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Global Issue & Regulatory Control of Pharmacovigilance System: A Standard Operating Procedure for a New Develop Organization

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Abstract— Occurrence of Adverse Drug Reaction (ADR) and other drug related issue vary from region to region and countries. This variation in occurrence may be due to demographics; races; dietary habits; genetics; prescribing practices; manufacturing quality with different standard and many more factors. These ADR (Adverse drug reaction) may be in the process of pre-marketing or post-marketing surveillance are reported to the regulatory agency and concerned regulatory agency may take action after the collection of ADRs. The reporting of safety information from clinical trials and with marketed products by pharmaceutical companies to regulatory authorities has been mandatory for many years but with each national authority having different requirements like the current in US all Serious and Unexpected adverse experience (Domestic and Foreign) should be reported within 15 calendar day.

Keywords : Pharmacovigilance, ADR, FDA, Regulatory Control.

INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The scope of the Pharmacovigilance has been to:

- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
- improve public health and safety in relation to the use of medicines
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use
- promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.

Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. Pharmacovigilance also concerns substandard medicines, medication errors, lack of efficacy reports, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines and adverse interactions of medicines with chemicals, other medicines, and food.[1]

Importance of Pharmacovigilance:

It highlights the need for critical examination of the Strengths and weakness of present Pharmacovigilance systems in order to increase their impact. It anticipates developments necessary to meet the challenges of the next ten years. It argues that the distinctive approaches adopted by different countries in response to their individual needs should be supported and fostered. The document also highlights the importance of collaboration and communication at local, regional and international levels, to ensure Pharmacovigilance delivers its full benefits.[2,3]

CONSTITUTES OF THE PHARMACOVIGILANCE PROCESS

Pharmacovigilance process starts at the way beginning of clinical development process of a drug product and continues throughout the life cycle of the product. Broadly it can be divided into two phases:

1) Pre Marketing Pharmacovigilance Process
2) Post Marketing Pharmacovigilance Process

Pre Marketing Pharmacovigilance Process:

The assessment of clinical data and Safety and Efficacy data during the drug product development known as the pre marketing Pharmacovigilance process. It involves the measuring of the adverse drug reactions in whole the phases of the clinical trials. On the basis of these data or case report form informs the agencies and manage the risk benefits ratio of the drug product. During the clinical data the adverse drug reaction occur are known as the expected adverse drug reaction and those which are comes during the post marketing Pharmacovigilance process are known as the unexpected adverse drug reaction.

Post Marketing Pharmacovigilance Process:

Phase 2nd of the Pharmacovigilance process after a medicines gets launched in the market and until the time that it remain in the market is the post approval Pharmacovigilance process. It is the post marketing Pharmacovigilance process that's the regulatory agencies of the world vigilant about the reporting of adverse events happens spontaneously. [4]

Pharmacovigilance in different countries/regions

All the regions of the world have their own particular Pharmacovigilance system, through based on WHO guidelines.

Pharmacovigilance in Europe

Pharmacovigilance system in Europe is coordinated by the European Medicines Agency (EMA) and conducted by the National Competent Authorities (NCAs). The EMA maintains and develops the Pharmacovigilance database comprising all suspected serious adverse drug reaction observed in the European region. Here, the Pharmacovigilance system is called EUDRA Vigilance and contains separate but similar database of human and veterinary reactions. EMA Pharmacovigilance legislation regulated by Article 106 of Directive 2001/83/EC, Directive 2001/20/EC & Article 26 of Regulation (EC) No. 726/2004 EMEA& EC.[5, 6]

Pharmacovigilance in United States

Here Pharmacovigilance has a multi faced approach. Three branches of the Pharmacovigilance in the USA has been defined by the FDA to evaluate product risks and promote the safe use of products by the American people. These three division / branches comes in the office of Surveillance and epidemiology (OSE).

