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PHARMACOVIGILANCE: CAUSALITY ASSESSMENT AND MONITORING OF ADVERSE REACTIONS

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ABSTRACT

Pharmacovigilance is an essential branch of healthcare that focuses on the detection, assessment, understanding, andpreventionofadversedrugreactions(ADRs)andotherdrug-related problems. Thisreport provides a comprehensive overview of pharmacovigilance, including its origin, development, objectives, scope, and importance in ensuring patient safety. The report discusses the historical evolution of pharmacovigilance from early drug-related tragedies such as the thalidomide disaster to the establishment of global monitoring systems by the World Health Organization (WHO). It explains important terminologies, causality assessment methods such as WHO-UMC scale, Naranjo Algorithm, and Bayesian approaches, along with ADR reporting systems and medical evaluation of adverse events.

The report also highlights the process of ADR monitoring, diagnosis, management, and reporting under national and international pharmacovigilance programs. Furthermore, it describes quality systems in pharmacovigilance, pharmacovigilance databases, signal detection,riskassessment,andriskmanagement strategies.Specialemphasisisgiventocase narrative writing, global and Indian perspectives of pharmacovigilance, and the significant roleofpharmacists in ADR monitoring and patient safety. Overall, pharmacovigilanceplays a vitalrole in promoting the safe and rational use of medicines, improving healthcare outcomes, and strengthening public health systems through continuous drug safety monitoring and reporting.

METHODOLOGY: The methodology of this report was based on reviewing textbooks,

journals, WHO guidelines, and online resources related to pharmacovigilance. Information regarding adverse drug reactions (ADRs), causality assessment methods, ADR reporting systems, signal detection, and risk management was collected and studied systematically. Different pharmacovigilance toolssuchas WHO-UMCscale and Naranjo Algorithmwere also reviewed to understand their role in drug safety monitoring

KEYWORDS: ADR-Adverse drug reactions, WHO-World health organization, UMC-Uppsala monitoring centre .ADE-Adverse drug event, PV-Pharmacovigilance, PvPi-Pharmacovigilance programme of India, FDA-Food and drugadministration, EMA-Europeanmedicineagencies, ICSR-Individual case report, CRF-Case report form, CDSCO-Central drug standard control organization, NCC-National coordinate centre,

INTRODUCTIONANDOVERVIEWOFPHARMACOVIGILANCE[1]

Pharmacovigilance isanimportantand integralpartofclinicalresearch.Pharmacovigilance is defined as "the pharmacologicalscience relating to detection, assessment ,understanding and prevention of adverse effect ,particularly long term and short-term adverse effect of medicines''.Theetymologicalrootsfortheword "Phamacovigilance" are;pharmakon(greek) medicinal substance, and vigilia (latin) to keep watch.

AIMSOF PHARMACOVIGILANCE

1. **ImprovePatientSafety&Care:** Theprimarygoalisto minimizerisksassociated with pharmaceutical products, enhancing overall patient safety and care.
2. **DetectAdverseDrugReactions(ADRs):** Earlyidentificationofpreviously unknown or rare side effects not detected during clinical trials.
3. **AssessBenefit-RiskRatio:** Continuouslyevaluatethebalanceofbenefitsandrisks, ensuring that for authorized medicines, the risk remains acceptable.
4. **PromoteRationalUseofMedicines:** Encourageevidence-based,effective,and, where possible, cost-effective prescribing and usage.
5. **PromoteRationalUseofMedicines:**Reducemedicationerrors,abuse, misuse,and adverse effects to prevent harm.
6. **SafetyCommunication&Education:**Providetimely,evidence-basedsafety information to healthcare professionals, patients, and the public.
7. **Post-MarketingMonitoring:** Continuouslymonitorthesafetyofdrugsafterthey have been approved and are in widespread use.

OBJECTIVESOFPHARMACOVIGILANCE

FIGURE 1:OBJECTIVESOFPHARMACOVIGILANCE.

ORIGINOFPHARMACOVIGILANCE[2]

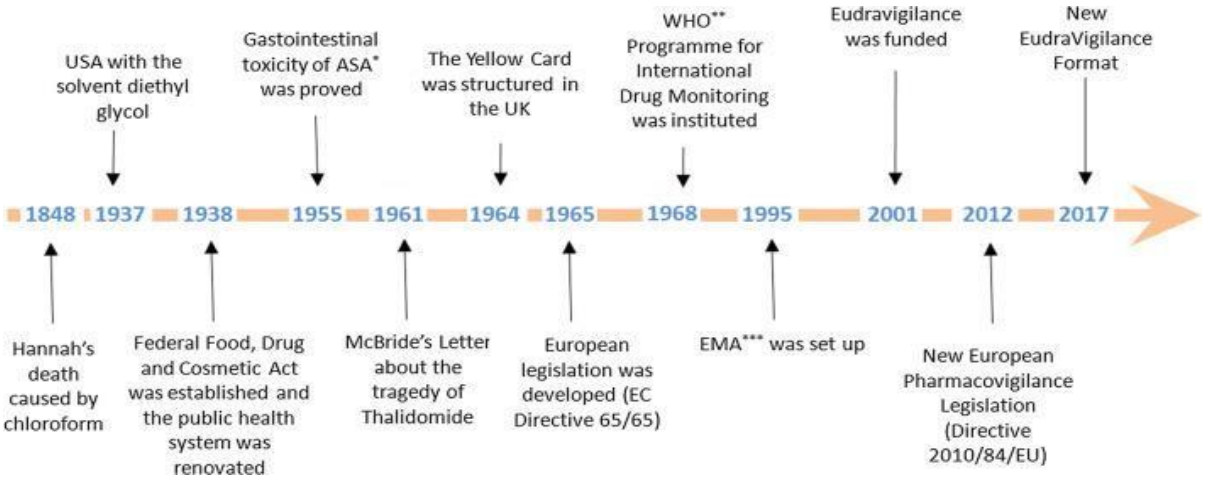


Figure2: Origin of pharm a covigilance.

