Module 1: Overview of Pharmacovigilance

Module 1

What are we going to learn?

- Basic concepts of Pharmacovigilance (PV)
- Need for Pharmacovigilance

Pharmacovigilance (PV)

Science and activities relating to the

Detection: Reporting/collection of Adverse Events by creating awareness/sensitizing the public, HCPs and MAH/ pharmaceutical companies

Assessment: Study on the aetiology of the adverse effect and establishing a causal relationship with the drug in question

Understanding: understanding the life cycle of the ADR and its severity to be able to take any preventive action for the same

Prevention: Taking necessary measures (risk mitigation strategies/communicating the risks to the HCP/ patient) to promote the safe use of products including submission of safety data before the drug approval or withdrawal of the drug from the market post identification of the risks as compared to the benefits of the drug.

of adverse effects or any other medicine-related problem.

The term "**medicines**" embraces both pharmaceutical and biological medicines, and vaccines.

Why and when was PV started?

THEN…

Drug Safety matters used to be conducted in secret to avoid alarming the public

Thalidomide disaster in 1961 : Drug prescribed in the 1950s as a mild sleeping pill and remedy for morning-sickness for pregnant women led to serious birth (limb) defects (birth of congenitally deformed infants as the result of exposure in utero to an **unsafe medicine**) and led to the start of modern **pharmacovigilance.**

Led to creation of the **WHO** Pilot Research Project for International Drug Monitoring in **1968** for **early action for rapid dissemination of information on ADRs**

NOW…

Public involvement is sought to enhance the performance of Pharmacovigilance.

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Stakeholders for PV

Sources (Spontaneous/Study/ Literature/NIPs/ Media)

Reported by HCPs, Patients, Sponsors/MAH, lawyers)

Pharmaceutical Companies

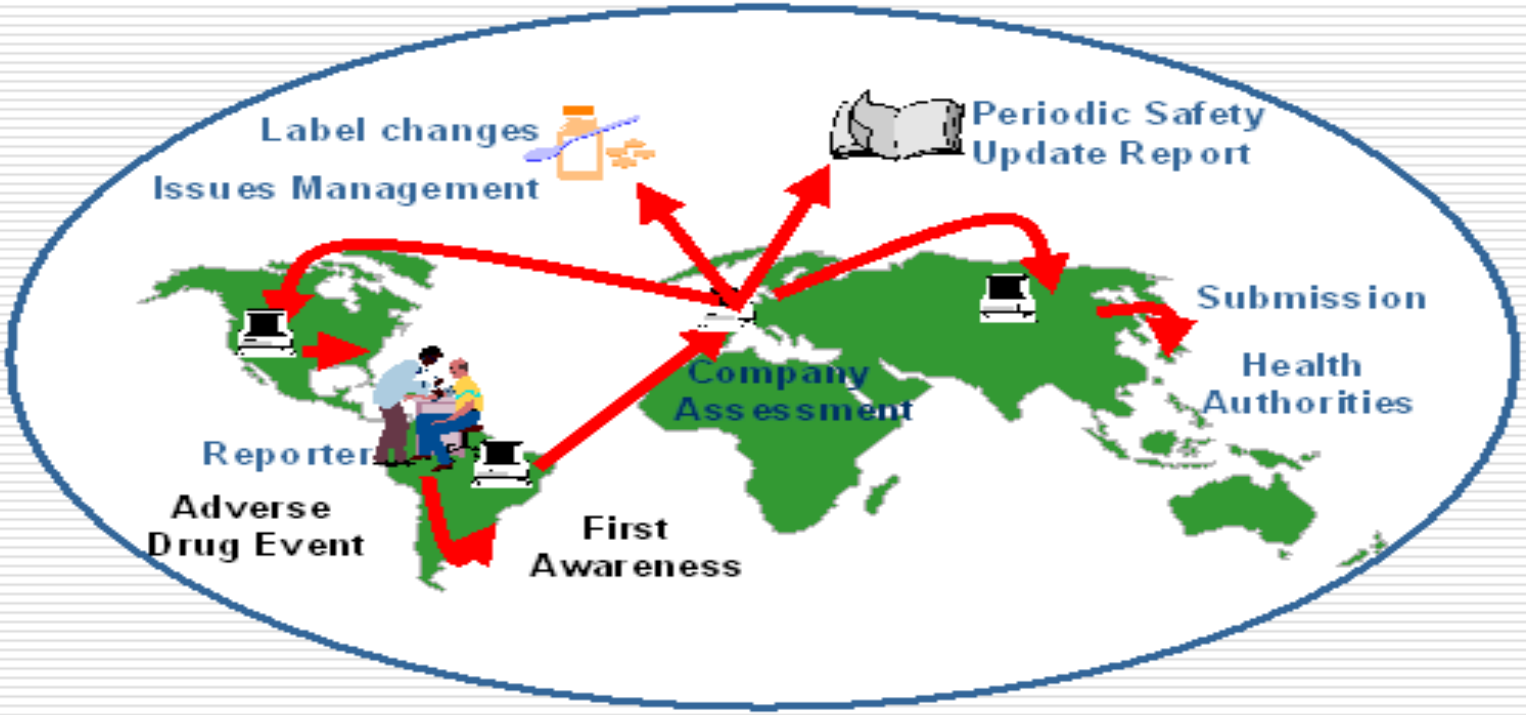
(MAH)

