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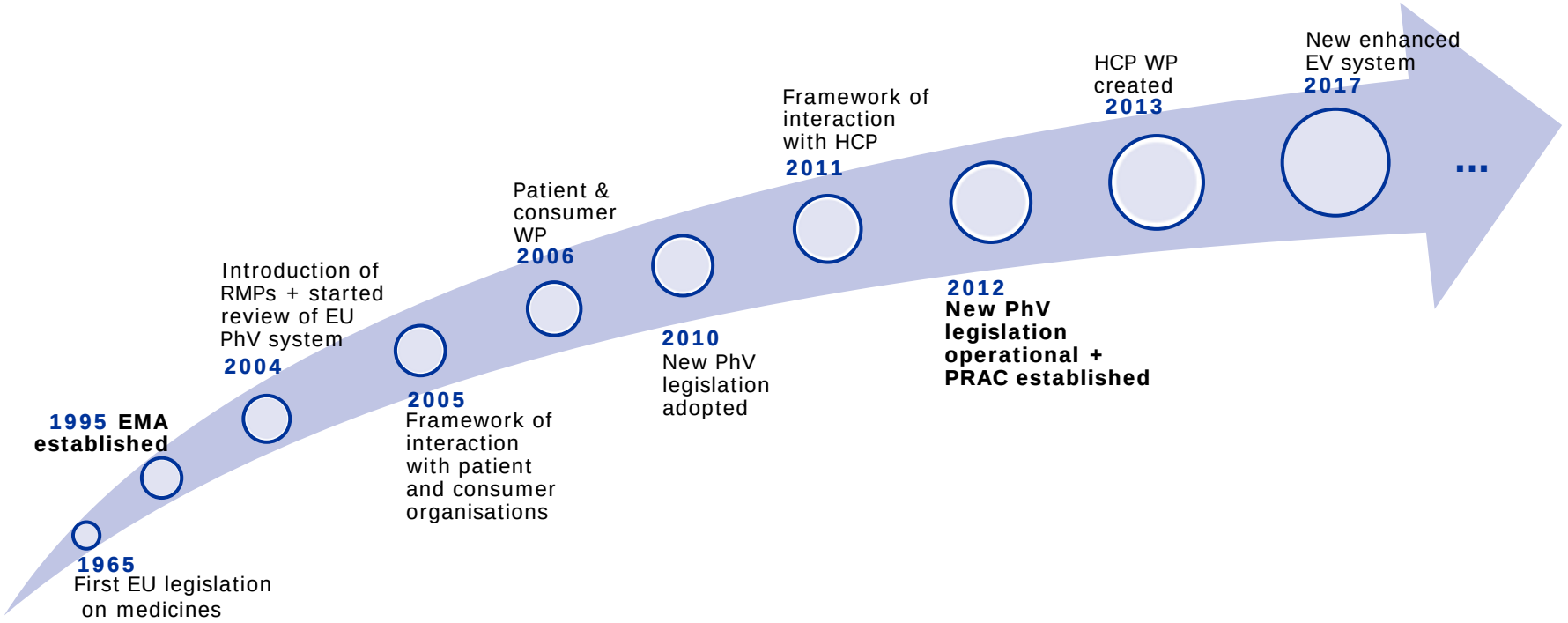
SCIENCE MEDICINES HEALTH

Overview of the EU Pharmacovigilance system

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Aniello Santoro on 9 March 2018
Pharmacovigilance and Epidemiology Department

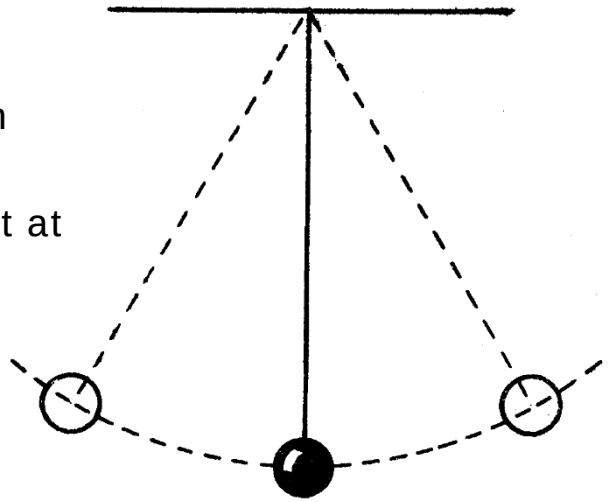
A bit of history



Goals of EU PhV System

Health Promotion

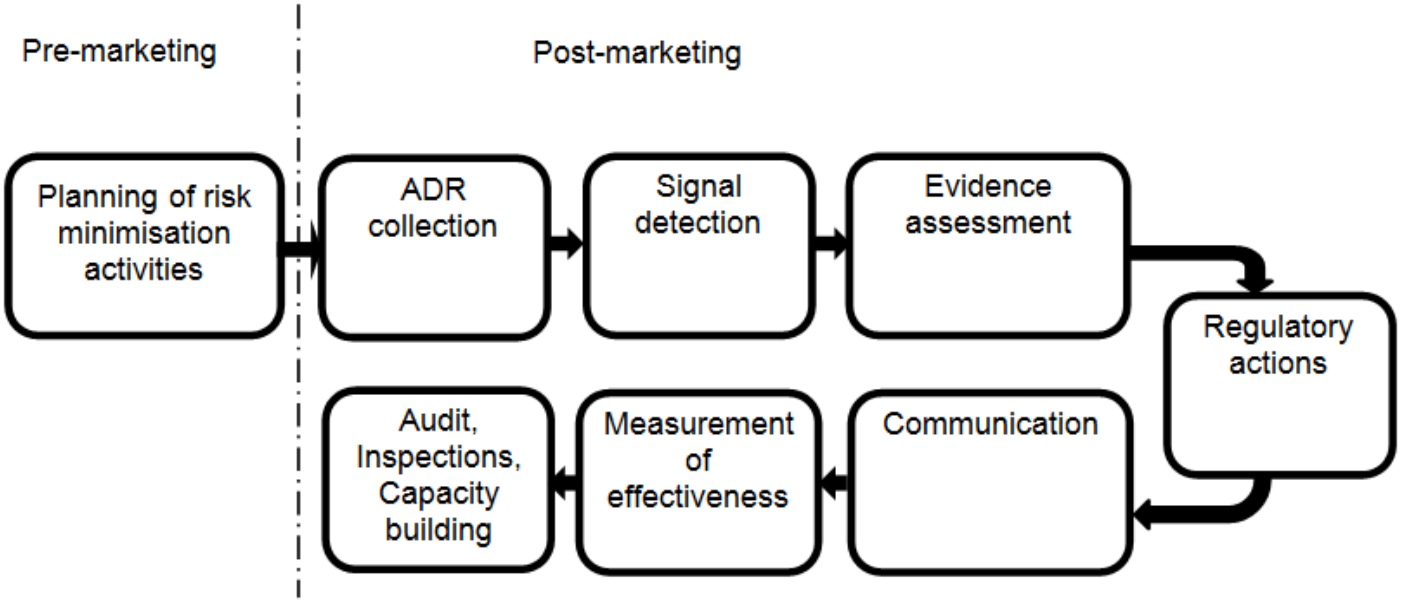
- Fulfill unmet medical needs
- Plan evidence generation through life cycle
- Plan for optimal risk management at authorisation
- Robust PhV systems support authorisation decisions



