Europharma – Training

Pharmacovigilance in 2015 - Current Perspectives and Future Challenges 02 December 2014

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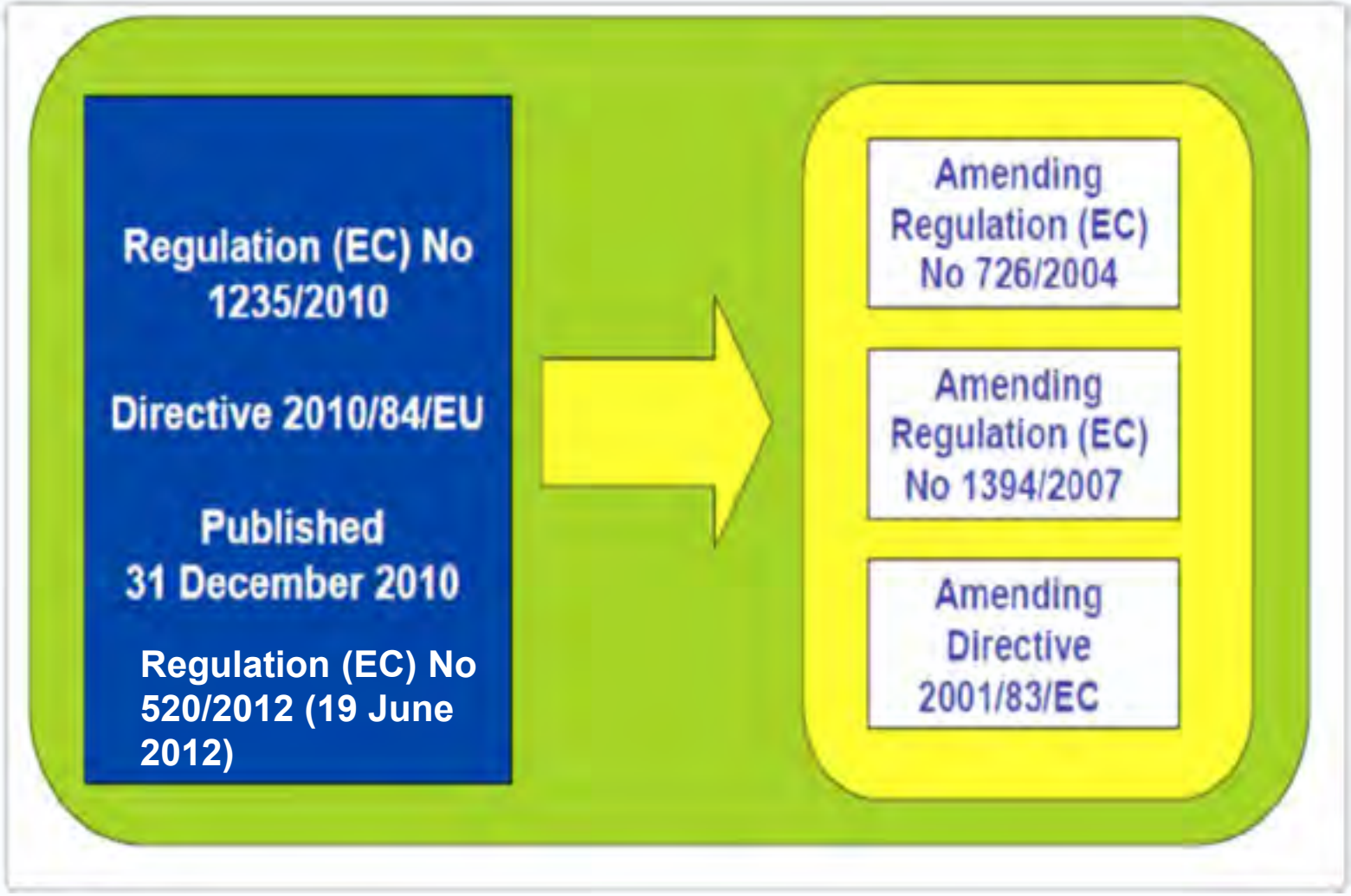
Objectives of Todays Session

- Background to the EU PV Legislation
- Purpose & Expectation of the EU PV Legislation
- Key Points of the EU PV Legislation
  - **Additional Monitoring**
- Regulatory Inspection Findings & Consequences
- Summary Observations