Regulatory Bodies

(Health Authorities like EMA, FDA, MHRA)

Marketing Authorisation Holders (MAH) are **legally** obliged to forward adverse events to the regulatory bodies.

Global Drug Safety Perspective

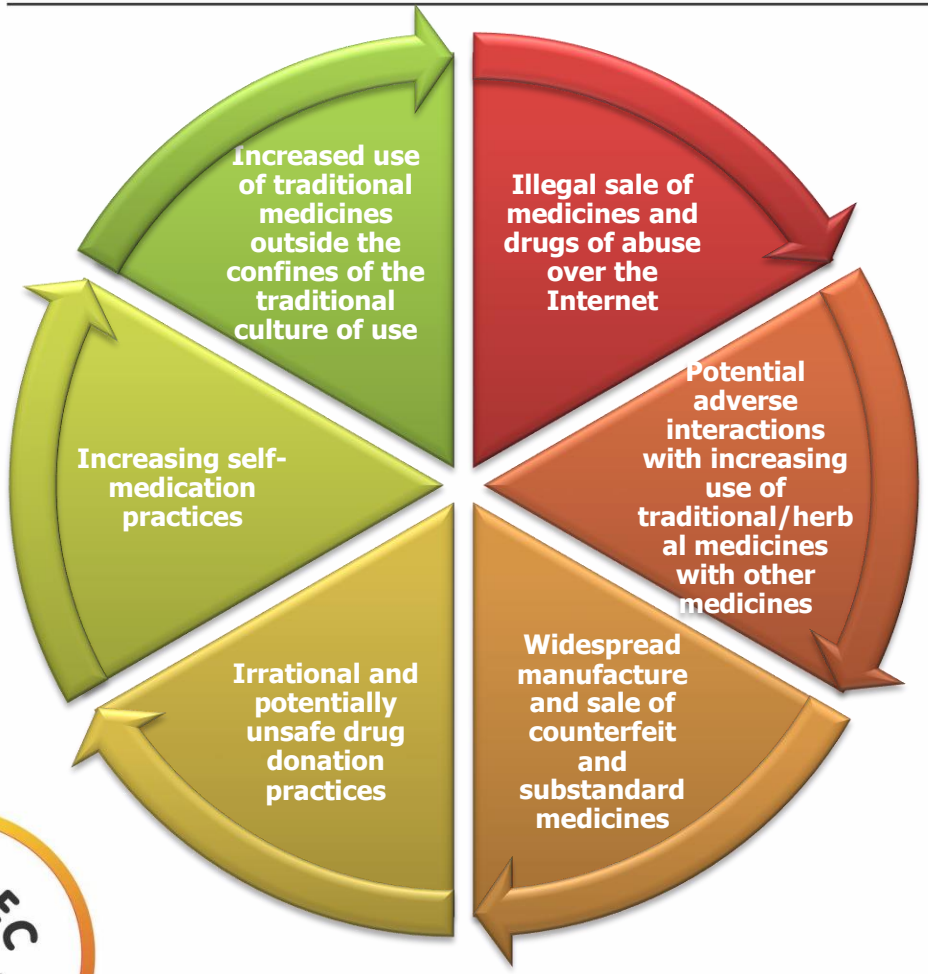


Objectives of Pharmacovigilance

Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and

Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public and promoting a more balanced risk/benefit assessment.

