

Overview of Pharmacovigilance

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Review Article

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ABSTRACT

Pharmacovigilance is drug safety process, it is also known as post marketing surveillance. Because at the time of clinical trials, the doses may differ from subject to subject and duration is also limited. For approval of drug product, Pharmacovigilance is necessary. In this adverse event reporting is the commonly associated. Any healthcare professional can report on this adverse event. After getting receipt or clinical study report, drug safety associate can triage the things, and information entered in database and finally reported to the drug regulatory authorities.

Pharmacovigilance

World Health Organization (WHO, 2014) defines "pharmacovigilance" as the science and its activities are regarding the collection, assessment, detection, monitoring, and prevention of Adverse Drug Reactions (ADRs), or any other drug-related problems [1-5].

Monitoring the safety and evaluation throughout whole life-cycle of a drug product and subjected by non-clinical, clinical, post marketing trails [6-8].

Need of Pharmacovigilance

1. There may be a need to monitor the effects of drugs during the clinical trials and after its in market.
2. Because adverse events can even happen during the clinical trials after its launch market [9,10].

Role of Pharmacovigilance

The goal of pharmacovigilance is to:

1. Monitor the quality of drugs.
2. Identify the health risks involved in the administration of certain drugs.
3. Prevent harm to people.
4. Research the efficacy of drugs [11-13].

Adverse Events (AE)

AE is any unfortunate medical occurrence that may present at the time of treatment with a pharmaceutical (drug) product but which does not have a causal relationship with this medicinal product [14,15].

Any AE can therefore be any unfavorable and unexpected sign (including abnormalities in laboratory reports), symptom, or disease temporally associated with use of a medicinal (Investigational) product, whether or not related to the medicinal (Investigational) product.

Adverse Drug Reaction (ADR)

ADR is a response which is harmful and unexpected, and which occurs at doses normally used in humans for the diagnosis, prophylaxis, or cure of disease, or for the modification of physiological function.

An ADR is distinguished from the adverse event by; the former has a supposition of a causal relationship between the drug product and the reaction, i.e., judged as being at least possibly linked to the reaction is reporting or the reviewing by healthcare professional, while the adverse event does not have such causal relationship^[16-20].

Adverse Drug Event (ADE)

Under this definition, the term ADE includes harm caused by the medicinal product (ADRs and overdoses) and harm from the use of the drug (including dose) reductions and stoppage of drug therapy^[21-25].

Importance of Pharmacovigilance

At the time of pre-marketing phase, the collected information regarding ADRs is incomplete because:

1. In clinical trials, patients are limited in number and number of patients may differ phase to phase. In clinical practice, the doses of medicine (Pharmaceutical ingredient) may changes and duration is limited.
2. Some of the information is incomplete. That is adverse reactions, chronic toxicity, drug interactions at that stage of clinical trials.

After reaching medicine to the public, sometimes it will^[26-30] cause very serious ADRs, so post marketing surveillance is important for avoid those conditions

So, worldwide health professionals should give report on ADRs, it can be reported by using individual case safety report (ICSR)

ICSR are mainly classified into four sections, they are:

An Identifiable Patient

1. Patient initials
2. Age at time of reaction or date of birth
3. Sex
4. Weight

Suspected Medicine

1. Name (INN and brand name)
2. Strength (concentration)
3. Dose, frequency
4. Dosage form
5. Route of administration
6. Indication for use
7. Duration of use, date started, date stopped
8. Batch number (especially for vaccines)

Suspected Adverse Reaction

1. Description of the reaction
2. Expectedness of the reaction (in accordance with the approved product information)
3. Seriousness of the reaction
4. Date the reaction started, stopped
5. Outcomes attributed to adverse reaction
6. Relevant tests/laboratory data (if available)

An Identifiable Reporter

1. Name, initials
2. Address
3. Contact details
4. Qualification (if healthcare professional) [31-35]

ADRs are difficult to distinguish from the drug, which is used for the treatment. Even though drug act through the same pathological and physiological pathways. The following assessment is useful for drug related ADR's:

1. Ensure that the patient use prescribed medicine at the dose advised.
2. Do a proper examination of patient and take a proper medical history a full medicine and medical history should be taken.
 - a) An ADR should be your first differential diagnosis at all times.
 - b) Ask if this adverse reaction can be explained by any other cause e.g., patient's underlying disease, other medicines including over-the-counter medicines or traditional medicines, foods or toxins.
 - c) Patient is thoroughly investigated for identify the actual cause of any new medical problem.
 - d) We can consider the medicine-related cause, because other causes do not explain the patient's condition [36-40].
3. Verify the time relationships, for some patients, the reaction occur immediately after administration of the medicine. Some patients take time to develop the reaction.
4. thorough physical examination of patient and appropriate laboratory investigations is needed, if necessary:
 - a) Remember: only a few medicines produce distinctive physical signs.
 - b) Exceptions include medicine eruptions, acute extra-pyramidal reactions, steroid-induced dermal atrophy.
 - c) Laboratory tests are important if the medicine is considered for improving patient care or if the laboratory tests results will improve the patient management.
 - d) We can describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis [41-45].

DETERMINATION OF DECHALLENGE AND RECHALLENGE

Dechallenge (withdrawal of the suspected medicine)

Positive dechallenge is the improvement/resolution of ADR when the suspected medicine is withdrawn in a strong, though not conclusive indication of medicine induced reaction [46,47].

Rechallenge (after dechallenge, re-introducing the suspected medicine):

Rechallenge is only justifiable when the benefit of reintroducing the suspected medicine to the patient overweighs the risk of recurrence of the reaction, which is rare. In some cases, on repeated exposure, the reaction may be more severe. Serious ethical considerations are required by Rechallenge [48-50].