Introduction to New EU Pharmacovigilance Legislation

Highlights of the New Pharmacovigilance Legislation



Good Vigilance Practice (GVP) Modules

17 Modules are proposed to replace previous Vol.9A guidance:

Main Modules

MODULE I - Pharmacovigilance Systems and their Quality Systems
MODULE II - Pharmacovigilance System Master File (Rev 1)
MODULE III - Pharmacovigilance Inspections (Rev 1)
MODULE IV - Audits
MODULE V - Risk Management Systems (Rev 1)
MODULE VI - Management and Reporting of Adverse Reactions (Rev 1)
MODULE VII - Periodic Safety Update Report s (Rev 1)
MODULE VIII - Post-Authorisation Safety Studies (Rev 1)
MODULE IX - Signal Management
MODULE X - Additional Monitoring
MODULE XV - Safety communication
MODULE XVI - Risk minimisation measures (Rev 1)

GVP Modules – next wave

Next wave of GVP Modules expected for release in 2014/2015:

MODULE XI - Public Participation in Pharmacovigilance – **Expected Q4-2014/Q1-2015**

MODULE XII - Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication – **Expected Q4-2014**

MODULE XIV - Referral Procedures for Safety Reasons renamed as International co-operation – **Expected Q1/Q2 2015**

Special Modules

Product or population specific considerations (GVP considerations chapters)

GVP P I Pharmacovigilance for vaccines for prophylaxis against infectious diseases (**released December 2013**)

GVP P II Biological medicinal products – **Expected Q4-2014/Q1-2015**

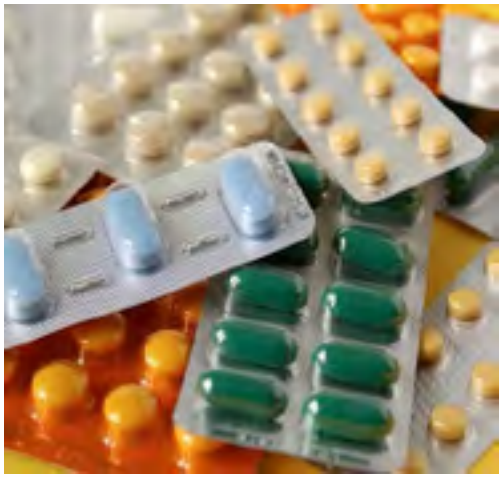
Key points to note about new PV Legislation

- New Conditions added to a MAA
- Quality systems for pharmacovigilance
- Pharmacovigilance System Master Files (PSMF)
- Risk Management Plans (RMPs)
- Effectiveness of risk minimisation
- **Post-Authorisation Studies (safety and efficacy)**
- Adverse Drug Reaction (ADR) reporting – broadening legal definition
- Patient reporting
- New Signal Management systems and procedures
- **Additional Monitoring requirements**
- New Periodic Safety Update Reports (PSURs)
- **Scientific Committees / Pharmacovigilance Risk Assessment Committee [PRAC]**
- Transparency and communication – ADR data in public domain
- **Coordination of inspections - sharing findings**
- Pharmacovigilance Audits and risk based planning

Drivers For Change

Main Drivers for the New EU Pharmacovigilance Legislation

- To strengthen and rationalise the community legislation with the overall objectives of:
  - Better protection of public health
  - Simplification of current rules and procedures
  - Integrate benefit and risk
  - Increase proactive planning to protect patient safety
  - Apply risk based and proportionate regulatory action
  - Engage patients and healthcare professionals
  - Increase transparency



Why Now?

Limitations to the basis for issuing a marketing authorisation (MA):

- Medicines authorised on the basis that likely benefits in respect of efficacy outweigh perceived risks
- Limited data available on which to assess risk (~1000 subjects per clinical trial)
- Animal toxicology data may be of limited relevance to human use
- Clinical trials have limitations:
  - medicines tested in small number of individuals
  - Not enough follow-up (most <1 year)
  - Trial subjects not representative of wider population (highly selected)
  - careful adherence to dosage regimen

Why Now (2)?

- Exclusion of patients who are:
  - frail,
  - of extreme age,
  - on multiple drug therapies,
  - reduced organ function
- Unlikely to detect ADRs occurring with incidence of lower than ~ 1/3,000

Real life situation:

- Large number of patients
- Less-controlled environment
- Unexpected and rarer ADRs may be observed

Estimate of ADR harm in Europe (EMA 2012)