Health Protection

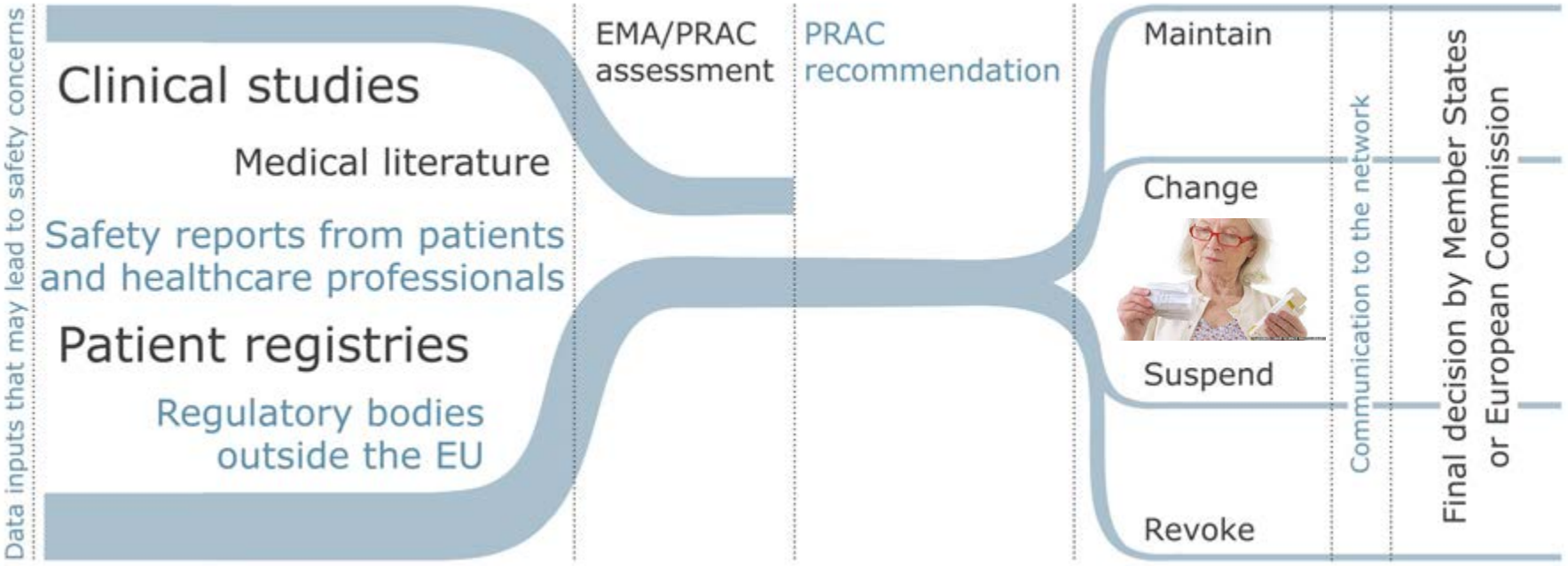
- Robust monitoring for new safety issues
- Rapid decision making
- Effective action to minimise risk
- Demonstrating positive impact

Continuum from pre- to post-marketing

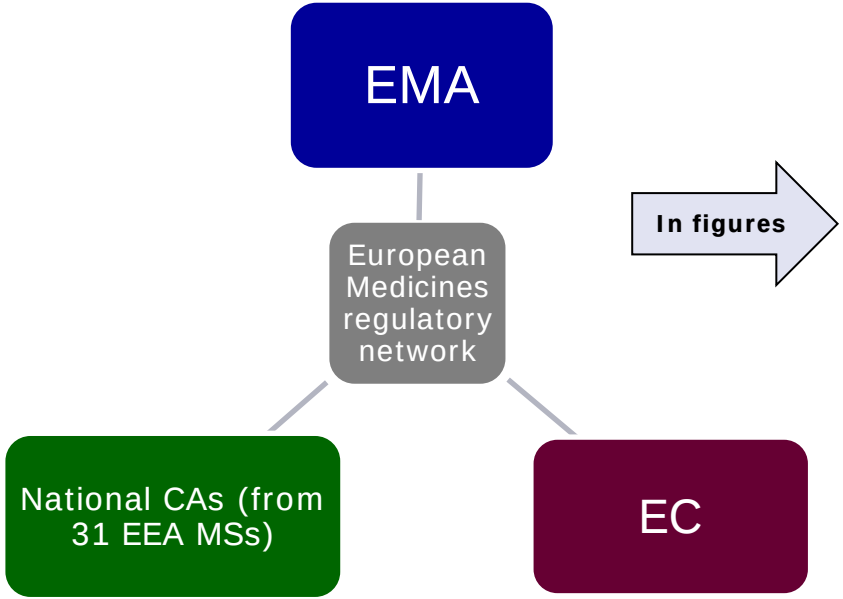


How do we monitor the safety of medicines

PRAC = Pharmacovigilance and Risk Assessment Committee



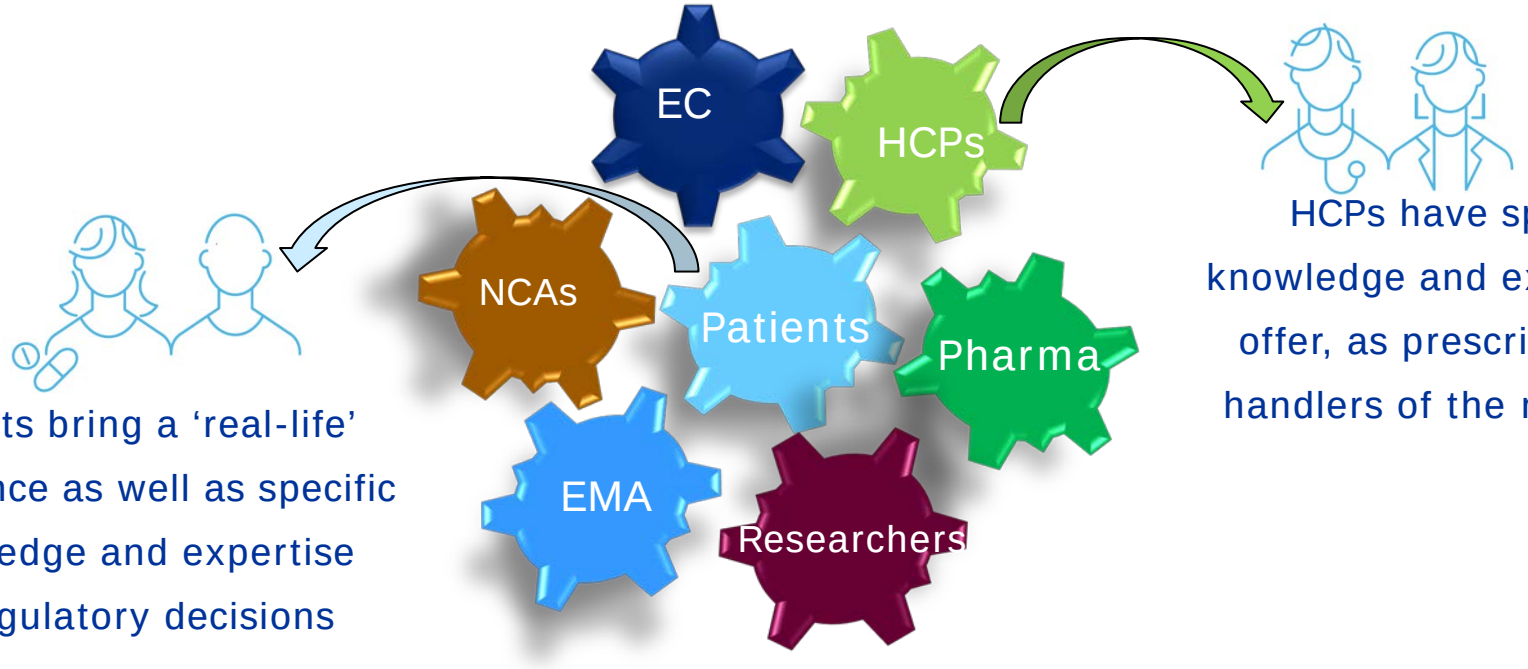
The European Medicines regulatory network



In figures

- 7 scientific committees (CHMP, CVMP, COMP, HMPC, PDCO, CAT, **PRAC**)
- 28 WPs
- ~ 4000 scientific experts across EU

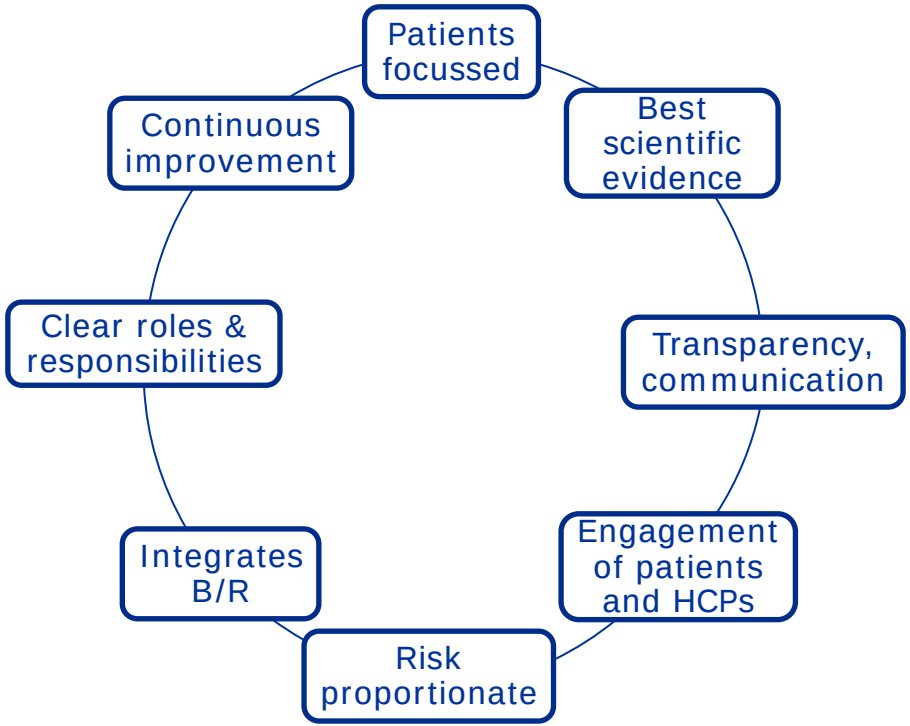
Pharmacovigilance stakeholders



Patients bring a ‘real-life’ experience as well as specific knowledge and expertise to regulatory decisions

HCPs have specific knowledge and expertise to offer, as prescribers and handlers of the medicines

Foundations of EU PhV system



Transparency, Communication, Engagement, Cooperation

Transparency

- ADR portal
- PRAC recommendations on signals
- EPAR (incl. summary of RMP)
- List of medicines (under evaluation, additionally monitored, withdrawn)
- Committee agendas, minutes, press releases, highlights
- Protocols / abstracts of final study reports of imposed PASS
- EU Referral (start, list of medicines, LoQ, TT, etc.)

