P95
TURNING DATA INTO EVIDENCE

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# An overview of regulatory guidance and requirements in pharmacovigilance

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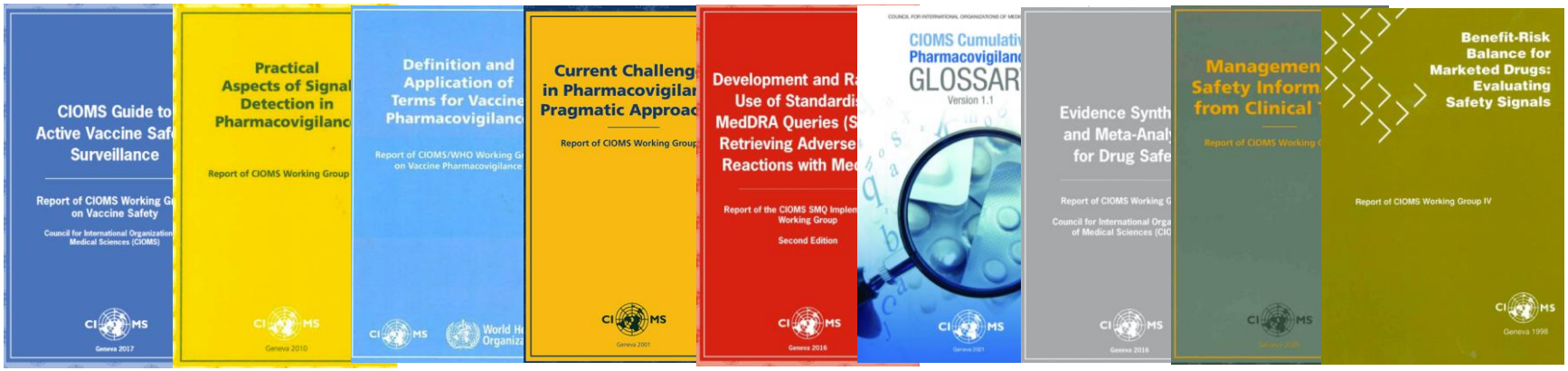
# Module content

- CIOMS
- ICH - International Council for Harmonisation guidelines – E2A-F, E6, M1 and M4
- Governing regulations in Europe & USA
- EU Good Pharmacovigilance Practice (GVP) overview
  - Pharmacovigilance System; Quality; Audits; QPPV
  - Risk Management Plan (RMP)
  - Aggregate safety reporting – periodic update reports
  - Expedited reporting of Individual case safety report (ICSR)
  - Signal detection and signal management
- WHO vaccine safety guidance; manuals; blueprints.

# Council for International Organizations of Medical Sciences (CIOMS)

- CIOMS - an international, non-governmental, non-profit organization established by WHO and UNESCO in 1949
- CIOMS mission is to advance public health through guidance on health research including ethics, medical product development and safety
- Collaboration between senior scientists from regulatory authorities, pharmaceutical industry and academia to develop consensus guidelines.
- Also conduct training, webinars, conferences etc.




https://cioms.ch/

# International Council for Harmonisation (ICH)

- ICH's mission is to:
  - achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered
  - bring together regulatory authorities from three regions (EU, USA, Japan) with experts from pharmaceutical industry
  - discuss scientific and technical aspects of product registration, leading to harmonisation to reduce duplicative effort during the development of new medicines
  - develop policy for the ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA).

