KATALYST
HEALTHCARES & LIFE SCIENCES

Pharmacovigilance Process Work Flow

Process of PV

- 4 ELEMENTS DETERMINING VALIDITY OF A CASE
- PHARMACOVIGILANCE WORKFLOW
- TYPES OF CASES
- SOURCES OF CASE REPORTS AND REPORTING FORMS
- **SINGLE CASE PROCESSING-ICSRS**
  - Basic Steps in the Case Handling Process
  - Case Management Workflow
  - Case Receipt
  - Triaging
  - Case Processing
  - Medical review
  - Follow up of adverse events
  - Case completion
- **AGGREGATE REPORTING**
- **SIGNAL DETECTION**
- **RISK MANAGEMENT PLAN**

A Valid Adverse Event Report:

4 Minimum data elements required

1- An identifiable patient

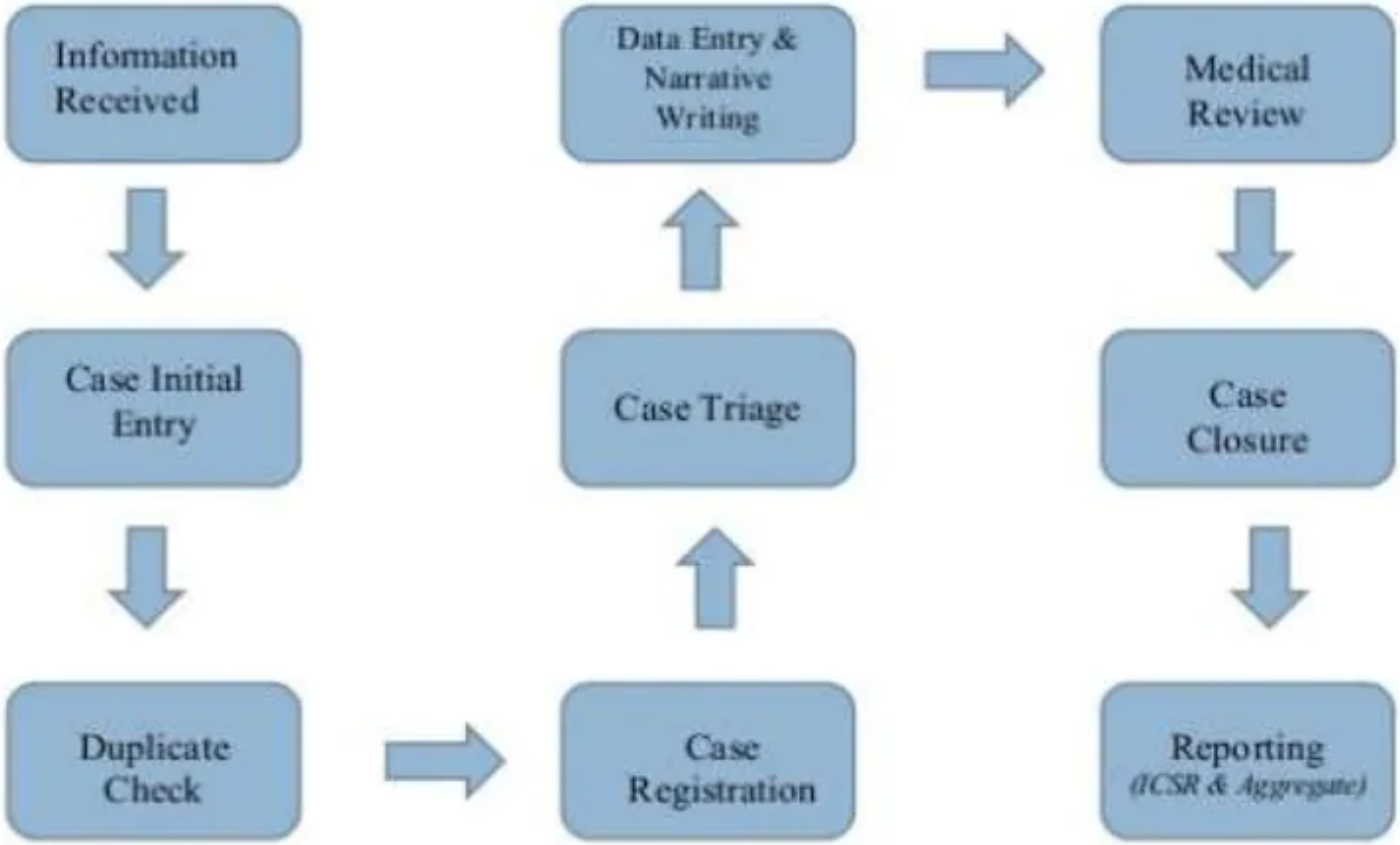
(initials, age, sex, birthday, or simply the knowledge that a patient exists)