Three Divisions within OSE:

1. Division of Drug Risk Evaluation (DDRE)
2. Division of Medication Errors and Technical Support (DMETS)
3. Division of Surveillance, Research and Communication Support (DSRCS)

In United State the Pharmacovigilance Legisation Regulated 21 CFR 314.80, 314.98 FDA, CDER, CBER.[7]

Pharmacovigilance in India

The central drugs Standard control organisation (CDSCO), ministry of health and family welfare, Govt of India launched the national Pharmacovigilance programmed (NPP) in November, 2004 based on the WHO recommendations made in the document titled" safety monitoring of Medicinal products-guidelines for setting up and Running a Pharmacovigilance Centre" the whole country is divided into zones and regions for the operational efficiency, CDSCO, new Delhi is at the top of the hierarchy by two zonal Pharmacovigilance centre viz. seth GS medical college , Mumbai and AIIMS, New Delhi.[8, 9]

COMPARATIVE FRAMEWORK FOR PHARMACOVIGILANCE

S.No.	Contents & Requirements	European Union	United State	India
1.	**Definitions**	According to WHO Collaborating Centre for International Drug Monitoring: Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.		
2.	**Legislation & Regulation**	Article 106 of Directive 2001/20/EC, Directive 2001/83/EC & Article 26 of Regulation (EC) No.726/2004	21 CFR 314.80,314.98 FDA,CDER,CBER	DGHS, Ministry of Health & Family Welfare
3.	**Regulatory Structure**	EMEA & EC	Office of Surveillance and epidemiology division of USFDA	CDSCO (DCGI), Schedule Y
4.	**Expedited Reporting Requirements**			
a.	**Spontaneous ADR case reports**	Should be reported by the MAH within 15 calendar day	Serious and unexpected, foreign and domestic should be reported by the MAH within 15 calendar day	No Specific Guideline
b.	**Case reports from the worldwide literature**	Should be reported within 15 calendar day	Serious and unexpected adverse experiences (domestic and foreign) should be reported within 15 calendar day	No Specific Guideline
c.	**Reporting from post-authorization studies / pharmacopidemiological study**	All serious adverse reactions within the EU should be reported within 15 days. All unexpected serious adverse reactions outside the EU should be reported within 15 days. Expected serious occurring outsides the EU should be reported in accordance with PSURs.	Serious and unexpected adverse experiences (domestic and foreign) should be reported within 15 calendar day	No Specific Guideline
5.	**Reporting Expedited Reporting**			
a.	**Fatal or Life Threatening**	As soon as possible but no later than 7 calendar days after first knowledge		

	Unexpected ADRs	followed by a complete a report as possible within 8 additional calendar days.		
b.	**All Other Serious, unexpected ADRs**	As soon as possible but no later than 15 calendar days		As soon as possible but no later than 14 calendar days.
6.	**Time Frame**	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
7.	**Risk Management Plans**	Risk managements plan is mandatory in the EU A valid EU-RMP must categorized as	FDA may determine Risk Evaluation and Mitigation Strategy (REMS) but this is not a requirements	No Specific Guideline
		Section-1: product information Section-2: safety specification Section-3: PVG plan Section-4 risk minimization plan if needed	Risk minimization action plans not mandatory in US but strongly advised at the time of filing especially for NCE	
8.	**Reporting Forms**	CIOMS IEU require the individual MAH (drug companies), to submit all received adverse reactions in electronic form	CIOMS I or Form FDA 3500A	Suspected Adverse Drug Reaction Reporting Form

9.	**Remarks**	The original words used by the reporter to describe the adverse reactions should be provided as well as the appropriate. Lowest level Terms from MedDRA. Qualified person responsible for Pharmacovigilance is mandatory in EU & Australia. MAH/Sponsor accessing a systematic literature data base, such as medicine, Excerpta Medica or Embase, no less.	No Specific Remark

A STANDARD OPERATING PROCEDURE FOR A NEW DEVELOP ORGANISATION

Purpose:

To describes the responsibilities for reporting of adverse drug events and ensure that the obligations for drug safety monitoring (Pharmacovigilance) are defined and implemented.

Scope:

Any Organization or licensee employee, distributor or agent who is made aware of an adverse reaction or event applicable to Healthcare products manufactured by an organization and an organization contract manufacturers for which an organization is the Market Authorisation Holder (MAH) or licenser.

