



# **Post Marketing Pharmacovigilance: Part 1: Passive PV**

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# Post-marketing pharmacovigilance

- **Governing laws**
- **Definitions**
- **Collection of post-marketing safety reports**
- **Processing of post-marketing safety reports**
- **Expedited reporting of post-marketing safety reports**
- **Periodic reports**



# Post-marketing pharmacovigilance

## Governing laws

### FDA rules and regulations

#### Marketed Products – 21CFR

- Subchapter D - Drugs for Human Use
  - 21 CFR 310.305 - AE reporting for marketed Rx products without NDAs (“grandfathered” pdts)
  - 21 CFR 314.80 - AE reporting for marketed products with NDAs (Rx and OTC)
- Subchapter F - Biologics
  - 21 CFR 600.80 - Post-marketing AE reporting



# Post-marketing pharmacovigilance

## Governing laws

### EU rules and regulations

Previously:

Directive 2010/84/EU

Regulation (EU) N° 1235/2010

### **New PV legislation in 2012**

→ Commission implementing regulation N° 520/2012 (June 2012)

Further amendment in Oct 2012

→ Regulation (EU) N° 1027/2012 (Jun 2013)

→ Directive 2012/26/EU (Oct 2013)



# Post-marketing pharmacovigilance

## Governing laws

Practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation are available in the **guideline on good pharmacovigilance practices (GVP)**. GVP apply to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States, and cover medicines authorised centrally via the Agency as well as medicines authorised at national level



# Post-marketing pharmacovigilance Definitions

## Unsolicited reports

- Spontaneous reports:  
unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation that does not derive from a study or any organised data collection system where AE reporting is actively sought
- Literature reports  
Reports of ADRs identified in the published medical and scientific literature by the MAH or competent authorities (e.g MLM by EMA)



# Post-marketing pharmacovigilance Definitions

- Reports from other sources  
Any other report the MAH becomes aware of originating from a non-medical source (ie.g lay press, social media, etc)
- Reports from the internet or digital media  
MAH should screen on a regular basis internet or digital media that are sponsored by the company. For the company sponsored websites, systems may be put in place to forward any information posted on these sites to a PV dedicated email address for example.



# Post-marketing pharmacovigilance Definitions

## Solicited reports

Are derived from organised data collection systems and include the following main sources:

- Clinical trials
- Non interventional studies\*
- Registries
- Post-approval named patient use programmes
- Patient support & disease management programmes
- Surveys of patients and HCPs
- Compassionate use
- \*elaborate on safety requirements





# Post-marketing pharmacovigilance Definitions

## **ICSR (Individual Case Safety Report)**

Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time

### **Valid ICSR**

ICSR for which the minimum criteria for reporting are present i.e

- An identifiable patient
- A suspect medicinal product
- An adverse event
- A reporter (person reporting the facts)



# Post-marketing pharmacovigilance

## Collection of reports

- Competent authorities and MAHs should have in place a PV system in order to collect and collate all reports of suspected adverse reactions/safety information associated with medicinal products from all sources.
- The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.
- All notifications that contain pharmacovigilance data should be recorded and archived in compliance with the applicable data protection requirements
- The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated in a timely manner and exchanged between competent authorities and marketing authorisation holders within the legal reporting time frames



# Post-marketing pharmacovigilance

## Collection of reports

- Organise the collection of reports in a way that allows a global overview of all cases received by any route and from any type of source (single/central collection point)
- Use standard forms for collection of initial and follow-up information
- Forms may be designed to meet product specific requirements/specificities
- Use of simplified forms for initial collection and more elaborate forms for follow-up information
- Use of targeted follow-up questionnaires (often as part of RMP)
- Use of pregnancy specific forms



# Post-marketing pharmacovigilance

## Collection of reports

- Collect the most accurate possible information upfront
- For consumer reports, obtain patient's consent to contact his HCP
- Organise and schedule follow-up queries
- Document all activities related to case processing
- Define the content of the case file



# Post-marketing pharmacovigilance

## Collection of reports

### Valid ICSR:

- An existing patient: Age, DOB or age\* group, initials, medical records number
- A reporter
- Adverse event/Safety information
- A suspect drug

But you still may create a valid case in your safety DB for cases where an HCP reports that he had a patient (no identifiers provided) who experienced a specific AE

\* At the time of the onset of the AE



# Post-marketing pharmacovigilance

## Collection of reports

### Adverse event information – what to collect

- AE/ADRs
- Drug interaction (drug-drug or drug-food),
- Exposure during pregnancy (with or without outcome) or lactation
- Lack of efficacy
- Overdose (intentional or accidental)
- Off-label use
- Suspected transmission of infectious disease via the medicinal product
- Drug abuse and misuse
- Accidental exposure
- Medication errors (established or potential)/dispensing errors/maladministrations
- Unintended beneficial effect
- Occupational exposure
- Non-compliance with the prescribed treatment



# Post-marketing pharmacovigilance

## Collection of reports

### Adverse event information

- Verbatim (original words of reporter)
- AE onset date and time\*
- AE stop date and time\*
- Outcome of the AE
  - Recovered
  - Recovering
  - Not yet recovered
  - Recovered with sequales
  - Patient died (as outcome of the AE)
  - Unknown