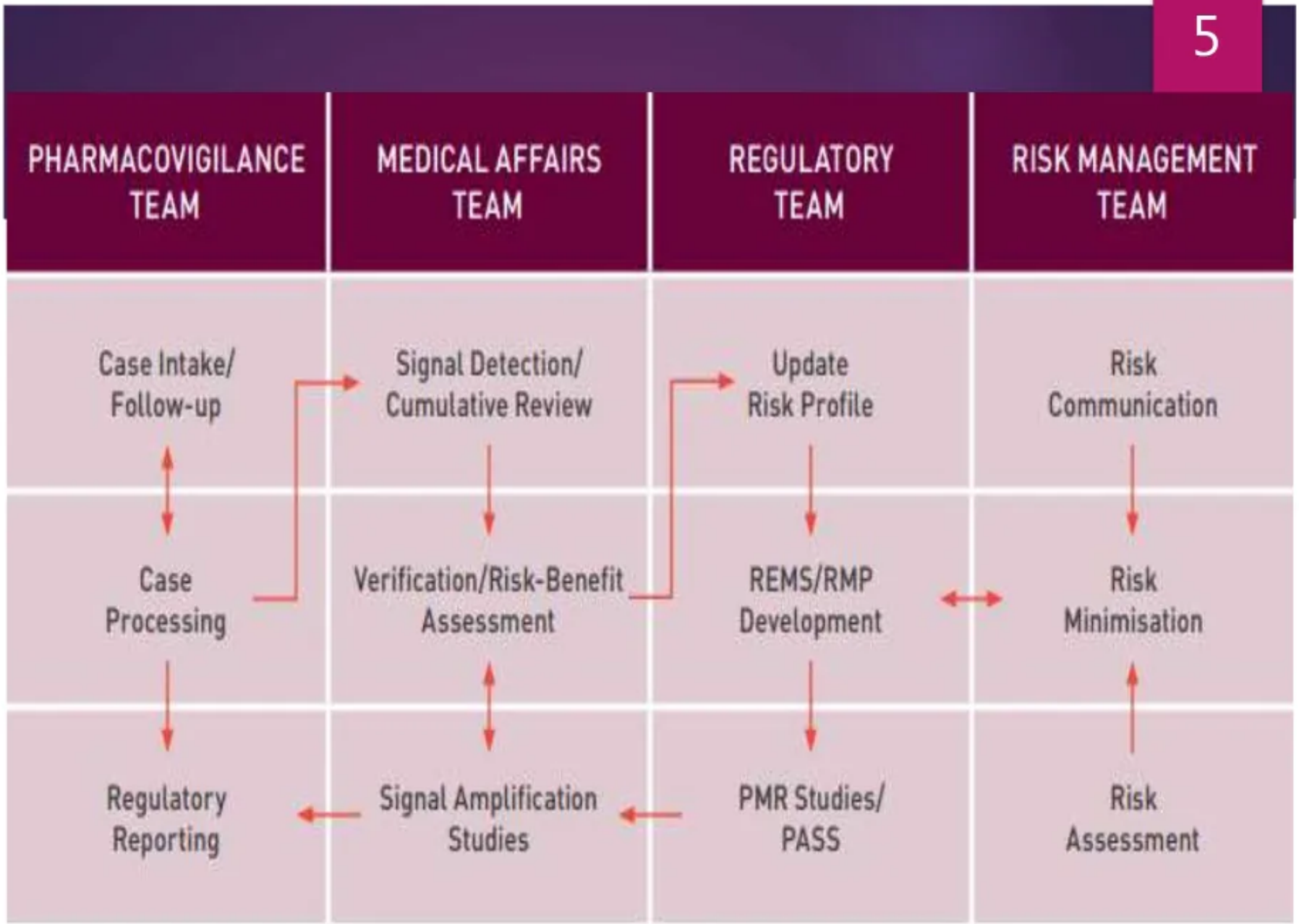
2- An identifiable suspected company product

3- An identifiable reporter (patient, physician, nurse, etc.)

*4- An adverse event**

Individual Case Data Flow




PHARMACOVIGILANCE TEAM
MEDICAL AFFAIRS TEAM
REGULATORY TEAM
RISK MANAGEMENT TEAM
Case Intake/ Follow-up
Signal Detection/ Cumulative Review
Update Risk Profile
Risk Communication
Case Processing
Verification/Risk-Benefit Assessment
REMS/RMP Development
Risk Minimisation
Regulatory Reporting
Signal Amplification Studies
PMR Studies/ PASS
Risk Assessment

1- An Identifiable Patient

Yes	No
<u>Enough evidence that a patient exists</u>	Medical inquiries about AEs with no patient
any knowledge of an individual patient: age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number.	Batch reports: specific patient number "Ten patients developed rash while on Diovan"
	Unspecified Number of patients "some patients had anaphylaxis"
	Non-human subject (pet)

2- An Identifiable Reporter

Yes	No
Initials, name of a person or relationship to the patient (e.g. parent),	*Email Address with no other identifiers*
name of an institution	*Telephone number with no other identifiers*
complete mailing address with no other information	*A reporter who refuses to give his/her name or address, professional qualifications and/or relationship to the patient*
The reporter's professional qualification (e.g. MD, Dr.)	*A letter not meeting the criteria of column "yes"*

3- A Suspect Product:

Yes	No
Any product registered, in-licensed, or co-promoted by company or MAH (globally or locally)	*A generic formulation of a company product (manufacturer known)*
A generic formulation of a company product (manufacturer unknown)	
A product from an unblinded SAE	

4- An Adverse Event:

Yes:

- a specific symptom or diagnosis laboratory finding kinetic interaction with plasma level change lack of efficacy or lack of expected therapeutic effect (as defined in the product label).
- Death with no other information pregnancy, overdose, abuse, accidental administration, disease aggravation.

No:

- ambiguous claims "patient suffered an injury" "irreparable damage" "patient hospitalized", with no symptoms or diagnosis that led to the injury hospitalization.

Desired Information:

- Patient: Initials, age, sex
- Company medication (therapy dates, dose, formulation, indication etc.)
- Adverse event (onset date, lab data, treatment, outcome)
- Reporter correspondence details

In addition:

- Medical history
- Concomitant medication (therapy dates, dose, indication, etc)
- Action taken (dechallenge/rechallenge, intervention)

Follow-Up Information:

- Any new information, or change in previous information
- provided by the reporter, or requested by local or central IMS
- Significant follow-up information expeditable within the SOP timelines*

Receipt of a Valid Adverse Event Report:

Date received by manufacturer
(Initial receipt date (IRD or MRD)):

- Date of receipt of a valid report with the 4 minimum date elements by <u>any company e</u>mployee or a designated person (e.g. a distributor)

- Triggers the regulatory clock!