# International Council for Harmonisation (ICH)

### Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

### Safety Guidelines

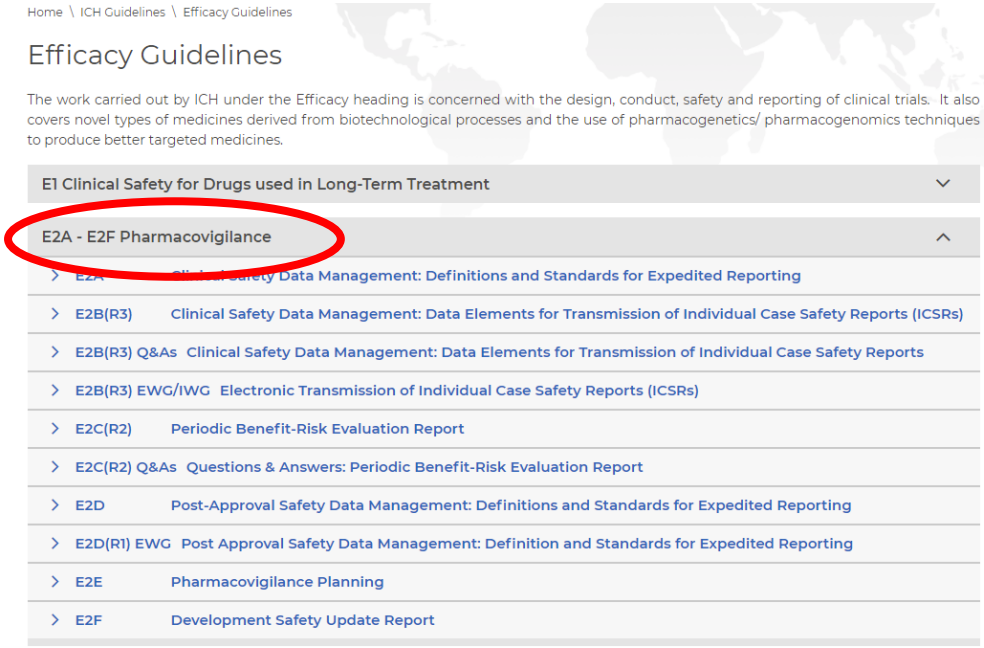
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

### Efficacy Guidelines

The work carried out by ICH under the Efficacy heading concerned with the design conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

### Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).




https://www.ich.org/page/efficacy-guidelines

# Members of ICH

- **Founding Regulatory Members**
- European Commission, Europe
- FDA, United States
- MHLW/PMDA, Japan

- **Founding Industry Members**
- EFPIA
- JPMA
- PhRMA

- **Standing Regulatory Members**
- Health Canada, Canada
- Swissmedic, Switzerland

- **Regulatory Members**
- ANVISA, Brazil
- COFEPRIS, Mexico
- HSA, Singapore
- MFDS, Republic of Korea
- NMPA, China
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- TITCK, Turkey

P95

# Regulatory observers of ICH

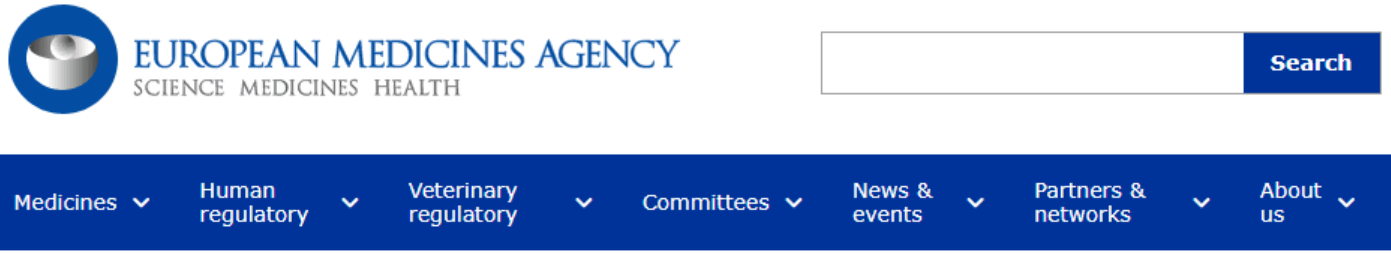
- AEC, Azerbaijan
- ANMAT, Argentina
- CDSCO, India
- CECMED, Cuba
- CPED, Israel
- EDA, Egypt
- Indonesian FDA, Indonesia
- INVIMA, Colombia
- JFDA, Jordan
- MHRA, UK
- MMDA, Moldova
- MOPH, Lebanon
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SECMOH, Ukraine
- TGA, Australia

# CIOMS and ICH

## Process flow

| CIOMS | ICH | Local regulatory authorities |
|---|---|---|
| Vision | Negotiation | Implementation |