Why is PV required?



To **decrease/prevent the harm** caused by medicinal products intended to **treat/benefit the condition/indication** for which the medicine is used

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Why is Post-marketing PV needed?

Rare AEs (which also might be serious enough to warrant additional precautions or even withdrawal of a medicine from the market) are unlikely to be uncovered by controlled clinical trials involving a few thousand patients at most.

Under representation of 'real-life' population (poorly represented groups) due to enrolment methods and inclusion/exclusion criteria for CTs

- Paediatric and elderly patients,
- Women, especially pregnant or breast-feeding women,
- Patients with one or more co-morbid conditions (and who are using other medicines concomitantly),
- Those with significant renal or hepatic impairment; and
- Patients from ethnic minorities

Non-revelation of long-term adverse/toxic effects of some medicines in CTs. A fuller pattern of adverse effects is revealed only after continuous monitoring for AEs. E.g. Bone fracture after long-term use of some anti-epileptics.

Basic concepts of Pharmacovigilance

Definitions in Pharmacovigilance (1)

Adverse Event (AE)—ICH

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). Any unfavourable and unintended sign (abnormal laboratory finding,), symptom, or disease temporal to the use of any dose of a medicinal product, (ICH E2A).

Definitions in Pharmacovigilance (2)

Adverse Experience/Event—Food and Drug Administration (FDA)

- For post marketing cases: Any AE associated with the use of a drug in humans, whether or not considered drug related, including the following: use of a drug product in professional practice; from drug overdose whether accidental or intentional; from drug abuse, from drug withdrawal; and any failure of expected pharmacological action (21CFR314.80(a)).
- For clinical trial cases, the FDA revised the definition effective March 2011 to read as follows (21CFR312.32): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Definitions in Pharmacovigilance (3)

Adverse Reaction

- In the pre-approval phase of a product, the definition is as follows: “All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.”
- This means “that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out” (ICH E2A).
- For post-approval products, the definition is as follows: “A response to a drug which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function” (ICH E2A).

Definitions in Pharmacovigilance (4)

Serious Adverse Event (SAE) and Serious Adverse Reaction

- A serious AE or serious AR is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening

Note: The term life-threatening in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe:

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect

SAE cont

Important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse (ICH E2A).

The FDA (21CFR312.32, 21CFR314. 80(a)) and EMA (Good pharmacovigilance practice) definitions are similar but do differ somewhat

Definitions in Pharmacovigilance (5)

Suspected Adverse Drug Reaction (SADR)

- A noxious and unintended response to any dose of a drug or biologic product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase “a reasonable possibility” means that the relationship cannot be ruled out (ICH E2A).
- The point here is the word suspected, which means some level of causality with the drug in question, is present. It may be serious or non-serious.

Serious, Unexpected, Adverse Drug Reaction

- An SADR that is serious and unexpected. See the definitions for serious and unexpected. The FDA does not use this definition formally for cases, though the concept is similar.

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Definitions in Pharmacovigilance (6)

Unexpected Adverse Reaction—EMA

- An adverse reaction, the nature, severity or outcome of which is not consistent with the SPC . This includes class related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product. These adverse reactions, when the SPC is used as the reference document, are referred to as unlabeled. This is quite different from unlisted (see below).

Unlisted Adverse Reaction—EMA

- An adverse reaction that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product.

Expected

As opposed to “unexpected,” any event that is noted in the investigator brochure or labelling (Package Insert or SPC) is termed as “expected”.

Pharmacovigilance System

In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the **safety of authorised medicinal products** and detect any **change to their risk-benefit balance**.

