Basic PV Terminologies and Concepts

Revisions and Approval

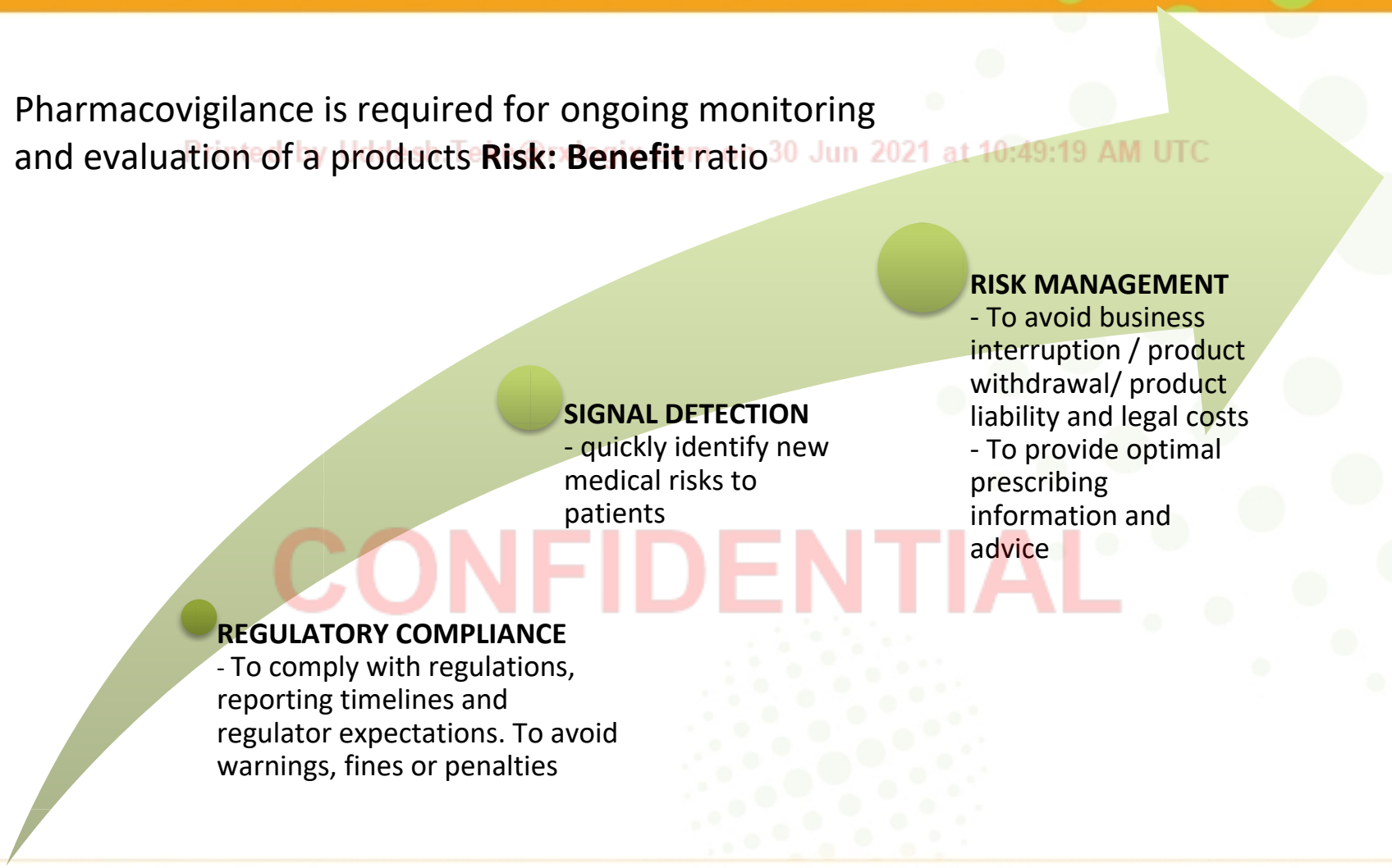
Author	Document ID	Version	Date	Change Description
Vandana Tanwar	RX-TRN-BUS-002	Version 4.0	06-Apr-2020	Reviewed and no changes in the content of the training material.
Deepika Dubey	RX-TRN-BUS-002	Version 3.0	08-Mar-2018	Addition of Event Terminologies and Source
Bhavana Pant	RX-TRN-BUS-002	Version 2.0	31-May-2016	Addition of Training assessment section
Bhavana Pant	RX-TRN-BUS-002	Version 1.0	15-Jan-2016	N/A

Agenda

- Why Pharmacovigilance?
- Side effects to meaningful Signals
- PV Process
- Event Terminologies
- Adverse Event Assessment
- Source
- Causality
- Seriousness
- Safety Information Carriers
- Expected, Listedness and Labeledness
- ICSR
- PV Terminologies - Exercise
- Assignment
- Appendix
- Assessment

Why Pharmacovigilance?

