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Overview of India's Current Pharmacovigilance System

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Abstract

Pharmacovigilance is becoming more prevalent in India. Given the scale of the Indian pharmaceutical business, it is critical to understand how pharmacovigilance affects pharmaceutical goods. Pharmacovigilance contributes to the safe use of pharmaceutical products, however under reporting is a big issue in India, either to a lack of information or a fear of the unknown. To develop a strong pharmacovigilance system in India, both the Indian pharmaceutical industry and the government must participate actively. Initiatives that can aid tiny privatised generic enterprises in dealing with changing laws, given their low budget, are required. This article presents an overview of India's current pharmacovigilance system, its difficulties, and how those problems can be overcome if India adopts the pharmacovigilance procedures used by other developed and developing countries.

Keywords: *- Adverse Drug Reaction, Central Drugs Standard Control Organization, Pharmacovigilance,*

INTRODUCTION

In terms of resources and legislation, India has seen tremendous progress in providing ideal circumstances for conducting clinical trials. Aside from the pharmaceutical industry, this trend may be found in the field of trials. Research and development is also progressing quickly, which is accelerating drug discovery in India.

The introduction of R&D in India has also enhanced the sensitivity to adverse drug responses. This vulnerability necessitated the implementation of pharmacovigilance policies, which did not play a part in the

earlier generic policies used by pharmaceutical corporations. The National Pharmacovigilance Programme was created and launched on January 1, 2005. Even though the bulk of pharmacovigilance rules were taken from international policies such as ICH and EU, there are still areas lacking clarity that require revision and specific attention.

This can be difficult in a resource-constrained country like India since several considerations must be addressed before adopting a law. The following discussion presents a summary of India's pharmacovigilance system and compares it to regulatory areas in other countries so that suitable change may be implemented in India.

National Pharmacovigilance Program in India

The Ministry of Health and Family Welfare started the National Pharmacovigilance Program (NPP) in July 2010, which is largely managed by CDSCO, New Delhi. The programme will be introduced in five stages, the specifics of which are shown in Table 1. ADR reports gathered from AMCs will be forwarded to the national co-ordinating centre. The coordinating centre will analyse causation and enter the results into the pharmacovigilance programme. Finally, the consolidated ADR data will be transferred via the vigiflow software interface into the ADR database at the Uppsala Monitoring Center, where signal processing will take place.

Table 1: Presented below is the roadmap for the Pharmacovigilance Programme of India. The programme will be implemented in five phases as depicted below:

Phase No.	Target for the five phases of pharmacovigilance program of India.	Description of national PVPI will be implemented infive phases as depicted below.
1	Initiation phase,2010-2011	Developing systems and procedures, enrolling 40 medical colleges, distributing data collection forms, developing and establishing training centers, training people working in pharmacovigilancecenters , linking with Uppasala monitoring centre in Sweden, initiating software development for national drug safety database, establishing zonal workshops for public awareness of

		drug safety and publishing drug safety news letter.
2	Expansion and consolidation phase2011-2012	Enrolling additional 60 medical colleges, identifing gapsthrough training, training pharmacovigilance centeremployees to operate softwares provided by Uppasala monitoring centre, WHO.
3	Expansion and maintenance phase,2012-2013	Enrolling additional 100 medical colleges, training of employees working in the pharmacovigilance centers, establishing zonal workshops for public awareness aboutdrug safety and publishing drug safety news letter.
4	Expansion and optimization phase, 2013-2014	Enrolling additional 100 medical colleges, interacting with international pharmacovigilance bodies, establishing zonal workshops for public awareness about drug safety and publishing drug safety news letter.
5	Excellence phase, 2014-2015	Creating centre of excellance for pharmacovigilance in Asia Pacific region

Approach

The approaches taken by rich and developing countries in formulating pharmacovogilance policies varied significantly. While regulations in industrialised nations such as the United States, the United Kingdom, and Japan are mostly concerned with ADR management, rules in India are primarily concerned with ADR collecting and reporting. The technique adopted in India is known as "pharmacodiligence," and it does not meet the primary goal of developing a pharmacovigilance structure. It is the inventors' primary job, i.e. pharmaceutical corporations, to regularly do a risk benefit evaluation and to primarily focus on risk management. However, the vast majority of pharmaceutical firms are generic. The Indian government is finding it difficult to persuade pharmaceutical companies to modify their strategy because developing an effective method to separate innovators from generics and draught rules appropriately is tough.