Verify the pharmacology of the drug product

- a) Verify the reaction occur due to the particular suspected medicine, it is sated in the PIL (Patient information leaflet) or other reference.
- b) If the reaction is not mentioned in the PIL (Patient information leaflet) it does not mean that the reaction cannot occur due to that particular suspected drug [51-53].

Seriousness of ADRs

A serious adverse event or reaction is any untoward medical occurrence associated with the use of a medical product in a patient that at any dose, the outcome is one of the following:

Death

Report if the patient's death is suspected due to drug product, direct outcome of the adverse reaction.

Life-threatening

Report if the patient was at serious risk of dying at the time of the adverse reaction or it is suspected that the use or continued use of the drug product would result in the patient's death.

Hospitalization (initial or prolonged)

Report if admission of patient to the hospital or prolongation of a hospital stay results because of the suspected adverse reaction.

Disability

Report if the adverse reaction resulted in a significant, persistent, or permanent disability/incapacity; (Change, deterioration, damage, or disruption in the patient's body function/structure, physical activities, or Quality of life).

Congenital anomaly

Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse reaction in the child (birth defect).

Medically important event or reaction

Medical and scientific assessment should be exercised in deciding whether other situations should be considered serious such as important medicinal events that might NOT be immediately life-threatening or result in death or hospitalization but might cause danger to the patient or might require intervention to prevent one of the other outcomes listed in the definition above [54-58].

Adverse Event Reporting

Adverse event reporting commonly associated with the Pharmacovigilance.

Adverse event reporting mainly involves receipt, triage, data entering, assessment, distribution, reporting (if appropriate), and archiving of adverse event data and documentation [59-63].

Receipt

Spontaneous SAE and non-SAE arrive by telephone, email, fax, company website, reports to sales representatives, and the legal departments etc. some other sources of arrival of AE is clinical studies, legal, literature reports [64-68].

AE Triage

1. After the arrival of case in drug safety department, it must be classified properly for case processing, the report should be date stamped upon under entry into the drug safety department, for paper cases manual rubber stamp and for electronic cases automatically date stamp. This should be done within 24 h.
 2. To determine the initial triage, whether the report needs urgent processing in order to transmitted to health authority.
 3. Triage should be done by someone with medical skills, many companies have dedicated nurses and pharmacists and health professionals for this role. For difficult or controversial cases traiger may take assistance from safety physician [69-72].
 4. Triage should cover at least the following:
 - a) Which drug is involved
 - b) Case type: clinical trial, spontaneous, stimulated, others
 - c) Serious and non-serious
 - d) Causality(for serious clinical trial cases, not for spontaneous)
 - e) Expectedness(labeledness) for serious for serious and non-serious cases
 - f) Determination of which report are expedited reports
-
- a. 7 days IND reports: Serious and life threatening, unlabeled.
 - b. 15 days IND reports: Serious, unlabeled.
 - c. 15 days NDA reports: Serious and unlabeled.

IND: Investigational New Drug; NDA: New Drug Application [73-76].

1. Pregnancy cases, with accompanying AE/SAE or not accompanying AE/SAE
2. Are the four elements of a valid case (reporter, patient, outcome, Drug) present and identifiable.
3. In general triage should be conservative so that serious cases, and in particular, 15 days expedited cases are not misclassified.
4. Some companies logon all cases into spread sheet or database to track them and ensure that they are not last in transit within the safety department [77-80].
5. After triage each case should be assigned to appropriate work channel. Each company develops various channels. They should roughly run along these line:
 - a) Rapid processing of death/ life threatening clinical trail cases within 7 calender days [81].
 - b) Processing of 15 days expedited reports to the IND and or NDA. These are serious cases for which processing must be completed by 15 calendar days [82].
 - c) Processing of other serious cases that are not expedited reports. These cases do not have to send to FDA within 15 calendar days. Rather they are sent in NDA periodic reports, IND annual reports and PSUR [83].
 - d) Sometimes case is not expedited report in one country but is an expedited case in another country (e.g. local labeling or reporting regulation is different there). This case must be transmitted to the subsidiary or business in time to meet 15 days reporting rules [84].
 - e) Non serious cases may be processed more slowly (e.g., 30 days) because they are not reportable only in aggregate reports [85].

Data Entry (DE)

1. At this point case should be entered in to computerized database. If a case number has not been assigned to the case at the triage level, it is assigned now.

2. If the data collection form used for collection of clinical trials and spontaneous data is standardized to one or two page form, then data entry should be fairly easy to do [86-90].
3. Some companies have initial review by medical professionals who highlights the items for data entry; other companies have the source documents sent directly to the data entry group (non-medical professionals) [91-94].

Data Review and Quality Checks

1. At this point, a drug safety specialist (nurses, pharmacist) reviews the data entry against the source documents and prepare or review the case narrative. Any addition or change in a case is made at this point [95,96].
2. A clear methodology should be developed so that it is done in standardized way. The quality review should look at contents, grammar and format, short simple English should be used because much reader (outside of United States) may not be a native English language speakers.
3. Follow-up information should be requested when the initial case is incomplete or unclear. Thus it is almost always requested when the initial case is incomplete or unclear. Thus it is almost always required that follow queries be sent to the reporter to complete the case data [97,98].
4. Care must be taken to ensure that data are not mistaken for a new case but rather are clearly identified as follow up to case already received [99,100].

CONCLUSION

Pharmacovigilance is comes under drug safety reporting and post marketing surveillance. In this pharmacovigilance we can report the adverse drug events for efficacy of the drug product. Drug safety associate can investigate the case and reported to the drug regulatory affairs. Many pharmaceutical companies across the globe will maintain this pharmacovigilance reports. So pharmacovigilance is key for maintaining the drug safety.

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