Pharmacovigilance is required for ongoing monitoring and evaluation of a products **Risk: Benefit** ratio

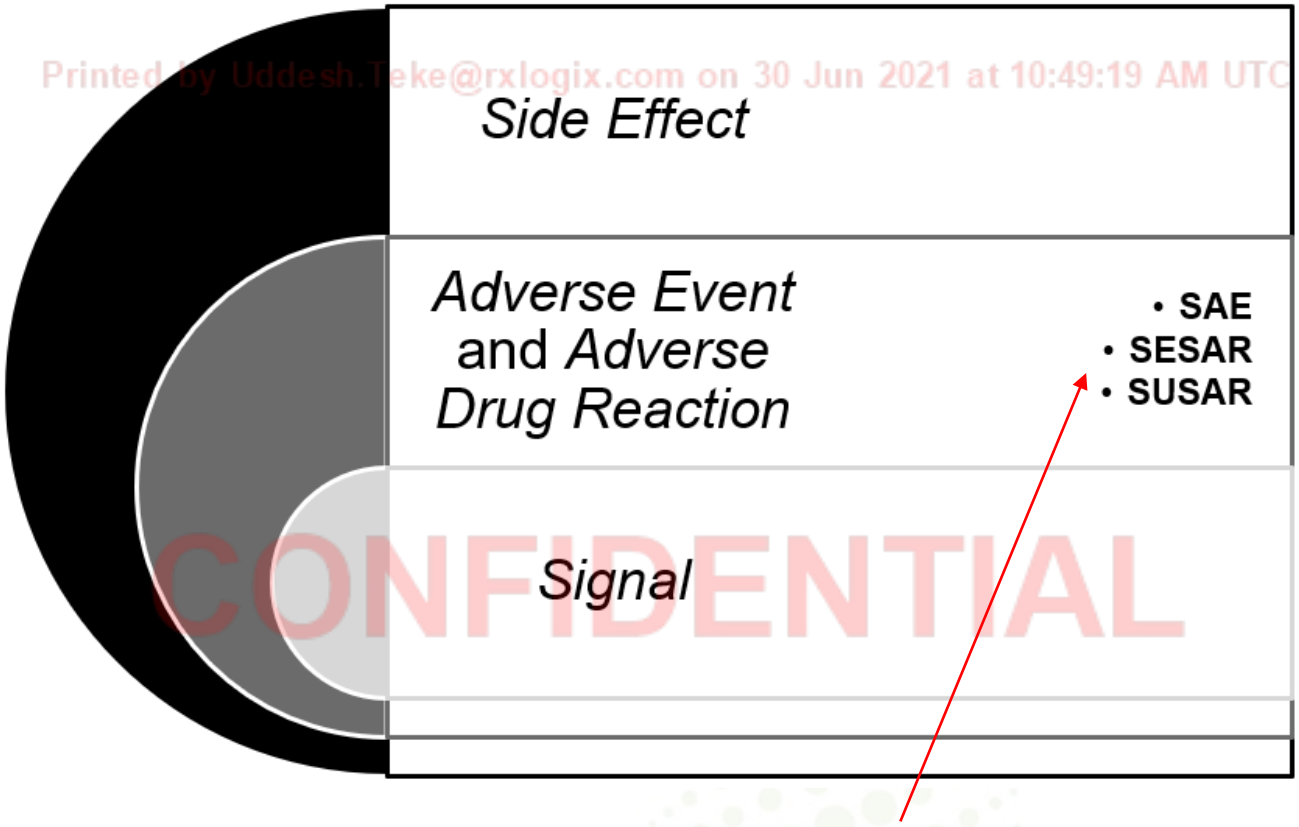


REGULATORY COMPLIANCE
- To comply with regulations, reporting timelines and regulator expectations. To avoid warnings, fines or penalties

