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PHARMACOVIGILANCE SYSTEM IN USA AND WHO

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ABSTRACT

Pharmacovigilance system is a branch of pharmacological sciences dealing with reporting of Adverse Reaction Events which are caused by medicines and/or medical devices. As a result, Pharmacovigilance System has been established which deals with collection, detection, assessment, monitoring and prevention of adverse effects of pharmaceutical products. US pharmacovigilance system is regulated by US Food and Drug Administration-USFDA Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug. The aims of PV are, to augment patient care and patient safety in relation to the use of medicines; to upkeep public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. UMC manages chief aspects of the mounting universal Pharmacovigilance set-up of the now more than 130 countries, known as the WHO Programme for International Drug Monitoring. WHO Collaborating Centre follows WHO policies and work in close relation with it does headquarter. UMC is organisationally and professionally discrete from WHO itself.. This article will focus on the pharmacovigilance programme in USA and WHO depicting its Adverse Drug Reaction Reporting system

INTRODUCTION

The thalidomide tragedy in the mid twentieth century triggered a chain of activities that were part of a global effort to avert a recurrence. Australia, Canada, several European countries, New Zealand and the United States of America established monitoring schemes based on reporting of suspected adverse drug reactions (ADRs). This culminated in the setting up of the WHO Programme for International Drug Monitoring. In the past fifty years, there has been a steady growth in the science now known as pharmacovigilance with an exponential turn in recent years. In the course of this growth, various terminologies and parameters have been introduced to enable communication and exchanges among workers in the field. The need for communication on drug safety has been further endorsed in the Erice declaration. However, little attention has been paid to

the development of indices which will provide a baseline and allow for an assessment or quantification of the growth and performance of pharmacovigilance, which will enable comparison within and between countries, regions and facilities. Pharmacovigilance has attained the maturity and stature of a discipline that has a significant impact on patient care and public health.[1] Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which do not reflect practice conditions as they are limited by the patient numbers and duration of trial as well as by the highly controlled conditions in which Clinical Trials are conducted. Pharmacovigilance is as a result one of the significant post-marketing tools in ensuring the safety of pharmaceutical and related health products. Apart from Drug Regulating Authorities Central Drug Standard Control Organization (CDSCO) for India and US-Food and Drug Administration (USFDA) for US, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Pharmacovigilance Planning (ICH E2E) and World Health Organization-Uppsala Monitoring Centre (WHO-UMC) also play contributes for developing, enhancing and monitoring Pharmacovigilance System around the globe.[2]

The purpose of Pharmacovigilance[4]

- To monitor all emerging information related to a medicinal product or substance.
- To analyze and report all relevant findings to regulatory authorities.
- Generate new insight that will expand our knowledge on the substance's effects.
- Use that knowledge to improve treatments and healthcare.
- Protect the public and prevent risks.

The products under consideration go beyond conventional medicines and also include herbal medicines, other traditional and complementary products, biological, vaccines, blood products and possibly medical devices.[1]

Reporting ADRS

Solicited Reports: They report information from clinical studies, patient support and disease management programs, surveys, non-interventional studies, and other organized systems of data collection.

Spontaneous Reports: When a consumer or healthcare professional communicates an ADR to a competent authority or MAH.

- This information does not come from organized data collection.

Literature Reports:

- They are composed of scientific and medical literature.
- Crucial for insights on the balance of risks and benefits.
- Information from literature is used for writing aggregate and potentially reporting/coding the individual case safety reports.

Reports from other Resources:

- Information that originates from non-medical sources.
- The reporter should make an effort to follow up on the information to get the minimum requirements for an ICSR.
- It is handled like a spontaneous report.

Internet and Digital Media:

- A recent form of ADR reporting.
- MAHs screen the Internet and digital media to for reports of potential suspected ADRs.
- They should also be handled as a spontaneous report.[4]

OBJECTIVES: The objectives of the study are: To understand the Pharmacovigilance System.

- To Apprehend and review the regulatory background of Adverse Event Reporting System in USA & WHO.

DISCUSSION: Many serious drug adverse events (AEs) only manifest well after regulatory approval. Therefore, the development of signaling methods to use with post-approval AE databases appears vital to comprehensively assess real-world drug safety. However, with millions of potential drug-AE pairs to analyze, the issue of focus is daunting.[5] FDA objective was to develop a signaling platform that focuses on AEs with historically demonstrated regulatory interest and to analyze such AEs with a disproportional reporting method that offers broad signal detection and acceptable false-positive rates. [5] FDA analyzed over 1500 US FDA regulatory actions (safety communications and drug label changes) from 2008 to 2015 to construct a list of eligible signal AEs. The FDA Adverse Event Reporting System (FAERS) was used to evaluate disproportional reporting rates, constrained by minimum case counts and confidence interval limits, of these selected AEs for 109 training drugs. This step led to 45 AEs that appeared to have a low likelihood of being added to a label by FDA, so they were removed from the signal eligible list. We measured disproportional reporting for the final group of eligible AEs on a test group of 29 drugs that were not used in either the eligible list construction or the training steps. [5]

I. Pharmacovigilance in USA [2]

History: After the Elixir Tragedy in 1937 and The Thalidomide Tragedy in1960, United States had revised the **Food and Drug Administration Regulations** to demonstrate the safety and efficacy of drug before issuing marketing Authorization.