Communication

- Advance notification of signals on PRAC agenda
- Preliminary AR on signals, PSURs etc. to MAHs
- Coordination between NCAs of safety announcements: harmonised message to patients / HCPs across EU
- Lines to take

Engagement

- Participation of patients and HCPs in Scientific Committees
- Patient and HCP WPs
- Public hearings

Cooperation

- Sharing of info on drug safety issues (regular teleconferences with FDA [HC/PMDA observers])
- Communication on any measure taken regarding CAPs that may have a bearing on public health protection in countries outside the EU (Confidentiality arrangement EMA / EC / WHO)

etc., etc.

Continuous improvement and capacity building

IMI PROTECT project	Developed evidence based methodologies in PhV
EU Network Training Centre	Spread good scientific and regulatory practices across the EU network
SCOPE (EC Joint Action Strengthening Collaboration for Operating PV in EU)	Collected info on how regulators in MSs run their national PhV systems (ADR collection, signals management, risk communication, quality management systems etc.); promoted best practice approaches in the EU network; developed wide-range training material accessible to PhV staff in MSs (via the European Union Network Training Centre)
ENCePP (EU network of Centres in PE and PhV)	Brings together expertise and resources in PE/PV and provides platform for collaboration; facilitates the conduct of multicentre, independent studies focussing on safety and on B/R balance of medicines

Some useful readings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Overview
Research and development
Marketing authorisation

▸ Home ▸ Human regulatory ▸ Post-authorisation ▸ Pharmacovigilance ▸ Good pharmacovigilance practices

Good pharmacovigilance practices

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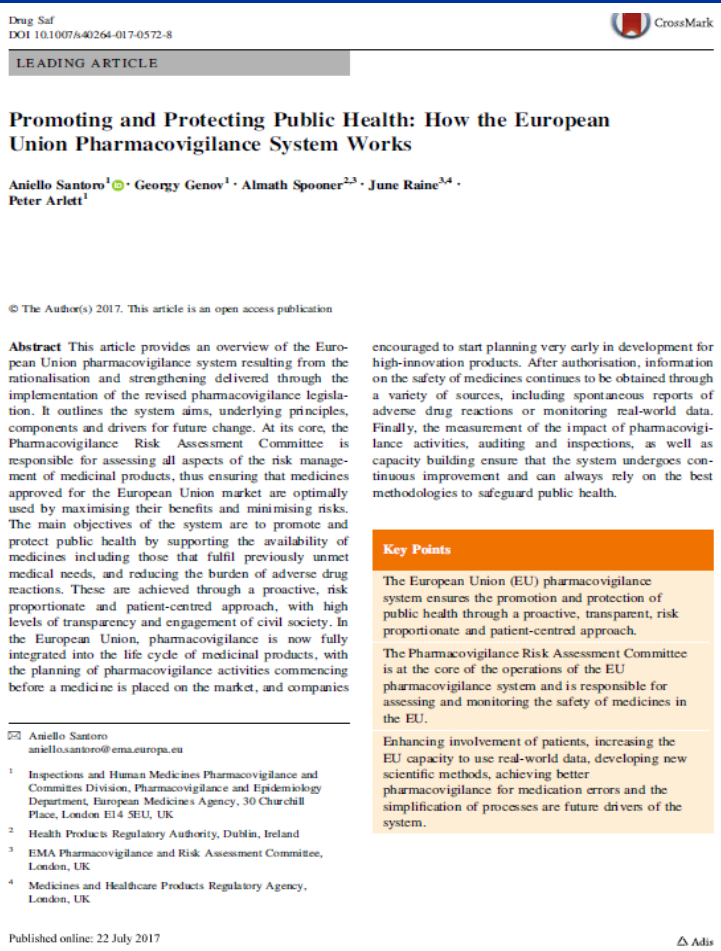
Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

Modules

- I: Quality systems
- II: PSMF
- III Inspections
- IV Audits
- V RMS
- VI ADRs
- VII PSURs
- VIII PASS
- IX SM
- X Additional monitoring
- XV Safety communication
- XVI RMM (tools, indicators)


Drug Saf
DOI 10.1007/s40264-017-0572-8

CrossMark

LEADING ARTICLE

Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works

Aniello Santoro[1] · Georgy Genov[1] · Almath Spooner[2,3] · June Raine[3,4] · Peter Arlett[1]

Abstract This article provides an overview of the European Union pharmacovigilance system resulting from the rationalisation and strengthening delivered through the implementation of the revised pharmacovigilance legislation. It outlines the system aims, underlying principles, components and drivers for future change. At its core, the Pharmacovigilance Risk Assessment Committee is responsible for assessing all aspects of the risk management of medicinal products, thus ensuring that medicines approved for the European Union market are optimally used by maximising their benefits and minimising risks. The main objectives of the system are to promote and protect public health by supporting the availability of medicines including those that fulfil previously unmet medical needs, and reducing the burden of adverse drug reactions. These are achieved through a proactive, risk proportionate and patient-centred approach, with high levels of transparency and engagement of civil society. In the European Union, pharmacovigilance is now fully integrated into the life cycle of medicinal products, with the planning of pharmacovigilance activities commencing before a medicine is placed on the market, and companies encouraged to start planning very early in development for high-innovation products. After authorisation, information on the safety of medicines continues to be obtained through a variety of sources, including spontaneous reports of adverse drug reactions or monitoring real-world data. Finally, the measurement of the impact of pharmacovigilance activities, auditing and inspections, as well as capacity building ensure that the system undergoes continuous improvement and can always rely on the best methodologies to safeguard public health.

Key Points

The European Union (EU) pharmacovigilance system ensures the promotion and protection of public health through a proactive, transparent, risk proportionate and patient-centred approach.

The Pharmacovigilance Risk Assessment Committee is at the core of the operations of the EU pharmacovigilance system and is responsible for assessing and monitoring the safety of medicines in the EU.

Enhancing involvement of patients, increasing the EU capacity to use real-world data, developing new scientific methods, achieving better pharmacovigilance for medication errors and the simplification of processes are future drivers of the system.

✉ Aniello Santoro
aniello.santoro@ema.europa.eu

[1] Inspections and Human Medicines Pharmacovigilance and Committee Division, Pharmacovigilance and Epidemiology Department, European Medicines Agency, 30 Churchill Place, London E14 5EU, UK

[2] Health Products Regulatory Authority, Dublin, Ireland

[3] EMA Pharmacovigilance and Risk Assessment Committee, London, UK

[4] Medicines and Healthcare Products Regulatory Agency, London, UK

Published online: 22 July 2017

Adis

Any questions?

Further information

Aniello.Santoro@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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Roles & Responsibilities through the product life cycle (I)

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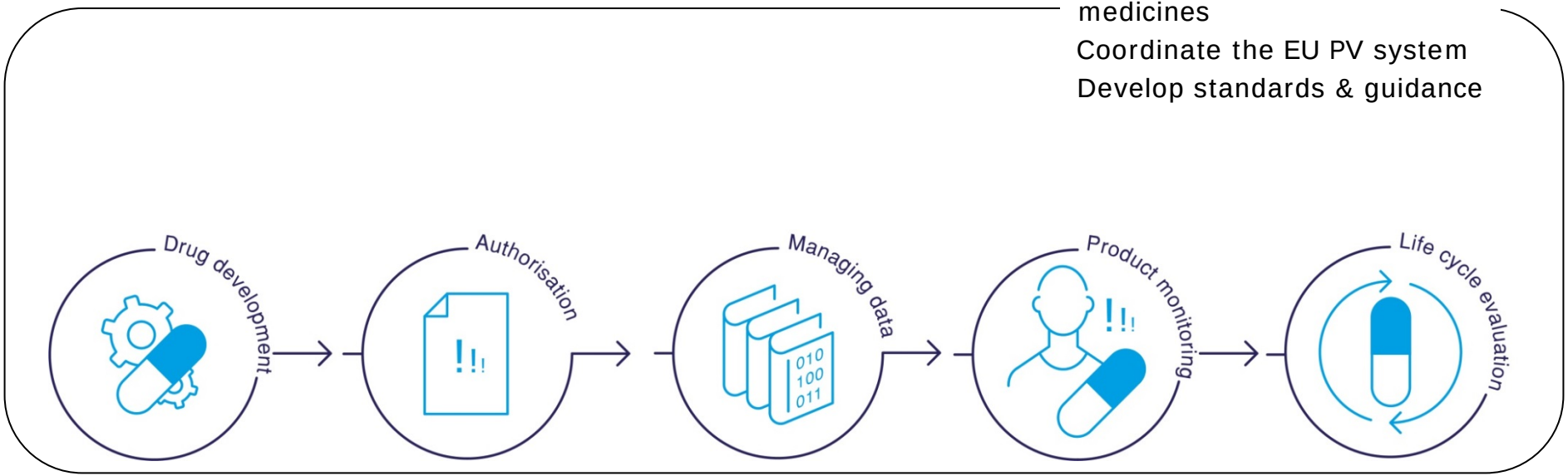
EMA / PRAC

Assess & monitor safety of medicines

Coordinate the EU PV system

Develop standards & guidance



Santoro A, et al. Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. Drug Saf. 2017 Jul 22.