SIGNAL DETECTION
- quickly identify new medical risks to patients

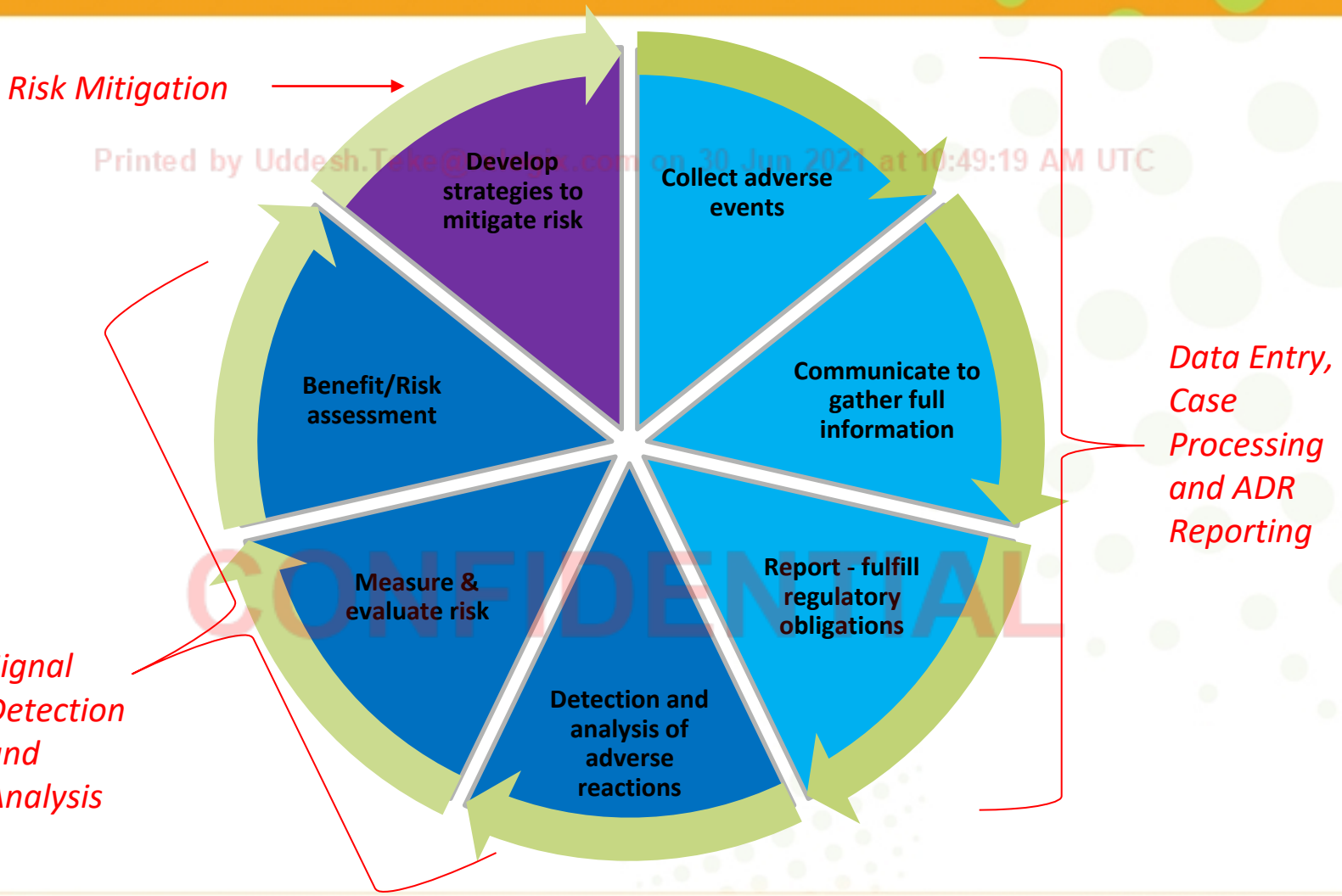
RISK MANAGEMENT
- To avoid business interruption / product withdrawal/ product liability and legal costs
- To provide optimal prescribing information and advice

Side effects to meaningful Signals



Serious adverse event, Suspected **Expected Serious Adverse Drug Reactions and Suspected **Unexpected** Serious Adverse Drug reactions*

PV Process



Events Terminologies

- **AE - Adverse Event (or Adverse Experience)**
  - 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.
- **ADR - Adverse Drug Reaction**
  - All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
- **Unexpected Adverse Drug Reaction**
  - An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).
- **SAE - Serious adverse event or reaction** is any untoward medical occurrence that at any dose:
  - results in death,
  - is life-threatening
  - requires inpatient hospitalisation or prolongation of existing hospitalisation
  - results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - requires intervention to prevent permanent impairment or damage.
- **Signal** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. (WHO, 1991; Delamothe 1992)