Pharmacovigilance Workflow:

AE Case Reports → **Aggregate Reporting** → **Signal Detection** → **Risk Management**

Serious and unexpected AEs are subject to expedited reporting

To review the cumulative safety information from a wide range of sources, on a periodic basis and submit to regulators worldwide.

Process of determining AEs associated with particular drugs and comparing the same to that for other similar drugs.

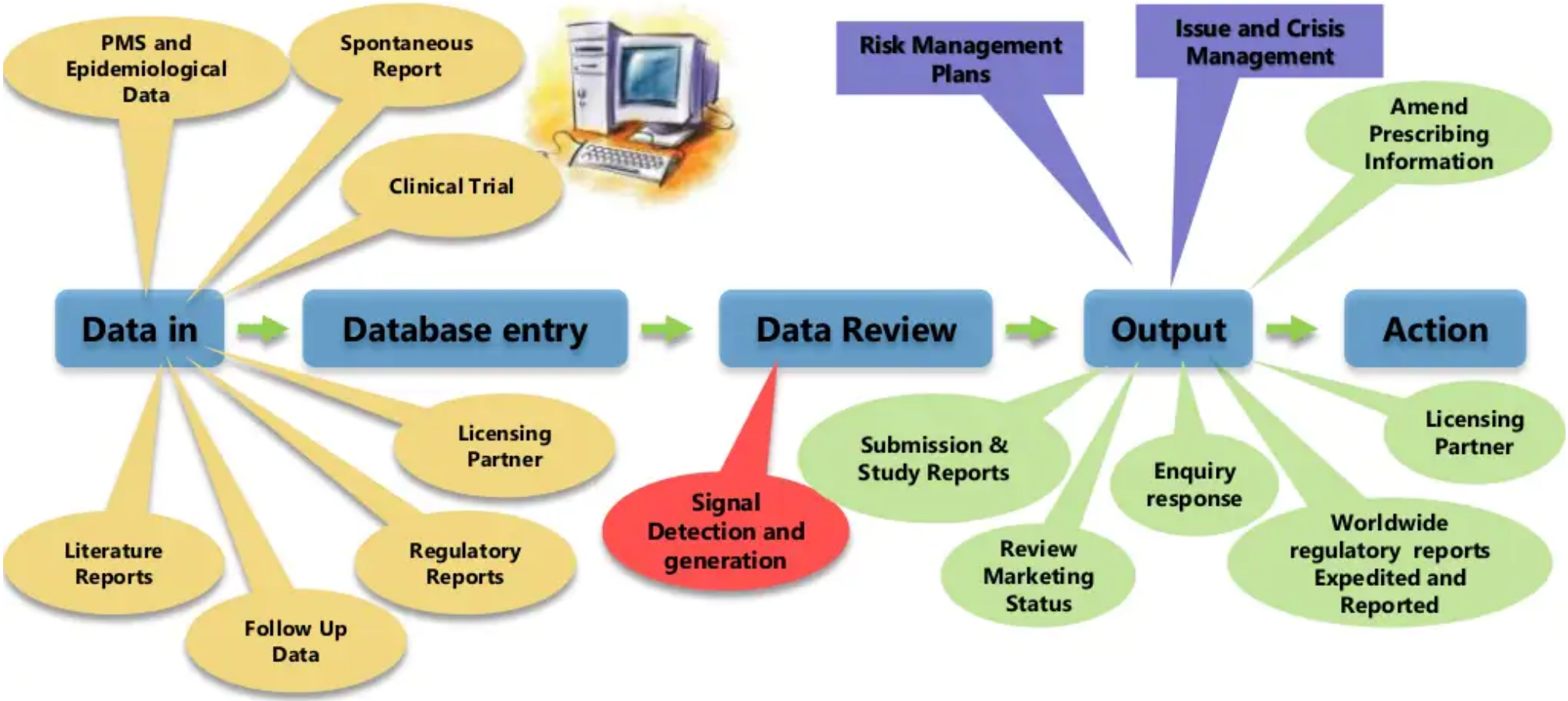
To monitor any reported AE of the product on a patient and to seek methods to minimise or remove such AE from the patient.

Case Management Flow:

- What is PV
- Adverse Drug reactions
- Regulations
- **Single Case**
- Aggregate Reporting
- Signal Detection
- Risk Management

Receive Case → Duplication Check → Logging the Case → Perform Triage to Assess Case → Data Entry in database → Medical Review → Validation & Close Case → Generate Report

Overview of Pharmacovigilance System:



SOURCES of AE Reports:

- Spontaneous reports (SRs):
  - Health Care Professionals (HCPs)
  - Non Health Care Professionals (non-HCPs)
  - Internet
- Solicited reports:
  - Clinical trials phases I-IV
  - Observational Post-Marketing Surveillance (PMS) studies

- Medical literature/ media
- Stimulated reports:
  - Patient support programs
  - Disease management
  - Marketing surveys
  - Patient Registries
  - Health outcome studies
  - Lawsuits
  - Quality of life questionnaires
  - Medical chart reviews

Sources of Individual Case Safety Reports

- **Spontaneous report acc. to ICH E2D:**

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional Centers, Poison Control Center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Definitions:

- **Healthcare professional (HCP):**

  Healthcare professionals are medically-qualified persons such as physicians, dentists, pharmacists, nurses, coroners, or as otherwise specified by local regulations.