DEVELOPMENT OF PHARMACOVIGILANCE

- **EarlyBeginnings(1848):**ThedeathofHannahGreenerduringchloroformanaesthesia prompted early investigations into drug-related deaths.
- **1937 Sulphanilamide Disaster:** The deaths caused by a toxic sulphanilamide elixir which contain diethyl glycol as the solvent that's led to the U.S requiring premarket drug safety testing.
- **Thalidomide tragedy (1957–1961):**The drug was prescribed to pregnant women as harmless treatment for nausea and vomiting and morning sickness. The tragic birth defectslinkedtothalidomideledtotheestablishmentoftheWorldHealthOrganization (WHO) Programme for International Drug Monitoring (PIDM) in 1968, marking the modern era of pharmacovigilance.
- **Standardization (1980s-90s):** The Council for International Organizations of Medical Sciences (CIOMS) createdst and ardizedreportingforms(CIOMSFormI)andmethods, forming

the foundation of global ADR reporting.

DevelopmentofRegulatoryFrameworks

- **1960s/70s:** Following the thalidomide crisis, many nations established national regulatory authorities (e.g., in the UK in 1963) to monitor safety.
- International Harmonization: Agencies such as the FDA and EMA enhanced PV through post-marketing surveillance and risk management, strengthened by International Conference on Harmonization (ICH) guidelines.

Evolution in India

- **1986-1998:**AformalADRmonitoring

SCOPEOFPHARMACOVIGILANCE

Thescopeofpharmacovigilance(PV) encompassestheentirelifecycleofmedicines,focusing onthedetection,assessment, understanding,andpreventionofadversedrugreactions(ADRs) andmedication-relatedissuestoensurepatientsafety.Itinvolvespost-marketingsurveillance, risk management, signal detection, and communication to healthcare stakeholders.

Aspectsofthescopeofpharmacovigilanceinclude:

- **ContinuousSafetyMonitoring:** Evaluatingdrugsafetypost-approval,asclinical trials may not detect rare or long-term adverse effects.
- **SafetyDataCollection:** Gatheringinformationfromvarioussources,includinghealthcare professional reports, clinical trials (phases 0-4), and real-world data.
- **RiskAssessment&Management:** Analysingthebenefit-risk balanceofpharmaceutical products and implementing mitigation strategies.
- **Signal Detection & Analysis:** Identifying new or changing safety information for early warning signs, often using advanced technologies like AI and data science methods.
- **RegulatoryCompliance&Reporting:** Submittingsafetydossiersandadverseevent reports to regulatory authorities (e.g., FDA, CDSCO).
- **BroadCoverage:**Monitoringnotonlyapproveddrugsbutalsovaccines,herbal medicines, blood products, and medical devices.
- **GlobalHealth Impact:**Enhancing public health by reducing the burden ofpreventable medication errors, which are estimated to be 50-75%

STANDARDTERMSANDTERMINOLOGY[3]

1. **Drug/Medicine:**It is any physiological and pathological change experienced by the beneficiary after having pharmaceutical product.
2. **Medicinal product:** Any substance or combination of substance presented as having properties for treating or preventing diseases in humans. Or any substance orcombinationofsubstancewhichmaybeusedinoradministeredtohumanbeings eitherwithaviewtorestoring,correctingormodifyingphysiologicalfunctionsby exerting a pharmacological, immunological or metabolic action, or to making a medicinal diagnosis.
3. **ADR :** Adverse drug reaction can be defined as any response to a drug which is noxious and unintended , and which occurs at doses normally used in a man for prophylaxis, diagnosisortherapyofdiseaseor forthe modificationofphysiological functions
4. **Signal :**Information that arises from one or multiple sources (including observationsandexperiments)whichsuggestsanewpotentiallycausalassociation, or a new aspect of a known association, between a drug and an adverse event that warrants further investigation.
5. **Benefit:**thepositive,therapeutic,orprophylacticeffectofamedicinalproducton anindividualpatient,orthenetpositiveeffectacrossapopulation.Itrepresentsthe "therapeutic good" or desired outcome of treatment, such as curing a disease, relievingsymptoms,slowingdiseaseprogression,orimprovingthepatient'squality of life.
6. **Efficacyandeffectiveness:**thesettinginwhichadrug'sperformanceismeasured, representing a transition from ideal, controlled trials to real-world application.
7. **Hazard:**any source of potential damage, harm, or adverse health effect on a person. It refers to the intrinsic capability of a medicinal product to cause unintended, noxious effects.
8. **Risk:** any adverse, unintended, or untoward clinical outcome with a reasonable possibility of a causal relationship to a medicinal product.
9. **Safety:**theacceptable,optimized,andcontinuouslymonitoredbenefit-riskbalance of a medicinal product, rather than absolute freedom from risk.
10. **Adverse effect and adverse reaction :** anAdverse Event (AE) is any untoward medicaloccurrenceduringtreatmentthatmaynothaveacausalrelationship,while anAdverse Drug Reaction (ADR) is a noxious, unintended response to a drug at normal doses with a suspected causal relationship
11. **MedDRA**:a standardized, clinically validated international medical terminology

usedbypharmaceuticalcompaniesandregulatoryauthoritiestocode,classify,and analyse adverse event data throughout a product's life cycle.

12. **Side effect:** It is an undersible physical symptom caused by taking drug or undergoing medical therapy.
13. **Casualty assessment:** It is the evaluation of the probability that the therapeutic drug can be the cause of an observed adverse reaction.
14. **Casereport:** theyarethereportofADR ofsinglepatient.
15. **Formulary:**Itincludesalistofmedicaldrugswiththeirmethodsofadministration, uses, available dose forms, side effect etc. it also sometime includes method of preparation also.

MATERIALSANDMETHODS

DIFFERENTSCALESUSEDINADRMONITORING(CASUALITYASSESSMENT TOOL) [4]

CAUSALITY ASSESSMENT

- It is the assessment ofrelationship betweena drug treatment and the occurrence ofan adverse event
- Basically,usedforestimationandtoinvestigatethattheparticulartreatmentisthecause of an observed adverse event or not
- It1stheessentialpartofADRreportingandimportanttask,conducted,National Pharmacovigilance Program in each country.