Good Pharmacovigilance Practices (GVP)

Good pharmacovigilance practices (GVP) are a set of guidelines for the conduct of **pharmacovigilance** in the European Union (EU).

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports.

The guideline on GVP consists of XVI chapters/modules covering major pharmacovigilance processes; product- or population-specific considerations.

Good Pharmacovigilance Practices (GVP)

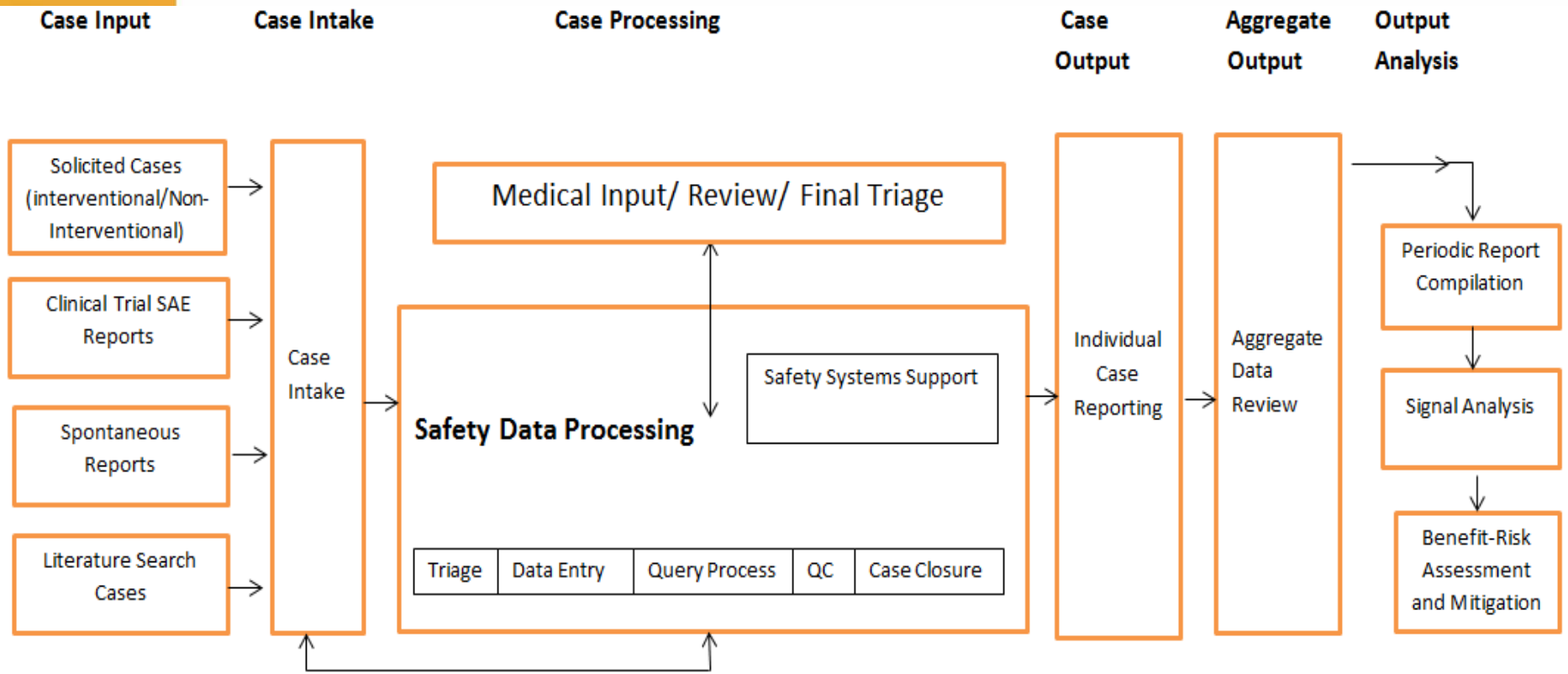
As of July 2012, volume 9A has been replaced by the good-pharmacovigilance-practice (GVP) guideline, published by the EMA. However, where GVP modules have not yet been finalised, the relevant parts of volume 9A remain the reference.