Regulations: U.S. Department of Health and Human Services and Food and Drug Administration (FDA) regulates pharmacovigilance with help of Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).[2]

Identifying and Describing Safety Signals: From Case Report to Case Series [6]

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

What is MedWatch? [7]

- A way to send information which applicant observe or experience from regulated medical products to FDA
- A way to stay up-to-date on recently reported safety information from FDA

Who can Report to MedWatch

- Healthcare Professionals
- Consumers and Patients

Why Report to MedWatch?

- "Every product that FDA approves carries some risk…Sometimes there are risks that only come to light after a medical product gets on the market and is used in a larger number of patients, for a longer period of time, and in patients whose health characteristics are different from those of the patients studied before approval."

Why Report to MedWatch?

- Not all products have clinical data/trials before clearance to market
- Limitations of clinical trials to identify safety signals before marketing

- Number of patients tested may be too small to detect serious but rare problems
- Trials are brief

MedWatch -What to Report

Serious events such as:

- Death
- Life threatening
- Permanently disabling
- Prolongs hospitalization
- Birth defect
- Requires intervention to prevent permanent impairment or damage
- Medication errors
- Product quality problems
- Potential for error
- Non-serious events

MedWatch – What not to Report

- Tobacco Products
- Vaccines
- Investigational Drugs
- Dietary Supplements
- Veterinary Medicine

Post-Marketing Surveillance

Safety Monitoring during the Post-Approval Phase of a Drug Product's Life Cycle

- Less frequent adverse drug experiences (ADEs)
- Patients with higher risk for ADEs
- Chronic and long term use
- Drug-drug interactions
- Drug-food interactions
- Expected ADEs
  - ➢ Increased severity or frequency
- Misuse or abuse of drug product
- Medication errors
  - ➢ Product packaging, labeling, other characteristics

Types of Post-Marketing Adverse Event Data

- Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Local or Regional (joint Comission Requirement)
  - Scientific literature publications
- Post-marketing studies (coluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials
- Active surveillance
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel initiative

Figure 1: Post-marketing Adverse Event Reporting and MED Watch[7]

Post – marketing safety reporting requirements

Under 21 CFR 314.80 post-marketing safety reports must be submitted to the agency for the following:

- ➢ **15-day Alert reports:** Serious and unexpected adverse experience from all sources (domestic and forign)
- ➢ **Periodic Adverse Events Reports:** domestic spontaneous adverse events that are:
  - Serious and expected
  - Non-serious and unexpected
  - Non-serious and expected
  - Quarterly for the first 3 years then annually

Serious Adverse Experience

- Results in any of these outcomes:
- Death
- Life-threatening adverse experience
- Inpatient hospitalization-new or prolonged
- Persistent/significant disability/incapacity
- Congenital birth defect

- Other serious: Based upon appropriate medical judgment, they may jeopardize the patient and require intervention to prevent a serious outcome

Spontaneous Reports and FAERS

- A communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority.
- Describe a suspected adverse event (s)
- Passive and voluntary reports

Spontaneous Reporting System Limitations

- Passive, voluntary surveillance
- Underreporting occurs and is variable from drug to drug and over time
  - ✓ Some literature cites 1-10%
  - ✓ Actual is unknown so FDA does not assume extent
- Reporting bias exists
- Quality of the reports is variable and often incomplete
- Duplicate reporting of the same case occurs
- Not population-based data source
- Cannot reliably estimate incidence or prevalence
- Numerator uncertain, denominator can only be projected from drug utilization data

FDA Adverse Event Reporting System

- Fully automated computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- 13 million reports since 1969
- Over 1.69 million new reports in 2016

Best Applications of FAERS[7]

- Events that are linked to specific diagnoses
- Events with a serious outcome that rarely occur in an untreated population
- Events with a short-to-moderate latency period following exposure
- "Safety signal" generation and descriptive case series

What is a Safety Signal

- Reported information on a possible casual relationship between an adverse event and a drug.
- The relationship being previously unknown or incompletely documented Usually supported by multiple case reports
- New unlabeled adverse events
- An observed increase in a labeled event or a greater severity or specificity
- New Interactions
- Newly identified at-risk population