Obligations

Before examining the policy formulation concerns, there are several key duties that need to be addressed. These

responsibilities are both therapeutic and industrial in nature. The nature of the requirements may be flexible or rigorous while retaining local operations. Some of the elements that impact policy implementation are addressed below:

Reporting

In India, there is a shortage of data on ADR reporting due to issues such as underreporting, a lack of openness in industry reports, a lack of separation between noise and signal, a lack of knowledge among health care providers, and a lack of assistance from local governing authorities. Under reporting may be common due to a lack of pharmacovigilance expertise among medical graduates and health care providers. To strengthen the knowledge base of healthcare practitioners, medical institutions should include pharmacovigilance material in their curriculum. Other causes for underreporting include inability to identify, fear of reputational harm, a lack of training, a lack of financial incentives, competence, and a sense of guilt. In a nation like India, where traditional medicines are widely used, a lack of attentiveness when practising alternative systems of medicine such as Ayurveda, Homeopathy, Unani, and Siddha is also a major issue.

Sensitivity

Emotional sensitivity is a critical issue to address since it impacts prescribers, patients, and businesses. Patients or the media may overreact to any ADR reported on the medicine if they lack enough information of the issue. In medical practise, a lack of awareness of the related risk factors, relative risk, and absolute risk can lead to a slew of unforeseen issues, particularly with drugs like oral contraceptives. On many times, even physicians are unaware of the need of ADR reporting and avoid it out of fear of jeopardising their image. The public impression in India is that a firm that regularly files ADRs delivers poorer products than a company that reports to a lesser level.

Collection of ADRs

ADR reporting is currently voluntary in many countries. In a nation like India, where the majority of the population lives in poverty and literacy rates are poor, many people are unfamiliar with pharmacovigilance terminology and reporting procedures. As a result, there is a need to educate both health care providers and the general public on the significance

of ADR reporting. In contrast to the Western world, where pharmacovigilance is done in accordance with established laws, Indian health care personnel are less encouraged to do so. This demonstrates the critical importance of providing some type of incentive to strengthen India's monitoring programme.

Industrial prospect

Pharmaceutical industries play an important role in forwarding pharmacovigilance by providing information about ADRs to the regulatory authorities through activities like signal detection, risk-benefit evaluation and risk management. It is not an easy job for industries to adhere to regulatory guidelines. Unfortunately industries encounter many problems in the process which require the attention of the regulatory authorities.[2,10,19]

For generic companies

Regulatory authorities or local governing bodies often see both the innovator and generic companies in the same light. It is mandatory for a generic company to adhere to the same regulations as an innovator company. Hence a generic company has to perform the base work associated with factors like cost and management to fulfill the pharmacovigilance related regulatory requirements.

Cost Implications

Any setup necessitates a financial investment. Some policies must be maintained indefinitely since termination might result in major consequences such as penalties, product recalls, and consumer law cases, eventually harming the brand's reputation. To maintain a competent vigilance system, every organisation must fulfil needs such as software, medical dictionary subscriptions for regulatory operations, WHO drug dictionary subscriptions, appropriate workforce, and efficient employees with good management abilities. Access to a regularly updated health database is also required to obtain balanced information. All of the aforementioned reasons need finance, which a generic manufacturer may find difficult to get.

Management issues

There are several obstacles to establishing a pharmacovigilance system, including a shortage of money and professionals. A pharmacovigilance setup necessitates input from a variety of departments, including regulatory affairs, information technology, sales, finance, marketing, legal, manufacturing, quality assurance, human

resources, and third-party vendors. These departments must collaborate in order to offer an effective output in areas such as:

1) Customer call receipt and triage
2) ADR case processing & reporting (electronic or hard copy)
3) Periodic safety updates reporting (PSUR)
4) Product quality complaints management (included by some companies)
5) Medical inquiries management (included by some companies)
6) Electronic safety database validation
7) Safety data exchange agreement management
8) Signal detection – risk-benefit evaluation
9) Risk management programs
10) Literature monitoring for ADR case reports
11) Training of company employees on ADR reporting
12) Global compliance monitoring
13) Audits and inspections management

A corporation will need a large financial expenditure to assure the effective operation of the above departments if it intends to oversee the operation of all departments directly, or it can outsource the job to CROs. Outsourcing is becoming increasingly popular since it provides companies with the certainty that the project will be completed in accordance with the required standards or guidelines.

Multinational operations

Companies want to spread their activities abroad for personal development, but in order to do so, they must follow local restrictions. However, it is very hard to develop a pharmacovigilance policy that is compliant with all authorities for managing both local and foreign operations. As a result, a globally approved harmonised pharmacovigilance policy is required.