# ICH E2A guideline




## ICH E2A Clinical safety data management: definitions and standards for expedited reporting

Share

| | |
|---|---|
| **Current effective version** | Adopted guideline |
| **Reference number** | CPMP/ICH/377/95 |
| **Published** | 01/06/1995 |
| **Effective from** | 01/06/1995 |
| **Keywords** | Clinical development, clinical safety reporting, expedited reports, adverse drug reaction (ADR) |
| **Description** | This document aims to develop standard definitions and terminology for key aspects of clinical safety reporting. I also provides guidance on the appropriate mechanism for handling expedited (rapid) reporting, in the investigational (i.e. pre-approval) phase. |

# ICH E2A guideline

- **Clinical safety data management: definitions and standards for expedited reporting**
- Includes definitions for key terms such as ADR, expectedness, seriousness
- Outlines standards for expedited (rapid) reporting of certain ADRs during drug development, e.g:
  - What should be reported
  - Reporting timeframes (7-days for fatal or life-threatening unexpected ADRs; 15 days for other serious unexpected ADRs)
  - Minimum criteria for reporting
  - Managing blinded cases.
- https://database.ich.org/sites/default/files/E2A_Guideline.pdf

# ICH E2B (R3) guideline

- **E2B(R3): Electronic transmission of ICSRs**
- Technical guidance that outlines specifications for ICSR data elements and data transmission
- Forms the basis of ICSR databases maintained by many RAs and MAHs.
- https://ich.org/page/electronic-standards-estri

# ICH E2C (R2) guideline

- **E2C(R2): Periodic Benefit-Risk Evaluation Report**
- Outlines a common standard and format for periodic benefit-risk evaluation reports (PBRERs) on marketed products (including approved drugs that are under further study)
- Includes concept of reference safety information (e.g. company core data sheet) to overcome potential differences in product information across different international jurisdictions.
- https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

# ICH E2D guideline

- **Post-approval safety data management: definitions and standards for expedited reporting**
- Key definitions: e.g. adverse event vs ADR
- Key concepts in post-market PV such as solicited vs unsolicited sources of individual case safety reports (ICSRs)
- Standards for expedited (rapid) reporting of serious ADRs
  - Minimum criteria for reporting
  - Timeframes (15 calendar days)
- Good case management practices
- Currently under revision: E2D (R1).
- https://database.ich.org/sites/default/files/E2D_Guideline.pdf

# Other ICH E2 guidelines

**ICH E2E: Pharmacovigilance planning**

- Provides guidance to help planning PV activities, especially in preparation for the early post-marketing period of a new drug.
- https://database.ich.org/sites/default/files/E2E_Guideline.pdf

**ICH E2F: Development safety update report**

- Provides guidance on the common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).
- https://database.ich.org/sites/default/files/E2F_Guideline.pdf

# ICH E6(R2) guideline

**ICH E6(R2): Good clinical practice**

- Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Unified standard to facilitate the mutual acceptance of clinical data by regulatory authorities (EU, US, Canada, Japan)
- Specifies responsibilities of ethics committees/institutional review boards, investigators and sponsors in conduct of clinical trials, including reporting of serious adverse events.
- https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

# ICH M1 guideline

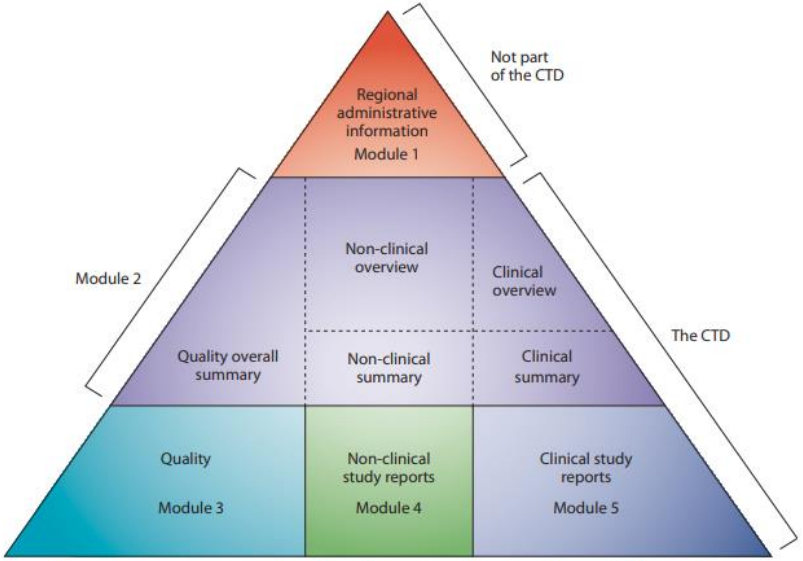
**ICH M1: MedDRA – medical dictionary for regulatory activities**