Components of a Good Post-marketing Report[7]

- Description of adverse event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, comorbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

Evaluation of Case Reports[7]

- Adverse event occurrence in expected time
- Absence of symptoms prior to exposure
- Positive dechallenge or rechallenge
- Consistent with pharmacologic effects
- Consistent with known effects in the class
- Support from pre-clinical studies, clinical trials
- Absence of alternative explanations[9]

ADR reporting procedure of USA[2] According to the Post Marketing Reporting of ADRs 21 CFR 314.80, FDA submit the Reports to the FDA Adverse Event Reporting System (FEARS). Reporting of ADR is done through following ways:

- Healthcare Professionals (Physicians, Pharmacists, Nurses and Others), Consumers (Patients, Family Members, Lawyers and Other), Regulated industries, Facility Users. Healthcare professionals, consumers, Regulated Industry and User facilities record the ADRs through either ADR form 3500A or ADR form 3500B and send these reports to FDA.
- Reporting is done online through MedWatch. FDA sends ADRs report to FDA Adverse Event Reporting System. Reports are assessed by clinical reviewers in the CDER and CBER.
- If a probable safety concern is acknowledged by FAERS, supplementary evaluation is performed this evaluation might include conducting studies using other large databases. The records are maintained for 10 years.

Figure 2: ADR Reporting System of USA[2] FDA provides drug and non vaccine biological product manufacturers, distributors, packers, outsourcing facilities, and other interested parties with information about FAERS electronic submissions and instructions on how to electronically submit postmarketing individual case safety reports (ICSRs) with and without attachments.[21] Since 2000, FDA has accepted electronic submissions of both expedited and non-expedited ICSRs for human drug and non vaccine biologic products. To date, FDA has only accepted electronic submissions of ISCRs in the XML format, prepared in accordance with International Conference on Harmonisation-E2B (ICH E2B) to transmit information directly from database-to-database using standardized (ICH E2B (M)) data elements. FDA is requiring that applicants electronically submit all ICSRs, ICSR attachments, and periodic safety reports. There are two options for submitting ICSRs electronically:

- Database-to-database transmission ("E2B")
- The Safety Reporting Portal (SRP) by manually entering the data via our SRP portal.
- Attachments: for both methods, FDA will only accept attachments in the PDF format.

Submitting ICSRs, ICSR Attachments, & Periodic Safety Reports (PSRs)

1. **Electronic submission of ICSRs [**11]
   Applicant have the 2 options for submitting ICSRs electronically.

   ICSR Option A: Database-to-Database Transmission ("E2B")

   - ICSRs must be submitted in the XML format.
   - Attachments must be in the pdf format.
   - Details are provided in the document "Specifications for Preparing and

Submitting Electronic ICSRs and ICSR Attachments". XML files are submitted to the FDA via the Electronic Submissions Gateway (ESG).

- For additional instruction on how to begin submitting ICSRs in the XML format, refer FDA document titled, "Steps to Submitting ICSRs Electronically in the XML Format."

ICSR Option B: Safety Reporting Portal (SRP): Applicants and non-applicants who do not have database-to-database capability may submit electronic ICSRs using the SRP. To submit via SRP, applicant must have an account to access the portal site. Those who are Gateway partners cannot use the SRP. Gateway partners are those companies that submit electronically via the Electronic Submission Gateway.

Steps for requesting an SRP account:
Contact FAERSESUB@fda.hhs.gov t o advise FDA of your intent to begin submitting via the SRP.

SRP account activation

- Applicant account will be activated in about 7 to 10 business days.
- Applicant will be notified via email with the subject line "SRP Account Activation" that will include the web link to the SRP portal along with account information.
- After receiving this email, Applicant account will be considered active and applicant may begin submitting reports.

2. **Submitting ICSR Attachments** Attachments to ICSRs include supporting information for ICSRs such as relevant hospital discharge summaries and autopsy reports, death certificate, and published articles for ICSRs based on scientific literature.

    - Database-to-Database Transmission ("E2B").
    - Submit attachments to ICSRs through the electronic submission gateway (ESG). FDA document "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments".
    - Safety Reporting Portal (SRP).
    - To submit ICSR attachments via the SRP, use the features within the portal that allows you to browse, select, and attach documents to an ICSR.[11]

3. **Submitting Periodic Safety Report** Periodic safety reports are comprised of a descriptive portion and non-expedited ICSRs (21 CFR 314.80 and 600.80), regardless of the format.

    1. **Descriptive Portion:**

        - Use Electronic Common Technical Document (eCTD) specifications to submit the descriptive portion electronically.
        - Indicate in the descriptive portion that the ICSRs have been submitted electronically as XML files to the FDA ESG or via the Safety Reporting Portal (SRP).