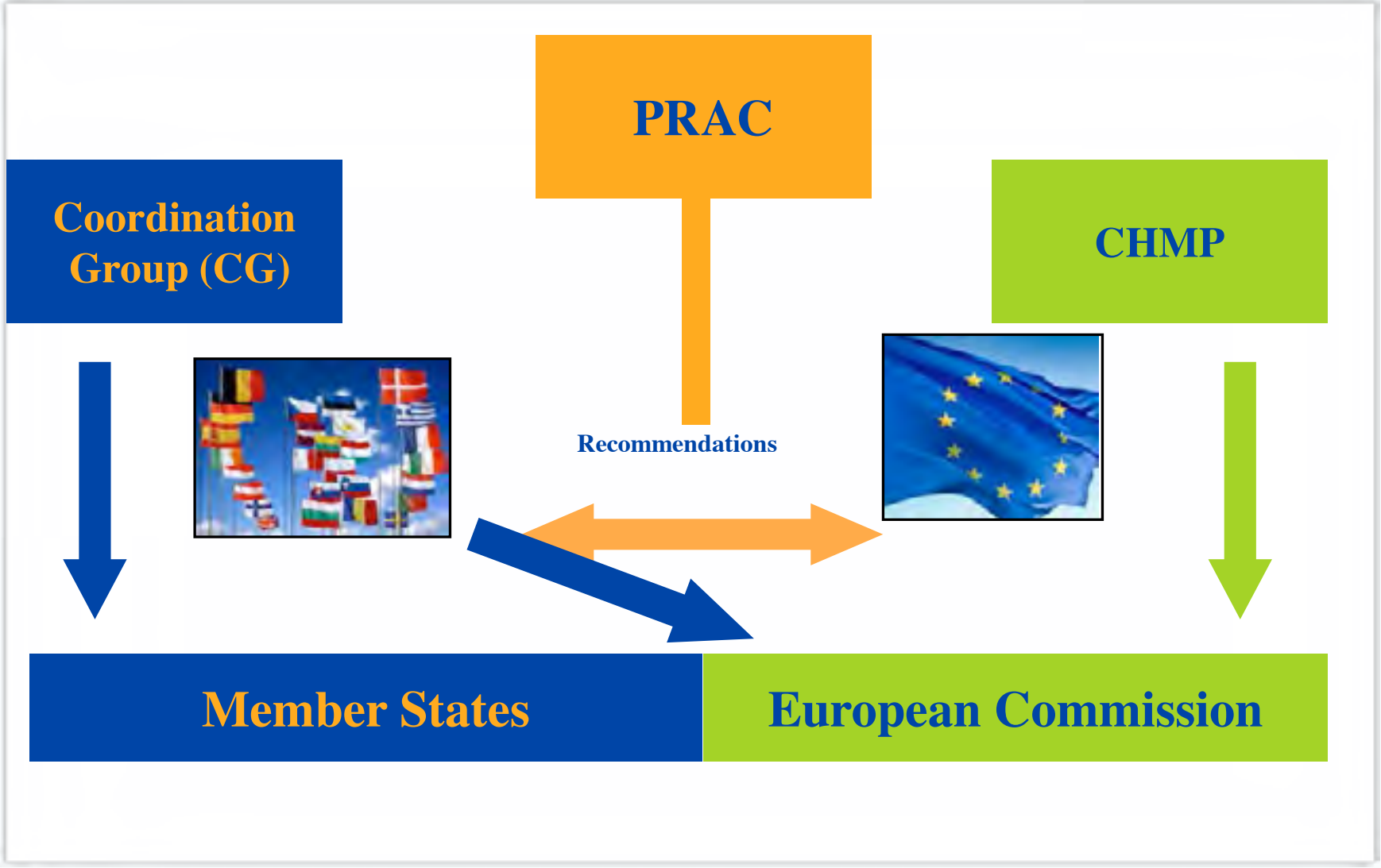
- 5% of all hospital deaths due to ADRs
- 5% of all hospital patients experience an ADR
- ADRs 5th most common cause of hospital deaths
- 197,000 deaths per year in EU caused by ADRs (EC, Brussels,10-Dec-2008)
- Total economic cost of ADRs to Europeans is ~ 79 billion Euros Annually
- USA - The direct medical costs of ADRs are US$30 to $130 billion annually (Pharmacoeconomics 1999;15:445-458; JAMA 1998;279:1200-1205; Pharmacogenomics 2003;4:231-239)