For the processing of all the information collected during the pharmacovigilance the following GVP Modules by EMA apply and serve as the guidelines:

ICSRs and Literature Cases: Module VI
Aggregate reports/ PSURs: Module VII
RMP: Module V
Signal Management: Module IX

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Operational Overview of PV



Data Submitted to Regulators

ICSRs

- Solicited (Clinical and Organised Data Collection from any of the sources including media and Literature)
- Unsolicited (Spontaneous including Literature, Social Media, Legal)

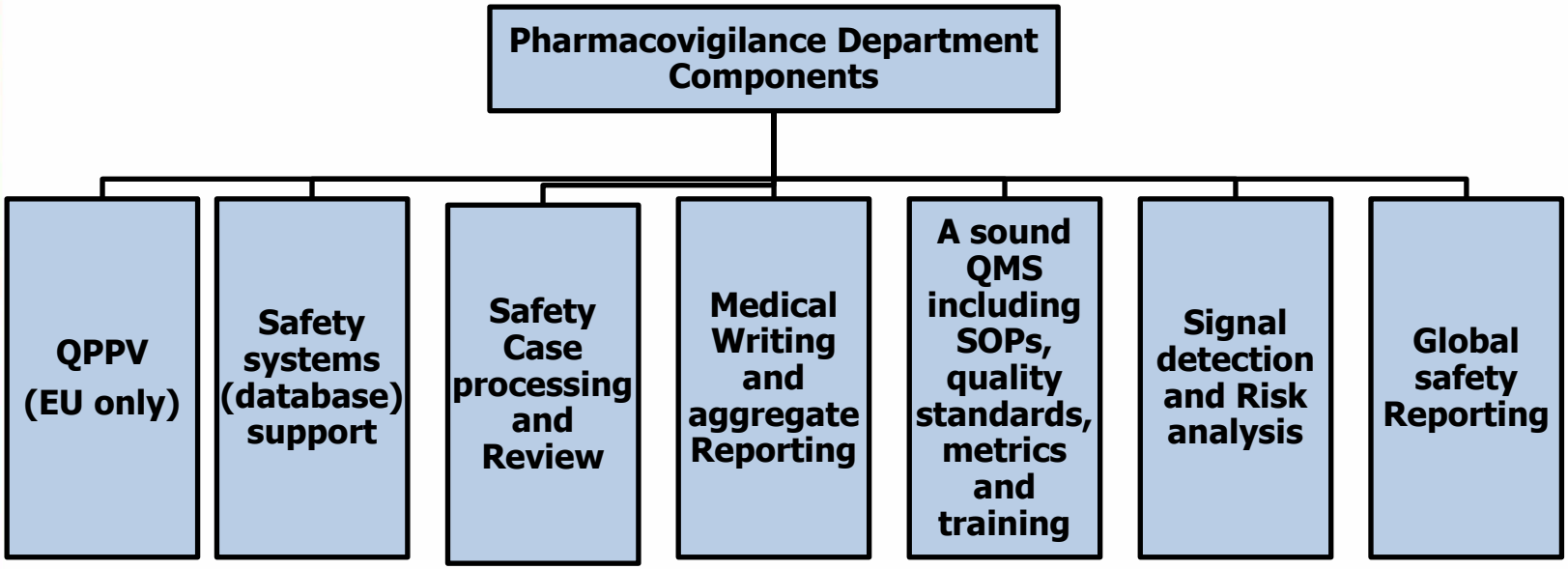
Aggregates

- PSURs/ PBRERs/PADERs
- Bridging Reports/COs/ASRs/DSRs/SUSARs
- Addendum PSURs
- Addendum COs

Signal Management

- Signal Detection
- Risk Evaluation
- Risk Evaluation and Mitigation Strategies (REMS)/Risk Management Plans (RMPs)
- DSRs

Components and Capabilities of a Complete PV system



QPPV: Qualified Person for Pharmacovigilance
QMS: Quality Management System
SOP: Standard Operating Procedures

Safety Databases

A safety database allows the pharmacovigilance department to monitor, assess, and report to the regulatory authorities serious safety information.