OBJECTIVES:

- Providerelationship betweendrugandevent
- Providea betterevaluation
- benefit/harmprofiles ofdrugs
- Playsan essential partof evaluatingADRreportsin early warningsystemsandfor regulatory purposes

METHODS:

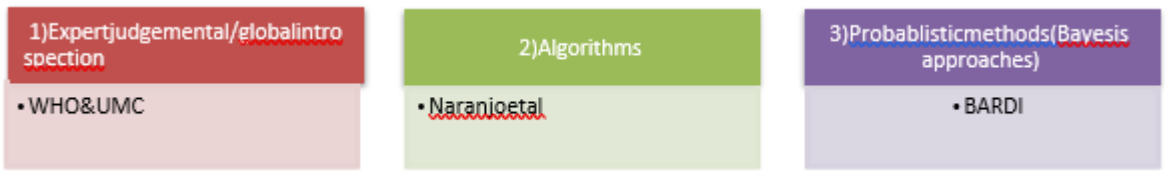


Figure3: causality assessment method.

❖ **Expertjudgement/globalintrospection:**

✓ Cliniciandiscussingobservedadversereactionand suspected medicine

✓ Causality assessment done by clinicians is purely based on previous knowledge andexperience of the clinician in the relevant field.

World Health Organisation (WHO)-Uppsala Monitoring Centre(UMC) scale

✓ .It isbasicallycombinedassessmenttaking into accounttheclinical -pharmacological aspects of the case history and the quality of the documentation of the observation.

✓ Includesthefollowing four criteria

a) Timerelationshipbetweenthedruguseandtheadverseevent

b) Absenceofother competingcauses

c) Responseto drugwithdrawalordosereduction(de-challenge)

d) Response todrugre-administration(rechallenge)

Causality association:

- **Certain**:Whenallcriteria(a,b,c,d)aremet
- **Probable**:Whencriteriaa, b,caremet
- **Possible**:Whenonlycriteriaaismet
- **Unlikely**:Whencriteriaaand barenotmet
- Besidesthe4 categoriesADRcanbecategorizedinto
- **Unclassified /Conditional**:Applied when more dataisneeded and suchdataisbeing sought or is already under examination
- **Unassessable/Unclassifiable**: Finally, when the information in a report is incomplete or contradictory and cannot be verified ,then it is Unclassifiable.

Algorithms

- An algorithm is a problem-specific flow chart with step-by-step instruction on how to arrive at an answer
- Itcontainssomequestionnairewhoseanswersprovidethecausalityofparticular ADR

Naranjoscale

- Anelementalquestionnairewithyesnoandunknownrepliesaredeveloped
- Basedonthereplies,thescorehasbeendeterminedintocategories

Table1:Casualtyassessmentquestionary.

QUESTIONS	YES	NO	DO NOT KNOW	SCORE
1.Are there previousconclusionreportsonthese reactions?	+1	0	0	
2.Didtheadverseeventappearimprovewhenthedrug was discontinued or a specific antagonist was administered?	+1	0	0	
3.Didtheadverseeffectreappear whenthedrugwas readministered?	+2	-1	0	
4.Didthepatienthavea similarreactiontothesameor similar druginanyprevious exposure?	+1	0	0	
5.Wastheadverse eventconfirmedbyanyobjective evidence?	+1	0	0	
6. didtheadverseeventappearafterthe suspected drugwas administered?	+2	-1	0	
7.aretherealternativecausesthatcouldontheir own havecausedthereactions?				
8.didthereactionreappearwhenaplacebowas given?	-1	+1	0	
9.wasthedrugdetectedin bloodorotherfluidsinconc knowntobe toxic?	+1	0	0	
10.wastheadverseeventconfirmedbyanyobjective evidence?	+1	0	0	

The Naranjo scale is a toolto help clarify how to evaluate a potentialcausalassociation. It is not intended to solve all the complex problems of identification and classification of ADRs.

Probabilisticmethods(BayesianApproaches)

- Bayesian methods for causality assessment make use of specific findings in a case to transform a prior into a posterior probability of drug causation
- Priorprobability-fromepidemiologicalinformation
- Posterior probabilitycombines this background information with the evidence in the individual case

BayesianAdverseReactionsDiagnosticInstrument(BARDI):

- BARDI is used to calculate the odds in favour of a particular drug causing an adverse event compared with an alternative cause.
- These odds are referred to as the posterior odds. The posterior odds factor is calculated by considering six assessment subsets: one deal: with background epidemiologic or clinical trials information (the prior odds) and the other five deal with case specific information (the likelihood ratios).

- **PsO=PrOxLR(Hi) xLR(Ti)xLR(Ch)xLR(De)xLR(Re)**

MedicalevaluationofadverseeventsinPharmacovigilance[5]

Pharmacovigilance is defined bythe World Health Organization (WHO) as "the science and activitiesrelatingtothedetection,assessment,understandingandpreventionofadverseeffects or any other drug-related problems."

Medicalevaluationofadverseevents(AEs)isa criticalstepinpharmacovigilancetodetermine:

- Causality
- Severity
- Seriousness
- Expectedness
- Risk–benefitbalance

Table2:Steps inMedicalEvaluationofAdverseEvents.

SINO	STEPS	EVALUATION
1	CaseValidation	• Checkcompletenessofreport • Identifypatient demographics • Confirmsuspectdrug • Verifyeventdescription • Checkreporterqualification
2	SeriousnessAssessment	• Death • Life-threateningcondition • Hospitalization(initial/prolonged) • Persistentdisability • Congenitalanomaly • Othermedicallyimportantcondition
3	CausalityAssessment	• who-UMCCasualtyassessment • NaranjoAdverseDrugReactionProbabilityScale
4	ExpectednessAssessment (Comparison)	• InvestigatorBrochure(clinicaltrials) • Packageinsert /SmPC (post-marketing
5	SeverityAssessment	• Mild • Moderate • Severe

AdverseEventReportingSystemandFormsused[6]

For new drugs, all suspected reactions including minors as well as major ones should be reported, for establishment or well know of the drug. While reporting an ADR health professional should keep in mind that only suspected association of drug which has caused a particular adverse event should be reported.