Key Changes to PV Legislation

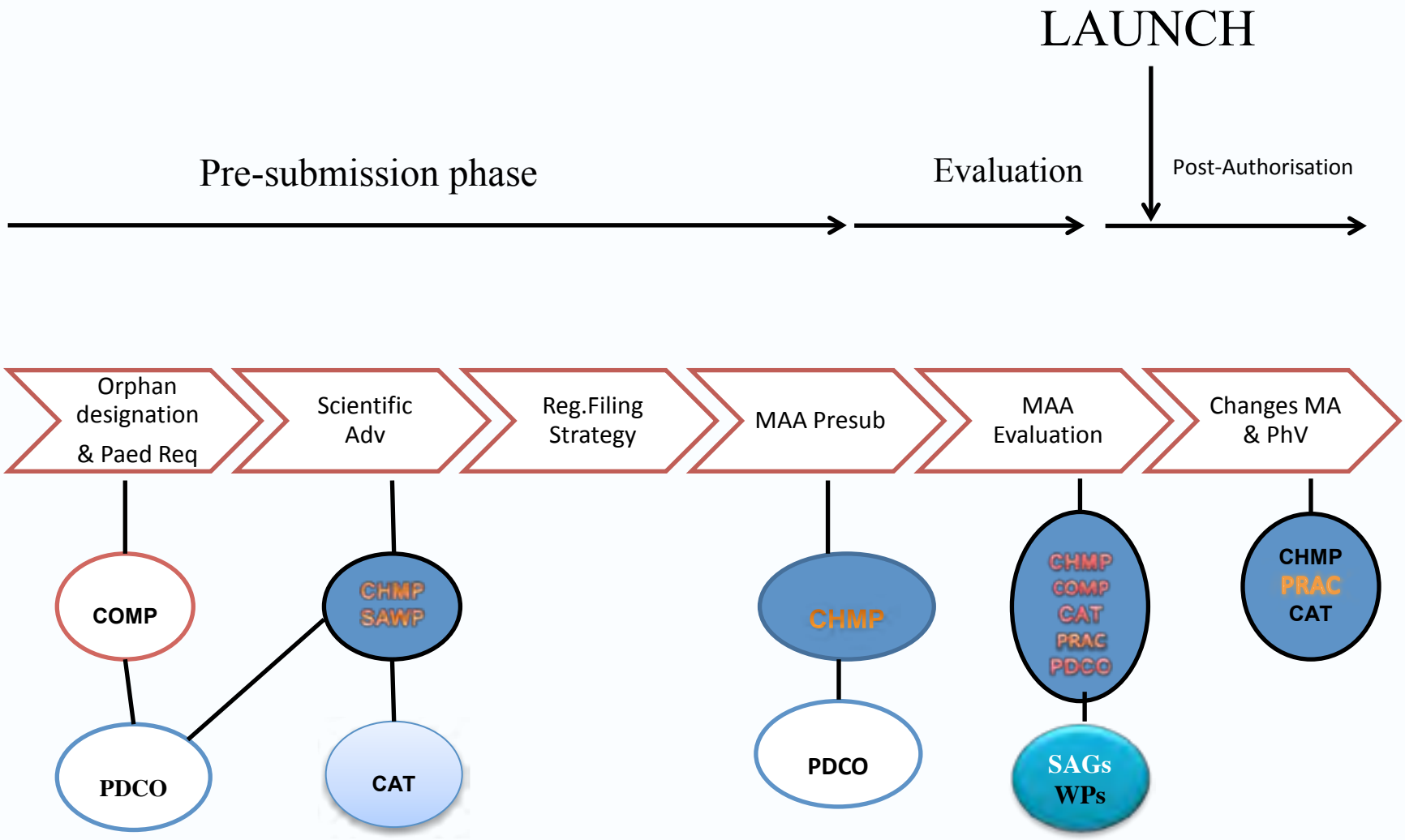
Pharmacovigilance Risk Assessment Committee (PRAC)

- Membership appointed by EU Member States and European Commission
- 1 Chair and 1 vice Chair (Dr J Raine (MHRA), Dr A Spooner(IMB)
- 27 Member States Representatives and EEA non voting members
  - 1 member and 1 alternate from each country
- European Commission Appointments
  - 6 members – expertise in pharmacoepidemiology and clinical pharmacology
  - 1 member and alternate representing patients
  - 1 member and alternate representing Healthcare professionals

PRAC and the other Groups/Committees



PRAC – Involvement with EMA Committees



PRAC (Continued)

- PRAC will specifically:
  - Agree and monitor RMPs
  - Supervise the design and evaluation of PASS
  - Agree Additional Monitoring (AM) requirements and will be involved in assessing the suitability for removal of AM at 5 years (Renewal)
  - Responsible for initial prioritisation and analysis of signals and where necessary agreement of the appropriate risk minimisation measures and communications
  - Review PSURs starting with Centrally Authorised Products (CAPs)
  - Review safety issues at the request of CHMP and CMD(h)
- **Minutes will be in public domain**

Expedited Safety Reporting

Management and reporting of ADRs

- The definition of an ADR has been widened to include:
  - Off-label use
  - Medication errors
  - Misuse
  - Abuse
  - Occupational exposure

- MAHs must submit all reports of suspected adverse reactions to medicinal products **independent of their condition of use** (overdose, misuse, abuse, medication error, occupational exposure, off-label use)

- Spontaneous reports from healthcare professionals and patients or consumers. (**Patient or consumer reports should be handled as spontaneous reports irrespective of any medical confirmation**)

Management and reporting of ADR reporting requirements – Post-Authorisation Safety Studies (PASS)

- MAHs should record all reports of suspected ADRs (EU/non-EU), including data from:
  - Non-interventional studies
  - compassionate use programmes
  - named patient use programmes
  - patient support and disease programmes
  - Registries
  - Surveys

Management and reporting of ADR reporting requirements – Social Media/Market Research

- MAHs should regularly screen **their internet and digital media pages** for reports of adverse reactions associated with their medicinal products e.g. Websites, blogs, forums etc.