Roles & Responsibilities through the product life cycle (II)

EUROPEAN MEDICINES AGENCY

Pharma
Discovers & develops medicines
Conducts studies to generate evidence

EMA / PRAC
Advise on evidence generation (studies)

EMA / CHMP
Assess EU-wide MAA

EMA / PRAC
Plan for optimal risk management (EU-RMP)

EC
Authorises medicines (CAP)

NCAs
Assess/authorise medicines (NAPs)

EMA
Maintains EV, PSUR repository and Art. 57 database of medicinal products

All
Support access to and analysis of real world data

Roles & Responsibilities through the product life cycle (III)

EUROPEAN MEDICINES AGENCY

EMA / PRAC
SD (CAPs)

NCAs
Promote & operate ADR reporting nationally
SD (NAPs)
Report ADRs to EV
Oversee national implem. of risk minimisation
Coordinate national safe & effective use of medicines

Industry
Monitors its medicines

Patients and HCPs
Use medicines
Use the product information
Report suspected ADRs

HCPs
Enact risk minimisation measures

EMA / PRAC
Assess PSURs, referrals, signals & study results
Coordinate safety announcements in EU
Coordinate inspections & monitor industry compliance

EMA / CHMP
Recommends to EC changes to MA, suspensions, withdrawals
Assess modifications/ extensions to MA

NCAs
Carry out PV inspections
Assess safety issues (NAPs)
Provide expertise to PRAC

Patients and HCPs
Participate in studies
Provide input in the assessment

Academia
Conduct studies

International regulators
Exchange information on safety issues

Abbreviations

ADR: Adverse Drug Reaction
B/R: Benefit/Risk
CA: Competent Authority
CAP: Centrally Authorised Product
CAT: Committee on Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
CVMP: Committee for Medicinal Products for Veterinary Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
EEA: European Economic Area
EMA: European Medicines Agency
EPAR: European Public Assessment Report
EU: European Union
EV: EudraVigilance
FDA: Food and Drug Administration
HC: Health Canada
HCP: Health Care Professional
LoQ: List of questions
MA: Marketing Authorisation
MAA: Marketing Authorisation Application
MAH: Marketing Authorisation Holder
MS: Member State
NAP: Nationally Authorised Product
NCA: National Competent Authority
PASS: Post Authorisation Safety Study
PDCO: Paediatric Committee
PE: Pharmacoepidemiology
PhV: Pharmacovigilance
PMDA: Pharmaceutical and Medical Devices Agency
PRAC: Pharmacovigilance Risk Assessment Committee
PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics
PSMF: Pharmacovigilance System Master File
PSUR: Periodic Safety Update Report
RMM: Risk minimisation Measure
RMP: Risk Management Plan
RMS: Risk Minimisation System
SD: Signal detection
SM: Signal Management
TT: Timetable
WHO: World Health Organisation
WP: Working Party

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EU Risk Management Plan

Module 10 - Patient safety and Pharmacovigilance

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Claire Espinasse on 9 march 2018
Scientific and Regulatory Management Department

Authorising medicines: What we know…

At the time of authorisation:

- Dossier of evidence submitted by the companies on quality, safety and efficacy
- Full assessment by the regulators
- Benefits must outweigh risks based on evidence from clinical trial program

What we know:

- Usually good evidence from clinical trials demonstrating efficacy in the specific indication and populations studied
- Good evidence from clinical trials on the most common adverse reactions

and what we don't know

- Effectiveness of the product in normal clinical practice: compliance, resistance, populations not included in trials
- Full safety profile including adverse drug reactions which are:
  - Rare
  - Delayed
  - From long-term exposure
  - Due to medication errors resulting in harm
  - Different in off-label use
  - Associated with abuse/misuse
  - Associated with populations not yet studied in trials, where a different safety profile is suspected (e.g. in children, very elderly, pregnancy, lactation, co-morbidity)

Table 1 — Chance that a very rare side-effect (0.01%) will not be observed

Number of patients treated	Chance of missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

Amery K Pharmacoepidemiology and Drug Safety, 8: 61±64 (1999)

Risk Management Definition

Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.

Risk management plan: a detailed description of the risk management system

Obligation is fulfilled by submitting a Risk Management Plan (RMP), in the format of the **EU-RMP** template, and maintaining it;

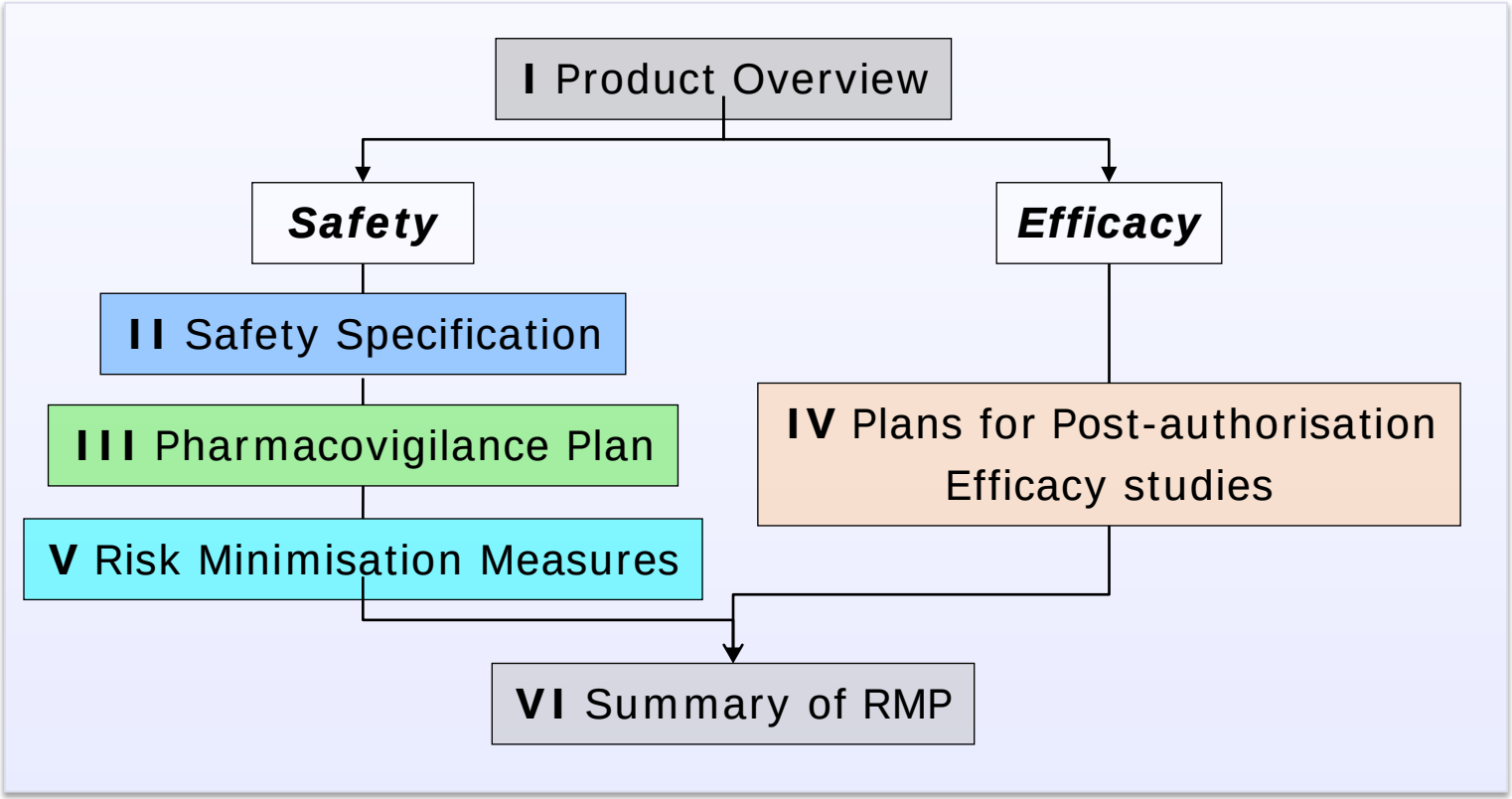
Key documents when preparing your EU-RMP:

GVP module V rev.2

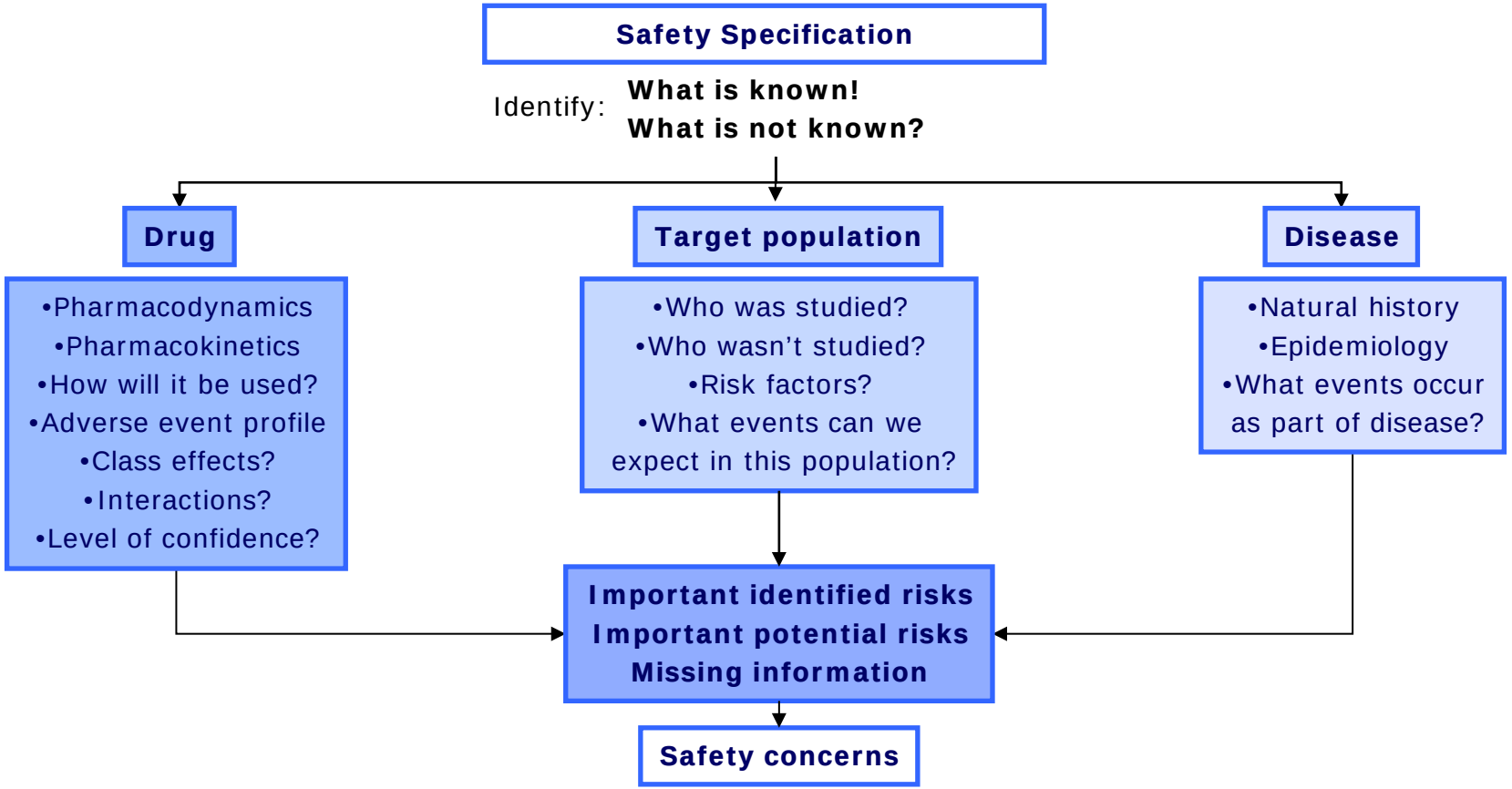
RMP template rev.2

both available on EMA website

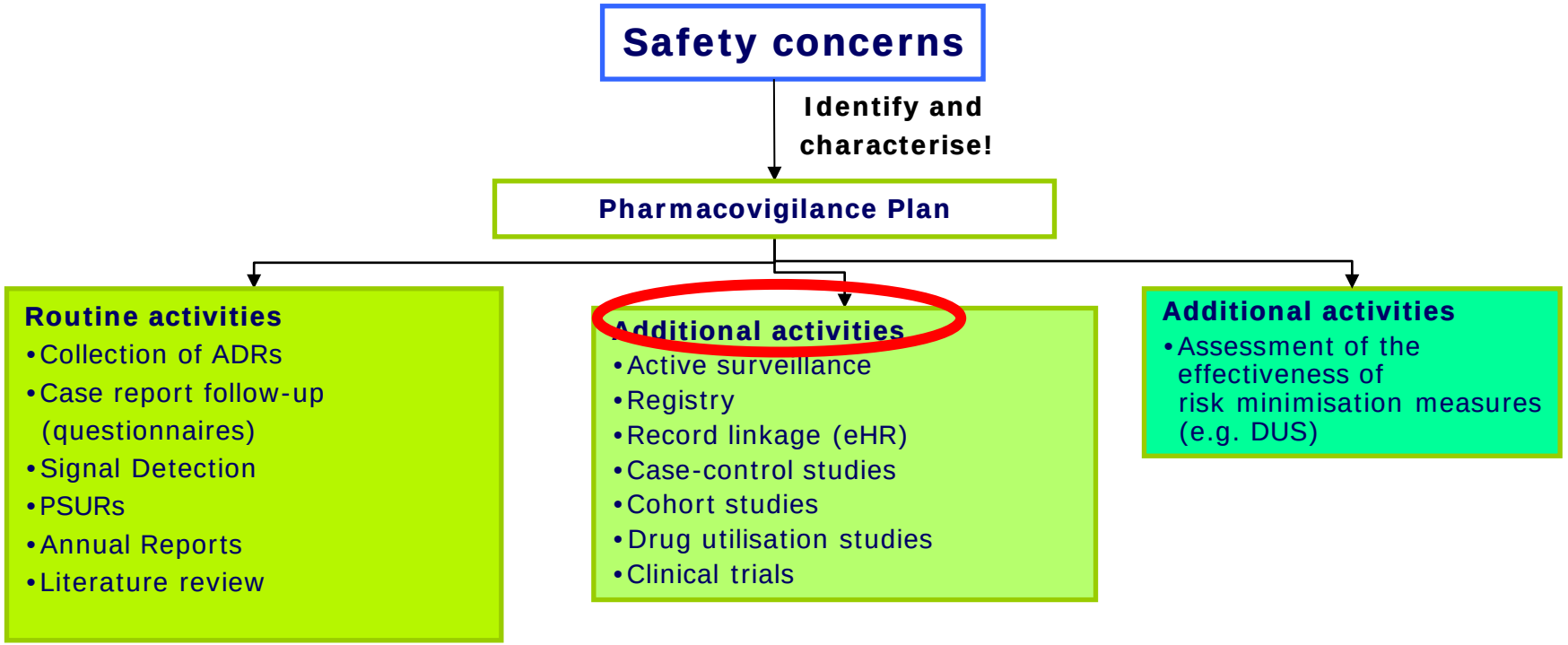
Information Flow in the RMP



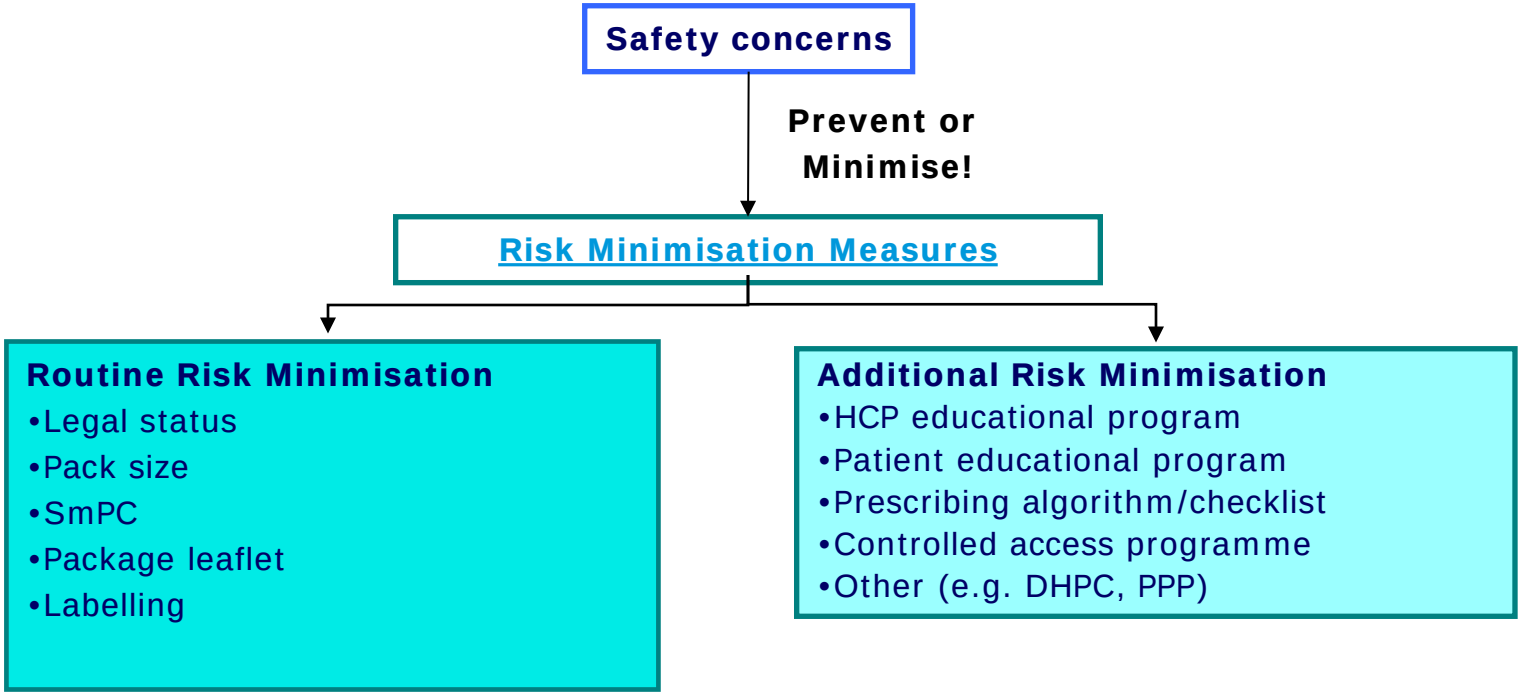
Part II Safety Specification Information



Part III Pharmacovigilance Plan



Part V Risk Minimisation Measures



Part V Routine Risk Minimisation Measures

- **Summary of Product Characteristics** (SmPC)

- **Product information** (PIL)

- **Pack size** (controlling the number of dosage units)
  - Limited validity/size of prescription

- **Legal status** of medicine (defined in Annex II.B as conditions or restrictions for supply or use of medicinal product)
  - Restricted medical prescription (e.g. administration in hospital only)
  - Special medical prescription (e.g. for narcotic or psychotropic substances; potential for addiction, abuse or use for illegal purposes)

Part V Additional Risk Minimisation Measures

- **Health Care Professional Educational Programme**
  - Dear Health Care Professional Letter
  - Physician's guide to prescribing
  - Pharmacist's guide to dispensing
  - Algorithm/checklist before prescribing/dispensing
  - Specific training programme
- **Patient Educational Programme**
  - Patient Alert Card
  - Patient Reminder Card
  - Patient Information Brochure/Booklet
- **Controlled access programme**
- **Other** (e.g. pregnancy prevention programme)

Reflected in **Conditions or restrictions for the safe and effective use** of the medicinal product (Annex II of the PI)
RMP Part V + Annex 6

Part V Effectiveness of Risk Minimisation

Effectiveness of risk minimisation activities should be **measured**

