

# A Study on Drug Safety Monitoring Program in India

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Pharmacovigilance is useful in assuring the safety of medicines and protecting the consumers from their harmful effects. A number of single drugs as well as fixed dose combinations have been banned from manufacturing, marketing and distribution in India. An important issue about the availability of banned drugs over the counter in India is that sufficient adverse drug reactions data about these drugs have not been reported. The most common categories of drugs withdrawn in the last decade were nonsteroidal antiinflammatory drugs (28%), antidiabetics (14.28%), antiobesity (14.28%), antihistamines (14.28%), gastroprokinetic drugs (7.14%), breast cancer and infertility drugs (7.14%), irritable bowel syndrome and constipation drugs (7.14%) and antibiotics (7.14%). Drug withdrawals from market were made mainly due to safety issues involving cardiovascular events (57.14%) and liver damage (14.28%). Majority of drugs have been banned since 3-5 years in other countries but are still available for sale in India. The present study compares the drug safety monitoring systems in the developed countries such as the USA and UK and provides implications for developing a system that can ensure the safety and efficacy of drugs in India. Absence of a gold standard for a drug safety surveillance system, variations in culture and clinical practice across countries makes it difficult for India to completely adopt another country's practices. There should be a multidisciplinary approach towards drug safety that should be implemented throughout the entire duration spanning from drug discovery to usage by consumers.

**Key words:** Adverse drug reaction, banned drugs, drug safety, pharmacovigilance

Adverse drug reactions (ADRs) are undesirable effects of medications that lead to large-scale morbidity and mortality in developed countries<sup>[1-3]</sup>. However, there is dearth of research that claims ADR presence in developing countries such as India. A few studies have examined the effects of ADRs mainly by looking at hospital readmissions<sup>[4,5]</sup>. Serious ADRs are seen in 6.7% patients in India on an average and the number can be as high as 8% in rural South India<sup>[6]</sup>. In South India, ADRs are responsible for 0.7-3.4% hospital admissions, 3.7% hospital readmissions and 1.3% mortality<sup>[5-7]</sup>.

ADRs can be detected by yellow card reporting, a cost effective method to monitor safe use of drugs. Yellow card reporting is useful in a number of ways. It identifies unidentified ADRs, risk factors for the occurrence of ADRs, drug safety issues and risk benefit comparisons among medications belonging to different therapeutic classes<sup>[8,9]</sup>.

All the medications targeted for clinical purposes have to undergo several rigorous preclinical and clinical testing as an evidence of their safety and effectiveness. At times, adverse events are seen only upon usage among general population. The process whereby adverse effects are detected through regular monitoring after the release of drug in market is called pharmacovigilance<sup>[7]</sup>. Drugs are often banned by the FDA or voluntarily withdrawn by the manufacturing pharmaceutical company when the adverse events pose a risk greater than the benefit provided by the drug. When drugs are used in combination with other drug(s) and if they cause adverse events, then the drug(s) combination and not the individual drug are banned by the FDA. Many drugs used as single dosage or in combination with other drugs are discontinued from being produced and provided in the Indian market. Single drugs banned in last one decade in India, are presented in Table 1<sup>[11-26]</sup>. The study intends to review the status of banned drugs in India. It also looks at the pharmacovigilance programs in UK

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and USA and provides implications for improving pharmacovigilance in India.

An observational study was conducted from February to April 2012. All drugs (single drug or fixed dose combinations) banned in India from 2001 to 2011 were considered in this study. The list of the medications was procured from the website of the central drugs standard control organization, Government of India<sup>[11]</sup>. An extensive review of the literature was done about the identified banned drugs for identifying the drug name (generic and Brands), drug class, pharmacological category (use), manufacturer of the drug, year of introduction in the Indian market, date of ban in India, the reason for ban and its availability in India and in abroad. We also document the common category of drugs banned, life span of the drug in the market. The search was conducted via databases such as PubMed, Scopus and Sciencedirect (research articles, letter to the editor, editorials, commentaries) and search engines such as Google and Google scholar (online news papers, and online providers of health information and services to consumers, physicians, healthcare professionals). Search terms indicating drug name (generic and brand name), pharmacotherapeutic use, manufacturer's name, reason for withdrawal from the market, year of introduction and withdrawal of the drug were used for researching individual drugs. The data was collected using the Statistical Package for Social Sciences (SPSS) version 20.