The database must be validated (e.g. CFR 21 compliant) and acceptable to all regulatory authorities on the global level.

It is also required to have the capability for reporting expedited cases electronically. The specifications for **electronic reporting** are detailed in **ICH E2B.**

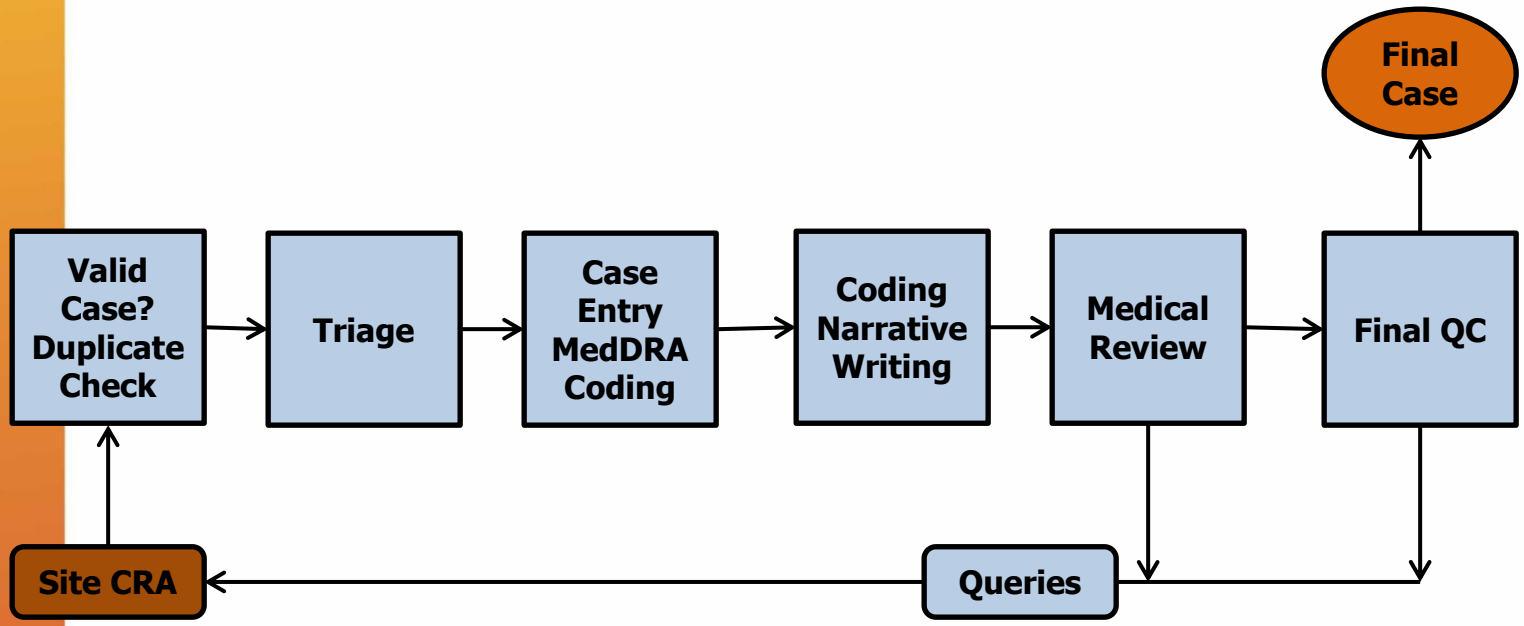
Such an “E2B compliant” gateway allows direct export of such expedited cases to the authorities’ databases such as EudraVigilance in Europe.

Safety Data Review and Assessment

Case Reports

Safety Data Review and Assessment is done through the combined processes of **individual subject data assessment** and **aggregate data review and assessment**. Each case is processed, assessed as to its relationship (causality) to the suspected product, and reported to the regulatory authorities and other stakeholders, based upon pharmacovigilance policies, regulations, and guidance documents.

SAFETY CASE PROCESSING AND REVIEW



CRA: Clinical Research Associate
MedDRA: Medical Dictionary for Regulatory Activities

ICSRs: What constitutes a valid report?