- Legislation requires **active monitoring of the outcome** of risk minimisation measures
- Crucial aspect of continuous pharmacovigilance
- Criteria to assess the effectiveness of each (additional) risk minimisation activity should be **outcome measures** that **indicate the success or failure** of the process implemented based on agreed standards
- Measurement of effectiveness is an additional pharmacovigilance activity of the RMP with defined milestones at regular intervals
- Consider burden on patients/prescribers and performance in healthcare system

→ **Further guidance provided in GVP Module XVI**

Thank you for your attention

Further information

Contact: claire.espinasse@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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EU Signal Detection and Management Procedure

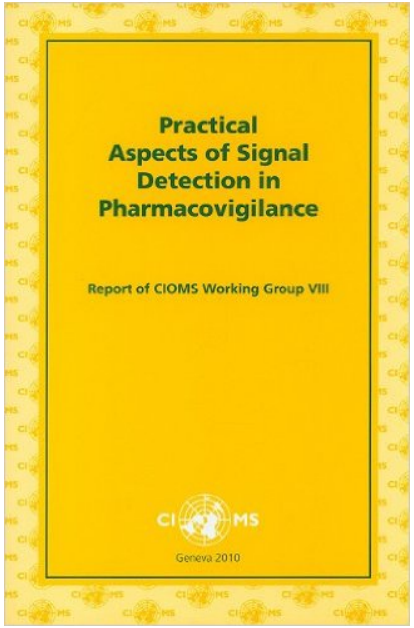
2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Rodrigo Postigo on 09 March 2018

Pharmacovigilance and Epidemiology Department

What is a signal

- *"Information that arises from one or multiple sources (including observations and experiments), which suggests a **new** potentially causal association, or a **new** aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to **justify verificatory action**".*



- Council for International Organisations of Medical Sciences Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010).
- In line with GVP Module IX and the Commission Implementing Regulation (520/2012) only signals related to an adverse reactions will be considered for the purpose of this presentation.