- **Consumer (non-HCP):**

  A consumer is defined as a person who is not a healthcare professional.

  Examples: user, spouse, relative, neighbor

Source of Individual Case Safety Reports:

- **Literature:**
  The Marketing Authorization Holder (MAH) is expected to regularly screen the worldwide scientific literature. Cases of ADRs from the scientific and medical literature, might qualify for expedited reporting.
- **Internet:**
  MAHs are not expected to screen external websites for ADR information but should regularly screen their websites for potential ADR case reports.
- **Regulatory Authorities:**
  Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are always subject to expedited reporting.

Spontaneous Reporting:

Strengths

- Cornerstone of 'PV'
- Cheap & Easy
- Encompass all clinical settings
- Life-time span
- Detection of rare ADRs

Weaknesses

- Underreporting
- Quality of reporting
- No denominator
- Subject to bias
- Delayed effects go undetected

How to Report:

- CIOMS-I form
- MedWatch 3500 – voluntary reporting
- MedWatch 3500A – mandatory reporting by MAHs
- CDSCO ADR form (India)

1. **Patient Details**
2. **Suspected Medicinal Product(s)**
3. **Other Treatment(s)**
4. **Details of Suspected Adverse Drug Reaction(s)**
5. **Details on Reporter of Event**
6. **Administrative and Sponsor/Company Details**

Pharmacovigilance Case Management Workflow:

2. AE Case Triage

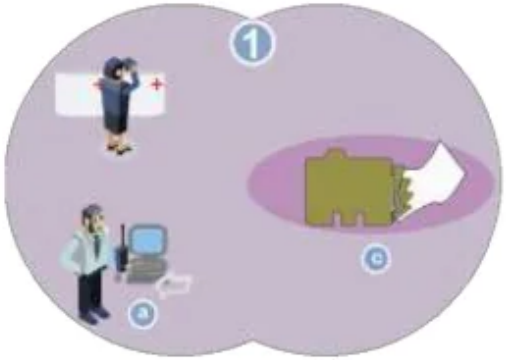
a. Identify duplicate AE cases
b. Assign case priority
c. Enter other case data into AERS system
d. Perform preliminary QA of data entered

3. Event Assessment

a. Prepare company narrative for review
b. Assess case from medical perspective
c. Perform final review of case for reportability

1. AE Case Reception

a. Receive AE Case
b. Document receipt
c. Index, file source documents



4. Processing Follow-Up Information

a. Identify additional Information required to analyze / report the case
b. Follow-up with case reporter to obtain additional information
c. Update additional case information in AERS

6.Regulatory Submission

a. Prepare safety report
b. Facilitate final review by Regulatory Affairs
c. Submit report to Regulatory Agency
d. Track submission date of report

5. Risk/Benefit Analysis

a. Perform risk benefit analysis based on AERS data
b. Perform risk benefit analysis based on data provided by regulatory agencies
c. Prepare analysis reports

Single Case Processing-ICSRs:

- Basic Steps in the Case Handling Process
- Case Management Workflow
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- Medical review
- Follow up of adverse events
- Case completion

AE Case Reception:

AEs received from variety of sources via wide range of methods (Telephone calls, Fax, Mail, Electronic Media).

The following information is captured:

- Case details
- Drug Details
- Patient Details
- Case Reporter Details

- Case details
  - Case number
  - Initial report or follow up report
  - Companies the drug belong to
  - Seriousness about the case
  - Date of receipt by the company becomes the **Regulatory Clock start date**

AE Case Reception:

- Drug details:
  - The reporter suspects that one of the drug is the cause. It is called **Suspect Drug**.
  - The other associated drugs are called **Concomitant Drugs**. Along with the name of the drugs, dose, frequency, regimen, indication are recorded where ever possible.
- Patient Details:
  - Patient's age, country, ethnicity, medical history , etc.
- Case Reporter Details:
  - About the person who reported the case.
  - When the case is reported when the drug is in clinical trial, it is **Clinical Trial Reporting**.
  - When the case is reported when the drug is in market, it is **Spontaneous Reporting**.
  - When the case is reported through publication, it is **Literature Reporting**.

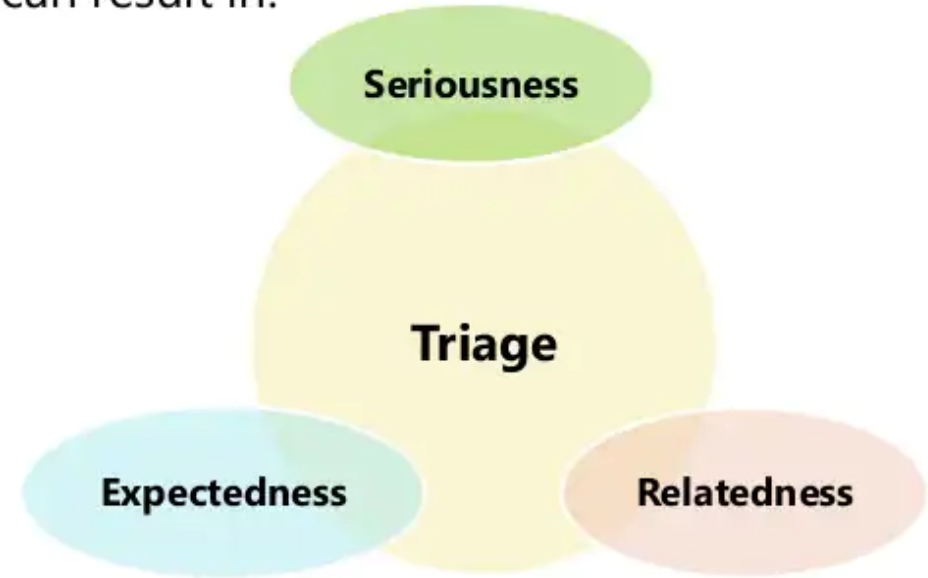
The reporters of cases are categorized : HCP and Non-HCP.