2. **Non-expedited ICSRs:** must be submitted as described above and on or before the periodic safety report due date. Do NOT submit expedited ICSRs previously submitted.[11]

II. PHARMACOVIGILANCE IN WORLD HEALTH ORGANIZATION-WHO[2] WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (WHO 2004,). Terms related to the science of pharmacovigilance are defined differently in different settings and by different organizations.

Procedure For Reporting Adverse Drug Reaction[15] Health care professional should bear in mind when reporting an ADR that ADR reports are, for the most part, only suspected associations that a drug has caused a particular adverse event. Reporting an ADR does not imply a causal association between the drug and the adverse reaction. However, in a doubtful case it is better to report than not to report.

1. WHAT TO REPORT

Any undesirable adverse event suspected to be associated with use of drug, biological (including blood products), herbal drugs, cosmetics or medical devices should be reported. They should include;

1. All ADRs as a result of prescription and non-prescription

2. All suspected adverse drug reactions regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product

3. Unexpected reaction, regardless of their nature or severity, whether not consistent with product information or labelling

4. An observed increase in frequency of a given reaction

5. A serious reaction, whether expected or not

6. All suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions

7. ADRs in special field of interest such as drug abuse and drug use in pregnancy and during lactation

8. ADRs occurring from overdose or medication error

9. Unusual lack of efficacy or when suspected pharmaceutical defects are observed

What information is required for an ADR case report?

The minimal standard information to be provided for proper assessment of the ADR case report are;

1. Patient information

2. Adverse reactions description (include laboratory results if available)

3. Information related to the suspected drug(s)

4. Information on management of the adverse reactions

5. Information about the reporter

Reporters are advised to study carefully and adhere to the guides on how to complete an ADR reporting form for proper interpretation. (See ADR reporting form annexure V).

Patient information

1. Patient identity: Indicate initials or record number of the patient in hospital, medical institution, dispensary, clinic or pharmacy.

2. Birth dates or age: Indicate date, month and year

3. Sex: Male or Female

4. Weight: Should be in Kilograms

I. Adverse reaction(s)

(1. Brief description of the ADRs) Indicate the adverse(s) reaction by marking X in the appropriate box. Preferably describe briefly the nature of the adverse reaction being reported but as clearly as possible, including the body site and severity.

(2. Time/date of onset of the adverse reactions) State the time of onset or the occurrence of the adverse reaction in relation to the administration of the drug. Indicate the date of onset in the following order; day, month and year. For example, did the drug reaction appear immediately following drug administration or there was temporal or spatial correlation with administration.

(3. Other relevant information)

i. Patient medical history or laboratory data including dates if available, considered relevant to the case or the adverse reaction being reported should be entered.

ii. Mention appropriate laboratory tests done to the patient and results to confirm the adverse reaction.

iii. State this concisely but clearly.

II. Suspected drug(s)

1. Name of the suspected drug (s): Trade name should preferably be used, if trade name not available, generic name may be used. Strength of the drug (s) should be stated

2. Dosage, frequency and route of administration should be clearly notified. For example;

- Dosage (specify dosage form; tablet, capsules, syrup, injection, cream, eye drops, etc. including total amount of drugs).
- Frequency: specify unit first i.e. mg, ml, mg/kg and number of time given e.g. 4 times daily or q.i.d.
- Route of administration by which the drug was administered. This should be entered in full term or abbreviated using the World Health Organisation (WHO) codes

3. Therapy date: The dates of beginning and termination of the administration of each drug should be stated, and preferably recorded as follows date, month and year. If dates are not available, record duration of treatment. If drug administration has not been terminated at the time of reporting, state 'Continuing'

4. Batch number and expiry date: Provide these information if are available

5. Reason for use: State indication or condition for which the drug(s) was given for.

6. Particular of concurrently drugs(or other treatment): state particulars of other drug (s) administered by the patient concurrently with the suspected drug, including drug administration for at least 1 month back with dosage, route of administration, duration of administration and indications.

7. Provide relevant information on medical devices

III. Management of the adverse reaction

1. Confirmation of the ADRs: Indicate what assisted in confirming the suspected adverse reactions. For example:

- Drug reactions confirmed by disappearance of the reaction after stopping administration of the drug or reducing the doses.
- Recovery on withdrawal of suspected drug(s) if no other drug is withdrawn and no therapy given.
- Recovery follows treatment of the reaction in addition to withdrawal of drug.

2. Mention the criteria for regarding the reaction as serious

3. Mention any treatment given to the patient after experiencing the ADRs.

4. Outcome: indicate the outcome of the adverse reaction by marking X in the appropriate box with dates in case of fatal outcome.