#### **Killer drugs still available in Indian market but banned in other countries:**

Table 2 shows some examples of medicines, which are banned in many countries but still available in India. Many of them are over the counter drugs (brands) are available with changed formulation but same brand name. They are available without prescription so the general population is ignorant about the serious side effects. India has serious issues with use, availability and distribution of banned drugs<sup>[27]</sup>. Some of the drugs are mandatorily banned by Drugs Controller General of India (DCGI) but are still available in the market (e.g. human placental extract). The manufacturers take the aid of pending court cases and continue distribution until decision is made. The answer to such unethical distribution and availability of banned drug may lie in the insufficient data about ADR and its reporting. Many studies about pharmacovigilance and ADR reporting have shown

very poor ADR reporting in India due to lack of knowledge and practice (Table 2).

Though each country has its own mechanism to ban and list banned drugs, it is worrisome that some drugs that are banned in other countries for proven adverse effects are still available in the Indian market and are profitable. Things get further complicated due to issues such as self medication, since it is not monitored by physicians, and patients miss the important step of getting warned about the side effects of the drug and the subsequent ADR reporting if any, is unavailable. There is lack of awareness about the safety issues associated with medications or about the discontinued nature of medications and the consequences upon their consumption in India.

#### **Medication safety programs in developed countries; United Kingdom (UK):**

In the UK, responsibility of public health and patient safety falls with the Department of Health, Government of UK<sup>[28]</sup>. The medicines and healthcare products regulatory agency (MHRA) is an executive agency that acts on the behalf of the Department of Health, Government of UK. This body assures the safety, quality and efficacy of medicines as well as healthcare products. MHRA employs the prescription event-monitoring (PEM) scheme through which the MHRA identify and monitor the first 10 000 patients who receive a newly introduced drug in the market for any adverse drug events<sup>[28]</sup>.

The general practitioner (GP) prescribes a newly introduced drug, which the patient takes to the pharmacist for dispensing. The prescription information received by the pharmacist is passed on to the prescription pricing authority (PPA). The PPA then sends electronic copies of the prescription of the drug under study to the Drug Safety Research Unit (DSRU). This process helps gather patient exposure data and is continued till data of about 20 000 to 30 000 patients is collected. The prescriber is sent a Green Form 3 to 12 months after the prescription is written. This form requests the details of any events that may have occurred to the patient since the prescription was written.

The forms are made anonymous to preserve patient confidentiality. The events information on the forms provides the outcome data. The details of events and