- Potential ADRs must be handled through the normal ICSR process – need valid criteria (e-mail address for Patient)

- **Practical implications:**
  - Pharmacovigilance must supervise market research activities
  - MAHs must have due process for review of **market research activities** and must have a medical information system which includes **policy for handling websites and social media**
  - QPPV must have oversight and be confident that processes are in place to capture all relevant information about ADRs

Signal Management Systems

Vision for Signal Management Systems

- MAHs must detect signals for any data source
- Set a **frequency and rationale** of how often these activities should be carried out based on risk, type of product and baseline cumulative reviews
- Put procedures in place that will support and ensure the QPPV has oversight of PV activities:
  - Signal detection and validation
  - Triage
  - Prioritisation
  - Review
  - Recommend action
  - Record and track signals

Additional Monitoring
The Black Triangle is born in Europe

What is Additional Monitoring (1)?

- Additional Monitoring is the requirement for close surveillance of some medicinal products to further investigate their safety profiles
- The types of products for Additional Monitoring are described in **Article 23 of Regulation (EC) No 726/2004** and includes:
  - **medicinal products with a new active substance,**
  - **biological medicinal products**
  - **products for which collection of specific post-authorisation data are required**
- All medicinal products that are subject to additional monitoring are included in a list that is set up and maintained by the EMA (EURD List)
- Products for additional Monitoring are denoted by an inverted black triangle ▼
- For Products included in the list, the summary of product characteristics (SmPC) and the patient information leaflet (PL) must include the statement “**This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions. See section 4.8 for how to reports adverse reactions**”.

What is Additional Monitoring (2)?

- The list of products shall include an **electronic link to the product information** and to a summary of the risk management plan on the new **EU web portal**
- Patients and healthcare professionals will be able to easily identify medicinal products that are subject to additional monitoring
- This will allow patients and Healthcare Professionals to **report suspected adverse reactions** and other information to regulatory agencies and the MAHs
- Regulators may remove a medicinal product from the **Additional Monitoring List** five years after the Community reference date
- PRAC can ask for the period of additional monitoring to be extended until such time as they conclude that the regulatory conditions have been fulfilled

Risk Management Planning

Risk Management Plans (RMPs)

- A RMP describing the Risk Management System (RMS) is required for all new MAAs
- Operation of a **Risk Management System** may be imposed in the Post-marketing phase if there are safety concerns
- Focus is on planning – which is prospective, dynamic and risk proportionate
- Effectiveness of Risk Minimisation Measures must be assessed
- **Summary of the RMP to be made public**
- RMPs must be continually updated
- Increased resource burden for generic and SMEs companies

Periodic Safety Update Reports/Periodic Benefit-Risk Evaluation Reports (PSUR/PBRER)

PSURs (PBRERs) – GVP Module VII

- Move from risk-based to **Benefit-risk** evaluation.
- Close links between signal detection, risk management, periodic safety reports and reference safety information (e.g. SmPC)
- PSUR (GVP Module VII) - Based on principles enshrined in ICH E2C(R2)
- PSUR linked to **EU Reference Date (EURD) List** agreed by PRAC, CHMP and CMDh – April 2013 Published 1 October – updated monthly
- A single PSUR report for one active substance
- More structured evaluation based on cumulative data but no mandated **quantitative** benefit-risk assessment.