Adverse Event Assessment

Source

- **Unsolicited**
  - Consumer reports: Should be regarded as spontaneous cases irrespective of medical confirmation.
  - Literature: The MAH is expected to screen world-wide scientific literature for such reports. The reporting clock begins once the Company has identified the 4 minimum item reporting criteria.
  - Internet: MAHs with websites should screen these regularly for ADRs and provide mechanisms of reporting e.g. ADR forms.
  - Other sources: Any reports from non-medical sources should be regarded as spontaneous
- **Solicited**
  - These arise from organized data collection systems e.g. clinical trials; postapproval named patient use programs; patient support and disease management programmes; surveys of patients or healthcare providers or programmes of efficacy and patient compliance

Clinical Trials - Blinding

- **Blinding**
  - The process through which one or more test subjects in a clinical trial are unaware of the treatment they are receiving (the actual study drug, a competitor's marketed drug, or a placebo)
  - In a single-blinded study, usually the subjects are unaware of the treatment
  - In a double-blinded study, both the subjects and the investigators are unaware of the treatment assignments.
  - Blinded studies are conducted to prevent the unintentional biases that can affect subject data when treatment assignments are known.
  - When a Serious adverse reaction is judged reportable on an expedited basis, it is recommended to break the blind for that particular subject (ONLY that subject)

Causality

Causality Determination:

- This is done to see if the adverse event a patient is reporting is caused by the suspect drug in question or not.

- Causality categories (as described by the Uppsala Monitoring Centre):

Certain	Unlikely
Probable / Likely	Conditional / Unclassified
Possible	Unassessable / Unclassifiable

- Methods of Determination for Clinical Cases:
  - De-Challenge (Stopping the use of a drug
    - Disappearance of the AE is referred to as a Positive Dechallenge and if the AE continues this is called a Negative Dechallenge.
  - Re-Challenge (Reintroducing the use of a drug)
    - Reproduction of the AE is referred to as a Positive Rechallenge and if the AE does not reoccur this is called a Negative Rechallenge.

Seriousness

- **Seriousness Determination**:
  - In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:
    - results in death,
    - is life-threatening (The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
    - requires inpatient hospitalisation or prolongation of existing hospitalisation
    - results in persistent or significant disability/incapacity
    - Is a congenital anomaly/birth defect
    - requires intervention to prevent permanent impairment or damage/ is a medically important event or reaction.

SAFETY INFORMATION CARRIERS

- **Investigator's Brochure**
  - This is a document that would be created before a drug goes under clinical trials and may change during the course of a clinical trial.
- **CCDS - Company Core Data Sheet**
  - This is a document prepared by the MAH (Marketing Authorization Holder) containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the product used worldwide not just locally.
- **Package Insert / Label**
  - The Document received with a Product containing information such as the Brand Name, Generic name of the product, Description, Clinical Pharmacology, Indications and Uses, Contraindications, Warnings (may include Drug Abuse and Dependence also), Precautions, Adverse Reactions, Over dosage, How Supplied, Dosage and Administration.
  - A Package Insert may contain more side effects (adverse events) than are listed in the CCDS
  - This is Local so different countries may have a different package insert

LISTEDNESS AND LABELLEDNESS - *All synonyms for EXPECTEDNESS*

- Package Insert of Cough Syrup X

CCDS
Drowsiness
Nausea
Rash

EMA Label
Drowsiness
Nausea
Rash

US Label
Drowsiness
Nausea
Rash
Dizziness

- Expedited Reporting of 'Dizziness' from Cough Syrup X in various scenarios:

Patient ABC experienced AE in
Country: **Italy**
CIOMS form will be filed
Unexpected adverse event