- MedDRA provides standardised medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans
- It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale
- Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products.
- https://www.ich.org/page/meddra

# ICH M4: CTD

- **ICH M4: The Common Technical Document**
- Harmonises the format of submissions to regulatory authorities
- 5 modules

1. Region-specific information (including local label/SmPC)
2. CTD summaries
3. Quality data
4. Nonclinical data
5. Clinical data.



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

- https://database.ich.org/sites/default/files/M4_R4__Guideline.pdf

# US Regulatory Framework

- The *Code of Federal Regulations* **(CFR)** contains general and permanent rules published in the *US Federal Register* (the Government's daily newspaper) by the Federal Government.
- The CFR is divided into 50 titles representing broad areas subject to Federal regulations
  - Each title is divided into chapters that usually bear the name of the issuing agency
  - Each chapter is further subdivided into parts covering specific regulatory areas
  - Large parts may be subdivided into subparts.
  - All parts are organized in sections, and most citations to the CFR will be provided at the section level
- Regulations that govern safety reporting to the FDA are found in **Title 21 of the CFR.**

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm

# EU regulatory framework

**Regulations**

- Regulations are legal acts that apply automatically and uniformly to all EU countries as soon as they enter into force, without needing to be transposed into national law. They are binding in their entirety on all EU countries
- Pre-authorisation PhV is governed by EU Regulation No 536/2014.

**Directives**

- Directives require EU countries to achieve a certain result, but leave them free to choose how to do so. EU countries must adopt measures to incorporate them into national law (transpose) in order to achieve the objectives set by the directive. National authorities must communicate these measures to the European Commission

- Post-authorisation PhV is governed by a combination of EU Regulations and Directives.

https://ec.europa.eu/info/law/law-making-process/types-eu-law_en
https://ec.europa.eu/health/medicinal-products/pharmacovigilance_en

# EU regulatory framework

**Guidelines**

- EMA guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in regulations and directives
- For practical purposes, the EU PhV requirements are laid out in **Good Pharmacovigilance Practices (GVP)**
- GVP is outlined in a series of modules, annexes and product/population specific guidelines.

# GVP modules

| Module | Topic |
|---|---|
| I | Pharmacovigilance systems and their quality systems |
| II | Pharmacovigilance System Master File |
| III | Pharmacovigilance inspections |
| IV | Pharmacovigilance audits (Rev. 1) |
| V | Risk Management Systems (Rev. 2) |
| VI | Collection, management and submission of reports of suspected adverse reactions to medicinal products [+ addendum on duplicate management] |
| VII | Periodic safety update report |
| VIII | Post-authorisation safety studies |
| IX | Signal management (Rev. 1) [+ addendum on methodological aspects of signal detection] |
| X | Additional monitoring |
| XV | Safety communication (Rev. 1) |
| XVI | Risk minimization measures: selection of tools and effectiveness indicators [+ addendum on educational materials |



https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section

# GVP annexes

- Annex I: Definitions
- Annex II: Templates
- Annex III: Other PV guidance
  - Guideline on the exposure to medicinal products during pregnancy
  - Guideline on conduct of PV activities for medicines used by paediatric population
  - Note for guidance EV Human – Processing of safety messages and individual case safety reports (ICSRs)
- Annex IV
  - ICH technical documents
- Annex V: Abbreviations.