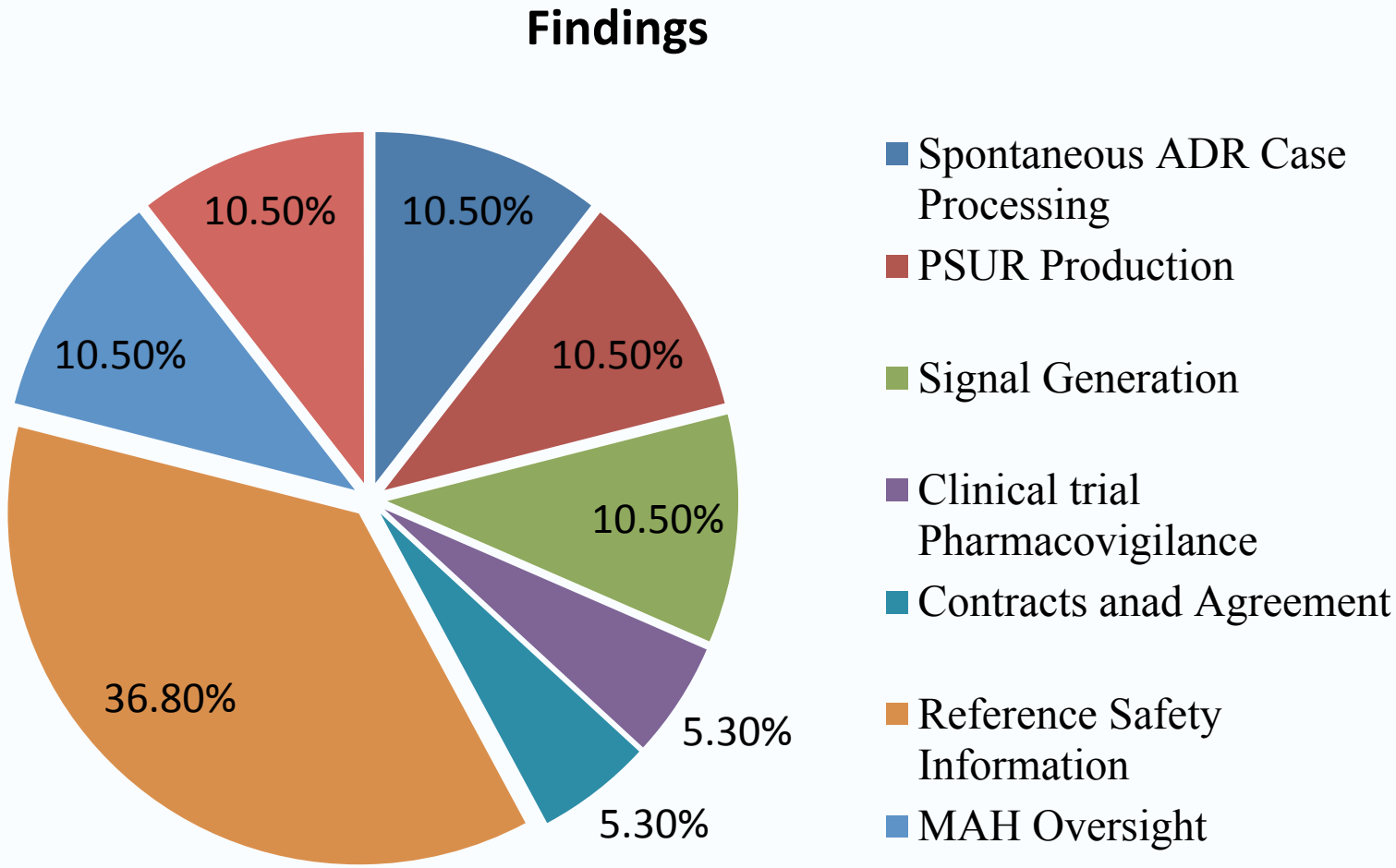
Inspection & Audit Findings & Penalties

Common Findings in Regulatory Inspections & Audits (1/8)

Update from MHRA Inspectors indicate that the most frequent inspection findings fall into the following categories:

- Overall PV System Failure
- Handling and processing spontaneous ADR reports
- PSUR production
- Signal generation
- Clinical trial pharmacovigilance (Handling SUSARs)
- Contracts and Agreements
- Reference safety information
- Lack of MAH oversight

Common Inspection & Audit Findings (2/8)



Common Inspection & Audit Findings (4/8) - Details

Processing of ADR Reports

- All information about suspected ADRs is not accessible from at least one point in the Community
- Lack of understanding of expedited reporting requirements
- Inadequate quality control procedures for ADR processing
- Lack of appropriate follow-up of ADR reports
- Failure to obtain pregnancy exposure outcomes
- Lack of reconciliation of safety data when information is exchanged between partners or other departments
- Significant back-log in ADR report processing

Common Inspection & Audit Findings (7/8) - Details

- **Handling Reference Safety Information:**
  - Poor control of Reference Safety Information (RSI)
  - Inappropriate reference document used to determine reportability for SAEs from clinical trials with authorised products
  - Lack of robust processes for implementing SmPC / PIL changes once safety variations are approved (e.g. notify HCPs & Update websites)
  - No clear translation of information in CCSI into Local Labels
  - IB not aligned with CCSI for marketed product

Role of Globalisation in patient safety (1)