1. Whattoreport?

Anyundesirable adverse event other thanthe therapeutic effect begins withthe use ofdrug whichcanbeherbal, cosmetics, ormedicaldevice should bereported.Theyshould include,

- AllADRs
- AllsuspectedADRsandproductdetailedprovidedbythe company
- Unexpected reactions
- ADRsassociatedwithdrug-drug,food-drug,drug-foodinteractions
- ADRoccurringfromoverdose

2. HowtoreportanADR

ForreportinganADR,oneshouldhave localCase ReportForm(CRF)whichisobtained from the National Drug Regulatory Authority. There is different case report format in different countries but all must have at least four major sections having:

a) Patientinformation

- Identifyofpatient
- Age/ DOB
- Sex
- Weight
- Gender

b) Adverseevent/reaction

- Briefdescriptionof ADR
- DateofADR
- TimeofADR
- Laboratorydata
- Patienthistory(medicalhistory)
- Outcomesattributedtoadverseevent

c) Suspectedmedication

- Name ofsuspectedmedication
- Dose?Routeofadministration/frequencyofdrug
- Dateoftherapyfromthesuspectedmedication
- Eventabatedafterdosedecreasedorstopped
- Expirydateof dose

- Providerelevantinformationonmedicaldevice

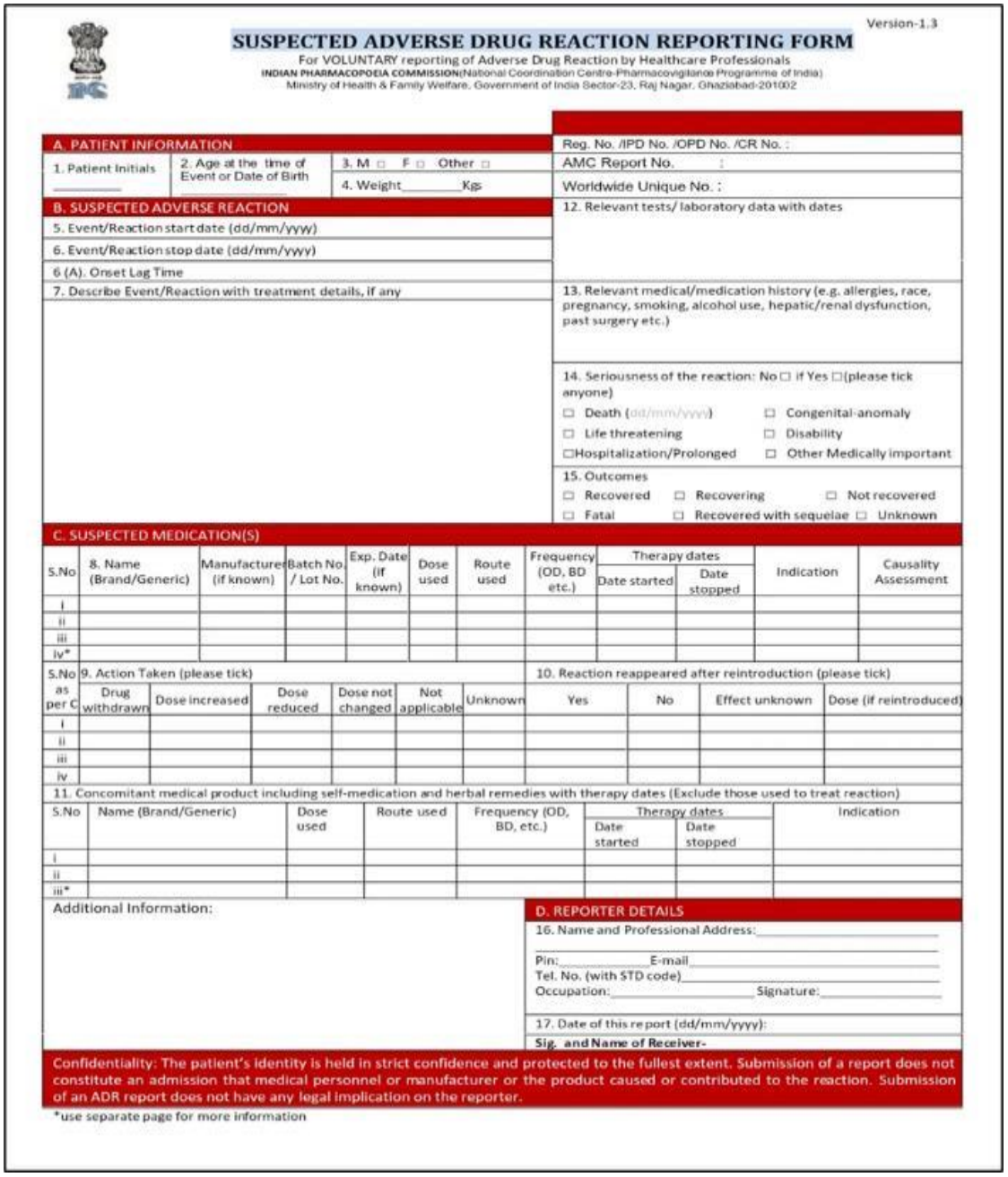
d) Reporter

- Detailedofreporter
- Nameofthereporter
- Address ofhealthfacility
- E-MAILAddress
- Signature,telephonenumber
- Dateofreportingthereactions

3. Whentoreport?

Allthe suspected adverse reactions that are clinically important should be reported as soon as possible, delay in the process of reporting will make the report inaccurate. If possible, report should be sent while the patient is stillunder examination, it willhelp the reporter to clear any ambiguity by re-examining the patient.

- Howtoreport?
- SendthereportinCRF,ifitasself-adhesivepostagepaid“yellowfrom”
- DullyfilledCRF, whenADRisencountered
- Useseparateformforeach patient’s
- FormshouldbesealedandmailedtoTanzaniaFoodandDrugAdministration(TFDA)
- This report can be submitted online with the help ofTFDAwebsite and follow up the indication.