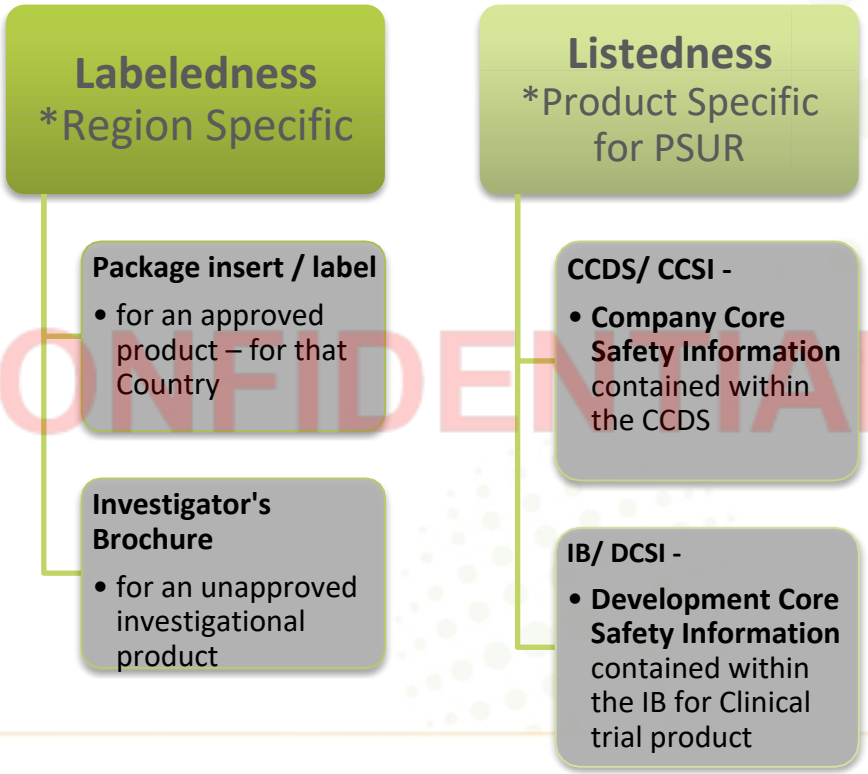
Patient MLR experienced AE in
Country: **USA**
MedWatch 3500 Drug form will be filed
Expected adverse event

- Periodic Reporting For Cough Syrup X (for Adverse Event: Dizziness)

UNLISTED

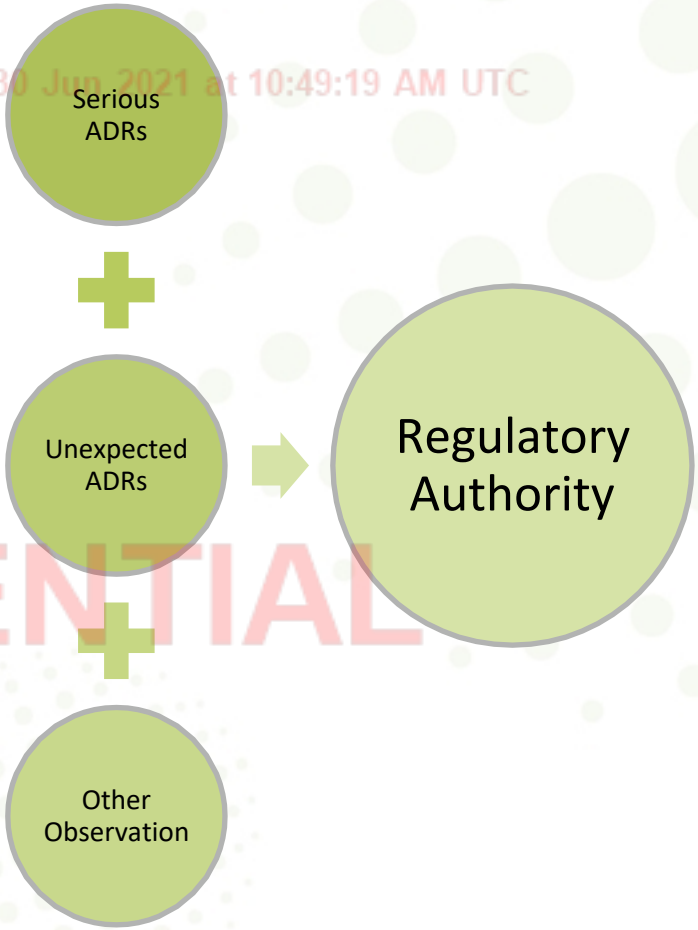
LISTEDNESS AND LABELLEDNESS - *All synonyms for EXPECTEDNESS*

- Listedness And Labeledness are Synonymous for Expectedness, but are used in different contexts.
- 'Listedness' is used to refer Expectedness in Periodic reports.
- 'Labeledness' is used to refer Expectedness in Expedited reports.



