Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/5294
DOI URL: http://dx.doi.org/10.21474/IJAR01/5294

RESEARCH ARTICLE

PHARMACOVIGILANCE: WHERE DO WE STAND?

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Manuscript Info

Manuscript History

Received: 01 July 2017
Final Accepted: 03 August 2017
Published: September 2017

Keywords:-
Pharmacovigilance, adverse drug reactions, healthcare professionals, toxic effects.

Abstract

Pharmacovigilance is a system, not only significant to the early detection of adverse drug reactions; but also facilitates identification of risk in post marketing period. Contribution to Uppsala monitoring database from developing countries including India is still negligible due to the poor reporting culture, lack of knowledge in healthcare professionals regarding pharmacovigilance etc. are so many reason which are barrier for emerging this essential department in pharmaceutical industry.

This article aims at bringing such issues into notice with respect to pharmacovigilance systems and look upon some measures that may be taken to safeguard the patients who take the drug for their better health, not for suffering the toxic effects, also some suggestion to improvising the health standards.

Introduction:-

Pharmacovigilance (PhV) (*pharmakon* (Greek for drug) and *vigilare* (Latin for to keep watch) is the system which constantly keeps monitors the latest move regarding patient care and safety in relation to the use of medicines and all medical and paramedical interventions [1].

When a patient's having adverse event, expected or unexpected, it is necessary that these events are reported, analyzed and their significance communicated effectively to the respective authorities to interpret the information and take further actions on it.

Why Pharmacovigilance?

1. **Leading causes of morbidity and mortality**: In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality e.g. in study by Lazarou in 1998 described ADRs 4-6 largest cause of death in the USA and cause of 3-7% of all hospital admissions. ADRs are one of the leading causes of morbidity and mortality, adding to overall healthcare cost [2].
2. **Company revenue**: Many drugs that were very successful and benefited thousands of patients, but were later found to have serious side-effects, resulting in their withdrawal. The most notable recent example was *Vioxx*, launched in 1999 and withdrawn in 2004 with total sales of $2.5 billion from 100 million prescriptions issued. The cost to Merck in terms of loss of revenue, personal injury lawsuits and reputation has been significant [3].
3. **Patient's safety**: It is estimated that approximately 2.9–5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay. The overall

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incidence of serious ADRs is 6.7% and of fatal ADRs is 0.32% in hospitalized patients, making these reactions between the fourth and sixth leading cause of death, respectively [4, 5].

Lack of Adverse Event Reporting:-
Dependence on voluntary submission of adverse events by Health Care Professionals (HCP), Manufacturers & consumer is the biggest barrier for pharmacovigilance.
As voluntary submission of Adverse event reporting depends on

Health care professionals and 2) Patient:-
1. Sometimes both patient and the health care providers are unaware of the adverse event reporting systems. This is due to the lack of knowledge.
2. ADR as its effects may be desirable to patients but are not medically needed (e.g. Opioid analgesics psychological effects).
3. Patient wants to conceal information in condition like HIV infection
4. Lack of interest, funding and knowledge pose challenges in effective post marketing drug surveillance in surgery. Lack of efficacy and medication errors can be is very common, can be life threatening at many cases or may cause even death.

The awareness towards the PhV can be understood by a study which demonstrated that in India only 35% of the resident doctors and 27% of nurses chose the correct definition of ADR. Resident doctors had better knowledge on the regarding "what to report." On the other hand, two-third of the nurses (75%) had better knowledge about "whom to report" an ADR.

The products which are already approved and marketed in the regulated markets of USA, Europe, Japan or other countries are mostly being launched in Indian market. For effective adverse event monitoring, the Indian Pharmaceutical companies are dependent on the experiences shared from these regulated markets, where the drug was already used for many years before coming into Indian market. Because of this reason, Pharmacovigilance system is not that strong in India [6, 7, 8].

Vulnerable Population:-
During the premarketing phase of the drug the pediatric patients, geriatric patients and pregnant women are not exposed to the drug due to the strict inclusion exclusion criteria followed in the trials. Adverse drug reactions in children constitute a significant health issue given their reported incidence of 9.5%. They also account for 2.1% of hospital admissions, with 39.3% of life threatening [9].

Causes for an Inadequate Reporting:-
Report" sounds unpleasant to Indian Population.
1. Busy schedule of healthcare professionals.
2. Greater emphasis on disease (rather than drugs).
3. Hardly any rewards or incentives [10, 11].

United States has 2.672 doctors per 1,000 people, and 3.1 hospital beds per 1,000 people, on the other hand, India has a mere 0.599 doctors and 0.9 hospital beds per 1,000 people.

The awareness regarding reporting can be well recognized by the fact that during one calendar year, not even a single ADR report was sent to Uppsala monitoring centre (UMC) from a country of 1billion thus, ADR reporting rate in India is below 1% as compared to world rate of 5% [12].

Difficulties faced by National PharmacovigilanceProgramme:-
Pharmacovigilance begins after episode occurring in 1937 with Prontosil (sulfanilamide) which is responsible for death of 105 individuals than Thalidomide (1962) tragedy make a milestone for its development. However in India it originates in 1986, but come into limelight a decade later in 1997 when India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was madeoperational.
1. The Indian pharmacovigilance system is not able to match the global adverse drug reporting dates.