**TABLE 1: SINGLE DRUGS BANNED IN INDIA OVER THE LAST DECADE (2001-2011)**

Drug Name (Brand name, drug class)	Pharmacol category (use)	Manufacturer	Year of drug		Reason for withdrawal
			Release	Indian ban	
Astemizole (Hismanal, 2nd gen antihistamine)	Antihistamine (allergies)	Janssen Pharmaceutical	1997	2003	Rare but fatal QT interval prolongation and related arrhythmia resulted in a market withdrawal in 2003 <sup>[10,11]</sup>
Cisapride (Propulsid, 5-HT <sub>4</sub> agonist)	Gastroprokinetic (antiemetic)	Janssen Pharmaceutical	1980	2011	Rare but fatal QT interval prolongation and related arrhythmia lead to issue of warning letters by US FDA and withdrawal in 2000 and in India in 2011 <sup>[10,11]</sup>
Diclofenac (Voltaren, NSAIDS)	Analgesic (pain relief)	Novartis	1973	2008	Liver toxicity in vultures and hence banned for animal use in India in 2008 <sup>[10,11]</sup>
Phenformin (Biguanide, Chlorformin in India)	Antidiabetic	Marketed by Ciba-Geigy (DBI)	1957	2003	Lactic Acidosis in the late 1970s which was fatal in 50% of cases and hence banned from the Indian market in 2003 <sup>[10,11]</sup>
Terfenadine (Seldane, 2nd gen antihistamine)	Antihistamine (allergies)	Sanofi-Aventis	1985	2003	Liver damages and severe cardiovascular complications resulting in withdrawal from the US, Canadian and Indian market in 97, 99 and 2003, respectively <sup>[10,11]</sup>
Gatifloxacin (Tequin, 4th gen fluoroquinolone)	Antibacterial (respiratory tract infections)	Bristol-Myers Squibb	1999	2011	Diabetes risk reported in a Canadian study published in NEJM 2006 <sup>[12]</sup> led to a FDA black box warning in 2006 <sup>[13]</sup> and withdrawn from Indian market in 2011 <sup>[11,14]</sup>
Rosiglitazone (Avandia, thiazolidinedione)	Antidiabetic	GSK	2006	2010	Increased risk of heart attacks by 43% and subsequent deaths led to a US FDA alert in 2007 <sup>[12,15]</sup> Suspension by the EMA in 2010 and withdrawal by India and New Zealand in 2011 <sup>[16]</sup>
Tegaserod (Zelnorm, 5-HT <sub>4</sub> agonist)	Gastric motility stimulant (IBS and constipation)	Novartis	2002	2011	Banned globally due to 10 fold increase in risk of heart attacks and strokes in 2007 and withdrawn from Indian market after a report DTAB in 2011 <sup>[10,11,17]</sup>
Nimesulide (Nimed, Nimedex, Nimesil, Nimulid, Nimutab, Nimdase, Nimopen-MPIndia (COX-2 selective NSAID)	Analgesic (acute pain, osteoarthritis and primary dysmenorrhea)	Helsinn Healthcare (original developer), By Dr. Reddy's Labs and Piramal Healthcare, India	1985	2011	liver toxicity and increased number of reports of adverse drug reactions in children led to its withdrawal in India in 2011 for pediatric use <sup>[11,18-20]</sup>
Sibutramine (Meridia, related to amphetamines)	Antiobesity (for anorexia)	Inventor is Knoll Pharma followed by Abbott	1998	2011	Increased heart attacks, strokes, and cardiac arrest led to withdrawal from the Indian market in 2010 <sup>[11,21]</sup>
Rofecoxib (Viox, NSAID)	Analgesic (osteoarthritis, acute pain, dysmenorrhoea)	Merck & Co	1999	2004	Increased risk of heart attack and stroke on long term use in high doses led voluntary withdrawal by Merck from the US market and in India agreement between Union Ministry of Health and Welfare and the National Pharmacovigilance Advisory Committee in 2004 <sup>[11,22]</sup>
Valdecoxib (Bextra, NSAID)	Analgesic (to treat osteoarthritis, rheumatoid arthritis, and painful menstrual symptoms)	Pfizer	2001	2005	Increased risk of heart attack, stroke, serious and sometimes fatal skin reaction led to market withdrawal in the US by its FDA in 2005 and in India in 2005 upon a report submitted to the National Pharmacovigilance Advisory Committee (NPAC) <sup>[10,11,23,24]</sup>
Letrozole (Femara, nonsteroidal aromatase inhibitor)	Antineoplastic (Hormonally responsive breast cancer after surgery and in postmenopausal women and infertility)	Novartis	2007	2011	Severe genetic abnormalities in babies born to infertile women led the Indian Union health ministry to withdraw the drug in 2011 after approving it for infertility therapy in 2007 <sup>[10,11,25]</sup>
Rimonabant (Acomplia, selective cannabinoid CB-1 receptor antagonist)	Antiobesity (Reduce hunger and appetite for weight reduction)	Sanofi Aventis	2006	2009	Serious suicidal tendencies led the European drug regulator and the National Health Regulator to recall in 2009 and in 2009 in India in agreement between the Health Ministry and DTAB <sup>[10,11,26]</sup>

NPAC: National Pharmacovigilance Advisory Committee, FDA: Food and Drug Administration, IBS: Irritable bowel syndrome, GSK: GlaxoSmithKline, NEJM: New England journal of medicine, NSAID: Nonsteroidal antiinflammatory drugs