2010/2012 EU Legislation

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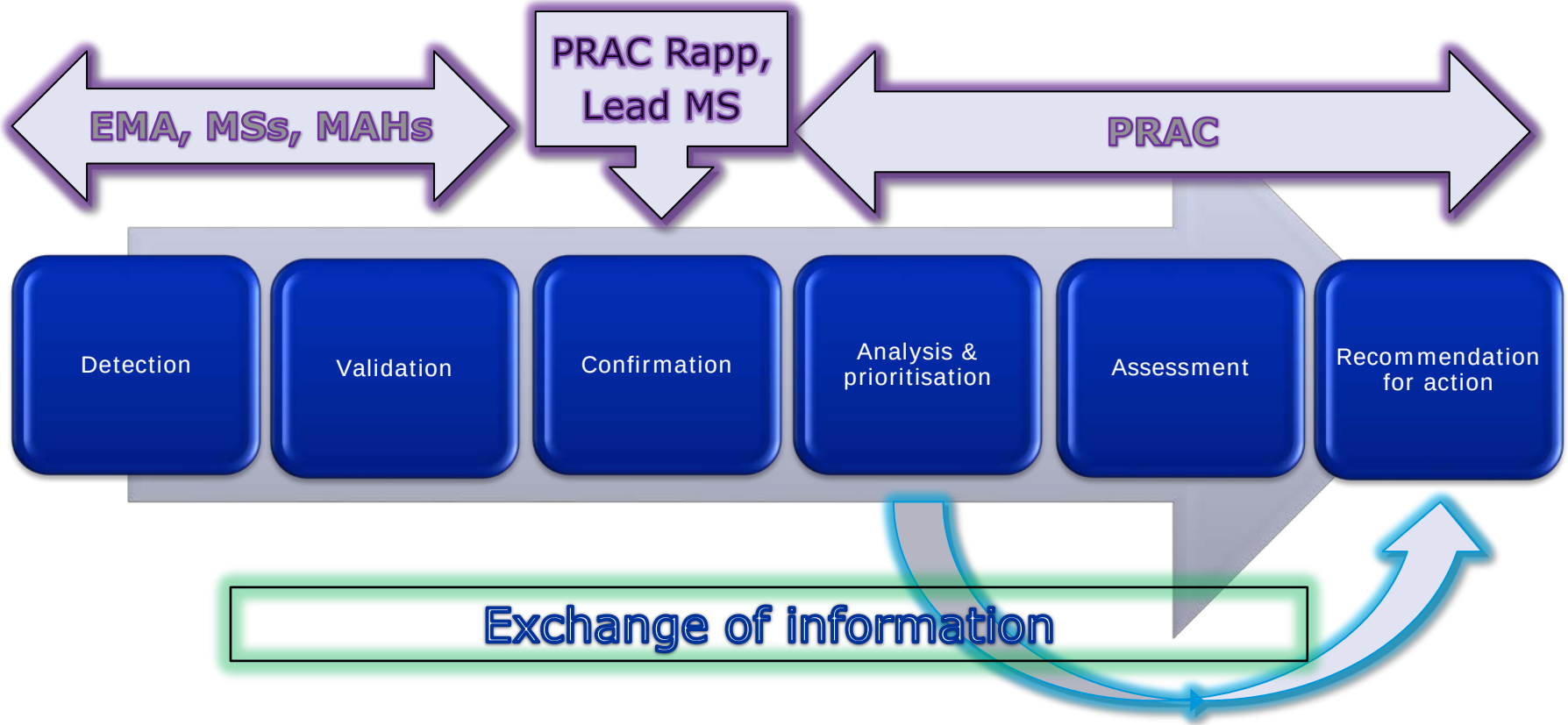
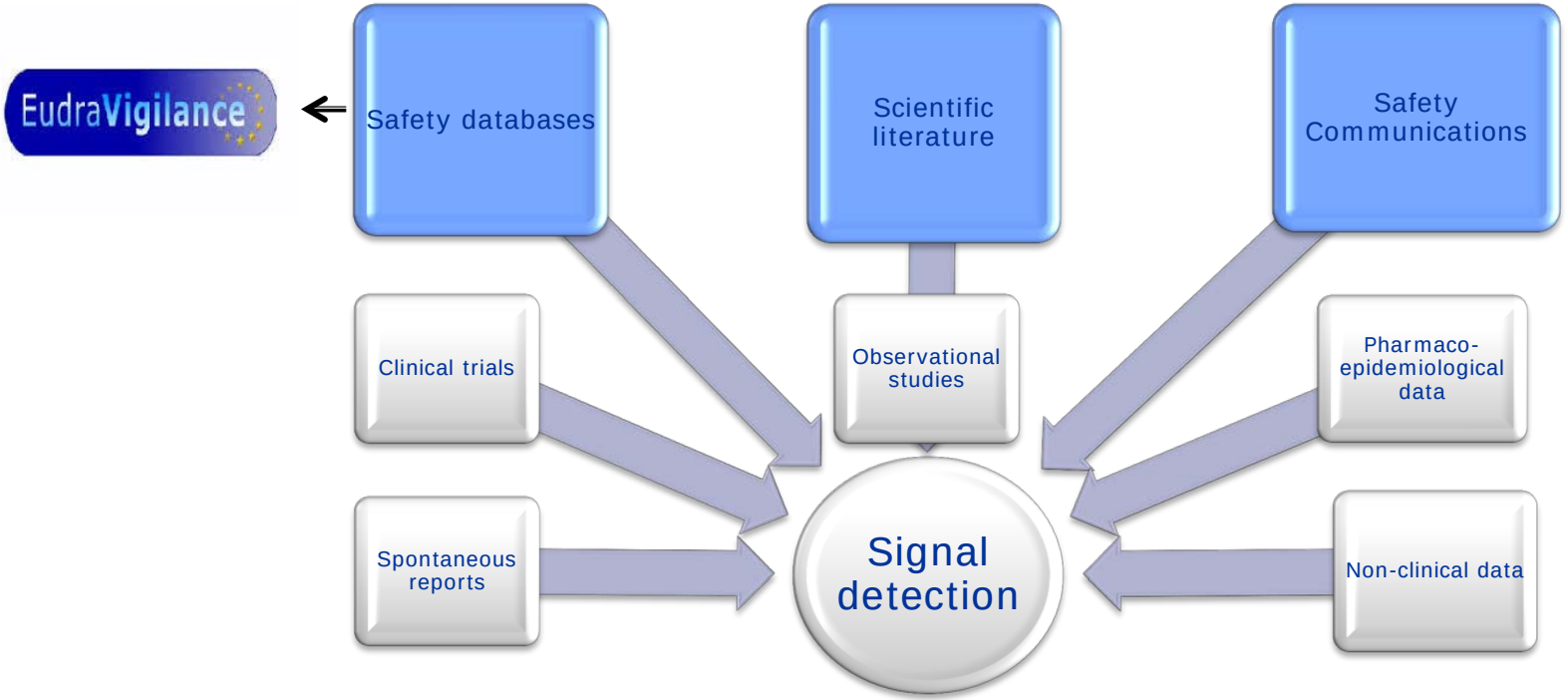
- Updated pharmacovigilance legislation published in 2010 and 2012 (amending Regulation 726/2004 and Directive 2001/83) and Commission Implementing Regulation (IR) 520/2012 established:
  - Principles for monitoring the data in the EudraVigilance database to determine whether there are new risks or whether risks have changed or whether those risks have an impact on the benefit risk balance of the medicinal product.
  - The PRAC shall perform initial analysis, prioritisation and assessment of signals and when necessary agree on any subsequent action concerning the marketing authorisation of the product.
  - The different steps in the Signal Management process.

- EU Guideline: Good Vigilance Practice Module IX on Signal Management

EU signal management process at a glance




EudraVigilance
Safety databases
Scientific literature
Safety Communications
Clinical trials
Observational studies
Pharmaco-epidemiological data
Spontaneous reports
Signal detection
Non-clinical data

What is EudraVigilance?

- EudraVigilance (EV) is a common pharmacovigilance database accessible at a single point within the European Community
- EV contains information on suspected Adverse Drug Reactions (ADRs) from both pre- & post-authorisation phases, transmitted securely by:
  - National Competent Authorities (NCAs)
  - Marketing Authorisation Holders (MAHs)
  - Sponsors of Clinical Trials
- EV also contains medicinal product information in the extended EudraVigilance Medicinal Product Dictionary (xEVMPD)

What is the main purpose of EudraVigilance?

- To support the protection of public health by:
  - Collecting suspected ADRs in the pre- and post-authorisation phases
  - Supporting the monitoring and evaluation of potential safety issues by EU regulators during clinical trials and following their marketing authorisation
  - Monitoring the reporting compliance (EU expedited reporting requirements) and the quality of data submitted by MAHs and NCAs
  - Monitoring identified/potential safety issues as outlined in the EU Risk Management Plan
  - Supporting the decision making process at the level of the EMA Committees

EudraVigilance key dates

- Key dates
  - December 2001: Launched (post-authorisation only - EVPM)
  - May 2004 : Extended to cover Clinical Trials
  - November 2005: Mandatory electronic reporting of PM ICSRs in the EEA
  - July 2007: EudraVigilance Data Analysis System (EVDAS) available to NCAs
  - November 2017: EV became central repository for all EEA ADR data
    - ➢ All cases to be transmitted to EV & EMA to forward EEA cases to NCAs

EV access to the general public

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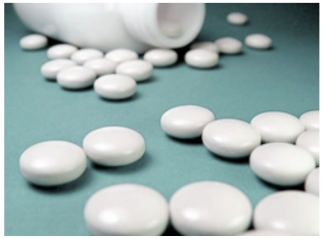
EudraVigilance - European database of suspected adverse drug reaction reports



bg Европейска база данни относно съобщенията за подозирани нежелани лекарствени реакции
es Base de datos europea de informes de presuntas reacciones adversas
cs Evropská databáze hlášení podezření na nežádoucí účinky léčivých přípravků
da Europæisk database over indberetninger om formodede bivirkninger
de Europäische Datenbank gemeldeter Verdachtsfälle von Arzneimittelnebenwirkungen
et Ravimite võimalike kõrvaltoimete teatiste Euroopa andmebaas
el Ευρωπαϊκή βάση δεδομένων αναφορών πιθ
is Evrópskur gagnagrunnur fyrir tilkynningar á
en European database of suspected adverse dr
fr Base de données européenne des rapports
ga Bunachar sonraí Eorpach na dtuarascálacha
hr Europska baza podataka prijava sumnji na
it Banca dati europea delle segnalazioni di sos
lv Eiropas ziņojumu par iespējamām zāļu blak
lt Pranešimų apie įtariamą nepageidaujamą re
hu Feltételezett mellékhatásokról szóló jelentés
mt Database Ewropea ta' rapporti dwar reazzjo
nl Europese database van rapporten over vern
no Europeisk database over rapporter om anta
pl Europejska baza danych zgłoszeń o podejrz
pt Base de dados europeia de notificações de
ro Baza europeană de date privind rapoartele
sk Európska databáza hlásení o podozreniach
sl Evropska podatkovna baza poročil o domne
fi EU:n tietokanta lääkkeiden epäiltyjä haittav
sv Europeiska databasen för rapporter om mis

Number of individual cases by Age Group

Age Group	Cases	%
Not Specified	230	17.0%
0-1 Month	10	0.7%
2 Months - 2 Years	8	0.6%
3-11 Years	45	3.3%
12-17 Years	54	4.0%
18-64 Years	545	40.3%
65-85 Years	395	29.2%
More than 85 Years	66	4.9%
Total	**1,353**	**100.0%**

Number of individual cases by Sex

Sex	Cases	%
Female	676	50.0%
Male	592	43.8%
Not Specified	85	6.3%
Total	**1,353**	**100.0%**

EVPM ICSR(s) **Individual Case Safety Report Form** EudraVigilance

General Information

EudraVigilance Local Report Number	EU-EC-10000733311
Sender Type	Pharmaceutical company
Sender's Organisation	NOVO NORDISK A/S
Type of Report	Spontaneous
Primary source country	European Economic Area
Reporter's qualification	Healthcare Professional
Case serious?	Yes

Patient

Age	Age Group	Sex
61 Years	Adult	Male

Reaction / Event

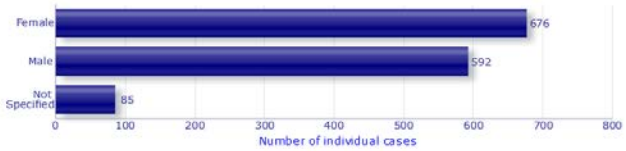
MedDRA LLT	Duration	Outcome	Seriousness[1]
Drug effect diminished		Unknown	life threat.
Product lot specific issue		Unknown	life threat.
Blood glucose increased		Not Recovered/Not Resolved	life threat.

