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REGULATORY ASPECTS OF PHARMACOVIGILANCE ALONG WITH COMPARISION IN UNITED STATES AND EUROPE

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ABSTRACT

Pharmacovigilance is studying the safety and effectiveness of drugs and practice to minimize the possible risk associated with the use of drugs. It has developed to the new challenges it faces. With the modernization there is a rapid increase in knowledge as well as safety about the drug and humans. Pharmacovigilance helps to improve public health and safety. There is a need for new global network to share information and intelligence about benefit and risk of medicinal products. Regulatory aspects of Pharmacovigilance become more specific and advanced. Different Countries follow their guidelines based on specifications.

Key Words: Pharmacovigilance, drugs, drugs.

INTRODUCTION

DEFINITION

Pharmacovigilance(abbreviated **PV** or **PhV**),known as **Drug Safety**, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.

"pharmacovigilance" = *pharmakon* (Greek for drug) + *vigilare* (Latin for to keep watch). pharmacovigilance focuses on adverse drug reactions, or ADRs, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy, which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Medication errors such as overdose, and misuse and abuse of a drug, are also of interest because they may result in an ADR. [(1)]

Adverse Event Reporting

The activity that is most commonly associated with Pharmacovigilance, and which consumes a significant amount of resources for drug regulatory authorities and drug safety departments in pharmaceutical companies, is that of adverse event reporting. Adverse event (AE) reporting involves the receipt, triage, data entering, assessment, distribution, reporting (if appropriate), and archiving of AE data and documentation. The source may include: spontaneous reports from healthcare professionals or patients ,solicited reports from patient support programs; reports from clinical or postmarketing studies; reports from literature sources; reports from the media (including social media and websites); and reports reported to drug regulatory authorities themselves. For pharmaceutical companies, AE reporting is a regulatory requirement in most countries. AE reporting also provides data to these companies and drug regulatory authorities that play a key role in assessing the risk-benefit profile of a given drug.

The "4 Elements" of an AE case

One of the fundamental principles of adverse event reporting is the determination of what constitutes an adverse event case. During the triage phase of a potential adverse event report, the triager must determine if the "four elements" of an AE case are present:

1. an identifiable patient
2. an identifiable reporter
3. a suspect drug
4. an adverse event

If one or more of these four elements is missing, the case is not a valid AE report.

Coding of Adverse Events

Adverse events is the process by which information from an AE reporter, called the "verbatim", is coded using standardized terminology from a medical coding dictionary, such as MedDRA (the most commonly used medical coding dictionary).

The purpose of medical coding is to convert adverse event information into terminology that can be readily identified and analyzed. For instance, Patient 1 may report that they had experienced "a very bad headache that felt like their head was being hit by a hammer" [Verbatim 1] when taking Drug X. Or, Patient 2 may report that they had experienced a "slight, throbbing headache that occurred daily at about two in the afternoon" [Verbatim 2]

while taking Drug Y. Neither Verbatim 1 nor Verbatim 2 will exactly match a code in the MedDRA coding dictionary. However, both quotes describe different manifestations of a headache. As a result, in this example both quotes would be coded as PT Headache (PT = Preferred Term in MedDRA). [2,3]

TYPES OF ADVERESE EVENT REPORTS

1. Expedited Reporting

This refers to ICSR (*Individual Case Study Report*) is that involve a serious and unlabelled event (an event not described in the drug's labeling) that is considered related to the use of the drug. Spontaneous reports are typically considered to have a positive causality. In most countries, the timeframe for reporting expedited cases from the time a drug company receives notification (referred to as "Day 0") of such a case is 15 calendar days.

2. Clinical Trial Reporting

Known as SAE (Serious Adverse Event) Reporting from clinical trials, safety information from clinical studies is used to establish a drug's safety profile in humans and is a key component that drug regulatory authorities consider in the decision-making as to whether to grant or deny market authorization for a drug.

SAE reporting occurs as a result of study patients (subjects) who experience serious adverse events during the conducting of clinical trials. (Non-serious adverse events are also captured separately.) SAE information , which may also include relevant information from the patient's medical background, are reviewed and assessed for causality by the study investigator. This information is forwarded to a sponsoring entity that is responsible for the reporting of this information, as appropriate, to drug regulatory authorities.