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-annex-i---definitions-section

# GVP product/population specific guidelines

| Module | Topic |
|---|---|
| I | Vaccines for prophylaxis against infectious diseases |
| II | Biological medicinal products |
| III | Pregnant and breastfeeding women (draft under consultation) |
| IV | Paediatric population |
| V | Geriatric population (not yet released) |

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-product--or-population-specific-considerations-section

# The PhV System (GVP I)

- The PhV system is the system used by an organization to fulfil its legal tasks and responsibilities in relation to PhV
- The PhV system must be adequately designed to monitor the safety of authorized medicinal products and detect any change in benefit-risk balance
- In the EU, GVP Module I outlines the establishment and maintenance of quality assured pharmacovigilance systems for MAHs, competent authorities of members states and the EMA.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# The PhV System (GVP I)

- GVP Module I – Overview:
  - Pharmacovigilance System
  - Quality cycle and overall Quality objectives in PV
  - Principles for good PV practices
  - Responsibilities for the system
  - Training of personnel
  - Record management and documentation
  - Critical pharmacovigilance processes and business continuity
  - Role and responsibilities of the Qualified Person for Pharmacovigilance
  - Subcontracting to other organizations.

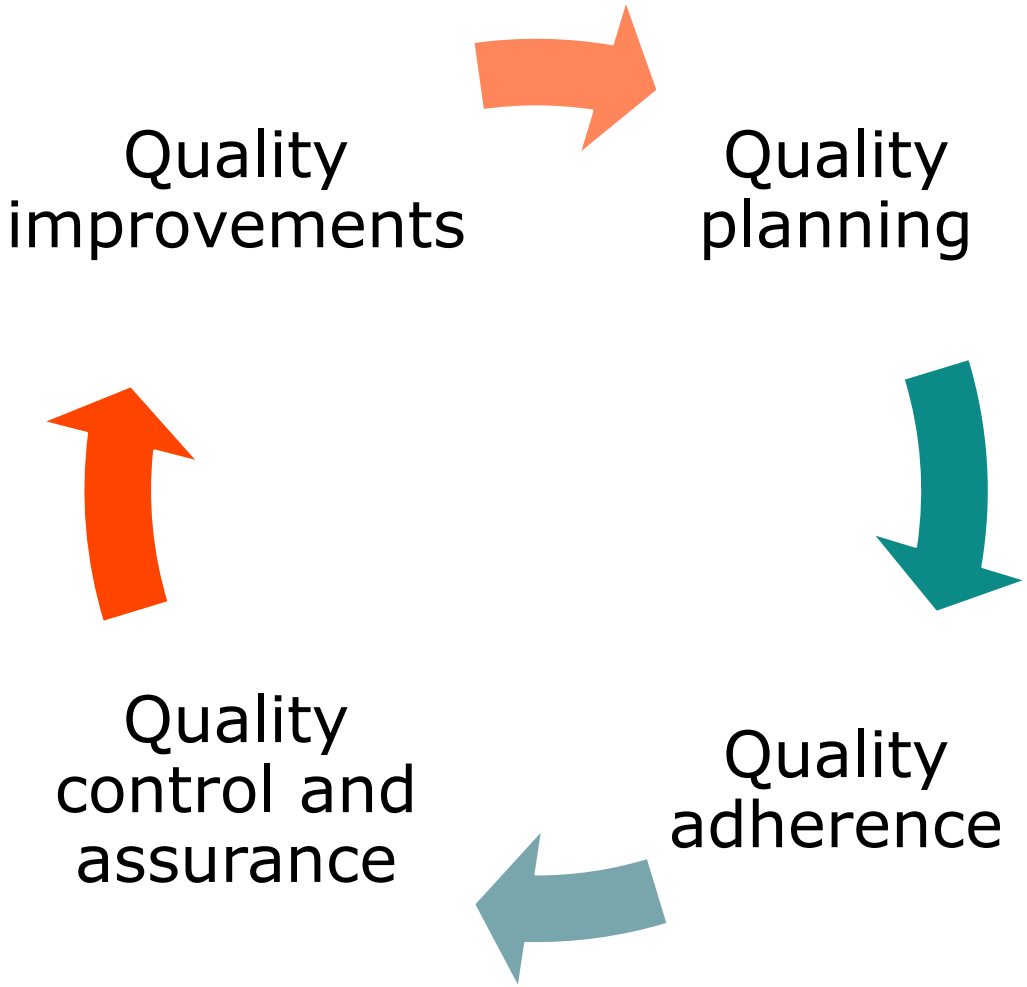
https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# Quality system in PhV (GVP I)