Serious AE/ADR (SAE)

A Serious Adverse Event/Reaction means an adverse reaction which:

- results in death,
- is life-threatening, The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe.
- requires in-patient hospitalization, or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect.
- is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. (ICH E2D)

Procedure:

It is the legal obligation of the Marketing Authorisation Holder (MAH) to set up a system to collect, collate, and evaluate information about suspected Adverse Events(s) (AEs) to ensure that all AEs are captured, reviewed, reported and acted on in accordance with the

regulations and legislation. The purpose of AEs recording and communication is to ensure that organization products are safe and can be used in an appropriate and rational manner.

PV activities should be handled at a centre (corporate office levels). These should be a dedicated group handling the Pharmacovigilance process preferable under organizations medical groups. This group and team may be called "Pharmacovigilance department" or "Drug safety group". if an organization is a multinational organization with business in several countries then each country business unit (CBU) should have dedicated person or team handling adverse events (AEs). This should be reportable to DSG (Drug Safety Group). The person handling adverse events at country level should be called "Drug Safety Officer" or "Drug Safety Cordinator (DSC)".

Basically, the DSO/DRC coordinator is responsible for collecting local safety data, reporting to the Regulatory Authority if applicable, and other local PV activities, and the DSG is responsible for processing safety data, and for all the other global PV activities.

1. COLLECTION OF AEs

Safety information originates from various sources which are classified as :

- Spontaneous (e.g. Health Care Professional, Consumer)
- Literature (e.g. : scientific & medical journals, newspapers, internet)
- Clinical Trial
- Regulatory Authority

Safety information will be collected by various means (e.g. phone, post/fax, email) either directly by an organization or through a third party (e.g. distributor, call centre)

Also, ICSRs (**Individual Case Safety Report)** could be received electronically from Regulatory Authorities and other MAHs. It is the DSG responsibility to download ICSRs onto the PV database.

1.1. Spontaneous

Spontaneous safety data are collected at a local level by the DSO/DSC and then forwarded to the DSG for processing. It is the responsibility of the DSO/DSC to follow up their local AEs.

1.2. Literature

The DSG at corporate office should be responsible for liaising with Business Intelligence of the organization for AE screening of the scientific literature.

The DSG then should review the literature paper and process any literature AEs. It is the DSG responsibility to follow up these AEs with the author.

However, if a DSO/DRC Coordinator becomes aware of an AE being published in a newspaper or scientific journal, it is their responsibility to forward it to the GDSG and to follow it up.

1.3. Clinical Trials

Clinical trials are being run by Medical or Clinical research departments of an organization. It is the responsibility of Clinical research departments to collect AEs and to forward the serious AEs to the DSG. Additionally, the DSG should be responsible for reviewing the coding of AEs entered in the study database before the clinical trial database lockpoint. The DSG will review SAEs

held on the clinical trial database and on the PV database to ensure consistency. If a clinical trial is being run by an CBU, it is the DSO/DRC responsibility to collect all AEs and forward them to the DSG.

1.4. Regulatory Authority

It is the DSO/DRC responsibility to have a system in place to obtain ICSRs related to an organization products from their local Regulatory Authority.

2. PROCESSING OF AEs

Upon receipt by email of an AE from a DSO/DRC, the DSG will email back the DSO/DRC to acknowledge receipt, and provide a reference if there was none.

Once the case has been databased, the DSG will email the unique number to the DSO/DRC. The unique number should be used in any further correspondence both internally and externally.

Only safety reports containing the 4 minimum data elements (Reporter, Event, Patient, Product), are called Individual Case Safety Reports (ICSR), will be processed by the DSG, with an exception for literature AEs referring to a number of patients.

Upon receipt of AEs reports, triage will take place as follow :

- ICSR
- serious
- product : 1/ drug, 2/ medical device, 3/ monograph and 4/ cosmetic
- date of receipt.

Healthcare Serious AEs (i.e. drugs and medical devices SAEs) should be entered in the database within 4 working days of receipt by the DSG, and Healthcare non-serious AEs within 30 calendar days. Personal care Serious AEs (i.e. cosmetics and monographs SAEs) should be entered in the database within 4 working days of receipt by the DSG, and Personal care non-serious AEs within 90 calendar days.

ICSRs will be entered and coded in the database by the DSG.The Medical Assessor will then evaluate each ICSR for seriousness and causality Finally, the DSG will check each ICSR for approval prior to local assessment and reporting .

3. REPORTING

3.1. Serious ICSRs

Further to the approval of each serious ICSR, the DSG will inform by email DSO/DRC to review this serious ICSR.