- **Inspection findings** will not be confined to EU situation; it has implications for **any territory** where a company is marketing their products
- Any issue which impacts patient safety in the EU is likely to have an immediate effect anywhere around the world because of globalisation
- All of the major regulatory agencies have agreements in place for exchanging regulatory information with other regulators (e.g. **EMA and FDA**)
- Examples are ICH which provides a regular forum through the **Global Cooperation Group (GCG)** for regulators across the world to exchange information rapidly in real time and for face to face meetings to discuss key regulatory issues such as product safety

Role of Globalisation in patient safety (2)

- The Members of GCG includes the EC/EMA, US-FDA, PMDA of Japan, TGA of Australia, Brazil, China, Chinese Taipei, India, South Korea, Russia, Singapore,
- Countries that belong to the following trading blocs: ASEAN, APEC, EAC, and GCC (including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates)
- Pan-American Network for Drug Regulatory Harmonization [(PANDRH) - covering Latin America and the Caribbean States]
- Southern African Development Community [(SADC) consisting of 15 Southern African Member States]

Consequences of Non-Compliance

Consequences of Non-Compliance With PV Legislation

- Increased frequency of Inspections
- Corrective and Preventative Actions (CAPAs)
- Referral Procedure
- Suspension/Withdrawal of Marketing Authorisation
- Naming and Shaming
- **Financial Penalties**
- Impact on Company Share Value/Investors

Consequences of Non-Compliance With PV Legislation

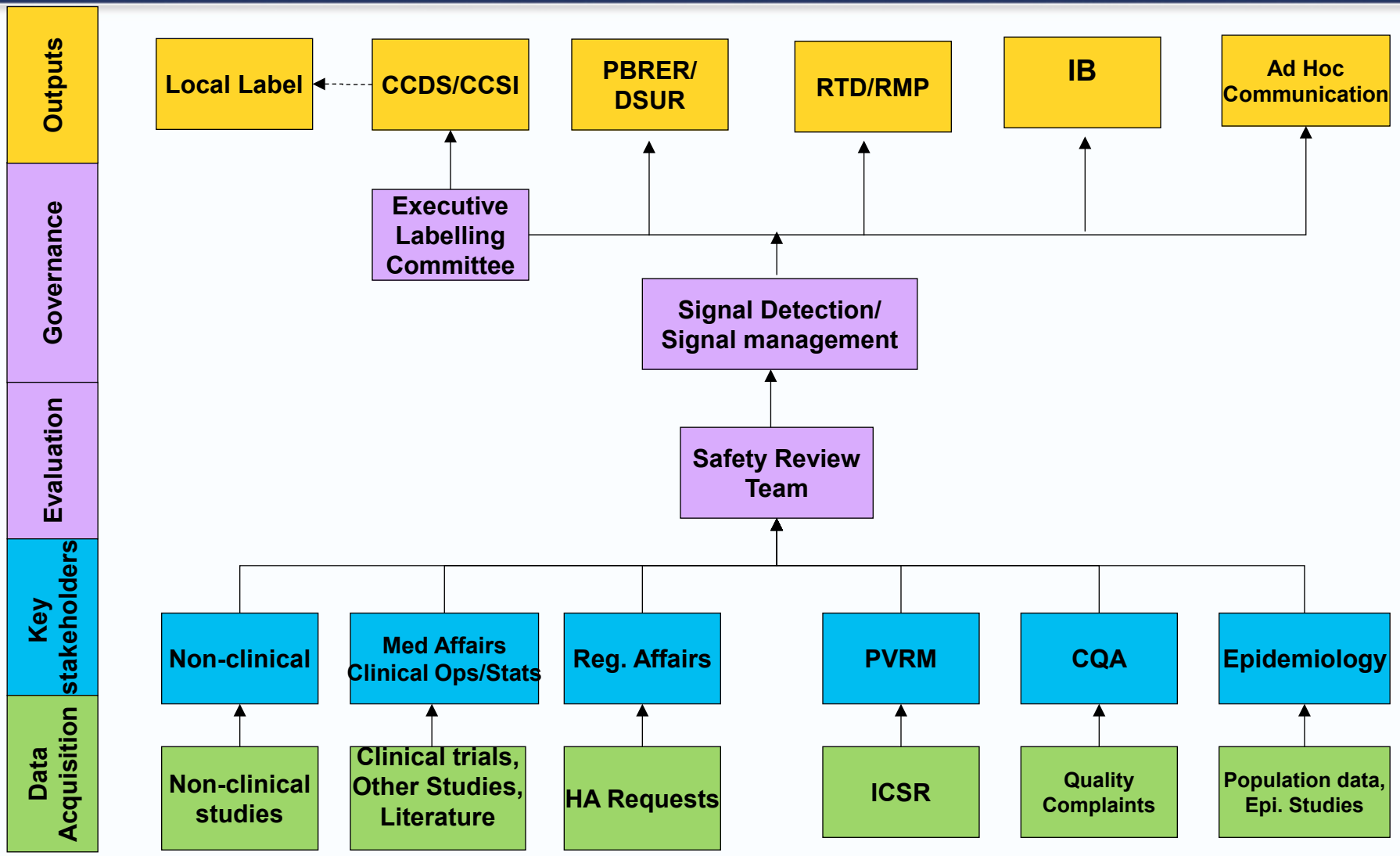
- **Financial Penalties Reg. (No. 658/2007), as amended by Regulation 488/2012 (Applies to CAPs), Art. 1: Failure to:**
  - Operate a comprehensive PV system, including maintenance of a PSMF and performance of regular audits (*Art. 1(11)*);
  - Record and report suspected adverse reactions (*Art. 1(14));*
  - Record and report suspected serious unexpected adverse reactions (SUSARs) (*Art. 1(17)*);
  - Have Appropriately qualified QPPV (Art. 1(21));
  - Submit PSURs (*Art 1(15)*);
  - Collate and assess specific PV data (*Art. 1(20)*); and
  - Communicate information relating to PV concerns to the general public (*Art. 1(23)*).

