



## A study on pharmacovigilance case processing

Y. Anil Kumar\*, A. Divya, B. Sayamma, Sk. Karishma, Konda Ravi Kumar, Ch. Santhosh Kumar

Dept. of Pharmaceutical Sciences, Hindu college of Pharmacy, Amaravathi road, Guntur - 522002, Andhra Pradesh, India

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### Abstract

Pharmacovigilance plays an vital role in modern technology which helps in monitoring and assessing the high-quality of Drugs, detection and stopping of any unfavorable outcomes of drugs. Pharmacovigilance starts with case processing: this involve safety data collection and coding, case management reporting and submission. In case of clinical trial, it is the investigator or in case of post marketing trial, it is either the physician or the prescriber or the patient himself who reports the adverse event or any drug related problem. Pharmacovigilance case processing helps to get clear information regarding the drug and outcomes by using various software technologies. Arugs database, cemflow, vigibase and ICSR are few software used nowadays. Case processing helps to monitor and track all serious adverse events, and medically significant ADRs and other medical related product information followed by timely processing and reporting of such information according with the company and regulatory reporting.

**Keywords:** Pharmacovigilance, high-quality of Drugs, ADRs.

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### \*Corresponding Author

Y. Anil Kumar



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### Introduction

Pharmacovigilance has been defined as the process of identifying and responding to drug safety issues [1] and has grown considerably as a discipline over the past 10 to 15 years. An educational survey in 1994 revealed that more than 320 people currently worked in company pharmacovigilance functions in the UK alone [2]. Pharmaceutical companies are international, hence the number of staff working in this field within the industry, particularly in other European countries and the USA, is far greater. A major pharmaceutical company such as Astra has over 100 permanent, experienced staff in pharmacovigilance within its research and development organisation in Sweden and the UK and a similar number in local operating companies worldwide. This development has been driven by an increased recognition of the role of pharmacovigilance, the investigation and marketing of a wider range of diverse medicinal products and more stringent and detailed regulatory requirements. The number of individual reports of possible adverse drug reactions (ADRs) can be considerable, for key marketed products often more

than 1000 case reports a year are received worldwide from health care professionals and other sources.

The aims of pharmacovigilance within the industry are essentially the same as those of regulatory agencies; that is to protect patients from unnecessary harm by identifying previously unrecognised drug hazards, elucidating pre-disposing factors, refuting false safety signals and quantifying risk in relation to benefit. Although the perspectives of companies and the regulatory agencies may be different they now work more and more closely together and share information. However, central pharmacovigilance units in major pharmaceutical companies in many instances are far better resourced and have much greater 'in-house' expertise on the safety of their particular products.

### Scientific characteristics

Although now seen as a discipline in its own right, pharmacovigilance is related to a number of scientific disciplines, the most important being clinical medicine, clinical and pre-clinical pharmacology, immunology, toxicology and epidemiology.

The identification and analysis of the safety characteristics of medicines falls into two distinct stages. During the first stage, before marketing, the main methodology is experimental with clinical trials comparing the new treatment to placebo or existing alternative treatments. After introduction of a new medicine into general use, the main safety methodology is observational, i.e. uses data from observation of patients treated in clinical practice rather than from experimental

situations. In general, the experimental data are of much higher quality than the observational, with better control of confounding factors. The challenge in pharmacovigilance, therefore, is to analyse and draw well-founded conclusions from observational data collected after marketing. In addition, data from observational epidemiological studies are playing an increasingly important role.

### **Aims and Objectives**

To study the pharmacovigilance case processing reports.

### **Methods used in pharmacovigilance**

The activities under the name of pharmacovigilance can be divided into three groups are regulatory, industry and academia. Under Regulatory pharmacovigilance is driven by the aim to provide drugs with a positive benefit-harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by a description of the methods used to detect new ADRs. Two forms of descriptive studies will be discussed here and are as follows:

1. Spontaneous reporting.
2. Intensive monitoring.

### **Spontaneous reporting**

In the year of 1961, Australian physician WG McBride was published a letter, and shares his observation that babies whose mothers had used thalidomide during pregnancy were born with congenital abnormalities more often than babies who had not been exposed to thalidomide in uterus. In the years to come it became evident that thousands of babies had been born with limb malformations due to the maternal use of thalidomide. In order to prevent a similar disaster from occurring, systems were set up all over the world with the aim of regulating and monitoring the safety of drugs. Spontaneous reporting systems (SRS) were created, and these have become the primary method of collecting post-marketing information on the safety of drugs. The main function of SRS is the early detection of signals of new, rare and serious ADRs. By means of a SRS it is possible to monitor all drugs on the market throughout their entire life cycle at a relatively low cost. With a SRS, it is not possible to establish cause-effect relationships or accurate incidence rates; it is also not possible to understand risk factors or elucidate patterns of use. Although critics say that spontaneous reporting is not the ideal method for monitoring the safety of drugs, it has proven its value throughout the years.

### **Data mining**

The term 'data mining' refers to the principle of analyzing data from different perspectives and extracting the relevant information. Algorithms are often used to determine hidden patterns of associations or unexpected occurrences i.e. signal in large databases. In the past, signal detection in spontaneous

reporting has mainly occurred on the basis of case-by-case analyses of reports. Several approaches of data mining are currently in use. Proportional reporting ratios (PPRs), which compares the proportion of reports for a specific ADR reported for a drug with the proportion for that ADR in all other drugs. The Bayesian confidence propagation neural network (BCPNN) method is used to highlight dependencies in a data set. This approach uses Bayesian statistics implemented in neural network architecture to analyze all reported ADR combinations. A related approach is the Multi-Item Gamma Poisson Shrinker (MGPS) used by the FDA for data mining of their spontaneous report's database. The MGPS algorithm computes signal scores for pairs, and for higher-order (e.g. triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pairwise associations would predict.

### **Intensive monitoring**

These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored. These data are collected and analyzed for new signals. In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (the Intensive Medicines Monitoring Programme) and the UK (Prescription Event Monitoring). The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spontaneous reporting because the former only monitors selected drugs during a certain period of time. Through its non-interventional character, intensive monitoring provides real world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. Intensive monitoring programmers also enable the incidence of adverse events to be estimated, thus enabling quantification of the risk of certain ADRs. Although the intensive monitoring methodology was developed more than 20 years ago, this methodology has received renewed interest in the last years. In the European Commission consultation 'Strategy to better protect public health by strengthening and rationalizing EU pharmacovigilance' intensive monitoring is mentioned as one tool that can improve the pharmacovigilance system.

Analytical studies can be conducted using a variety of approaches, including case-control studies, cohort studies and clinical trials. In order to be able to conduct retrospective cohort and case-control studies, data which have been collected in a reliable and routine manner needs to be available. To provide an example of such studies, we describe here two European databases frequently used for analytical studies, the General Practitioners Research Database (GPRD) in the UK and the PHARMO Record Linkage System in the Netherlands.

## GPRO

In any given year, GPs (general practitioners), who are members of the GPRD, collect data from about 3 million patients (about 5% of the UK population). The data collected include demographics (age and sex), medical diagnoses, along with the date and location of the event, date of prescription, formulation strength, quantity and dosing instructions, indication for treatment for all new prescriptions and events leading to withdrawal of a drug or a treatment. Data on vaccinations and miscellaneous information, such as smoking, height, weight, immunizations, pregnancy, birth, death, date entering the practice, date leaving the practice and laboratory results, are also collected. There have been over 250 publications in peer-reviewed journals using the GPRD.

## PHARMO

PHARMO links community pharmacy and hospital data within a specific region on the basis of patient birth date, gender and GP code. The system now includes drug-dispensing records from community pharmacies and hospital discharge records of about 2 million people in the Netherlands. Recently, PHARMO has also been linked to other data, such as primary care data, population surveys, laboratory and genetic data, cancer and accident registries, mortality data and economic outcomes. In the early 1990s, the PHARMO system of record linkage was developed in The Netherlands. The system has well-defined denominator information that allows incidence and prevalence estimates and is relatively cheap because existing databases are used and linked. In the past the database has been used for studies on drug utilization, persistence with treatment, economic impact and ADRs.

## Research methodology of pharmacovigilance

Pharmacovigilance (PV) is the process of detecting and monitoring adverse drug reactions (ADR), adverse events (ADE), detecting potential 'signals' throughout the drug/medical device lifecycle, and also tracking trends in consumers' sentiments regarding a particular product (drug/medical device) over time.