IV. Reporter information

Details on reporter of an ADR: mention applicant particulars:-name, address of the health facility (hospital, institution, dispensary, clinic, company, pharmacy or maternity home). E-mail address (optional), signature, telephone number and date of reporting the reaction (indicate date, month and year)

2. WHO SHOULD REPORT

Submission of a report does not constitute an admission that a health care professional or the drug or the product caused or contributed to the ADR in any way as all reports are termed as suspected.

Reporters should bear in mind that any information related to the reporter and patient identities shall be kept confidential.

The following should provide reports of any case of suspected ADRs when encountered to the patient as part of their professional responsibility:-

1. All health care professionals including specialists, doctors, dentists, pharmacists, nurses, assistant medical officers, clinical officers, pharmaceutical technicians, pharmaceutical assistants, traditional medicine practitioners and others health care providers

2. Manufacturers or Product registrants they should develop system for ADR follow-up within their company and assessment of impact of notification of significant safety data on their products.

3. All government hospitals, private hospitals, health centres, dispensaries private clinics, private pharmacies and private nursing homes have obligation to report all ADR cases encountered or reported to them by the patients.

Incharge of the following facilities; government and private hospitals, health centres and dispensaries they are required to nominate a focal person who will coordinate the ADRs collection and reporting within the facility.

This person will be a link between the institution and Regulatory Authority

It is vital to report an ADR to Regulatory Authority even if you are doubtful about the precise relationship with the given medication or you do not have all the facts. What is required is to report all SUSPECTED ADRs. Collection of reports from several healthcare providers in different parts of the country assists in making associations (strengthening of signal) between a particular drug and the adverse reaction.

Therefore, you must ensure that all necessary information for submission of ADR reports are obtained and reported through the reporting forms.

3. WHEN TO REPORT

Any suspected ADR should be reported as soon as possible. Delay in reporting will make reporting inaccurate and unreliable. If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient

4. HOW TO REPORT

Reporters should send accurate information to achieve a better and efficient program on ADRs monitoring in WHO. Send the report in a standardised form for reporting ADRs. The reporting form is self adhesive postage paid “yellow form”

Dully fill in the ADRs reporting form (annexed) when encountering an ADR to the patient.

Use a separate form for each patient (refer to filling guides)

4. A completed ADRs case report form should immediately be sealed and mailed preferably directly to Regulatory Authority within three days or through other

reporting centres for onward transmission to the Regulatory Authority

5. Reports can also be submitted online by going to the Regulatory Authority website http://www.Regulatory Authority.or.in and clicking on "adverse drug reaction reporting" on the bottom-right

6. Reports may be sent by e-mail through the following e-mail address; adr@Regulatory Authority.or.in

7. ADR reports may be faxed in cases of perceived urgency

8. Any follow-up information for an ADR case that has already been reported can be sent on another ADR form, or communicated by telephone, fax or e-mail. To enable this information be matched with the original report it is very important that follow-up reports are identified and the following should be indicated in the report;

a. that it is a follow-up information,
b. the date of the original report and
c. The patient identities.

Basic principles of efficient reporting

1. Report the adverse reaction immediately after it occurs.
2. If possible, take the decision to report whilst the patient is still with you, so that the details can be filled in at once on the reporting form.
3. Think about any other factors which may contribute in causing the event such as other prescribed drugs, self-medication, herbal products, food, chemicals, ask the patient particularly about other medicines taken.
4. If you get any supplementary data later, e.g. if the same patient develops the effect again or if something happens which increases your suspicion or seem to exclude the reaction, please send in a supplementary note immediately using ADRs reporting form with the patient identifiers.
5. All reports must have the following four data elements
    - An identifiable patient
    - A suspected adverse effect
    - A named suspected drug (s)
    - An identifiable reporter
6. Always write legibly.

5. WHERE TO REPORT

Report any suspected ADRs for pharmaceutical products marketed in WHO to the appropriate channels as follows:-

- Preferably directly to Regulatory Authority by post or online
- Via Zonal Drug Information Centres at National Hospital, Consultant Hospital, Bugando Medical Centre (BMC) and Kilimanjaro Christian Medical Centre (KCMC), for onward transmission to Regulatory Authority
- Via a focal person in the following health facility; government hospitals, private hospitals, health centres, dispensaries for onward transmission to Regulatory Authority

How to obtain the reporting form?

The ADR reporting form is obtained free of charge from;

- Regulatory Authority offices
- The website of Regulatory Authority, downloaded at http://www.Regulatory Authority.or.in
- Zonal Drug Information Centres.
- Regional hospital, district hospitals and ADRs focal persons in hospitals, health centres, clinics and dispensaries.[13]

PROCESSING OF COLLECTED ADVERSE DRUG REACTION DATA[14]

1. ASSESSMENT OF ADR CASE REPORTS

Assessment of case report aim at identifying national drug safety problems and respond to these through communication and or scientific risk/benefit assessment.