Local organisations in nations such as India and China, which have long been generic producers, are compelling their companies to meet local norms. However, because these businesses operate in several nations throughout the world, it is impossible to meet both local and international rules at the same time. Given these criteria, it is natural for a company to establish a pharmacovigilance department or extend its current skills.

Table 2: Many countries recently updated their regulations [22]

REGULATORY AGENCY	YEAR OF LAST UPDATE
Brazil	February 2009
Vietnam	March 2009
EU	Vol-9a September 2008
Russia	November 2008
US	Though CFR are final, however the guideline for post marketingpharmacovigilance was released in 2001 as a draft guideline.
Mexico	2007
Ukraine	2007

Evolving Regulations

Adherence to regulations is must for any company to continue its operations in any part of the world but evolving regulations present an ongoing challenge in terms of making changes to already well-established policies and resources. These evolving policies force any company to follow the newly established regulations. The companies might feel helpless since the evolving regulations are often accompanied by new problems. Companies in countries that have recently updated their regulations are listed below.

Funding

Finance is always a major issue to address. Implementing a policy is more difficult compared to framing a policy and it requires a lot of investment, in terms of both human efforts and capital. Such investment is difficult cannot be successfully made possible in many countries. This factor can limit the number of pharmacovigilance centers to be established. Sources providing continuous support throughout the nation at all times, are necessary. The capital should be based on the population to be served by the center and support should be provided by institutions, insurance companies, government and other organizations which are health based.

Local governing bodies

Local governing bodies play a key role in framing the pharmacovigilance policy mainly in countries, where the policy is

still in the emerging phase. The pharmacovigilance system is well framed and very stringent in the US, Europe and Japan. So, regulations from such authorities should be considered while framing regulations in India. However, local bodies in India do not provide much freedom to committees for framing policies.

Collaboration of the Indian governing bodies with international bodies should be encouraged in order to frame the necessary policies.

Harmonized pharmacovigilance

Need for harmonization

Although common regulations are framed, differencesin ideology still persists in different regions, creating challenges for companies to perform their activities. The ultimate goal of these regulations is to provide a uniform and standard platform to the industries to carry out their activities effectively and share the collected information through a database so that it is possible to reap collective benefits.

Table 3: Variations in regulations

S.NO.	ACTIVITY	VARIATIONS	EXAMPLES
	Start of Pharmacovigilance responsibilities for a product		
1	Pharmacovigilance	From date of authorization	US, Canada, EU
	obligations start date	From date of launch of product in the market	India, Australia (expedited reporting)
	Variations in Expedited reporting standards		
2	Timelines for submission	15 calendar days	US, EU
		10 working days for dometic cases	Vietnam
		5 calendar days	business partner exchange
3	Requirement for foreign/ domestic reports	Both foreign and domestic	US, EU, Japan, Ukraine (Only serious unexpected, fatal/ life threatening cases from confirmed company products
		Foreign reports not required	Mexico, South Africa, Malaysia, Brazil, Australia, Singapore, Thailand, China, Russia
4	Medically confirmed versus unconfirmed cases	Accepted	US
		not accepted	EU

5	Published Literature	Required	US, EU, Australia (domestic only), Canada, Japan
	monitoring for ADR cases	not required	India, Latin America, Africa, Russia, CIS
6	Different ADR reporting forms	Med Watch/ Council for International Organizations of Medical Sciences or CIOMS (for foreign cases only)	US
	CIOMS		Japan
7	Electronic (E2B) reporting requirement	Mandatory	EU Competent Authorities and European Medicines Agency (EMEA)
		not mandatory	rest of world
Differences in Periodic reporting standards			
8	PSUR submission Requirements	Mandatory requirement	US, EU, India
		On request by regulatory agencies	Canada, South Africa
		At license renewal only	United Arab Emirates
9	PSUR submission cycles	Quarterly, annually	US
		Quarterly, semi-annually, annually, re-registration	Mexico
		Three years (harmonized birth date based)	EU
		Annually	Australia
		Registration, re-registration	Kazakhstan, Ukraine Russia, Belarus, Iran, UAE, China
10	Content of PSUR	The following sections of a PSUR are not required: patient exposure, literature search, detailed marketing authorization status	US
		Comprehensive data is required per volume 9A, including all sections listed above	EU
		Literature search not required	India
		Additional requirement of write up about company's pharmacovigilance systems	Kazakhstan
		Additional requirement of executive summary in Portuguese. PSUR content can be in English	Brazil
11	Timelines for submission of PSUR from the Data Lock Point (DLP)	30 – 60 days (quarterly/annual)	US
		60 days	EU, brazil
		30 days	India
Variations in Risk Management Plan/Program requirements			
12	Risk management program e.g., Isotretinoin risk management	iPledge program mandatory	US, Canada, EU
		Not mandated by any other agency	Rest of the world
13	Risk management plan submission mandatory	For all new registrations	EU
		Not mandatory for all registrations	Rest of the world