Version-1.3

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reaction by Healthcare Professionals
INDIAN PHARMACOPOEIA COMMISSION(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India Sector-23, Raj Nagar, Ghaziabad-201002

A. PATIENT INFORMATION

1. Patient Initials	2. Age at the time of Event or Date of Birth	3. M ☐ F ☐ Other ☐
		4. Weight_____Kg

Reg. No. /IPD No. /OPD No. /CR No. :
AMC Report No. :
Worldwide Unique No. :

B. SUSPECTED ADVERSE REACTION

5. Event/Reaction start date (dd/mm/yyy)
6. Event/Reaction stop date (dd/mm/yyyy)
6 (A). Onset Lag Time
7. Describe Event/Reaction with treatment details, if any

12. Relevant tests/ laboratory data with dates

13. Relevant medical/medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction, past surgery etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐(please tick anyone)
☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Disability
☐Hospitalization/Prolonged ☐ Other Medically important

15. Outcomes
☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv*											

S.No as per C	9. Action Taken (please tick) Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Reaction reappeared after reintroduction (please tick) Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication
i							
ii							
iii*							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____Signature:_____

17. Date of this report (dd/mm/yyyy):

Sig. and Name of Receiver-

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction. Submission of an ADR report does not have any legal implication on the reporter.

*use separate page for more information

Figure4:ADRreportingform.

ADRREPORTINGPROCESS

1. DetectionofADR

ADRmaybeidentifiedby:

- Doctors
- Nurses
- Pharmacists
- Otherhealthcareprofessionals
- Patients

AnADRissuspectedwhenthereisany**unintended,harmfulreaction**occurringafter administration of a medicine at normal doses.

2. InitialDocumentation

Essentialdetailstorecord:

- Patientinformation(age,gender,weight,ID)
- Suspecteddrug(s)(name, dose,route,duration)
- Descriptionofreaction(onset,severity,outcome)
- Concomitant medications
- Relevantmedicalhistory
- Reporter details

3. FillingADRReportingForm

InIndia,ADRsarereportedusing:

- **SuspectedADRReportingForm(PvPI)**
- Forglobalreporting:**IndividualCaseSafetyReport(ICSR)**format

Under the**PharmacovigilanceProgrammeofIndia(PvPI)**,ADR formsaresubmittedto:

- NearestADRMonitoringCentre(AMC)
- Viatoll-freehelpline(1800-180-3024)
- Throughmobileapp
- CDSCOwebsite

4. SubmissiontoNationalCentre

ADRMonitoringCentresforwardreportstothe **IndianPharmacopoeiaCommission (IPC)**, which functions as the National Coordination Centre (NCC) for PvPI.

5. DataEntry&CausalityAssessment

- Dataenteredinto**VigiFlow**(WHOdatabase system)
- Causalityassessed using:
  - WHO-UMCscale
  - NaranjoAlgorithm

Reports are then forwarded to the **Uppsala Monitoring Centre (UMC)** for inclusion in the global database (VigiBase).

6. SignalDetection&RegulatoryAction

- Signaldetectionbyexperts
- Riskevaluation
- Regulatorydecisions(labelchanges,warnings,restrictions,withdrawal) In India, regulatory decisions are taken by **Central Drugs Standard Control Organization (CDSCO)**.

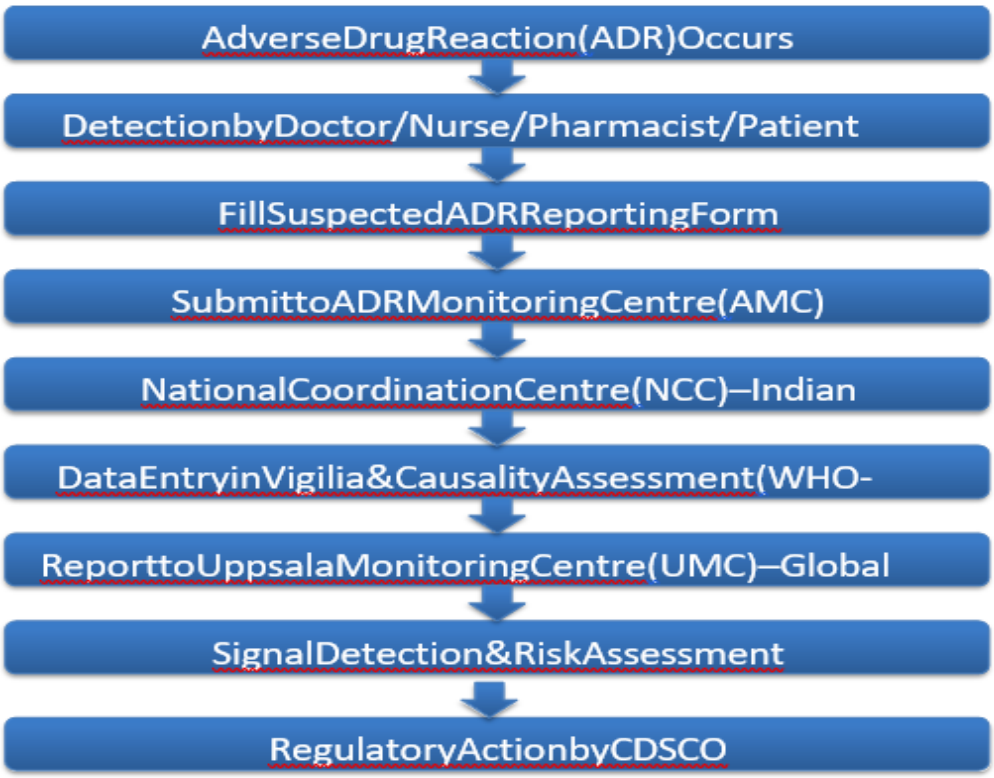


Figure5:ADRreportingprocess.