ICSRs: Individual Case Safety Reports

- **An identifiable patient**
- **An identifiable reporter**
- **At least one suspect drug**
- **At least one suspected reaction**

Information Collected in the ICSRs

- Patient
- Reporter
- Event
- Drug
- Medical history including concomitant medications and conditions
- Laboratory Data
- Narratives/texts
- Special situations: Lack of effect, overdose, drug abuse, drug dependence, medication error, technical complaints; pregnancy cases

Types of ICSRs

Solicited

(Interventional studies)Reports

Clinical trials

Registries, post-authorisation named-patients use programmes

Post-authorization safety studies (PASS)

Other patient support and disease management programmes

Surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

A patient support programme is an organised data collection system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products.

For the purpose of safety reporting, solicited reports **should not be considered spontaneous but** classified as ICSRs from studies and therefore **should have an appropriate causality assessment by a healthcare professional or the MAH** (see Annex IV, ICH-E2D).

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

Non-interventional trial reports

- A study where the medicinal product(s) is (are) prescribed in the **usual manner** in accordance with the terms of the marketing authorisation.
- The assignment of the patient to a drug is not as per a **trial protocol** but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
- No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data
- Non-interventional studies are defined by the **methodological approach** used and **not by the scientific objectives**.
- Retrospective studies also are noninterventional

Types of ICSRs

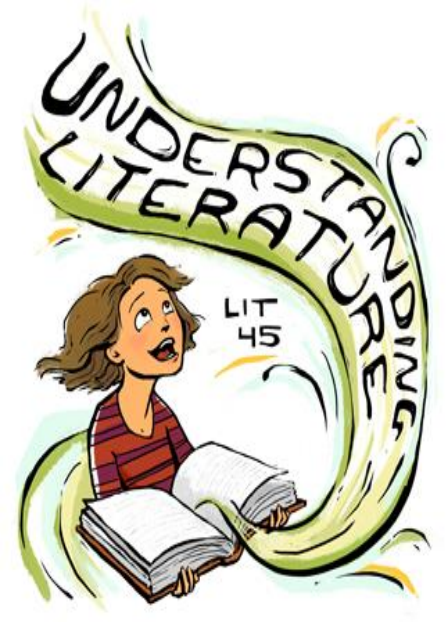
Unsolicited Reports

- An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that **does not derive from a study or any organised data collection scheme** (see Annex IV, ICH-E2D).
- **Spontaneous Reports**
- **Stimulated Reports**
- Literature reports
- Other sources: e.g. law suit (**Legal**) cases, **media** cases: e.g. lay press /internet/digital media.

Consequently AEs arising from the use of social media to gather market research information i.e. digital listening will be unsolicited reports **whilst** those cited during any other form of online market research, face to face, telephone or postal market research will be solicited reports.

Academy

Literature Reports



As the literature and scientific material serve as a significant source of information for detecting new safety signals and emerging safety issues, MAH (Marketing Authorisation Holders) are expected to maintain awareness of possible publications through **a systematic literature review** of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) **no less frequently than once a week.**

Global literature databases such as Pubmed (MedLine) or Embase (or any other client specific databases) are searched to identify **VALID** articles and abstracts to:

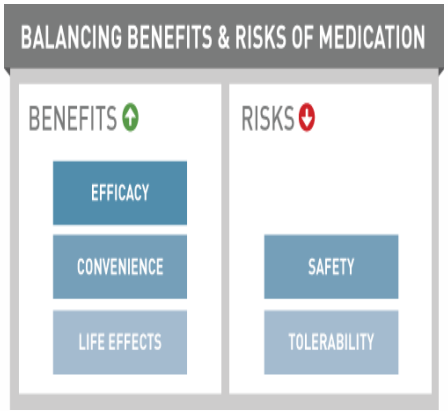
- Be processed as ICSRs
- Be included in PSURs/PBRERs
- NDA AR (New Drug Application Annual Report)
- DSUR (Development Safety Update Report)

Understanding “Safe”, “Safety” and “Risk/Benefit” Balance

Safe: “**Doesn’t mean harmless**”. It means decreasing the risks/preventable harm and getting the most benefits from your medicine for which it is intended to be used.