Individual Case Study Report (ICSR)

- A document providing the most complete information related to an individual case at a certain point in time
- Minimum Criteria For Reporting
  - Identifiable patient
  - Suspect medicinal product
  - Identifiable reporting source
  - In event or outcome (in clinical investigation cases, there is a reasonable suspected causal relationship)
- Initial Report
  - The first set of information that the company receives regarding a particular ICSR
- Follow-up Report
  - Additional details that the company becomes aware of regarding an ICSR that is already in their database



Exercise:

Identify the PV terminologies in the following excerpts

Scenario 1

Dr. Rachel In England reported that a 23 year old female patient experienced Swelling in her hands

while taking Antibiotic Azythromycin at a dose of 250 mg / day , starting 01-Oct-2011

for Cough

Along with Vitamin C tablets

On 10-Oct-2011, she discovered skin inflammation on her left hand.

She immediately stopped taking Antibiotic Azythromycin and Applied Soframycin

The skin inflammation gradually healed over the following week.

Additional information has been requested.

Scenario 1

Dr. Rachel In England reported that a 23 year old female patient experienced **Swelling** in her hands Symptom

while taking **Antibiotic Azythromycin** at a dose of 250 mg / day , starting 01-Oct-2011 Suspect Drug

for **Cough** Indication

Along with **Vitamin C tablets** Concomitant Drug Diagnosis

On 10-Oct-2011, she discovered **skin inflammation** on her left hand.

She immediately stopped taking Antibiotic Azythromycin and Applied **Soframycin**

The skin infla Treatment Drug al De-challenge Result following week.

Additional information has been requested.

Follow-up Report

Scenario 2

T-DM1 is an antibody-drug conjugate

developed by Genentech

for Treatment of certain types of Metastatic Breast Cancer

Phase II Double-Blinded- trial for this product was conducted

by CRO X, who managed all the staff, patients, devices and other resources needed for clinical research.

FDA has given approval for a Compassionate study since T-DM1 shrank tumours in comparison to Placebos, in one-third of women who had received extensive prior treatment for advanced breast cancer.

Scenario 2

T-DM1 is an antibody-drug conjugate Intervention

developed by **Genentech** Sponsor

for Treatment of certain types of **Metastatic Breast Cancer** Indication

Phase II **Double-Blinded**- trial for this product was conducted Blinding

by **CRO X**, who managed all the staff, patients, devices and other resources needed for clinical research. CRO

FDA has given approval for a **Compassionate study** since T-DM1 shrank Compassionate study tumours in comparison to **Placebos**, in one-third of

women who had received extensive prior treatment for advanced breast Placebo cancer.

For understanding Terminologies in Argus Safety System refer the following code-list values

Reporter	Patient	Product	Event
Intermediary	**Age Groups**	**Accidental Exposure**	**Causality Category**
Case Form> General tab>Reporters Area	Case Form > Patient tab > Patient Information Screen, Age Group drop-down list.	Case form >Products tab> Dosage Regimen	Case Form > Events tab >Events Assessment tab
Occupations	**Condition Type**	**Action Taken**	**Event Frequency**
Case Form>General tab>Reporter information area	Case Form > Patients tab > Patients sub tab>Other relevant history area	Case Form > Product tab > Product Details	Case Form> Events tab>Events sub tab
Report Media	**Birth Type**	**Anatomical Location**	**Event Intensity**
CASE form> General tab> Reporter information	Case Form > Patient tab >Pregnancy Information screen	Case Form > Product tab > Vaccines> Anatomical location drop-down list.	Case Form> Events tab>Events sub tab
Reporter Type	**Delivery Type**	**Dosage Frequency**	**Event Outcome**
CASE form> General tab> Reporter information	Case Form> Patient tab>Patient sub tab> Pregnancy details	Case Form> Products tab>Dosage Regimen area	Case Form> Events tab>Events sub tab
	Fetal Outcome	**Formulation**	**Nature of Event**
	Case Form> Patients tab>Pregnancy information	Case Form> Products tab>Product Information area	Case Form> Events tab> Events sub tab
	Medical Status	**Route of Administration**	
	Case Form> Patients tab	Case form> Products tab> Dosage Regimen	

Appendix:

Pharmacovigilance: Basic Terms

- Comparator (Product)
  - An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.
- Contract Research Organization (CRO)
  - A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
- Randomization
  - The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
- Sponsor
  - An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Pharmacovigilance: Basic Terms

- Concomitant Drugs
  - drugs that were taken at the same time as the drug suspected of causing the adverse event or where in the person's system at that time.
  - All the known concomitant drugs taken by the patient should be on the MedWatch form
- Indication
  - In medicine, an indication is a valid reason to use a certain test, medication, procedure, or surgery.

The End

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None

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4.0

DOCUMENT ELECTRONIC SIGNATURES

DOCUMENT APPROVAL WORKFLOW

Author Approval

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