DiagnosisandManagementsofADRs[7]

DiagnosisofAdverseDrug Reactions(ADR)

Table3:DiagnosisofAdverseDrugReactions(ADR) Management of Adverse Drug Reactions (ADR)

Component	**Details**
Drug History	Completemedicationhistory(dose, duration,OTC,herbal drugs)
TemporalRelationship	Reactionoccurredafter startingthedrug
Dechallenge	Improvement afterstoppingthedrug
Rechallenge	Reactionreappearsafterre-administration(ifsafe)
CausalityAssessment	**UseNaranjoAdverseDrugReactionProbabilityScale orWorld HealthOrganization**-UMCscale
LaboratoryTests	CBC, LFT,RFT,serumdruglevels
SeverityAssessment	HartwigandSiegelseverityscale

Table4:managementofadversedrugreactions(ADRs)

severity	Action	Example
mild	Continuedrug/reducedose +monitoring	Mild nausea
moderate	Stopdrug+symptomatic treatment	Drug-inducedrash

QualitySysteminPharmacovigilance[10]

A **Quality System in Pharmacovigilance (PV)** is a structured framework of policies, procedures,processes,andresponsibilitiesdesignedtoensurethatpharmacovigilanceactivities areconsistent,reliable,andcompliantwithregulatoryrequirements.Themaingoalistoensure patient safety by detecting, assessing, understanding, and preventing adverse drug reactions (ADRs)**.**

APharmacovigilanceQualitySystemensuresthat allPVactivitiesareperformedaccordingto GoodPharmacovigilancePractices(GVP)andregulatoryguidelinestomaintainhighstandards of drug safety monitoring**.**

ObjectivesofQualitySysteminPharmacovigilance

- Ensurepatientsafetyandprotectionofpublichealth
- Maintainaccuracyandreliabilityofsafetydata
- Ensurecompliancewithregulatoryauthorities
- Promotecontinuousimprovementinpharmacovigilanceprocesses
- Ensuretimelydetectionand reporting ofadversedrugreactions

ComponentsofPharmacovigilanceQualitySystem

Figure6:componentsofqualitysystem

1. **Quality planning:** establishing structures and planning integrated and consistent processes (ex: Clear written standard operating procedures, Safety reporting timelines, Risk management plans)
2. **Quality control:** Quality control focuses on monitoring pharmacovigilance processes to ensure accuracy and completeness

Examples: Case processing checks, Verification of Individual Case Safety Reports (ICSRs), Data validation in safety databases

3. **Quality assurance:** monitoring and evaluating how effectively the structures and processeshavebeenestablishedandhoweffectivelytheprocessesarebeingcarried out

Eg**:**Internalaudit,Compliancemonitoring,Correctiveandpreventiveactions(CAPA)

4. **Qualityimprovement:** correctingand improvingthestructuresandprocessesand the carrying out of those processes as necessary

ImportanceofQualitySystemin Pharmacovigilance

Improvesdrugsafetymonitoring

Ensuresregulatorycompliance

Helpsinearlydetectionofsafetysignals

Enhancesdatareliabilityandtransparency

Protectspublichealth

PharmacovigilanceDatabaseandSignaldetection[11] Pharmacovigilance Database

A Pharmacovigilance database is an electronic system used to collect, store, manage, and analyse reports of adverse drug reactions (ADRs) and other drug-related safety information. Thesedatabases helpregulatoryauthoritiesandpharmaceuticalcompanies monitorthesafety of medicines after they are marketed.

Pharmacovigilancedatabasesgather IndividualCaseSafetyReports(ICSRs) submittedby healthcare professionals, patients, pharmaceutical companies, and regulatory agencies.

MajorGlobalPharmacovigilanceDatabases

1. **UppsalaMonitoring Centre(UMC)– VigiBase**
   - GlobaldatabaseforADRreports.
   - ManagedfortheWorldHealthOrganization(WHO) Programmefor International Drug Monitoring.
   - ContainsmillionsofICSRsfrommorethan150 countries.

2. **U.S.FoodandDrugAdministration(FDA)– FAERS**

- **FDAAdverseEventReportingSystem(FAERS)** collectsadverseeventand medication error reports in the United States.

3. **EuropeanMedicinesAgency– EudraVigilance**

- Europeandatabaseforsuspectedadversedrugreactionreports.
- UsedbyEUregulatoryauthoritiesforsafetymonitoring.

4. **IndianPharmacopoeiaCommission–PvPIDatabase**

- MaintainsthepharmacovigilancedatabaseunderthePharmacovigilance Programme of India (PvPI).
- ADRreportsaresubmittedthroughADRMonitoring Centres(AMCs).

TypesofDataStoredinPharmacovigilanceDatabases

- Patient information(age, gender)
- Suspecteddrugdetails
- Concomitantmedications
- Descriptionofadverse event
- Laboratoryandclinical findings
- Outcomeofthe reaction
- Reporter information

Thesedatabasesallow**continuoussafetymonitoring,signaldetection,andrisk assessment** for medicines.

SignalinPharmacovigilance[12]

In pharmacovigilance, a **signal** is: Information that suggests a new possible causal relationship betweenadrugandanadverseevent,oranewaspectofaknownreaction, that requires further investigation.

“Information that arises from one or multiple sources (including observations and experiments), whichsuggestsanewpotentiallycausalassociation, oranewaspectofa knownassociation, betweenaninterventionandaneventorsetofrelatedevents, either adverse orbeneficial, that is judged to be ofsufficient likelihood to justifyverificatory action.”

Types of Signals

- **Newsignal**–Unknownadverseeffect
- **Knownsignal**–Alreadyknownbutwithnewinformation(e.g.,increased severity)
- **Potentialsigna**–Needsmore data

Clinical Signals

- Indicationsofpotentialsafetywitha medicalproduct (drugordevice),that are observed during clinical research
- Indicativeofadversedrugreactions(ADRs)
- Indicativeofothersafetyconcernslike,druginteractions,contraindicationsormisuse/ abuse of the products
- Identifiedthroughanalysisofadverseevent data(AED),laboratorytests,imaging, etc.
- Detectionandevaluation:statisticalanalysis, expertopinionandregulatoryguidance

Safety Signals

- Indicationsofpotentialsafetyissueswitha medicalproduct,that canbe identified during clinical research, post-marketing surveillance, etc.
- It'simportanttocarefullymonitorforsafetysignalsthroughouttheproduct lifecycle, to ensure that the medical products are safe and effective for use by patients
- Aneffectivesafetydetectionand management isa criticalaspect of pharmacovigilance (PV)