Triaging:

Triage is the assessment, classification & prioritization of the information received according to key regulatory, scientific and medical criteria.

Triage errors if not corrected in time can result in:

- **Late regulatory reports**
- **Missed safety signals**

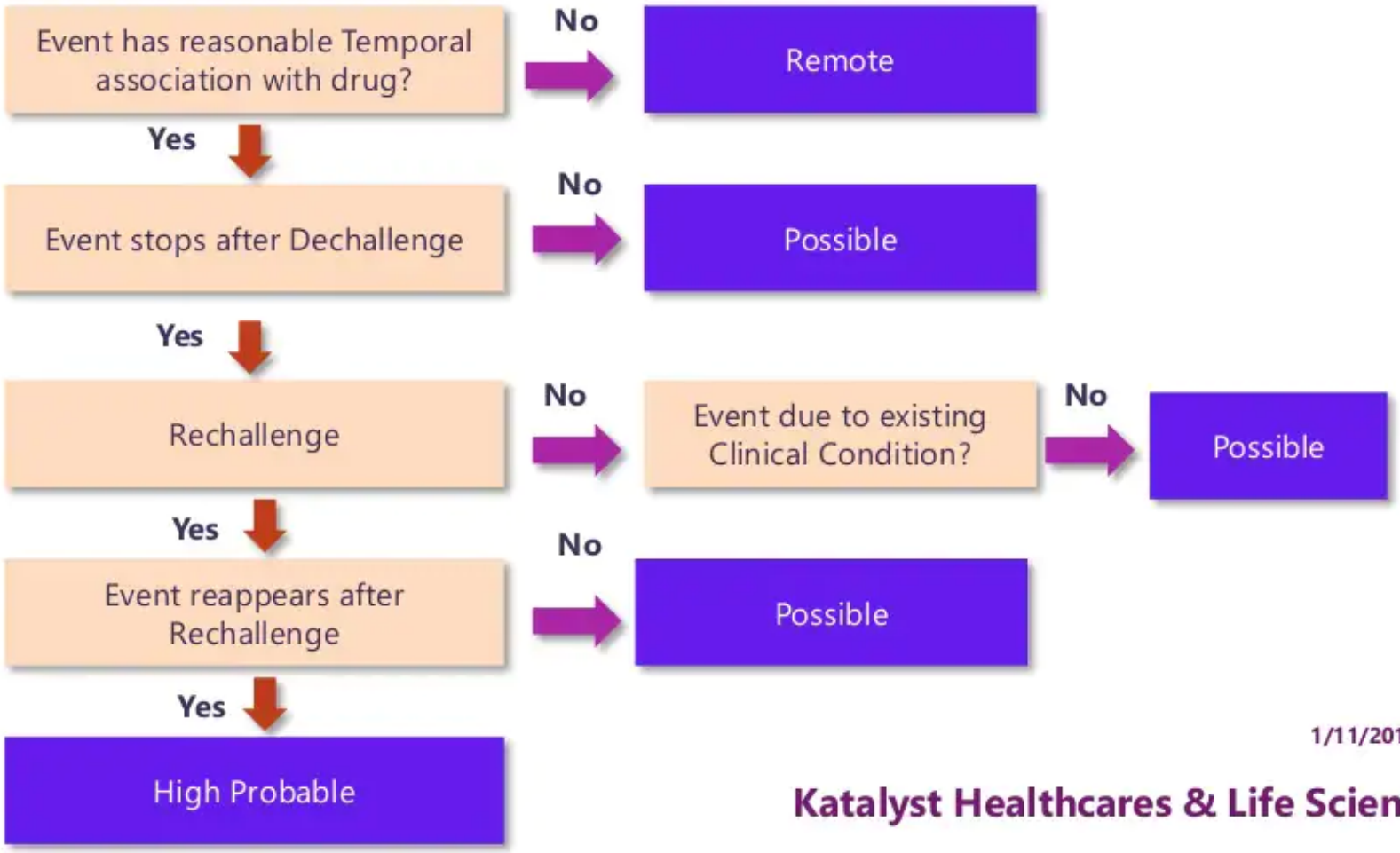


Methods of Causality Assessment:

- Kramer scale
- Bayesian Neural network
- Yale algorithm
- Spanish quantitative imputation system
- WHO assessment scale
- Naranjo's scale
- European ABO system
- Karch and Lasagna's scale

Relatedness/Causal Relationship

Doctors review the data and finds out the causality of the case, i.e., why this adverse event happened.



Relatedness:

"Suspect Causal Relation" WHO Causality Algorithm

Classification	Definition
Definitely related	Events *have no uncertainty* in their relationship to test drug administration: meaning that a re-challenge was positive.
Probable	Event *follows* a reasonable temporal sequence from drug administration, increases upon discontinuation of the drug
Possible	Event *may or may not* follow a reasonable temporal sequence from drug administration but seems to be the type of reaction that cannot be dismissed as unlikely.
Unlikely	No reasonable temporal association between the study drug and the suspected event
Definitely unrelated	Events which occur prior to test drug administration or events which cannot be even remotely related to study participation

Causality:

To determine likelihood of a causal relationship between drug & adverse events:

- Association in time/place between drug use and event.
- Pharmacology (current knowledge of nature).
- Medical/pharmacological plausibility (signs, symptoms, tests, mechanism).
- Likelihood or exclusion of other causes.