- The quality system is part of the PV system and consists of its own structures and processes
- Defined as 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
- Covers organisational structure, responsibilities, procedures, processes, resource management, compliance management & record management
- Responsibility for the MAH but also competent authorities of member states and the agency to establish and use quality systems that are adequate and effective for this performance.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# Quality cycle in PhV



# Principles for good PhV practices

- Meet needs related to safety of medicines for patients, HCPs and public
- Strong leadership from upper management
- Involvement of all members of the organisation and engagement in continuous quality improvement
- Adequate organisation of resources and tasks
- Collection of all information related to benefit-risk balance
- Good collaboration between MAH, competent authorities, public health organisation, HCPs, patients, etc.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# Oversight of quality systems (GVP I)

- Organisational management should ensure that:
  - The quality system is **documented**
  - Documents are subject to **control** (creation, revision, approval and implementation)
  - Adequate **resources** (including human, facilities, equipment etc.) are available
  - Ensure staff are appropriately **trained**
  - Adequate **records** are kept
  - Timely and effective **communication** mechanisms are incorporated into the system with pathways for escalating concerns
  - The PV system and quality system is **reviewed** periodically
  - **Deviations** from requirements are identified and the **root cause** is investigated
  - **Corrective and preventative actions** are identified, implemented and appropriated documented
  - **Audits** of the system should be conducted.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# Qualified Person for Pharmacovigilance (QPPV)

- In the EU, MAHs must nominate a qualified person responsible for pharmacovigilance (QPPV)
- The QPPV must have oversight over the functioning of the system in all relevant aspects e.g:
  - standard operating procedures
  - contractual arrangements
  - database operations
  - compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports
  - audit reports
  - training of personnel in relation to pharmacovigilance
  - An overview of signal management activities.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

# Pharmacovigilance System Master File (PSMF): GVP Module II

- The PSMF is a collection of documents that describes an MAH's pharmacovigilance system and its compliance with regulatory requirements
- The PSMF also aides the planning and conduct of audits and inspections of the PhV system
- The PSMF includes sections covering:
  - QPPV
  - Organisational structure of MAH
  - Sources of safety data
  - Computerised systems and databases
  - PhV processes
  - PhV system performance
  - PhV quality system.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

# PhV audits (GVP IV)

- GVP Module IV (Guideline on Pharmacovigilance audits) provides methods and processes for the EMA, competent authorities and MAHs to audit their PhV systems
- Risk-based approach that focuses on areas of highest risk to a PhV system, including the quality system
- Risk factors to consider include:
  - Changes to legislation and guidance
  - Major organisational restructures
  - Risk to availability of appropriately trained staff
  - Changes to the system since last audit (e.g. new database)
  - Medicinal products that have additional monitoring requirements
  - Criticality of different process areas
  - Information from compliance metrics/KPIs.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-iv-pharmacovigilance-audits-rev-1_en.pdf

# PhV audits (GVP IV)

- Audit findings categorised as 'critical', 'major' or 'minor'
- Importance of CAPA management and follow-up of audit findings
- PSMF must contain figures on audit findings, system performance including key performance indicators, list of completed audits for a period of 5 years and a list of the planned audits
- A note on any critical or major audit findings must be included in the PSMF
- Role of competent authorities is to ensure compliance by means of conducting inspections of MAHs.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-iv-pharmacovigilance-audits-rev-1_en.pdf

# Risk Management Plans (GVP V)

- MAHs are required to submit a risk-management plan (RMP) when applying for authorization in the EU many international jurisdictions
- EU Guidance:
  - GVP module V (and also Module XVI and addendum): https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
  - RMP format: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-format-risk-management-plan-rmp-eu-integrated-format-rev-201_en.pdf
  - COVID-19 vaccines: https://www.ema.europa.eu/documents/other/consideration-core-requirements-rmps-covid-19-vaccines_en.pdf
- Regulatory authorities outside the EU may accept the EU RMP with an additional country-specific annex.