Table 4: Variations in Information Dissemination [12,23]

COUNTRIES	INFORMATION DISEMMINATION
Australia	Regular bulletins are published
Brazil	Conducting training and courses for health care team by national agencies
India	In the form of published reports
Jordan	Workshops for health care teams in both public and private sector
Malaysia	Manuals, talks, publications in official newsletter Berita-ubat-ubatan
Singapore	Newsletters and published reports
South Africa	As official document like gazette
Ukraine	Information bulletins are prepared and recommendations are made to healthprofessionals, investigators and health ministry

Table 5: Variations in Regulatory Action Taken[12,23]

COUNTRY	REGULATORY ACTION TAKEN
Australia	Withdrawal from market or modification of contraindications, warnings, precaution to product
Brazil	Identifying the global scenario of drug withdrawals, specially on drugs with irrational active ingredient combinations, products requiring restrictions and with no therapeutic value and implementing changes accordingly
India	Suggest to regulatory for intervention related to drug/class
Jordan	Required changes to be introduced in product information
Malaysia	Making changes to product information, contraindications,precautions, warnings and also to dosages and in advertising
Singapore	When ADRs occur more frequently than previously expected then changes are to be made in marketing authorization and when it leads to effects that are unacceptable it is withdrawn from market
South Africa	Changes to product information or labeling
Ukraine	Center shall propose to ministry of health to take decisionregarding temporary or permanent ban on product until further

	trials result in disapproval of the unsafe properties of the drug

Areas to review

Compared to the regulations prevalent in different countries with regards to the timeline for submission of PSUR, the content to be included in PSUR, risk management strategy, information dissemination and the regulatory actions performed as part of the Indian pharmacovigilance programme need changes in different aspects such as

1) Literature search not being presently required for submission of PSUR, even though it improves the possibility to search for a possible new ADR.

2) Informing about the PV policy in Kazakhstan to the Indian regulatory bodies as it will provide information about their policies and allow for improvement of Indian policies.

3) Adoption of electronic reporting system due to its e
stablished superiority in other fields.

4) Mandatory implementation of ipledge like EU since it will enable us to come out with a robust pharmacovigilance plan with a main focus on risk management.

5) Inclusion of updated risk management plan in periodic submission.

6) Issuing an acknowledgement receipt with a reference number for all further correspondence to avoid any duplication of reports. There should be timely and easy feedback for all the cases reported.

7) Harmonizing the conditions for approval of drugs with phase IV clinical trial data to enable safety evaluation, contrary to the present process of approval based on special conditions like finalization. Sharing of information should be encouraged.

8) Reporting of ADRs to limit the confidentiality of the investigator and avoiding the involvement of the media and the patient, in addition to informing the safety issues of the drugs.

9) Taking regulatory action after receiving a signal similar to the process employed in Ukraine since delaying in decision making may put the patient's health at risk.

10) Disseminating information similar to Brazil and Jordan since making the information public and providing recommendations to the health ministry will have more beneficial effects.

11) Introducing ADR monitoring and reporting issues in school and college curriculum and combining ADR monitoring with public health programmes. [14,20,22,21]

Implementing all the above factors might be challenging to the companies since there is an immense need to employ a universally acceptable harmonized pharmacovigilance system. Such a system should be governed by a universal body like UPPASALA that has links with local organizations all over the globe. This will also allow more companies to carry out their pharmacovigilance activities without much difficulty. Thus, a more active vigilance programme can be constructed than the previous one. Harmonization, similar to globalization can lead to the formation of a more widely accepted programme that can ensure good progress.

CONCLUSION

The ultimate purpose of pharmacovigilance regulatory organisations is patient safety. As a result, while developing legislation to promote patient well-being, it is critical to examine variables that create barriers for various stakeholders in the system. It is also the regulatory authorities' job to be more actively involved in conducting educational programmes for both health care teams and the general public, as underreporting of medication errors/adverse drug events is a major impediment.

Harmonizing legislation allows more companies to participate and exchange necessary information with the healthcare community.Pharma firms will be able to prevent sensitivity by educating healthcare providers. Minor variations can be worked out by taking into account the local circumstances of certain members. Incentives can be useful in motivating individuals to report in poor nations.

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