“Safety" is a relative concept and decisions about a particular drug's use must be evaluated as a **balance between the benefits and the risks** of the medication use for an individual patient

Safety concern : could be an important identified risk, important potential risk or missing information.



Anticipating and minimising adverse reactions to medicines can have a very substantial effect on morbidity, hospitalisation, and on mortality.

Risk and Risk-Benefit Balance

Risk:

Preventable or endured undesirable or **harmful effects related to a drug therapy** (assessed by their causality, severity, certainty of likelihood, longevity, preventable or not and certainty about the information used for characterization of risks)

It is the probability of harm being caused; the probability (chance, odds) of an occurrence.

Risk/Benefit Balance: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health).

RA may withdraw an approved drug from the market if the balance goes otherwise.

Regulatory agency (RA) approves a drug when the drug's benefits outweigh its risks for the conditions outlined in the product label

Benefit:

Positive outcomes or favourable effects associated with a drug.
May be due to a drug **having greater efficacy**, treating a broader range of patients or symptoms, or being easier for a patient to use.

CIOMS Working Group IV is working on harmonization of risk benefit balance evaluation methods

Risk Vs. Benefit

The efforts put in continued monitoring with the aim of *minimizing the "safety hazards" and maximizing the "benefits "* of treatment even after the drug is marketed is **pharmacovigilance**.

Two treatments for obesity are described in the table below.
Please imagine that you have an option of receiving one of the treatments, and consider which one you would prefer to receive.

		Treatment A	Treatment B
Benefits (higher is better)	Physician's view on **HDL Cholesterol levels**	Mild improvement	No change
	Number of people who experience a **10% weight loss**	10 out of 1000	450 out of 1000
Risks (lower is better)	Number of people who experience **psychiatric conditions**	100 out of 1000	1 out of 1000
	Number of people who experience **cardiovascular conditions**	1 out of 1000	100 out of 1000
	Number of people who experience **gastrointestinal conditions**	1 out of 1000	None

Considerations for Benefit-Risk Assessment

- **Assessment of Benefits**
  - What is the expected and actual benefit for a specific patient?
  - Adequacy of Dose response
  - Clinical relevance
  - Strength of evidence of Benefits
  - Duration of effect
  - Comparative efficacy
  - Generalizability of treatment response (response in patient populations)

- **Assessment of Risks**
  - What is the weight of evidence that supports that a risk exists? (how much uncertainty exists)?
  - How serious is the risk (including sequelae)?
  - How often is it that the risk will occur? (Frequency)
  - Is the risk preventable? (Preventability)
  - Will it decrease/disappear after a drug is stopped or will the risk increase over time? (Reversibility)
  - Impact on patient Quality of life and public Health

Considerations for Benefit-Risk Assessment

- **Benefit–Risk Assessment**
  - Does the benefit outweigh the risk?
  - Strengths, weaknesses and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation
  - Cost effectiveness

- **Improving the Benefit-Risk Balance**
  - Are there any other treatment options (drug or non-drug) where the benefit/risk balance is more favorable?
  - Routine (Drug Labels, PIL, RMP, Guided Questionnaires) Risk minimization activities
  - Additional Risk minimization activities (Dear Doctor Letter (DDL)/Direct Healthcare Professional Communication (DHPC), Post-Authorization Safety studies (PASS), Educational material for physicians)

Withdrawal of a products on Benefit-Risk Grounds

When the regulatory authority believes that a drug no longer has a place in treatment, it will ask the manufacturer to withdraw the drug E.gs.

Accutane (Isotretinoin) indicated for Acne -on market for 27 years (1982- June 2009)

Cause for recall:

increased risk of birth defects, miscarriages, and premature births when used by pregnant women; inflammatory bowel disease; suicidal tendencies

Bextra (Valdecoxib) indicated for pain relief -on market for 3.3 years (Nov 2001-April 2005)

Cause for recall:

serious cardiovascular adverse events (like death, MI, stroke); increased risk of serious skin reactions (like toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme); gastrointestinal bleeding

Thank you!

Questions?