# Risk Management Plans (EU)

- RMPs include information on:
  - a medicine's safety profile;
  - how its risks will be prevented or minimised in patients;
  - plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine;
  - measuring the effectiveness of risk-minimisation measures.
- RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available
- Companies need to submit an updated RMP:
  - at the request of EMA or an NCA;
  - whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

# Risk Evaluation and Mitigation Strategy (US)

- A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.
- REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.
- Examples:
  - Lenalidomide (to prevent risk of embryo-foetal exposure)
  - Alemtuzumab (to prevent risk of autoimmune conditions, infusion reactions, stroke and malignancies).

https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems

# Expedited ICSR reporting: EMA (GVP VI)

- According to Article 107(3) and 107a(4) of Directive 2001/83/EC:
  - serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within **15 days** from the date of receipt of the reports;
  - non-serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within **90 days** from the date of receipt of the reports.
- **GVP Module VI** (Rev. 2) gives detailed guidance on the collection, management and submission of suspected adverse reactions to medicinal products.

# Expedited ICSR reporting: FDA

- Under 21 CFR 314.80 post-marketing safety reports are categorised as 15-day alert reports or Periodic Adverse Experience Reports
- 15-day Alert reports
  - Serious and unexpected adverse experience from all sources (domestic and foreign)
  - For post-marketing studies, only required if causally related
- Periodic Adverse Experience Reports:
  - Domestic spontaneous adverse events that are:
    - Serious and expected
    - Non-serious and unexpected
    - Non-serious and expected
  - Quarterly for the first 3 years then annually.

# Aggregate safety reporting

- Aggregate safety reports provide an evaluation of the risk-benefit balance of a medicinal product at defined timepoints in the life-cycle of the product

- Pre-authorisation:
  - ICH E2F: Development Safety Update Report
  - Provides a common standard for aggregate safety reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions.
  - Submitted annually.

# Aggregate safety reporting

Post-authorization:

- ICH EC2 (R2): Periodic benefit-risk evaluation report (PBRER)
- GVP Module VII: Periodic Safety Update Report (Rev 1)
- Other terminology/formats:
  - Periodic Safety Update Report (PSUR – ICH E2C R1)
  - Periodic Adverse Drug Experience Report (PADER) – US FDA
- PBRERs may be required on 6-monthly, annual, and less frequent submission timetables simultaneously across different regions
- Authorities determine the periodicity and data-lock points (ideally should be harmonized, but not always!)
- An ad hoc PBRER may be requested by a regulatory authority
- FDA has provisions for accepting aggregate reports in PBRER or PSUR format instead of PADER format.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf

# PBRERs/PSURs (GVP VII)

- Main focus is the evaluation of **relevant new safety information,** placed within the context of any pertinent efficacy/effectiveness information that may have become available since the international birth date
- The PBRER should include cumulative knowledge of the product while retaining focus on new information
- Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf

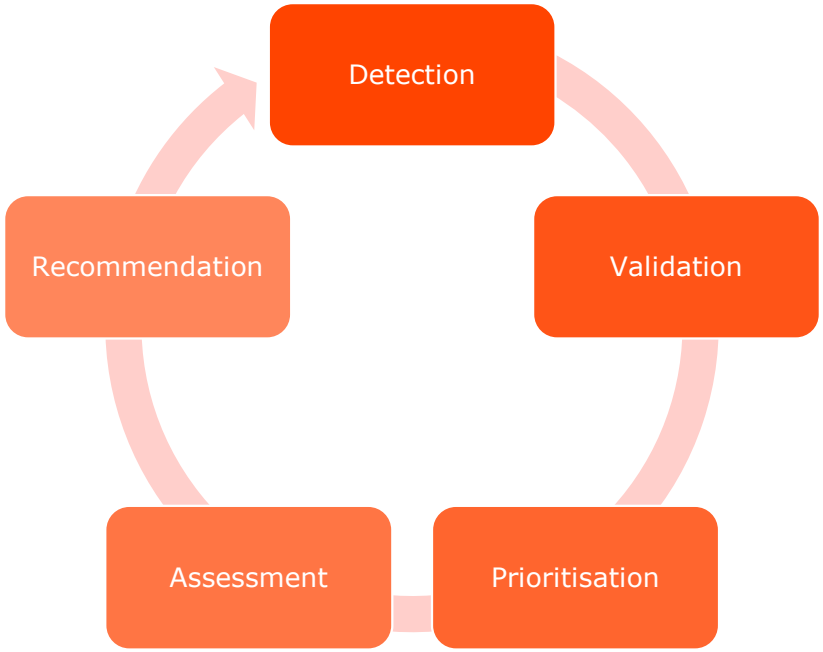
# PBRERs/PSURs (GVP VII)