3. Spontaneous reporting

Spontaneous reporting is the core data-generating system of international pharmacovigilance, relying on healthcare professionals to identify and report any adverse events to their national pharmacovigilance center, health authority (such as EMA or FDA), or to the drug manufacturer itself.[5]

The rule-of-thumb is that on a scale of 0 to 10, with 0 being least likely to be reported and 10 being the most likely to be reported, an uncomplicated non-serious event such as a mild headache will be closer to a "0" on this scale, whereas a life-threatening or fatal event will be

closer to a "10" in terms of its likelihood of being reported. In view of this, medical personnel may not always see AE reporting as a priority, especially if the symptoms are not serious. And even if the symptoms are serious, the symptoms may not be recognised as a possible side effect of a particular drug. In addition, medical personnel may not feel compelled to report events that are viewed as expected.

4. Aggregate Reporting

Aggregate reporting involves the compilation of safety data for a drug over a prolonged period of time (months or years), as opposed to single-case reporting which, by definition, involves only individual AE reports. The advantage of aggregate reporting is that it provides a broader view of the safety profile of a drug. Worldwide, the most important aggregate report is the Periodic Safety Update Report (PSUR). This is a document that is submitted to drug regulatory agencies in Europe, the US and Japan (ICH countries). [(4)]

Risk Management

Risk Management is the discipline within Pharmacovigilance that is responsible for signal detection and the monitoring of the risk-benefit profile of drugs. Other key activities within the area of Risk Management are that of the compilation of Risk Management Plans (RMPs) and aggregate reports such as the Periodic Safety Update Report (PSUR), Periodic Benefit Risk Evaluation Report (PBRER), and the Development Safety Update Report (DSUR).

- **Causality Assessment**

Causality refers to the relationship of a given adverse event to a specific drug. Causality determination (or assessment) is often difficult because of the lack of clear-cut or reliable data.

- **Signal Detection**

Signal detection (SD) involves a range of techniques (CIOMS VIII).

The WHO defines a safety signal as: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

- **Risk Management Plans**

A Risk Management Plan (RMP) is a document that describes the risks (adverse drug

reactions and potential adverse reactions) associated with the use of a drug. The overall goal of an RMP is to assure a positive risk-benefit profile once the drug marketed. The document is required to be submitted, in a specified format, with all new market authorisation requests within the European Union. Although not necessarily required, RMPs may also be submitted in countries outside the EU.

The risks described in an RMP fall into one of three categories:

- Identified Risks,
- Potential Risks,
- Unknown Risks.

RMP are the measures that the Market Authorisation Holder, usually a pharmaceutical company, will undertake to minimise the risks associated with the use of the drug. These measures are usually focused on the product's labeling and healthcare professionals.

In the US, under certain circumstances, the FDA may require a company to submit a document called a **Risk Evaluation and Mitigation Strategies (REMS)** for a drug that has a specific risk that FDA believes requires mitigation. While not as comprehensive as an RMP, a REMS can require a sponsor to perform certain activities or to follow a protocol, referred to as **Elements to Assure Safe Use (ETASU),**to assure that a positive risk-benefit profile for the drug is maintained for the circumstances under which the product is marketed.

Risk/Benefit Profile of Drugs

Pharmaceutical companies are required by law in most countries to perform clinical trials, testing new drugs on people before they are made generally available. This occurs after a drug has been pre-screened for toxicity, sometimes using animals for testing. The manufacturers or their agents usually select a representative sample of patients for whom the drug is designed – at most a few thousand – along with a comparable control group. The control group may receive a placebo and/or another drug, often a so-called "gold standard" that is "best" drug marketed for the disease.

The purpose of clinical trials is to determine:

- if a drug works and how well it works
- if it has any harmful effects, and
- if it does more good than harm, and how much more? If it has a potential for harm, how probable and how serious is the harm? [5]

Pharmacoepidemiology

Pharmacoepidemiology is the study of the incidence of adverse drug reactions in patient populations using drug agents.

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics is generally regarded as the study or clinical testing of genetic variation that gives rise to differing responses to drugs, including adverse drug reactions. Pharmacogenetics will eventually provide information as to which genetic profiles in patients will place those patients at greatest risk, or provide the greatest benefit, for using a particular drug or drugs.