WHO is responsible with continuous collection, assessment and storage of reports of, suspected adverse reaction to medicinal products marketed in the country.

Reports are initially separated according to their source. All case reports will be individually assessed and the following shall be considered: -

1. Quality of documentation in respect to completeness on the four elements of a case report as possible, integrity of data, quality of diagnosis and follow-up.
2. Analysis; this shall be based on the temporal relationship between the reaction and the drug, whether there was positive dechallenge/rechallenge, the seriousness of the reaction, whether the current labelling lists the reaction and whether the reaction is reported on the medical literature.
3. Clinical relevance in respect to detection of new reaction especially for new drugs, unknown reactions or serious. If similar cases are found, the report becomes a monitored adverse drug reaction.
4. Quality control in respect to identification of duplicate reports. Certain characteristics of a case report for example; sex, date of birth or age, name of the suspected drug, dates of drug exposure etc. shall be used to identify duplicate reporting or follow up report.
5. Causality assessment and transmission of the assessed reports in suitable format to the WHO database of International Drug Monitoring at Uppsala Monitoring Centre (UMC) shall be done monthly.

The causality assessment and ADR coding shall be based on WHO causality categories. The categories are based on four considerations:-

i. The association in time between drug administration and event
ii. Pharmacology (including current knowledge of nature and frequency of adverse reactions)
iii. Medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings, mechanism)
iv. Likelihood or exclusion of other causes

The Coding; drug names shall be entered in a systemic way by using the WHO Drug Dictionary and preferably the trade name of the suspected product shall be used. Diseases will be classified based on International Classification of Diseases (ICD) developed by WHO. The adverse events description shall be entered based on the WHO Adverse Reaction Terminology (WHO-ART).

6. Generation of hypotheses or the identification of signals. This activity shall be strengthened by a search from the cumulative data in the global WHO database for similar report.
7. Presentation of analysed case reports to the WHO Drug Committee. This committee of experts shall be responsible for evaluation and interpretation of the compiled coded case reports and giving advice on appropriate interventions.
8. Receipt and communication of appropriate safety information

resulting from analysis of local reports, from UMC, other national Centre, regulatory agencies and literature.

2. HANDLING OF ADR DATA [14]

An acknowledgement letter or note will be sent to the reporter for every ADR report received with an additional reporting form.

The ADR reports shall be stored in a confidential database at WHO and analysed report sent to the WHO database of International Programme on safety monitoring of drugs to which all case reports received by the National centres are sent.

The names of reporter and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. Publications will not disclose trade name of products unless regulatory actions have been taken. In this regard information obtained from spontaneous ADR monitoring system will not be used for commercial purposes. The information is only meant to improve our understanding on use of medicinal products by reducing the risks associated with drug prescribing and administration and to ultimately improve patient care, safety and treatment outcome. In the same way suspected ADR reports cannot be used in a court of law under any circumstances. WHO is responsible for providing reporting forms, collecting, analyzing and communicating the findings and evaluation reports. WHO shall use the finding from the reporter for making regulatory decisions on how to prevent or minimize the risk of ADRs from the use of pharmaceutical products circulating in the country. WHO may communicate the findings, recommendations and directives to appropriate organizations or individuals. These include, healthcare professionals, pharmaceutical manufacturers, public health programmes within the country, other public and private health institutions, the media and the public.

Provision of feedback to reporters

The outcome of the report, together with any important or relevant information relating to the reaction reported, will be communicated to the reporters and other parties as appropriate. After a significant ADR is detected and a decision on the course of action determined, the information shall be communicated rapidly and systematically to healthcare providers and product registrant. In addition, healthcare professionals will have an increased advantage of access to feed back information on reaction to drug within the same pharmacological class reported within the country and internationally and availability of additional database for further investigation.[14]

3. UTILISATION OF ADR DATA[14]

Data collected will be used for provision of timely advice to health-care professionals and consumers on drug safety issues at facility level, national and international level. A well documented adverse drug reaction case could result in one or more of the following;

1. Further investigation of signals. For example, identifying `at risk' group, a dose range which might be more suspected, suggesting a pharmaceutical group effect, pharmacological mechanisms, lack of effect by a particular drug or investigation into the use of a drug in the country

2. Drug regulation and dissemination of information of current importance

3. Education and training initiatives to improve the safe use of the medication and other health promotion interventions as the situation may warrant including change in supply status or withdrawal

Report on drug problems from healthcare provider can prevent new drugs tragedies or can reduce suffering and save lives of thousands of patients.