Quality signals

- Indicationsofpotentialqualityissueswitha medicalproduct,that canbe identified during manufacturing, testing, etc.
- Indicativeofproblemswithmanufacturingprocess –contamination, impurities,or deviation from established procedure
- Indicativeofproblemswithproducttesting–inaccurateor unreliable results
- Detectionandevaluation:inspectionofmanufacturingfacilities,producttesting,and analysis of AED

Efficacy Signals

- Indicationsoftheeffectivenessofa medicalproduct,intreatingaparticularcondition or disease
- Identified:Clinicaltrials,postmarketingstudies,andreal-worlddataanalyses
- Indicativeofpositivetreatmentoutcomes–improvement insymptoms,disease progression,

or patient survival

- Dependingonthenatureandstrengthoftheefficacysignal, it willbeusedto support regulatory approval, labelling claims, or marketing strategies

Source of Signals

- ClinicalTrials
- Spontaneousreporting
- Activemonitoringsystem
- Pharmaco-epidemiologystudies
- Non-clinicalstudies

(Eg:animaltoxicologystudies)

- AdverseEventReporting
- PostmarketingSurveillance
- LiteratureReview–systematicreviewsandmeta-analysis

RISKASSESSMENTS&MANAGEMENTS[13]

Risk assessment isthesystematicprocessofidentifying, evaluating, and analysing potential risks associated with a particular activity, process, or product . in the context of pharmacovigilance., riskassessment acriticalcomponent ofensuringthesafetyofdrugsand medical product. It involves the identification and evaluation of both known and unknown risks determine the like hood and severityofadverse events orother drug related problems.

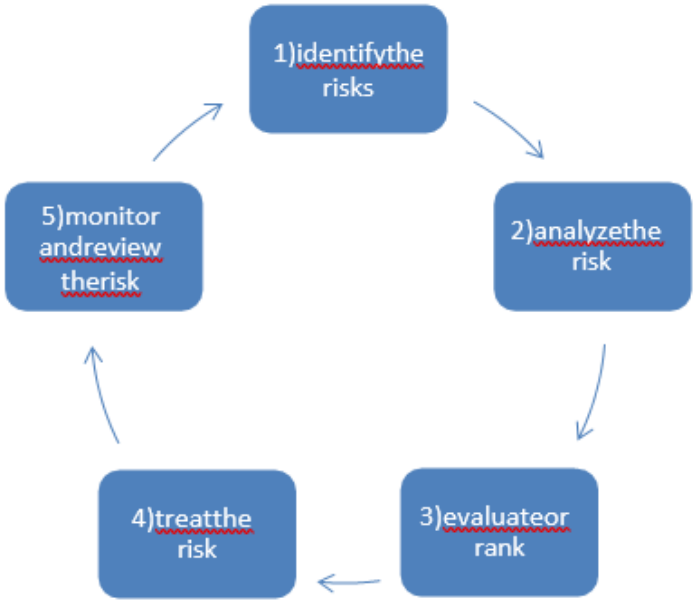


Figure7:riskassessmentprocess.

TYPESOFRISKSMANAGEMENT

1) KnownRisks

Discussingrisksthat arewell-establishedanddocumented inthedrug'ssafetyprofile. Explaining how known risks are identified through clinical trials, post-marketing surveillance, and scientific literature.

2) unknown risks

Exploringrisksthat arenotonlyyet fullycharacterizedorunderstood.Discussingthe challenges in detecting and assessing unknown risks. Highlighting the role of pharmacovigilance in identifying and manging emerging or unexpected risks.

RISK-ASSESSMENTMETHOD

1) Benefit -risk assessment: describing the process of weighing the potential benefitsofdrugagainst itsrisks.Discussingthe importanceofconsideringthe therapeutic value of the drug in relation to its safety concerns.

2) Quantitative risk assessment: Explaining the use of quantitative methods to estimatetheprobabilityand magnitudeofspecific risks.Discussingtechniques such as mathematical modelling and simulation to quantify risks.

3) Qualitative risk assessment: Describing qualitative methods for assessing risks,suchasexpert judgement andriskmatrices.Discussingtheadvantages and limitations ofqualitative approaches .

Case Narrative Writing[14]

Casenarrativewriting isastructuredwayofdescribingarealpatient caseorevent ina clear, detailed, and chronological manner. It is commonlyused in healthcare fields like **Pharmacovigilance**, medicine, and clinical research.

A**casenarrative** isa**writtensummaryofapatient'sclinicalcase**, includingwhat happened, when it happened, and how it was managed.

Whereitisused

- AdverseDrugReaction(ADR) reporting
- Clinicaltrials
- Medicalcasereports
- Drugsafetymonitoringsystems

ComponentsofCaseNarrative

1. **PatientInformation**
   - Age,gender(nopersonalidentifiers)
2. **MedicalHistory**
   - Pastdiseases,allergies,ongoingconditions
3. **DrugDetails**
   - Nameofdrug,dose,route,duration
4. **Event Description**
   - What happened(e.g.,sideeffects)
   - Timeline ofevents
5. **TreatmentGiven**
   - Actionstaken(drugstopped,dosechanged,etc.)
6. **Outcome**
   - Recovered,notrecovered,fatal, unknown
7. **CausalityAssessment**
   - Relationshipbetweendrugandreaction

Example:case;A45-year-old femalepatientwasprescribedamoxicillinforarespiratory infection. After two days of treatment, she developed a skin rash and itching. The drug was discontinued, and antihistamines were given. The symptoms resolved within three days. The reaction was assessed as "probable" according to causality criteria.

Purpose

- Toclearlycommunicateclinicalinformation
- Tosupportdrugsafetyevaluation
- Tohelp healthcareprofessionalsunderstandandpreventrisks

Causality Assessment

UsingtheWHO-UMCCausalityAssessmentScale,thereactionwasclassifiedas

"Probable"because:

- Reasonabletimerelationship betweendrug intakeandevent
- Improvement ondrugwithdrawal(positive dechallenge)
- Noalternativeexplanation
- Rechallengenotrequired

Global And Indian Perspective of Pharmacovigilance[15]

Global Perspective of Pharmacovigilance

- **WHOProgramme:** Sincethe1960s,theWorldHealthOrganization(WHO)hasrun the Programme for InternationalDrug Monitoring, connecting national centres tothe Uppsala Monitoring Centre.
- **RegulatoryFramework:** Strict regulations(e.g.,FDA intheUSA,EMAintheEU) require rigorous, mandatory safety reporting for clinical trials and post-marketing, often using tools like EudraVigilance.
- **FocusonSignalDetection:**GlobalPVheavilyusesdatamining, pharmacogenomics, and informatics to identify risks rapidly, aiming to advance knowledge about drug safety, not just identify harm.