- Major topics covered:
  - Worldwide marketing approval status
  - Actions taken in reporting interval for safety reasons
  - Changes to reference safety information
  - Estimated exposure and use patterns
  - Data summary in tabulations
  - Findings from clinical trials during reporting period
  - Findings from non-interventional studies
  - Non-clinical data
  - Literature
  - Overview of signals
  - Risk evaluation
  - Benefit evaluation
  - Integrated benefit-risk evaluation.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf

# Signal management (GVP IX)

- Set of activities to detect, assess and respond to changes in the benefit-risk profile of a product
- Based on analysis of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources
- Signal detection may a review of ICSRs, statistical analyses, or a combination depending on the size of the data set.




GVP module IX: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf

# EMA IME and DME lists

- The EMA maintains a list of IME MedDRA terms to facilitate the classification of AEs and aggregated data analysis:

https://www.ema.europa.eu/documents/other/meddra-important-medical-event-terms-list-version-241_en.xlsx

- The EMA also maintains a list of designated medical events (DMEs), corresponding to serious medical conditions that are often causally associated with drugs (e.g. acute kidney injury, rhabdomyolysis, Stevens-Johnson syndrome):
- https://www.ema.europa.eu/documents/other/designated-medical-event-dme-list_en.xlsx
- EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews.

# GVP module P1 - vaccines

- Focusses on vaccine-specific aspects and unique challenges that should be borne in mind when designing and implementing PhV activities for vaccines
- Special considerations for vaccines
  - Given to healthy individuals (prevention rather than treatment)
  - Multiple vaccines may be given at one time
  - High uptake means that coincidental AEs will occur with temporal association to vaccination
  - Complex biological products
  - Benefit-risk balance influenced by epidemiology of disease at the population level
  - Anti-vaccination campaigners and persistence of vaccination myths.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf

# GVP module P1 - vaccines

- GVP module P1 provides additional guidance on:
- RMP requirements for vaccines relating to the product overview, safety specification, pharmacovigilance plan, plans for PASS and risk minimization measured
- Content of the PBRER, with inclusion of sections on vaccination errors and vaccination failure Monitoring for batch-related AEs
- Signal management, including:
  - use of standardized AE case definitions published by the Brighton Collaboration
  - Use of age-specific disproportionality analyses for signal detection
  - Observed vs expected analysis for signal detection.

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf

# WHO vaccine safety guidance

- WHO plays a very active role in vaccine safety monitoring and capacity building for vaccine safety surveillance.
  - Global Vaccine Safety Blueprint 2021-2023 https://apps.who.int/iris/rest/bitstreams/1392676/retrieve
  - Causality assessment guidelines https://www.who.int/vaccine_safety/publications/CausalityAssessmentAEFI_EN.pdf
  - COVID-19 vaccine safety surveillance manual https://www.who.int/publications/i/item/10665345178
  - WHO vaccine safety basics e-learning course https://vaccine-safety-training.org/home.html
  - WHO vaccine safety basics learning manual https://www.who.int/vaccine_safety/initiative/tech_support/Vaccine-safety-E-course-manual.pdf

# Thank you!

# Muchas gracias !

# Questions & Answers session (in Spanish)