**TABLE 2: DRUGS THAT HAVE BEEN GLOBALLY DISCARDED BUT ARE STILL AVAILABLE IN INDIAN MARKETS<sup>[27]</sup>**

Drug name	Indication for use	Reason for ban	Few available brands in market
Analgin	Analgesic	Bone marrow depression	Novalgin, Baralgan M
Droperidol	Antidepressant	irregular heartbeat	Droperol
Furazolidone	antidiarrhoeal	Cancer	Furoxone, lomofen
Nimusulide	NSAIDS	liver failure	Nise, Nimulid
Nitrofurazone	antibacterial cream	Cancer	Furacin, Megacin
Phenolphthalein	Laxative	Cancer	Agarol
Phenylpropanolamine	cough and cold	Stroke	D.Cold, Vicks Action 500
Oxyphenbutazone	NSAIDS	bone marrow depression	Sioril
Piperazine	antiworms	Nerve Damage	Antipar
Quiniodochlor	Antidiarrheal	Damage to sight	Enteroquinol
Human Placental extract	Human placental extract is used in the medicines and cosmetic industry in the form of lotion, gel and injection	It is not permitted in some countries since it can transmit diseases to the user	Placentrex

their incidences are then analyzed, and may result in the generation of signals, hypotheses or the initiation of follow-up studies. Thus, PEM in UK assists the pharmacovigilance agency with an assessment of a newly introduced drug in terms of its clinical outcomes and adverse events an uncontrolled real world environment<sup>[28]</sup>.

#### **United States:**

The United States, Food and Drug Administration (FDA) is the Federal public health agency that has regulatory responsibility for ensuring the safety of all marketed medical products, including pharmaceuticals (drugs and biologics). The availability of safe and effective pharmaceutical products depends on reporting of ADRs by all the parties involved i.e. the consumers or the patients, the healthcare providers and the drug manufacturers. The manufacturers have to compulsorily report ADRs<sup>[29]</sup>.

All unsolicited reports from health care professionals or consumers, received by the FDA via either voluntary or mandatory route, are called spontaneous reports. Spontaneous reports are a part of a clinical observation that originates outside of a formal study. The individual spontaneous reports of ADRs, medication errors, and product quality problems, sent directly to the FDA through the Med Watch program or to the manufacturer and then indirectly from the manufacture to the FDA, combined with data from formal clinical studies and from the medical and scientific literature, comprise the primary data source upon which post marketing surveillance depends. The FDA continuously strives to implement newer surveillance techniques for

detecting, reporting and evaluating adverse events. Another approach that might be used by FDA to detect adverse events is analyzing claim databases with a large sample size. These databases have prescription claims that can provide a link to occurrence of adverse events<sup>[29]</sup>. In March 2005, three separate guidelines were issued by the FDA including, (1) premarketing risk assessment; (2) development and use of risk minimization action plans (RiskMAP); and (3) good pharmacovigilance practices and pharmacoepidemiologic assessment<sup>[29]</sup>. According to the Guidance for Industry, drug safety risk-management is defined as an iterative process designed to optimize the benefit-risk balance for regulated products<sup>[30]</sup> and RiskMAP is defined as a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits<sup>[31]</sup>. RiskMAP tools for risk minimization include physician education and awareness programs and access to reminder systems that cross check and provide assistance to the healthcare personnel in reducing risk related to prescribing, dispensing, receipt and usage of a product. Identification of drug safety signals, investigation and interpretation of risk signals beyond case review, specification of pharmacoepidemiologic research methods for risk assessment, development of disease and drug registries, conducting patient or health provider surveys are some of the measures undertaken by the FDA guidance to promote good pharmacovigilance practices and pharmacoepidemiologic assessment<sup>[30,31]</sup>.