### 1. Data entry

Data must be accurate. Data processors must be trained and supervised until their level of skill is acceptable.

### 2. Quality control

Use field controls and standard formats as in E1.2. The use of codes, e.g. ICD-10 or ATC codes results in fewer errors than does typing in names.

### 3. Coding of medicines and diseases

CemFlow is the preferred method of data entry. The clinical reviewer can enter clinical details directly on a "reviewer's screen" during the review process. The head of the PvC or the

CEM Clinical Coordinator can apply to the UMC for access and user registration for CemFlow or Select drug names or codes from the WHO Drug Dictionary.

## 4. Software used in Pharmacovigilance

- Oracle Argus Safety.
- Cem work flow
- Vigi data flow
- Clinovo database

### Oracle Argus Safety

Oracle Argus is a comprehensive pharmacovigilance platform which enables pharmaceutical companies and clinical trial organizations to make faster and better safety decisions, optimize global compliance, and easily integrate risk management. Argus is a systems and network monitoring application.

- Logging in: Enter your username and password.
- Entering Case Data:
  - Creating a New Case
  - Finding an Existing Case
  - Updating a Case.

#### I. General tab

General tab captures the case information in categorized sections for category-specific information. It also enables you to enter or view information such as type of report, literature information, and so forth.

- General Information
- Study Information
- Reporter Information
- Literature Information

#### II. Patient tab

Patient tab gives clear information regarding the patient details, history and information of medicaments. This includes 2 subtabs:

- **Patient Tab:** For details on entering data in each section of the Patient tab, see:
  - Patient Information
  - Patient Details
  - Event Death Details
  - Other Relevant History
  - Lab Data
  - Relevant Tests

- **Parent Tab:** For details on entering data in each section of the Parent tab, see:
  - Parent Information

#### III. Products tab

Products tab consists of 3 subtabs:

- Drug Tab  
For details on entering data in each section of the Drug tab, see:
  - Product Information
  - Product Indication

- Quality Control
- Dosage Regimens
- Product Details

- Device Tab

For details on entering data in each section of the Device tab, see:

- Product Information
- Product Indication
- Device Information
- Quality Control

- Vaccine Tab

For details on entering data in each section of the Vaccine tab, see:

- Product Information
- Product Details
- Vaccine Administration
- Prior Adverse Events
- Vaccine History

#### IV. Events

The Events tab has the following sub-tabs:

- Event Tab

The Event information tab lets you encode adverse events, record criteria for event seriousness, and display results of automated assessments that determine whether events are listed in data sheets.

- Event Information
- Event Coding
- Seriousness Criteria
- Nature of Event

- Event Assessment Tab

For details on entering data in each section of the Event Assessment tab, see:

- Product
- Event PT
- Datasheet

- Product- Event details tab

- Onset from first dose
- Onset from last dose

#### V. Analysis

The Analysis tab enables you to generate or view a narrative description of the case along with other notes. It also enables you to enter information required for generating the MedWatch 3500A, BfArM, and AFSSaPS reports. Use this tab to:

- Make a medical assessment of the case
- Approve the case for completeness and accuracy.

These consists of:

- Case analysis
- Case summary

#### VI. Activities

The Activities tab presents detailed information about the

- Contact Log,
- Routing Comments,
- Action Items, and
- Case Lock/Closure.

#### VII. Additional information

On the Case Form page, click the Additional Information tab. Enter information in the Notes and Attachments and References sections

#### VIII. Regulatory reports

The following procedures describe tasks for Expedited Reports. You can also schedule, review, generate, and transmit Periodic reports in a similar manner.

#### Vigi Base

VigiBase is the single largest drug safety data repository in the world. Since 1978, the Uppsala Monitoring Centre (UMC; established in Uppsala, Sweden) on behalf of WHO, have been maintaining VigiBase. VigiBase is used to obtain the information about a safety profile of a medicinal product.

#### Conclusion

Numerous articles are published on pharmacovigilance concept, history and terminologies. This article provides clear information about the software and usage of the software in pharmacovigilance regarding drug safety monitoring. This helps to identify rigorous testing of clinical drugs to improve patient care and reduce the risk of negative side effect. Pharmacovigilance workflow useful to get easy outcomes of the regulatory reporting and ensures drug safety monitoring.

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