The DSO/DRC will assess each serious ICSR for local labelling (i.e. local assessment), and will report it to the Regulatory Authority if applicable.

The DSO/DRC will capture their local assessment directly on the PV database. It is the responsibility of the DSG to submit ICSR to the country regulatory authorities.

3.2. Periodic Safety Update Report (PSURs) and other reports

The DSG is responsible for writing all PSURs. Where possible, PSURs will be written by active ingredient and in accordance with the International Birth Date. Once written, each PSUR will be distributed electronically as a pdf file to all DSOs. It is then the DSO/DRC responsibility to submit it or not to the Regulatory Authority. The DSO/DRC will acknowledge receipt of the PSUR and inform the DSG of submission/non submission.

If there is any additional local reporting requirements, e.g. a quarterly update report, the DSO will request it from the DSG at least 12 weeks prior to the submission deadline.

4. FILING/ARCHIVING

All safety data will be stored in a secure location, indefinitely and referenced, both at the DSG and the CBU. Each DSO/DRC is responsible for ensuring that all documentation is stored indefinitely at their CBU. At the DSG, all information related to a single ICSR will be filed in a specific file dedicated to that ICSR only. The world-wide number reference allocated to the ICSR once entered on the PV database will be annotated on each page of the documentation.

Hard copies of e-mails and other correspondence regarding this case will be retained with the source documentation. Each ICSR file will have a front sheet on which a written entry is made each time a new event related to that case is actioned. ICSRs will be filed by world-wide number. Every 6 months, ICSR files will be archived.

5. SIGNAL DETECTION

The DSG is responsible for screening the database for signal detection. Signal detection reports will be run quarterly by active ingredient and reviewed during the regular DSG meeting.

6. AN ORGANIZATION PRODUCT LISTS

The DSG will keep a list of organization products world-wide (Healthcare and Personal care products).

To ensure this list is up-to-date, DSO/DRC will be asked to review it twice yearly. This list will be used by the DSG for updating the WHO dictionary to ensure appropriate coding in the database, and also to update the database key ingredient code list.

7. SOPs

An organization has SHOULD have a single world-wide policy in PV. However, to ensure that an organization complies with local regulation, it might be necessary to write local SOPs to supplement an organization global procedures. Local SOPs are the responsibility of the local DSO/DRC within each CBU.

8. TRAINING

All GDSG staff and all DSO/DRC will receive appropriate training on :

- PV,
- the global PV SOPs,
- how to use the PV database.

Training will be tailored to the individual needs.

The QP will keep a record of the DSG staff and DSO/DRC who have been trained.

It is the responsibility of the DSO/DRC to inform all an organization employees at the CBU of their legal obligations in terms of Pharmacovigilance. All training information (e.g. slides/training materials, training record form) must be documented and retained by the DSO/DRC at the CBU .

CONCLUSION

Continuous monitoring of their effects, side effects, contraindications and outright harmful effects which can result in a high degree of morbidity and in some cases, even mortality, is essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the Country and outside. Because clinical trials involve several thousand patients at most; less common side effects and ADRs are often unknown at the time a drug enters the market. Even very severe ADRs, such as liver damage, are often undetected because study populations are small. Post marketing Pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have the responsibility of having a well-established Pharmacovigilance system to monitor adverse reactions of drugs. During the drug development phase and later during the life time of a marketed drug.

The reporting of safety information from clinical trials and with marketed products by Pharmaceutical companies to regulatory authorities has been mandatory for many years but with each national authority having different requirements as mentioned in earlier pages for comparative studies in European agencies, United state and Indian agencies.

List of Abbreviation

Sr.No	Abbreviations	Full Form of Abbreviations
1.	MAH	Market Authorization Holder
2.	SAE	Serious Adverse Effect
3.	COL	Corporate Office Level
4.	CBU	Country Business Unit
5.	AEs	Adverse Events
6.	DSG	Drug Safety Group
7.	DSC	Drug Safety Coordinator
8.	DSO	Drug Safety Officer
9.	DRC	Drug Regulatory Coordinator
10.	ICSR	Individual Case Safety Report
11.	PSUR	Periodic Safety Update Report
12.	SOP	Standard Operating procedure

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