#### **Pharmacovigilance in India, the need:**

According to the 2011 census, India has the second highest population in the world with over 1.21

billion people<sup>[6]</sup>. The pharmaceutical industry in India is valued at 18 000 million dollars and its growth is estimated at the rate of 12-14 % per annum. Pharmaceutical exports are also growing at 25% compounded annual growth rate (CAGR) every year. The total export of pharmaceutical products amounts to 8000 million dollars, which makes India a global pharmacy of generic drugs since it is a distinct entity providing generic drugs, which have quality and are affordable. On a global scale, India is being viewed as an emerging hub of clinical trials, drug discovery, research and development<sup>[32]</sup>. After years of clinical trials and step by step approval by drug regulatory authorities, a drug is introduced for curing a particular disease. Prior to introduction in the market, despite several checks in the drug discovery and development process, certain drugs are withdrawn from the market when ADRs associated with them are discovered. Drugs might be withdrawn even after they are available in the market for a decade or longer. Examples of such drugs are rosiglitazone, rofecoxib, gatifloxacin, rimonabant and especially nimusulide formulation used in the market since 12 years<sup>[16-18]</sup>. Some of the ADRs are avoidable. Spontaneous reporting by healthcare professionals is an important step for preventing or reducing ADRs<sup>[33]</sup>. The ADR reporting rate in India is below 1% compared to the worldwide rate of 5%<sup>[7]</sup>. Given the lower rate in India, one of the reasons might be attributed to the awareness about pharmacovigilance and ADR monitoring among the Indian healthcare providers.

#### **National pharmacovigilance program of India:**

The national pharmacovigilance program (NPP) was established by the Ministry of Health and Family Welfare in New Delhi in 2010 as a means to gather ADR reports throughout the nation. The NPP comprises of a national coordinating center that receives ADR information from individual pharmacovigilance centers about the cause, source and the personnel involved in an adverse drug event via a vigiflow software interface operated by Uppsala Monitoring Center<sup>[32,34]</sup>. The NPP has developed and expanded through five phases of development since its initiation in 2010. In its initiation phase from 2010-2011, 40 medical schools were established as pharmacovigilance centers and personnel were trained in these pharmacovigilance centers. In the expansion and consolidation phase from 2011-2012, additional 60 medical colleges were enrolled as part of NPP

and gaps in training the personnel working in the pharmacovigilance centers were identified. In the expansion and maintenance phase from 2012-2013, another 100 medical colleges were enrolled as part of NPP. In the expansion and optimization phase to be implemented in the future from 2013-2014, the NPP plans to enroll an additional of 100 medical colleges. The NPP will also establish the Centre of excellence for pharmacovigilance in Asia Pacific Region as part of the excellence phase to be implemented in 2014-2015. Throughout the five phases, the NPP has and will coordinate public awareness workshops for promoting drug safety and efficacy<sup>[32]</sup>.

#### **Sub-committee to monitor banned drugs in India:**

Each country has its own organization that monitors its individual circulation of banned drugs. In India, prior to drug marketing, its safety and efficacy is ascertained in accordance with the Schedule Y of Drugs and Cosmetics Act. Even after market approval, the safety and efficacy of the drug is continuously examined on the basis of information gathered via Pharmacovigilance, Post-Marketing Surveillance and information reported from other countries. In order to examine such information, the Drugs Technical Advisory Board (DTAB) under Drugs and Cosmetics Act has constituted a sub-committee, consisting of experts on the subject who examine the information received from the sources mentioned above and take a final view as to whether to prohibit the manufacture, sale and distribution of drugs or to restrict its use and accordingly recommend the Government to make suitable amendments under Section 26 A of the Drugs and Cosmetics Act which empowers the Central Government to prohibit the manufacture, sale or distribution of such drug or cosmetics<sup>[34]</sup>.

#### **The role of pharmacist in drug safety:**

A multifaceted approach is required for safety of medicine regulation in the Indian market. A useful first step is to establish transparency, which is not apparent presently. The pharmacist can play a very important role in drug safety. Hence every state drug control officer should strictly abide by the Drug and Cosmetic Act 1940, which mandates every pharmacy to have a pharmacist at all times during business hours. Pharmacist can educate assistant pharmacists as well as patients visiting the pharmacy by writing labels in easy and understandable language, patient counseling, providing leaflets and stick posters about certain ADRs related to the obtained medications

and advice to report ADRs to pharmacists or other healthcare professionals.