Common Questions to assess causality:

Are there previous conclusive reports on this reaction?
Did the ADR appear after the suspected drug was administered?
Did the ADR improve when the drug was discontinued?
Did the ADR appear with re-challenge?
Are there alternative causes for the ADR?
Did the reaction appear when placebo was given?
Was the drug detected in blood at toxic levels?
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
Did the patient have a similar reaction to the same or similar drug in any previous exposure?

NARANJO Algorithm

For assessing the causality-

- definite = ≥9
- probable = 5-8
- possible = 1-4
- doubtful = ≤ 0

Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			TOTAL SCORE:	

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

Hartwig and Seigels Scale:

For assessing the severity-

1. Mild ADRs-are self limiting and do not contribute to prolongation of length of hospital stay.
2. Moderate ADRs- require therapeutic intervention or hospital admission or prolonged hospital stay by at least one day.
3. Severe ADRs- life threatening, requiring intensive medical care or produce disability or lead to death.

Reporting Time Frames

Post-marketing 15-day "Alert reports"

The applicant shall report each adverse drug experience that is both serious and unexpected, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

SUSAR (suspected unexpected serious adverse reaction)
This reporting needs to be done not later than **seven** days after the Sponsor was first aware of the reaction. Any additional relevant information should be sent within **eight** days of the report.
-FDA

Data Processing:

- The main functions of these steps are:
  - **Data entry** into safety database from source document
  - **Coding** (AEs & Products)
  - Writing the case **narrative**
  - Identifying missing information that should be pursued as queries for **Follow Up**

Case Processing:

- **Duplicate search:** Due to, greater awareness , stringent regulations and multiple reporting sources, duplicate reports is a common phenomenon. Every safety management software has a facility to identify and delete duplicates. Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, clinical trial code, country, etc.) may be used to identify duplicate reporting. This action is of significance for further processing of the case. The duplicate could actually be follow up information that could alter the seriousness and hence reporting timeline of the case. Missed out duplicates could send misleading information to signal detection systems.

- **Data Entry:** Details of the four pillars of a valid case have to be reported meticulously. Patient information has to follow the HIPPA code for confidentiality. Reporter information has to clear and detailed enough to be able to contact the person if necessary. Drug identifiers like name, formulation and dose have to be captured correctly. Event report has to be detailed enough for the evaluator to decide on the cause of the adverse event. This would include chronological description of the event or events, nature, localization, severity, characteristics of the event, results of investigations and tests, start date, course and outcome, concomitant medications and other risk factors .

Dictionary Coding:

Medical classification, or **medical coding**, is the process of transforming descriptions into universal **medical diagnoses** & **Procedure** terms.

Purpose:

- To **code** new and amended dictionary terms for purpose of **standardization**
- These terms could be Drug terms, Adverse Events, Diseases, Medical Procedures.
- To ensure **consistent** data classification across all protocols within a project as well as globally across all projects
- To **classify** similar verbatim text into predefined categories that represent medical concepts so that **statistical reports** can be generated for data analysis.

Dictionary Category:

MedDra

Medical Dictionary for Regulatory Activities

- Symptoms
- Signs
- Diseases
- Diagnosis
- Therapeutic Indications
- Names & Qualitative results of investigations
- Surgical & Medical Procedures
- Medical/Social/Family History

WHO Drug

World Health Organization - Drug Dictionary

- Study Drugs
- Concomitant Drugs
- Previous Drugs

WHO -ART

World Health Organization - Adverse Reaction Terminology

Adverse Events

- Serious
- Non-Serious

-Maps to COSTART for reporting purposes

WHOART-WHO:

Adverse **R**eaction **T**erminology is dictionary for coding adverse reactions . This system is maintained by the UMC.

COSTART:

COding **S**ymbols for a **T**hesaurus of **A**dverse **R**eaction **T**erms developed by USFDA . But recently COSTART was replaced by MedDRA.

- **MedDRA** is managed by MSSO (**M**aintenance and **S**upport **S**ervices **O**rganization)
- **MSSO** releases new version in twice a year (March & September)
- March release is the main ,contains changes at the HLT level & above
- September release contains changes at the PT level
- Latest version (17.1) was updated in sept 2014

Example of Coding an Event:

Verbatim	MedDRA
redness at the injection site	Erythema
itchiness at injection site	Pruritis
lack of efficacy	Drug inefficient
reduced effect	Drug nefficient
reflux	Acid reflux

Coding for drugs: Both the suspect drug and concomitant medication have to be coded. The principle is again to be talking the same language across countries, companies and regulatory bodies. Most common dictionary is the WHO Drug Dictionary enhanced. This is provided as a product by the Upsala Monitoring centre of the WHO. Entries are updated 4 times a year. The majority of entries refer to prescription-only products, but some over-the-counter (OTC) preparations are included. The dictionary also covers biotech and blood products, diagnostic substances and contrast media. For chemical and therapeutic groupings the WHO drug record number system and ATC classifications are considered.

Causality assessment:

- ✓ Non spontaneous case reports usually indicate whether an adverse drug reaction is suspected due to the administered drug.
- ✓ In these circumstances and even otherwise, a causality assessment is required to be conducted.
- ✓ Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events.

These systems are largely based on following considerations:

- ➢ the chronology or association in time (or place) between drug administration and event current knowledge of nature and frequency of adverse reactions due to the suspect molecule; or the pharmacology
- ➢ medical or pharmacological plausibility based on signs and symptoms, laboratory tests, pathological findings, mechanism of action
- ➢ likelihood or exclusion of other causes for the same adverse events; often the disease condition or concomitant medication.