Pharmacogenomics, on the other hand, is the broader application of genomic technologies to new drug discovery and further characterization of older drugs. [(1)]

International collaboration in Pharmacovigilance

CIOMS

The Council for International Organizations of Medical Sciences (CIOMS), through its Working Groups, is a globally-oriented that provides guidance on drug safety related topics. CIOMS is part of WHO and prepares reports that are used as a reference for developing future drug regulatory policy and procedures. Over the years, many of CIOMS' proposed policies have been adopted.

Examples of topics these reports have covered include:

- Current Challenges in Pharmacovigilance:
- Pragmatic Approaches (CIOMS V);
- Management of Safety Information from Clinical Trials (CIOMS VI);
- Development Safety Update Report (DSUR):
- Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials (CIOMS VII);
- Practical Aspects of Signal Detection in Pharmacovigilance:
- Report of CIOMS Working Group (CIOMS VIII). [(6)]

ICH

The ICH (the International Conference on Harmonisation) is a global organisation with members from the European Union, the United States and Japan.

The ICH Steering Committee (SC) is the governing body that oversees the harmonisation activities. Since its establishment in 1990, each of its six co-sponsors—the European Union (EU), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Ministry of Health, Labour and Welfare (MHLW, Japan), the Japanese Pharmaceutical Manufacturers Association (JPMA), the US Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA)—has had two seats on the SC. Other parties have a significant interest in ICH and have been invited to nominate Observers to the SC.

The three Observers are the World Health Organization (WHO), Health Canada and the European Free Trade Association (EFTA). The International Federation of Pharmaceutical Manufacturers Association (IFPMA) participates as a non-voting member of the SC. [5]

WHO

The principle of international collaboration in the field of pharmacovigilance is the principal basis for the WHO International Drug Monitoring Programme, through which over 100 member nations have systems in place that encourage healthcare personnel to record and report adverse effects of drugs in their patients. These reports are assessed locally and may lead to action within the country. Through membership of the WHO Programme one country can know if similar reports are being made elsewhere. Member countries send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database. When there are several reports of adverse reactions to a particular drug, this process may lead to the detection of a signal – an alert about a possible hazard communicated to members countries. This happens only after detailed evaluation and expert review. [7]

National and Regional Drug Regulatory Authorities

Canada

is regulated by the Marketed Health Products Directorate of the Health Products and Food Branch (Health Canada). [8]

Egypt

is regulated by the Egyptian Pharmacovigilance Center of the Egyptian Ministry of Health. [9]

European Union

is coordinated by the European Medicines Agency (EMA) and conducted by the national competent authorities (NCAs). (10)

India

National Pharmacovigilance protocol, Ministry of Health and Family Welfare, Government of India (11)

Japan

is regulated by the PMDA and MHLW. (12)

Kenya

is regulated by the Pharmacy and Poisons Board. (13)

Uganda

is regulated by the National Drug Authority.(14)

Latin America

Most Latin American countries have high or medium levels of regulatory pharmacovigilance requirements, in line with international standards.[15]

United States

In the U.S., the drug industry is regulated by the FDA. (16)

Regulatory Guidelines of Pharmacovigilance in different countries: (17)

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 reactions observed in the European region. The pharmacovigilance system is called **EudraVigilance** and contains separate but similar databases of human and veterinary reactions.

Pharmacovigilance in United States

Three branches of pharmacovigilance in the USA can be defined as the FDA; the pharmaceutical manufacturers; and the academic/non-profit organizations like RADAR and Public Citizen. The US Food and Drug Administration (FDA) receive reports about adverse drug reaction and takes appropriate actions for drug safety.

Pharmacovigilance in India

The Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Govt. of India launched the National Pharmacovigilance Programme (NPP) in November, 2004. The pharmacovigilance in India was 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 operational efficiency. CDSCO, New Delhi is at the top of the hierarchy followed by two zonal pharmacovigilance centers viz, Seth GS Medical College, Mumbai and AIIMS, New Delhi.