Figure no 1: Post-marketing Adverse Event Reporting and MED

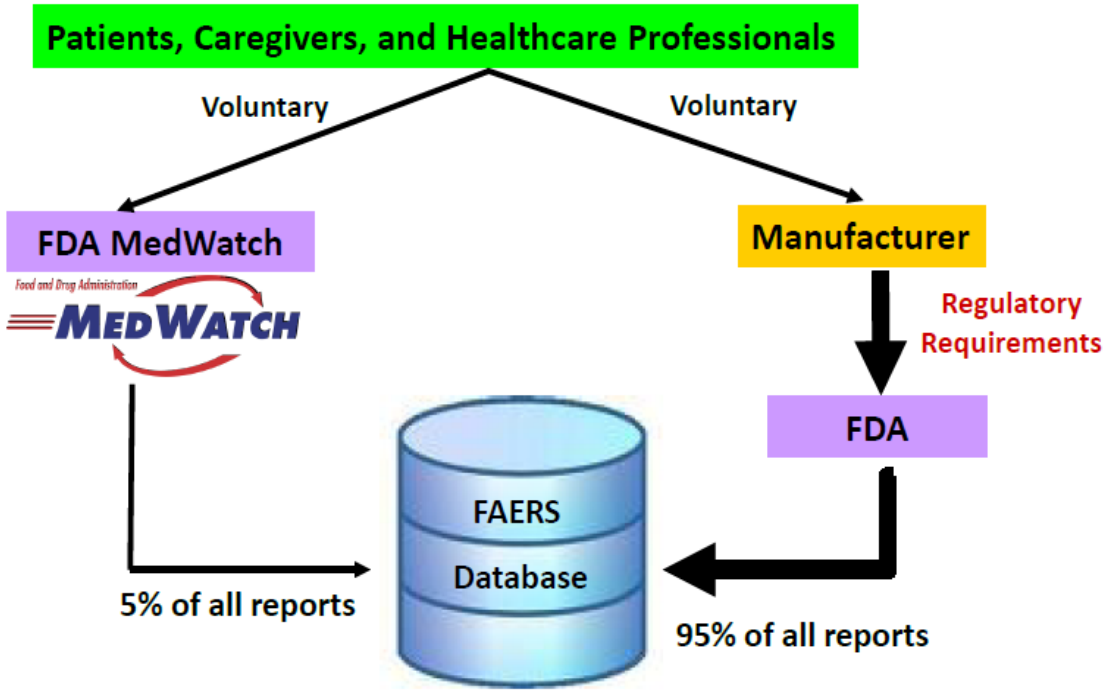
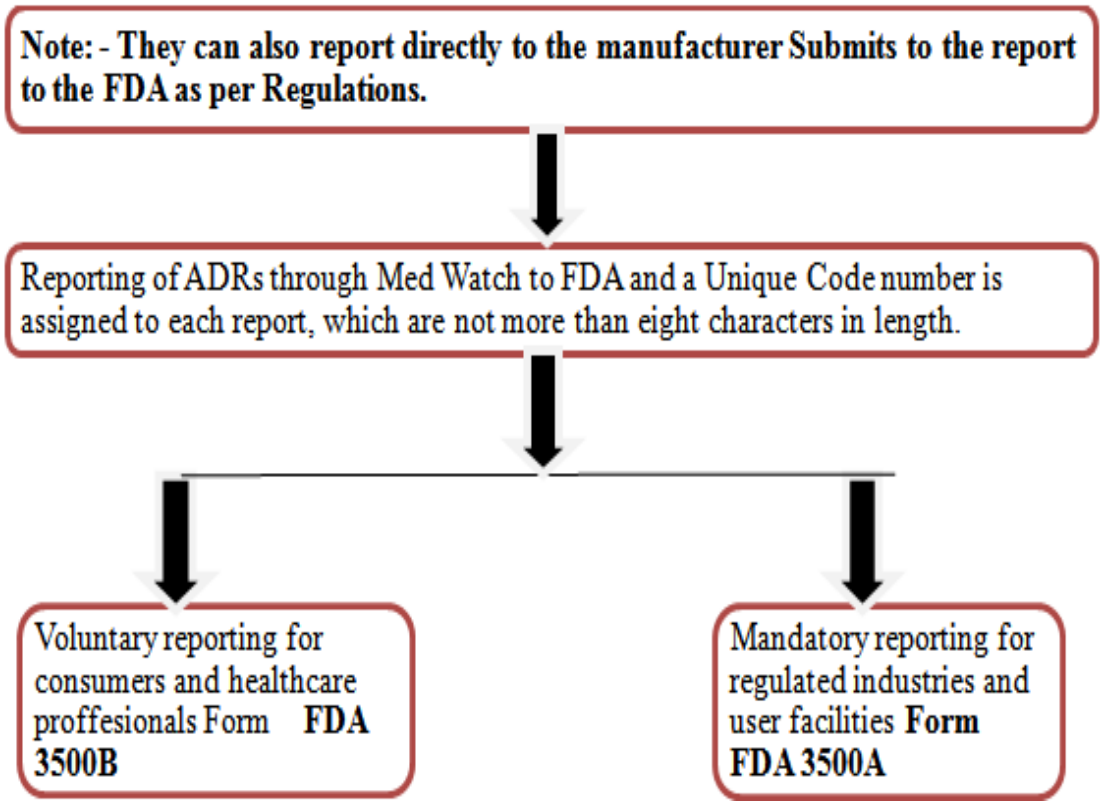
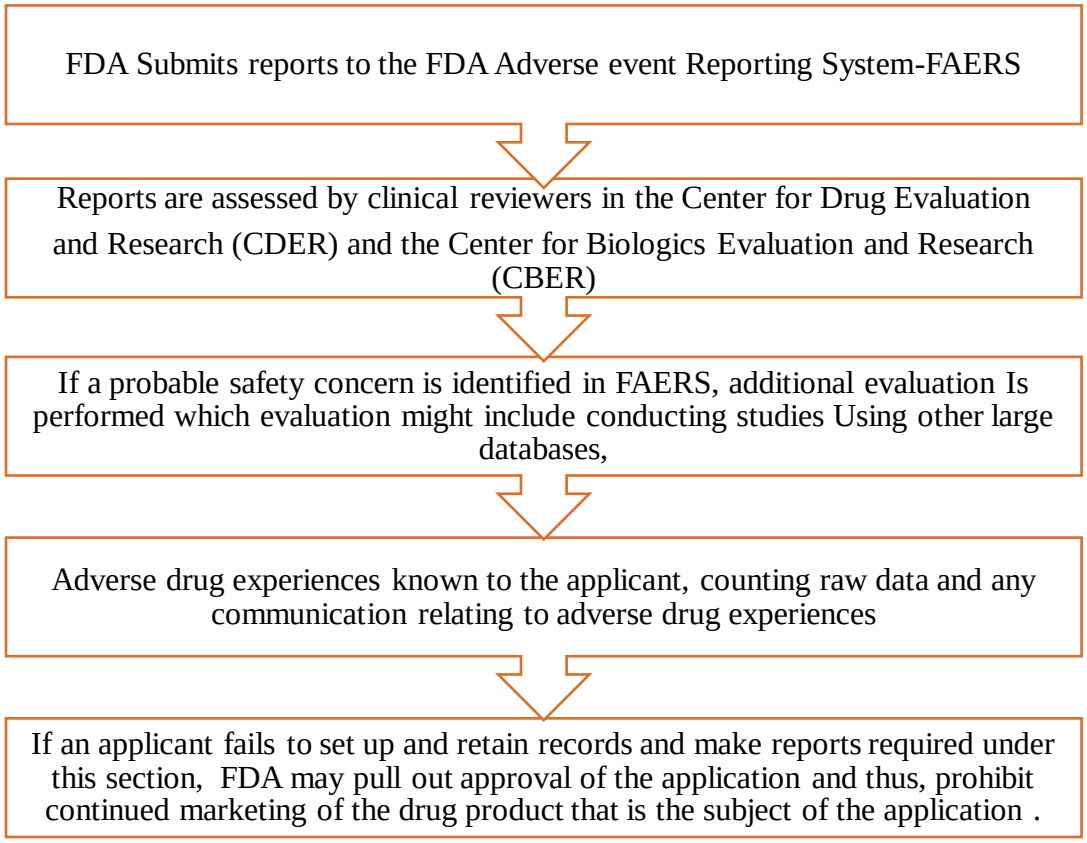


Figure 2: ADR Reporting System of USA





CONCLUSION

Analysis of voluntary AE reports in the US FAERS database has shown the characteristics of spontaneous reporting in the US. Voluntary reports tended to include AEs related to subjective symptoms, as in some previous studies on patient reporting in the EU. Voluntary reports by consumers seemed to be different from reports by healthcare professionals in demographics and outcomes of patients, and suspect drugs Pharmacovigilance regulations of USA are well developed and stricter. They have two separate ADR reporting for applicant for reporting of Adverse Drug Reactions. WHO-UMC gives regulations for setting up Pharmacovigilance Plan in member state. It maintains one database which has Adverse Drug Reactions that has occurred around the globe among member state. The Pharmacovigilance system will help country to maintain the ADRs data which will be Stored in one database and help to prevent and monitor further ADRs incidence.

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