nurses, pharmacists, HCP's, need to be aware of the reporting adverse drug reactions (ADRs). This is the main concern in India, where the awareness of reporting ADR is very poor (Yadav *et al.*, 2008) and lack of time, training has been accounted for underreporting of ADRs amongst physicians. (Radhakrishnan *et al.*, 2011) Furthermore, when a new drug is prescribed, physicians play a very vital role in reporting adverse events. Medical representatives (MRs) and Business executives (BE's) from pharmaceutical companies approach physicians for the promotion of their drugs. While a new drug is promoted to physicians, it is also very important to discuss the reporting of Adverse Drug Reactions. But, there is no valid data on whether such information is discussed. A study data which was conducted on 500 doctors, shows that only (10.2%) physicians stated that they were given details regarding the need to report AE's for a new drug. Only (5%) doctors said that they were informed by MRs that they should be more vigilant in reporting AE's for new products especially when used in vulnerable populations (children, pregnant and lactating women, elderly) and Additionally, (91.6%) participants said that the MRs told them that the new drug is completely safe as it has been thoroughly evaluated (Bhati *et al.*, 2015).

Conclusions

Till a few years back, in India, there was not a compulsion and no strict regulatory action to have a strong pharmacovigilance system in place to detect adverse events of the company marketed drugs. nevertheless, the increased interest of the Indian regulatory authority in pharmacovigilance is reflected by several instances

including of the amendment Schedule Y, organizing several workshops and conferences, and press releases or notification from DCGI from time to time, showing the importance of a strong pharmacovigilance system in India. Hence, the Indian Generic pharmaceutical companies are now facing higher regulatory reinforcement and increased accountability demands to ensure and manage a favorable benefit-risk balance of the products. This includes reporting and monitoring spontaneous adverse events, PSURs submission, risk-benefit ratio analysis, and relevant communications. For the clinical trials being conducted in India, the regulatory timelines for reporting and the conditions for expedited reporting have been clearly defined. As there was limited guidance available in Schedule Y, the CDSCO has drafted and published a pharmacovigilance guidance document for MAH on the website. It has become more imperative for the Indian pharmaceutical companies to consult the guidance documents available from the Indian regulatory authority to conduct pharmacovigilance activity. Challenges are faced by the pharmaceutical companies in India are Underreporting of AE's, lack of training of HCP's and MR's (medical representatives) on drug safety and adverse event reporting, non-availability of staff trained in pharmacovigilance.

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Conflict of interest

None of the authors had any conflict of interest that could affect the performance of the work or the interpretation of the data.

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