Indian Perspective of Pharma covigilance

- **HistoricalEvolution:** PVinIndia beganformallyin1986,but it failedduetolackof funding until the current PvPI was launched on July 14, 2010.
- **Regulatory Structure:** The Central Drugs Standard Control Organization (CDSCO)governsPV,withtheIndianPharmacopoeiaCommission(IPC) in Ghaziabad acting as the National Coordination Centre.
- **Current Status & Challenges:** While the IPC was recognized as a WHO Collaborating Center for safety monitoring in South East Asia, challenges remain, suchaslowreportingratesamong healthcareprofessionals, lackoftraining,andthe need for strengthening the culture of spontaneous reporting.
- **Recent Trends:** There is a growing focus on integrating PV in clinical trials and adaptingtoelectronicreportingmethods,suchasthe VigiFlowsystem,toenhance compliance.

Table4:comparisonsofIndianandglobalprospective

Aspect	Global	India
Coordination	WHO& UMC	IPC(PvPI)
Database	VigiBase	ContributestoVigiBase
Reporting	Advanceddigitalsystems	Developingbutimproving
Awareness	Highindeveloped countries	Moderate,improving
Challenges	Dataintegration, AI	Underreporting,training

RoleofPharmacistinADRmonitoring[16]

1. DetectionofADRs

PharmacistsareoftenthefirsthealthcareprofessionalstoidentifysuspectedADRsduringdispensing

or patient counselling. They:

- Observeunusualsymptomsor complaints
- Review medicationhistoryandidentifypossibledrug-relatedcauses
- Monitorhigh-riskdrugsand vulnerablepopulations(children,elderly)

2. AssessmentandEvaluation

Pharmacistsevaluatewhetheradrugisresponsibleforthereactionby:

- AssessingcausalityusingtoolslikeNaranjoAlgorithm
- Checkingdose, duration,anddrug interactions
- DifferentiatingADRsfromdiseasesymptoms

3. Documentation

Properrecordingisessential.Pharmacists

- Maintaindetailed ADRrecords(patientdetails,drug,reaction,outcome)
- UsestandardizedreportingformslikeWHO ADRReporting Form

4. ReportingADRs

Oneofthemostcriticalroles

- Report ADRstonationalpharmacovigilance centressuchasPharmacovigilance Programme of India
- Submitreportstoglobaldatabases like VigiBase
- Encouragespontaneousreportingamonghealthcareprofessionals

5. PatientCounselingandEducation

- Pharmacists:Educatepatientsaboutpossiblesideeffects
- Adviseonwhat todoifanADR occurs
- Promotemedicationadherenceandsafedruguse

6. Preventionof ADRs

- Reviewprescriptions forpotentialdruginteractions
- Ensureappropriatedosingandcontraindications
- Recommendsaferalternativeswhennecessary

7. Participationin Pharmacovigilance Programs

- Involvement inhospitalADRmonitoringcommittees

- Conductdrugsafetystudiesand audits
- Contributetosignaldetectionandriskmanagement

8. Communication with Healthcare Team

- Informdoctorsand nursesabout suspectedADRs
- Suggesttherapymodifications
- Ensurecoordinatedpatientcare

RESULTS AND DISCUSSION

Pharmacovigilance originated from historical drug safety tragedies including the sulphanilamide disaster and thalidomide tragedy. Its major objectives are early detection of ADRs,preventionofmedicationerrorsandpromotionofrationaldruguse.Thescopeincludes post-marketing surveillance, signal detection, safety communication, risk management and monitoringofmedicines,vaccinesandmedicaldevices.Causalityassessmentmethodsinclude WHO-UMC scale, Naranjo algorithm and Bayesian approaches such as BARDI. ADR reporting involvesdetection,documentation,submissionto monitoringcentresandevaluation by regulatory authorities.Quality systems in pharmacovigilance consist of quality planning, qualitycontrol,qualityassuranceandqualityimprovement.GlobaldatabasessuchasVigiBase, FAERS and EudraVigilance support signaldetectionand safetymonitoring.Risk assessment evaluates known and unknown risks through benefit-risk analysis and quantitative or qualitative approaches. Pharmacists contribute significantly through ADR detection, assessment, reporting, patient counselling and participation in pharmacovigilance programs.

CONCLUSION

ADRs_have a perspective to provoke_harmful effect in patients. Health-care workers and pharmacovigilance constrain being more conscious of perceive the ADRs in the patient. Pharmacisthadanacceptableknowledge,attitudeandbehaviouronADRreportingandrelated aspects, a good number ofthem had below than acceptable knowledge on drug safety related aspects ofspecific drugs.Educationalprograms have to be continued to generate awareness on how to report ADR and stimulate pharmacists more active participation in the pharmacovigilance programme. Each and every pharmacy store should keep a copy of suspectedAdverse Drug Reaction fromfor easy availabilityto patients. Reporting ofadverse drugreactionhadaddedagreatvalue byimprovingtheaccuracyandefficiencyforevaluation of unwanted effects. The intention is to increase awareness of the different approaches for

diagnosis ADRs as well as to stimulate researchers to continue to collect pharmacoepidemiologic information, studyofpharmacologic, and genetic factors involved in thepathogenesisofdrugreactions, anddevelopandtest newdiagnosticunder variousclinical condition. Causalityassessment to assessthe relationship orconnectionbetweenthe drugand adverse events is a keycomponent for benefit-risk assessment and identification/ assessment ofsafetysignals. Despite various methods developed and standardized, no specific method is accepted universally, although the expert judgement/global introspective method is most commonlyused,asalgorithm-basedandprobabilisticmethodshavebeenshowntobetoughto reliably implement in real situations.

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