Continued education (CE) is very important for pharmacists for updating and refreshing their knowledge about recent advancements and changes in pharmaceuticals. CE also helps in educating pharmacists about the NPP including how to report and whom to report ADRs in their practice. The government of India can also educate general population about black box warnings via a media. Presently, only one Pharmacy College affiliated with the J.S.S. Medical College and part of J.S.S. University, Mysore is involved in the NPP, but previously even community pharmacies located in the state of Goa and many pharmacy colleges located in south India acted as peripheral pharmacovigilance centers. Unfortunately, the NPP focuses only on medical colleges and not on other healthcare facilities. Pharmacists and nurses are an integral part of improving awareness about pharmacovigilance in India. Their efforts contribute to the smooth running of the NPP and maintenance of up-to-date documentation hence they should be given due recognition and considered an integral part of NPP.

The pharmacovigilance system in India is very poor and the increased workload on physicians, nurses and pharmacists does not bring to their notice most of the ADRs occurring in practice. Pharmacists are supposed to dispense accurate medications and they possess prime knowledge on medications. Unfortunately in India the qualification for a pharmacist to work in a pharmacy is a diploma (diploma in pharmacy a 2 year study plus 500 hour practical training in hospital), and not a baccalaureate degree in pharmacy.

Moreover the educational curriculum in India for pharmacist is more focused on industry rather than on community pharmacy. However, things are changing and courses based on pharmacy practice are being taught in many pharmacy schools in South India as

part of programs such as Pharm. D. and M. Pharm. pharmacy practice. If the current generation of pharmacists get involved in the NPP, we can expect an increase in the future detection of ADRs being reported back to the concerned authorities, which in turn will help the government to take the needed action at the earliest (Table 3)<sup>[35]</sup>.

#### **Suggestions for improving ADR reporting:**

Electronic reporting of ADRs, inclusion of ADR education in the professional curriculum, legal protection for healthcare professionals, information exchange about ADRs between healthcare professionals, incorporating ADR information in patient charts, establishment of pharmacovigilance centers at individual healthcare facilities, improving knowledge and awareness about ADR reporting among patients and healthcare professionals and better coordination among pharmacovigilance centers at the local, state and the national levels are some of the steps that can affect the mindset about ADR reporting in India<sup>[7,34]</sup>.

#### **Recommendations to improve drug safety in India:**

Some recommendations to enhance drug safety in India include physicians prescribing medications whose ADR profile is known, informing patients when new drugs are prescribed and to be alert about possible ADRs, approval of new drugs with caution for diseases for which safe alternatives are already existent, mention of drug approval date and black box warnings on the label of medications, penalizing physicians and pharmacists involved in prescribing or distribution of banned drugs, generation of awareness by the NPP about banned drugs in the market and constituting a committee by the DTAB to regulate banned drugs and medications with severe ADRs. The issue of circulation of banned drugs in the Indian market is severe and public awareness about the safety concerns associated with using banned drugs is imperative.

**TABLE 3: QUALIFICATIONS REQUIRED FOR REGISTERED PHARMACIST IN INDIA**

Qualification	Duration of course	Training needed for registration as pharmacist	Subjects related to drug safety	Current employment
D.Pharm	2 year full time	500 hour in Hospital (3 months)	None	Community Pharmacy/Hospital pharmacy
B.Pharm	4 year full time	One month in pharmaceutical industry	None	Pharmaceutical industry/hospital pharmacist, community pharmacy
Pharm.D.	5 year full time	One year Internship	ADRs, pharmacoepidemiology and drug safety	Pharmacovigilance Industry, CROs, Academia

ADRs: Adverse drug reactions, CROs: Contract research organizations

## CONCLUSIONS

If all healthcare professional including physicians, nurses, pharmacist and others including the patient report all ADRs then regulatory authority can take action as soon as possible, and drugs which are banned worldwide may be not available in India too. The importance of encouraging physicians, pharmacists, other health-care professionals, and patients to continue to report serious suspected adverse drug reactions, whether unknown or known, to manufacturers and their local regulatory agencies cannot be over emphasized. Drug development is becoming increasingly difficult. Continued attrition of potentially useful drugs because of serious unwanted effects will not help. Careful premarketing screening should reduce the problem but may also reduce the number of potentially useful drugs available for full development and subsequent licensing. Better risk management strategies are needed to handle problems when they arise, by means other than revocation of licenses.

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