To summarize the basic knowledge about pharmacovigilance, it can be said that the information obtained from reports about adverse drug reactions promote drug safety on a local and national level. These reports are entered into the national adverse drug reaction database and analyzed by expert reviewers justifying the whole pharmacovigilance system.

Comparision of Pharmacovigilance in US and EU

EU	**US**
Regulations Governing Pharmacovigilance	
2001/20/EC Clinical Trials Directive 2005/28/EC Good Clinical Practice Medicinal Products for human use in clinical trials –Volume 10-Clinical trial Volume 9A Pharmacovigilance.	US-IND Annual Reporting 21CFR 312.33 Post-marketing Reporting of ADRs 21CFR314.80 PDUFA Reenactment with U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007, FDA. FDA Guidance Documents 1)Premarketing Risk Assessment 2)Development and Use of Risk Minimization Action Plans (RiskMAPs) 3)Good PVG Practices and Pharmaco-epidemiologic Assessment

		4)Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection.
	Pre-Marketing Safety Reporting	
Recipient	EMEA,EC,MS	FDA
Purpose	Benefit-risk assessment	Progress Report (focus on clinical development program)
Content	Benefit-risk assessment	Study data & summary information
Adverse event included	Format SUSARs; serious, associated, +/- expected	Listings of all SAEs, deaths, ESRs, and withdrawals due to AEs for the reporting period Adverse
Format	Concise global analysis Benefit-risk evaluation Implications for trial subject costs.Proposed measures to minimize risk Supporting results of non-clinical studies	Tabular summary of most frequent and most serious AEs by body system List of completed non-clinical studies and result summary Summary of foreign marketing developments General Investigational Plan for next year Outstanding IND business Description of IB revisions

Post-Marketing Safety Reporting	
Eudra-vigilance Mandatory electronic reporting Only include Medically Confirmed Reports Require QPPV Rapid Alert System EU, there are no harmonized rules for post-marketing studies. In the United Kingdom, reports of such events are actively solicited through the	AERS MedWatch Program (Voluntary and Mandatory) Optional Electronic Reporting NDA Annual Reports to FDA . Consumer Reports ‘ Dear HCP’ Letters Expedited Reporting of all Class Action

Prescription-Event Monitoring system, which surveys prescribers regarding any adverse experiences among the first 10,000 people who use a given drug. The European Medicines Evaluation Agency (EMEA) requires PSURs every 6 months for 2 years, annually for the 3 following years, and then every 5 years (at the time of renewal of registration	lawsuits Clinicians are encouraged, but not required, to report drug-related adverse events either to drug manufacturers or directly to the FDA NDA Periodic Reports quarterly during the first 3 years after the medicine is approved and annual reports thereafter
. Risk Management Plans	
NCE Risk management plan is mandatory in the EU A valid EU-RMP must Section 1: Product Information Section 2: Safety Specifications Section 3: PVG Plan Section 4: Risk minimization Plan if needed	FDA may determine Risk Evaluation and Mitigation Strategy (REMS) but this is not a requirement (FDAAA) Risk Minimization Action Plans (RiskMAPs) not mandatory in US but strongly advised at the time of filing, especially for NCE
Pharmacovigilance Audits	
Focus on Systems (Summary of Pharmacovigilance Systems) Variable resources but includes PV inspectors 4 months notice Detailed agenda/plan in advance of the audit Interview driven 3-4 inspectors for 5 days	Focus on reporting of data to FDA Field investigators 0 to 3 days notice for domestic inspections No clear agenda/plan Document/data review 1-2 inspectors for 1-3 days Focus on Systems (Summary of Pharmacovigilance Systems) Variable resources but includes PV inspectors 4 months notice Detailed agenda/plan in advance of the audit Interview driven 3-4 inspectors for 5 days

CONCLUSION

Pharmacovigilance has emerged over time as an essential part of public health program. Its range is increasing with number and diversity of pharmaceutical products rising. The globalization of world economy and increased public exposure to large number of medicines, calls for a better coordination between drug regulators. A complicated and essential relationship exists between numbers of partners in drug safety monitoring. Partnership and commitments are necessary between partners to meet the future challenges in pharmacovigilance. Different countries follow different guidelines for Pharmacovigilance. There should be harmonization between all countries to represent it in a better way and helpful to health of humans.

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