2. Lack of the adverse drug reporting software for reporting the ADRs to the UMC.
3. Central Drugs Standard Control Organization (CDSCO) lacks the Basic infrastructure needed for having an efficient pharmacovigilance system.
4. Lack of proper training and inefficient staff.
5. The basic infrastructure requirement for setting up these cells i.e. space, trained workforce and funds, is huge and will take a lot of planning and management.
6. Proper training of the staff for the good pharmacovigilance practice and funds is must.
7. The SOPs for harmonized working of the pharmacovigilance cells have to be drafted and implemented.
8. Absence of validated standard working procedures is one of the greatest hurdles which national pharmacovigilance program is facing.
9. Schedule Y states that all cases involving SUSARs must be reported to the licensing authority within 10 calendar days (only clinical trials) of initial receipt of the information by the applicant.
10. According to the schedule Y, The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years the PSURs need to be submitted annually, No guideline afterwards regarding PSUR submission [2, 11].

Suggestion to improvising reporting:-

1. Availability of ADR reporting forms or adverse event reporting form drop boxes at health care centers, hospitals & dispensaries may definitely benefit the adverse event reporting rate. Since around 80 percent of human population resides in such countries a small increase in reporting will boost up the pharmacovigilance data and drug safety.
2. Proper training of health care professionals (HCP) and sales personnel regarding pharmacovigilance and safety reporting may help in increased reporting.
3. Increasing awareness regarding risks and adverse events through media or other communication channels may encourage patients to report the adverse events.
4. Involve professional organizations of healthcare providers to educate their members about the program and there by sustain their participation.
5. Use news- letters and pamphlets to inform healthcare providers about the program's activities.
6. Assign the job of pharmacovigilance to an independent unit which is full time dedicated to the job of ADR monitoring.
7. Pediatrician should co-opt for Pediatrics-recommended pediatrician on its panel.
8. Website relating Pharmacovigilance should be more informative by providing the latest data about the adverse events/adverse drug reactions reported.
9. Allow healthcare providers working in rural areas and at primary health centers to avail Internet and facsimile facilities to report adverse events: This would encourage reporting from remote areas, help expand the program's coverage and cut the red tape.
10. A healthy database will help the Indian pharmacovigilance system greatly and will play a great role in the safety analysis of the drugs. Clarity regarding the reporting of AEs is needed as the Schedule Y presently is pretty ambiguous in terms of reporting timeframes and needs to be completely overhauled [13, 14].

Table 1:-Comparison of the Pharmacovigilance Regulatory Requirements For EU, USA and India.

Contents & Requirements	**European Union**	**United States**	**India**
Phv System	MAH must ensure that it has an appropriate system of pharmacovigilance and risk management in place	An appropriate Pharmacovigilance system is required	Not mandatory
Description of Phv System	Pharmacovigilance Master file is required	In accordance with CFR	Not required
Regulatory Structure	EMEA & EC	Office of Surveillance and epidemiology division of USFDA	CDSCO (DCGI), Schedule Y
Legislation& Regulation	Regulation (EC) No 726/2004 Directive 2001/83/EC	21 CFR 314.80,314.98	DGHS, Ministry of Health & Family

		FDA,CDER,CBER	Welfare
Spontaneous Cases	To be reported by MAH within 15 Calendar days	Serious and unexpected, foreign and domestic, reported by the MAH within 15 calendar days	No Specific Guideline (Only specify for Clinical Trial)
Case reports from the worldwide literature	To be reported by MAH within 15 Calendar days	Serious and unexpected, foreign and domestic, reported by the MAH within 15 calendar days	No Specific Guideline
Reporting from postauthorization studies / pharmacopidemiological study	All serious adverse reactions within or outside the EU should be reported within 15 days.	Serious and unexpected adverse experiences (domestic and foreign) should be reported within 15 calendar day	No Specific Guideline
Fatal or Life Threatening Unexpected ADRs	As soon as possible but no later than 7 calendar days after first knowledge followed by a complete a report as possible within 8 additional calendar days.		
All Other Serious, unexpected ADRs	As soon as possible but no later than 15 calendar days		As soon as possible but no later than 10 calendar days.
Periodic safety report submission cycles	6-monthly continued until two full years then, once a year for the following 2 years and thereafter at 3- yearly intervals	Quarterly for first three years, then annually	Submitted every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 years
Risk Management Plans	Risk management plan is mandatory in the EU	FDA may determine Risk Evaluation and Mitigation Strategy (REMS) but this is not a requirement	No Specific Guideline
CFR: Code of Federal Regulations; FDA: Food and Drug Administration; EU: European Union; MAH: Marketing Authorization Holder; EMEA: European Medicines Agency; DGHS: Directorate General of Health Service; DCGI: Drug Controller General of India; CDER: Center for Drug Evaluation and Research; CBER: Center for Biologics Evaluation and Research			

Conclusion:-

Pharmacovigilance is still in its infancy in India, this is likely to expand in the times to come. As the newer drugs hit the market, the need for pharmacovigilance grows more than ever before. The pharmacovigilance also important as the most drugs invented in western countries. For improvement there should be an involvement of all categories of healthcare professionals in ADR and pharmacovigilance planning to incorporate the sense of ownership. It should be ensured that the reporting forms are always available. India has only a small section of Schedule Y dedicated to drug

safety, which when viewed in light of contemporary global practice, seems to have many lacunae. Good PV system will identify the risks within the shortest possible time. When communicated effectively, it will ultimately help each patient receive optimum therapy at a lower cost to the health system.

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