\* Depending on the product and the AE



# Post-marketing pharmacovigilance

## Collection of reports

- AE seriousness (ICH criteria)
- AE latency (i.e time elapsed between last dose of drug and 1st onset of symptoms)

### Suspect drug information

- Drug proprietary name or API if not known
- Dates of administration (start & stop dates)
- Dosage, form
- Route
- Lot number
- Indication for use
- Rechallenge/dechallenge information





# Post-marketing pharmacovigilance

## Collection of reports

### Patient's medical history information

- Focus on relevant medical history
- Try to obtain information on whether conditions were ongoing or not at the time of the onset of the adverse event(s)

### Patient's concomitant drugs information

- Focus on relevant concomitant drugs
- Administration dates
- Indication for use
- Check consistency between indications for use and reported medical history



# Post-marketing pharmacovigilance

## Collection of reports

### Lab tests and exams

- Try to collect structured data
- Most widely used tests and exams
- Dates of tests and exams
- Test and exam results should be expressed in internationally used/accepted units whenever possible



# Post-marketing pharmacovigilance

## Collection of reports

### Administrative information

- Collect and record all receipt dates (dates 1st received) for all pieces of information
- Crucial for expedited reporting (clock start date) and compliance metrics
- Collect and record contact details and document all attempts to follow-up a case until case closure (SOPs should define number and intervals for FUPs and definition of case closure)
- Patient information where the patient is the reporter should only be collected for administrative purposes and identification of duplicates and transmitted according to local laws on data privacy (use database functionalities to 'hide' some of the patient details)



# Post-marketing pharmacovigilance

## Processing of reports

- Acknowledge receipt
- Triage
  - Seriousness
  - Listedness/expectedness
  - Reportability
- Duplication check
  - Patient identifiers
  - Reporter
- Enter all information available in safety database and allocate company case ID



# Post-marketing pharmacovigilance

## Processing of reports

- Create also cases for non-valid reports for tracking purposes and follow-up as these cases may become valid upon follow-up
- General rule: create 1 case per patient and per medical occurrence
- All information related to 1 patient and the same medical occurrence must be recorded in the same case with receipt dates for initial and every single follow-up information



# Post-marketing pharmacovigilance

## Processing of reports

- Pregnancy reports may result in the creation of 1 single case or 1 mother and child case(s)
  - Prospective pregnancy reports: information on pregnancy is provided during the course of the pregnancy → usually 1 mother and 1 (or more) child case(as) are required except in cases of spontaneous abortion (no foetal anomaly), or normal outcome (no AE in the child)
  - Retrospective pregnancy report: information is provided after the outcome of the pregnancy is known → usually only 1 mother case is required even in case of abnormal outcome

**Mother and child cases should be linked to each other**



# Post-marketing pharmacovigilance

## Processing of reports

- Importance of accurate MedDRA coding for adverse event and laboratory data/examination
  - Suspect and concomitant drug coding (WHO DD and company product dictionary or xEVMPD information if using the EVWEB functionality)
  - Diagnostic tests
    - Useful to confirm or exclude a diagnosis
    - Useful to exclude alternative etiologies
    - Enter relevant positive and negative results
- ➔ Medical advice is often required to determine the relevance of tests



# Post-marketing pharmacovigilance

## Processing of reports

- Narrative
  - Is a complete medical description of the case
  - Is a comprehensive, stand alone medical story of what happened to the patient
  - Is a summary of all relevant clinical and other related information
  - Should be concise and written in a chronological order
  - Mandatory only for reportable cases
  - For non-reportable cases, company decision as to whether a narrative is written





# Post-marketing pharmacovigilance

## Processing of reports

- Usually not written for non-valid cases
- Use of auto-narratives when possible
- Use of templates if no auto-narratives are available in the safety database



# Post-marketing pharmacovigilance

## Processing of reports

- Patient information
  - Depending on safety database features, all PII\* may be recorded but fields may need to be anonymised for further transmission to CA
  - Medical history & concomitant drug details may be restricted to relevant data (medical advice often required)
- Listedness/expectedness assessment
  - Identify the RSI against which the assessment will be done (CCSI, SmPC, USPI, etc) and local responsibilities if any
  - Automation possible in some databases
  - Importance of documenting label changes and subsequent assessments changes

\* Personally Identifiable Information



# Post-marketing pharmacovigilance

## Processing of reports

- Drug event association
  - Some databases allow a specific link between a suspect drug and one or more specific events
  - Relevant in case of multiple suspect drugs
  - Drug/Event association is relevant for causality assessment and signal detection
  - Allows also specific drug/event related latency (time to onset between last dose of suspect drug and onset of a specific event)



# Post-marketing pharmacovigilance

## Processing of reports

- Expedited reporting
  - Format
    - CIOMS – EEA and all ICH adopting countries also accepted by FDA for non domestic cases
    - Medwatch (FDA 3500 A) for US domestic cases
  - Output
    - Xml for electronic E2B reporting
    - Pdf for conventional reporting
  - Means
    - EEA: Eudravigilance
      - Gateway for bigger organisations
      - EVWEB or EVPOST for smaller organisations
    - US: ESG
    - NON EEA and non US: need to check local requirements. Often pdf CIOMS by email