Listedness/Labeldness/Expectedness:

- Listedness is based on the CCSI which is the core information on safety profile of molecule available with MAH.
- Expectedness is based on SmPC or PI which is a local label and is related to particular nation.
- It may happen that molecule A is having 10 SmPCs but as a rule each molecule is always has one CCSI. Also, CCSI may contain the less safety information which is available in each and every SmPC but vice-a-verse is not true. So rarely it may happen the event is unlisted but may be expected as per the local label (SmPC).

- CIOMS V provides a very elaborate explanation of Listedness/Labeldness/ and Expectedness.
- The purpose of Expectedness/Labeldness is to assess the reportability of the case to health authorities, whereas listedness, based on CCSI is for the generation of line-listings for PSURs.

Case Review:

- All cases should be reviewed after processing to ensure regulatory, scientific and medical standards are met

- Case review is a 2 step process:
  - **Quality review**
  - **Safety Assessment**

Focus of Case Review:

- Completeness and Accuracy of data.
- Consistency of data entry with source documents
- Confirmation of the triage assessment of regulatory reportability
- Consistency with established report standards (ICH)
- Queries and Follow up information

What is a Narrative?

- Summary of all relevant clinical information relating to an adverse event
  - **Relevant** information*
  - Presented in logical **time sequence** (medical story)
  - Comprehensive **details** of individual cases (stand alone)

*Electronic reporting currently limit on characters (20,000 characters)

Key Elements of a Narrative:

- This is a **spontaneous non serious** report.
- A **nurse** reported that a **29 year** old **male** consumer experienced **stomach ache** on **14Jun2008**. while on therapy with oral aspirin
- The patient stated that he experienced burning type of stomach ache. The patient could not eat due to the pain in the stomach. The patient also could not sleep until early morning due to the stomach pain.
- He was taking aspirin 75mg two times a day orally for the **treatment** of **low back pain from an unknown date**.

Key Elements of a Narrative...Contd

- **Medical history** included high blood pressure and ulcerative colitis from an unknown date.
- **Concomitant medications** included oral acetaminophen 500mg, Vitamin B complex 180mg, from an unknown date.
- **Investigations data;** endoscopy was carried out on 19Jun2008 and the results were normal.
- Therapy with Aspirin was continuing at the time of the report.
- At the time of the report the **clinical outcome** of the event was **unknown**.

Medical Review:

- Adverse Event (AE) Capture
  - Appropriateness of the AE terms selected
- **Sequencing** of the AEs
- Confirmation of Coding
- Confirmation of the **Seriousness** classification of the AE Terms
- Confirmation **Listedness**/**Expectedness** classification of AE Terms
- Reviews concurrent conditions, medical history
- Identification of any specific additional information needed for medical assessment
- Company causality assessment, wherever appropriate
- Identification of potential safety signals

- **Timely reporting to authorities:** this is the end goal for which all the above has to be done in a timely manner. The reporting could be by sending data back to the sponsor or by a click of a button based on the software used. The latter will provide an extra couple of days for case processing

- Safety data management is the most basic step in pharmacovigilance. This is often outsourced so that internal company resources can focus on the domain related, mentally stimulating activities like signal detection, regulatory responses, information to stakeholders

Case Completion:

- Case considered ready for completion when it has gone through **triage**, **processing**, **review** and **approval**

- Case completion process includes:

  - any updates to the case as required by the **review cycle**

  - incorporation of **additional** information requests into standard follow-up requests

  - **generation** of final report & **distribution** of the final report to appropriate internal & external parties, including regulatory submission

  - **Archiving** the report and accompanying source documents (both paper & electronic documents)*

Follow up Information:

Recommendation to prioritize case reports by importance:

- Serious and unexpected
- Serious and expected
- Non-Serious and unexpected
- Cases of special interest (ADRs under surveillance; non-serious ADRs which may develop into serious ADRs (mild blood alterations indicating dyscrasias; liver enzyme fluctuations etc..)

Follow up can be obtained by:

- Telephone; site visit; written request
- Written confirmation should be obtained wherever possible for the data supplied

Follow up Information:

- Judgement should be exercised for the extent of follow up and should be placed
- alongside the seriousness of the reported reaction and the known outcome
- (condition stabilized; resolved)
- It is recommended that MAHs should collaborate together if there is more than
- one MAHs drug suspected as a causal agent (interactions)
- ICH E2D has a list of key data elements which should be included wherever
- possible in expedited reports

Follow up related to pregnancy:

- Any pregnancy outcome where the reporter or Company decides may be related
- to the Company product, this should be reported as an expedited report under 15
- calendar day rules
- All pregnancy cases should be followed to term
- If the Company product has long half life (or metabolites) even though the
- product was stopped before conception there is a possibility that drug/metabolite
- exposure could occur and recommendations in the label and for Company
- monitoring should occur

What is Aggregate Reporting:

- Aggregate Reporting is the process that reviews the **cumulative safety information** from a **wide range of sources**, on a **periodic basis** and submit the findings to **regulators worldwide.**

- Aggregate report examines and summarize all existing safety experience with a medicinal product. Report includes benefit risk assessment of SAEs and ADRs, pregnancy reports, overdose and Lack of Efficacy reports.

- The aggregate safety reports are submitted to regulators for as long as the medicine is marketed anywhere in the world and enables understanding of risk benefit profile of product over a period of time.