Consequences of Non-Compliance With PV Legislation

- **Financial Penalties Regulation No. 658/2007, as amended by Regulation 488/2012, Art. 1:**
  - Art. 16(1) – fine of **5%** of the MAH’s Community turnover in the preceding business year;
  - Art. 16(2) – periodic penalty payment per day of **2.5%** of the MAH’s average daily Community turnover in the preceding business year
  - In the case of MAH’s non-cooperation by refusing to provide information, a daily financial penalty of 0.5% of the MAH’s daily turnover for the preceding business year will be imposed

The New PV Legislation & How to Avoid Penalties

How Should an Ideal Safety Surveillance Process look?



Relationship between functional groups in a company and patient Safety

Summary (1) - Key changes that will affect MAA process

In Summary- New legislation provides greater clarity on the information related to PV to be submitted at time of MAA including:

- All key measures of risk management system are now conditions of the Marketing Authorisation including **PASS** and **PAES** (**e.g. Conditional Approval, Exceptional Circumstances, Special Situations**)
- MAHs to update Risk Management System annually on their progress in meeting post-authorisation commitments
- Follow-Up measures being phased out to one of the following:
  - conditions in Annex II of Marketing Authorisation (specific obligations to fulfil post-authorisation measures);
  - additional pharmacovigilance activities in the Risk Management Plan;
- Follow-up Measures and **timeframes will be measurable** and regulatory action will be taken if obligations are not met e.g. Financial penalty, MA suspension or MA withdrawal/Revocation

Summary (2) – Benefit of Changes

- A chance to link life cycle management from clinical development through to post-authorisation monitoring.

- More joined-up working in Pharmaceutical Companies

- Improvement of data collection and data quality (critical for success)

- Allows companies to predict adverse events earlier and put strategies and plans in place to:
- To provide a proactive approach to **risk management planning** which will **ensure patient safety** by helping to rapidly detect new/changing risks

- Development of better methodologies and tools to help with communication of benefit risk concepts to patients and prescribers/healthcare providers

Glossary

- **CMDh** – Coordination Group for Mutual Recognition & Decentralised Procedure – human
- **CHMP** - Committee for Medicinal Products for Human Use
- **DDPS** – Detailed Description of the Pharmacovigilance System
- **EC** – European Commission
- **EMA** – European Medicines Agency
- **ENCePP** – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
- **EU** – European Union
- **EURD list** – List of European Union Reference Dates and frequency of submission of Periodic Safety Update Reports
- **GVP** – Good Pharmacovigilance Practices
- **ICSR** - Individual Case Safety Reports
- **MA** – Marketing Authorisation
- **MAH** – Marketing Authorisation Holder
- **MedDRA** – Medical Dictionary for Regulatory Activities
- **MS** – Member State
- **PAES**-Post Authorisation Efficacy study
- **PASS** – Post-authorisation Safety Studies
- **PRAC** – Pharmacovigilance and Risk Assessment Committee
- **PSMF** – Pharmacovigilance System Master File
- **PSUR** – Periodic Safety Update Report
- **PV** - Pharmacovigilance
- **QPPV** – Qualified Person responsible for Pharmacovigilance
- **RMP** – Risk Management Plan
- **XEVMPD** – eXtended EudraVigilance Medicinal Product Dictionary
- **XEVPRM** – eXtended EudraVigilance Medicinal Product Report Message