Examples of Aggregate Reports

Pre-marketing Reports

- NDA Annual Reports
- IND annual reports
- Clinical Study Reports (CSR)

Post-marketing Reports

- Periodic Safety Update Report (PSUR)
- Summary Bridging Report (SBR)
- Development Safety Update Report (DSUR)
- Annual Safety Reports (ASR)
- Periodic Adverse Drug Experiences Reports (PADER)

Periodic Reporting in US (PADER)

- PADER- Periodic adverse drug experience report or PAER- Periodic adverse experience report _periodic report in US. The U. S. Food and Drug Administration (FDA) generally requires NDA Periodic Reports

- Quarterly during the first 3 years and
- Annual reports thereafter

Periodicity of reporting In Europe (PSUR)

The European Medicines Evaluation Agency (EMEA) requires Periodic Safety Update Reports (PSURs)

- Every 6 months for 2 years
- Annually for the 3 following years, and then
- Every 5 years

Periodicity of reporting In Japan: (Anzenteikihoukoku)

In Japan, the authorities require a survey on a cohort by a number of identified institutions

- Annually for 6 years on this cohort

Adverse reactions that are **non serious**, but **both mild in severity and unlabeled**, must be reported

- Every 6 months for 3 years and
- Annually thereafter

What is PSUR:

- ✓ The Periodic Safety Update Report (PSUR) is a report that summarizes interval safety data covering short periods of time and is used in overall safety evaluation of a product.
- ✓ It is a tool for Marketing Authorization Holders (MAHs) to conduct systematic analyses of safety data on a regular basis.

The deadlines for the submission of PSURs are as follows:

- Every 6 months in the first two years following authorization and/or marketing.
- Every year in the next two years.
- Every 3 years thereafter.

ICH & CIOMS Background:

- CIOMS II Working Group
  - Began work in November 1989 after completing CIOMS I
  - Harmonize report format for aggregated safety information
  - Published Report in 1992
- ICH Topic E2C
  - Step 4 November 1996
- ICH E2C Addendum
  - Step 4 February 2003

Source of Information:

Generally, data from the following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

- Spontaneous notifications from HCP's and non-HCP's
- Clinical Studies
- Literature
- ADR reporting systems of regulatory authorities
- Other sources of data:

(reports on ADRs exchanged between contractual partners (e.g., licensors licensees), data in special registries, such as maintained in organ toxicity monitoring centers, reports created by poison control centers and epidemiologic data bases)

General Principles:

- One report for one active substance
- All indications, dosage forms and regimens
- Separate PSURs
  - fixed combinations
  - two or more different formulations, e.g., systemic vs topical
- One report to reach regulatory authority for the same time period
- Six-month interval data from international birth date (first approval anywhere)
- Report all relevant new information from appropriate sources
- Use of CCSI as reference product information

Source: ICH E2C PSUR

PBRER-Periodic benefit risk evaluation report

- PSUR is replaced by PBRER
- The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or
- emerging information on the risks of the medicinal product, and on its benefit in approved indications,
- to enable an appraisal of the product's overall benefit-risk profile.

- The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:
- Summarizing relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- Summarizing any important efficacy/effectiveness information that has become available during the reporting interval;
- Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile; and
- Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

The MAH should continuously evaluate whether any revision of the reference product information/RSI is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI made during the interval should be described in Section 4 of the PBRER ("Changes to Reference Safety Information") and include:

- Changes to contraindications, warnings/precautions sections of the RSI;
- Addition of Adverse Drug Reaction(s) (ADR) and interactions;
- Addition of important new information on use in overdose; and
- Removal of an indication or other restrictions for safety or lack of efficacy reasons.

Timelines for PBRER:

Ad hoc ("for cause") PBRERs

Ad hoc PBRERs are reports outside the routine reporting requirements, and may be requested by some regulatory authorities. Where an ad hoc report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the MAH.

Time Interval Between Data Lock Point and the Submission

As a result of the expanded scope of the PBRER, the time interval between the DLP and submission of PBRERs should be as follows:

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days;
- PBRERs covering intervals in excess of 12 months: within 90 calendar days;
- ad hoc PBRERs: 90 calendar days, unless otherwise specified in the ad hoc request.

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission.

Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.

TERMINOLOGY

- ✓ SIGNAL-reported information on a possible causal relationship which is being unknown or incompletely documented previously.
- ✓ Usually more than 1 report is required to generate a signal
- ✓ before signals are published they are first clinically assessed by PV experts at UMC(Uppsala monitoring Centre ,Sweden)

To qualify as a signal through the current routine signal detection process, a drug-ADR combination has to go through and meet the criteria in the following procedure:

1. The relative reporting rates for all drug-ADR combinations reported in VigiBase are calculated. The IC value highlights the drug-ADR combination as being reported "unexpectedly" more frequently relative to the database background.

2. For the highlighted drug-ADR combinations the triage algorithms (filtering methods) select combinations for which the ICSRs derive from at least two countries and meet one of the following criteria:
   • new drug and serious reaction (drug first entered into the database in the last five years and ADR is a WHO-ART critical term) [Glossary of terms]
   • significantly increased IC value since the previous quarter

3. Drug-ADR combinations filtered out by the triage algorithms are subsequently checked by UMC staff for occurrence in available product information and literature. If the reaction is not found or not described well enough, the individual case reports are retrieved from VigiBase.

4. A thorough clinical assessment of the individual case reports is then done either internally by UMC staff or externally by members of the UMC Signal Review Panel.

There are 3 Types of Signals:

1. Confirmed signals-causal relationship between the drug and adverse event.

2. Refuted(false) signals-no causal relationship.

3. Unconfirmed signals-require further investigation.