Drug Information

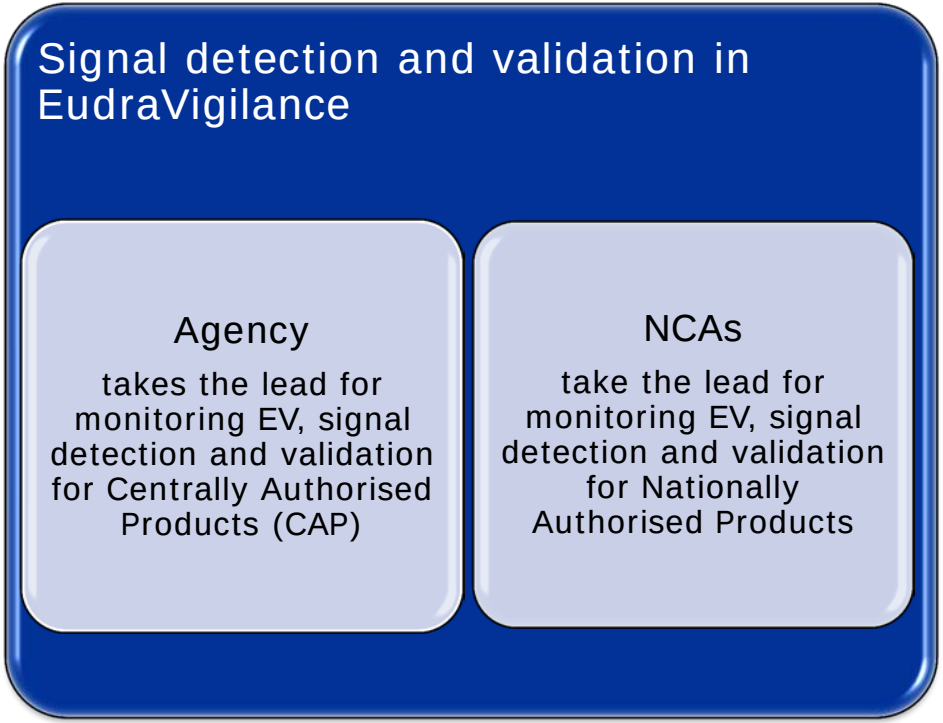
Role[2]	Drug	Duration	Dose	Units in Interval	Action taken
S	ACTRAPID PENFILL - INSULIN HUMAN, INSULIN HUMAN (RDNA)				Drug withdrawn
C	- CLINDAMYCIN, CLINDAMYCIN HYDROCHLORIDE, CLINDAMYCIN PHOSPHATE				

Drug Information *(cont.)*

Info[3]	Drug	Indication	Pharm. Form	Route of Admin.
	ACTRAPID PENFILL - INSULIN HUMAN, INSULIN HUMAN (RDNA)	Diabetes	Solution for injection	Subcutaneous
	- CLINDAMYCIN, CLINDAMYCIN HYDROCHLORIDE, CLINDAMYCIN PHOSPHATE	Inflammation		Unknown



- Signal validation is the process of evaluating the current data available for the detected signal to verify that further analysis is needed (e.g analysis of individual cases)

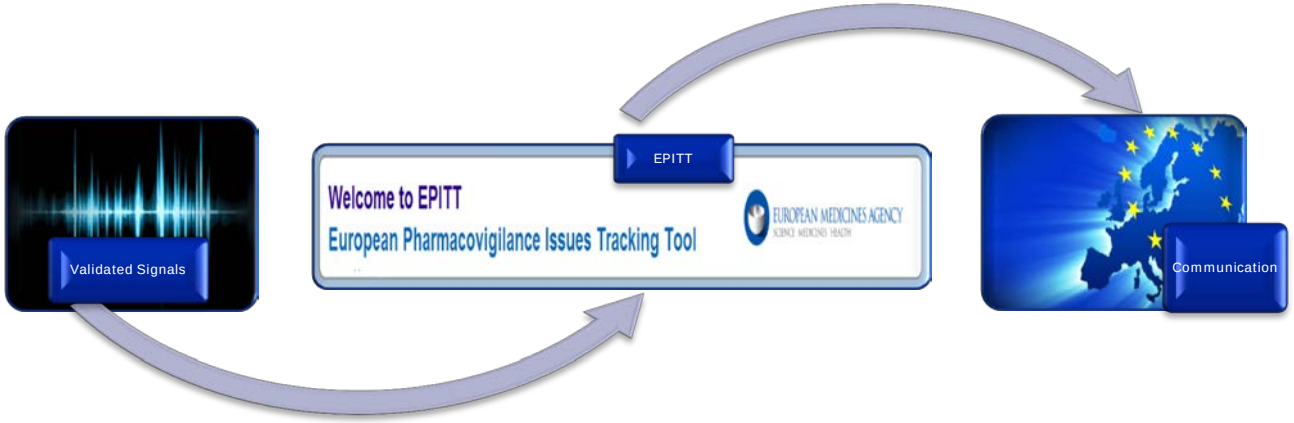


The electronic Reaction Monitoring Report (eRMR)

provides aggregated data, incorporates statistical analysis

Active Substances	SOCs	SMQ Narrow	PTs	IME / DME	New EV	Tot EV	New Fatal	Tot Fatal	New Spontaneous	Tot Spontaneous	PRR (-)	Priority	Changes	SDR	Signal Status
active substance	Nerv	Convulsions	Petit Mal Epilepsy	Ime	0	19	0	0	0	16	0.26				
active substance	Nerv	Convulsions	Grand Mal Convulsion	Ime / Dme	1	85	0	0	0	73	0.20	Pr 1	Increased		PSUR
active substance	Nerv	Convulsions	Postictal Paralysis	Ime	0	3	0	0	0	3	0.75				
active substance	Nerv	Convulsions	Complex Partial Seizures	Ime	0	5	0	0	0	2	0.03				
active substance	Nerv	Convulsions	Psychomotor Seizures	Ime	0	1	0	0	0	0					
active substance	Nerv	Convulsions	Temporal Lobe Epilepsy	Ime	0	1	0	0	0	1	0.05				
active substance	Nerv	Convulsions	Simple Partial Seizures	Ime	0	1	0	0	0	0					
active substance	Nerv	Convulsions	Clonic Convulsion	Ime	0	1	0	0	0	1	0.01				
active substance	Nerv	Convulsions	Convulsion	Ime / Dme	5	750	0	12	5	609	0.42	Pr 1	Increased		Linked
active substance	Nerv	Convulsions -- Drug Abuse, Dependence &	Drug Withdrawal Convulsions	Ime	0	1	0	0	0	1	0.02				
active substance	Nerv	Convulsions	Epilepsy	Ime / Dme	3	117	0	2	3	112	0.52	Pr 1	Increased		Closed
active substance	Nerv	Convulsions	Partial Seizures	Ime	0	3	0	0	0	3	0.03				

- Number of cases (interval and cumulatively)
- Disproportionality (Reporting Odds Ratio)
- Clinical relevance
- Biological plausibility
- Temporal association
- Dechallenge / rechallenge (+/-)
- Confounders, alternative explanations
- Drug interactions
- Previous awareness (SPC, PSUR, RMP…)
- Other sources (literature, CTs…)



- Where it is considered that a validated signal requires further analysis, it shall be confirmed no later than 30 days by the PRAC Rapporteur or the Lead Member State.

Any confirmed signal shall be entered in the tracking system administered by the Agency and shall be transmitted to the Pharmacovigilance Risk Assessment Committee for the initial analysis and prioritisation of signals

- The initial analysis and prioritisation by PRAC is follow-up by a recommendation
- 3 main categories of PRAC recommendations:
  - No specific action
  - Need to additional information
  - Need for regulatory action

- Evaluation of all evidence gathered following initial analysis and prioritisation:
  - MAH responses
  - Additional analyses performed by regulators or other stakeholders, in EV or other sources
- Led by Rapporteur appointed by the PRAC
- According to an agreed timetable
- Leads to a further PRAC recommendation

Standard timetable for the assessment of additional data from MAHs for signals

Day	*Action*
Day 1	Start of procedure
Day 30	Preliminary PRAC Rapporteur AR
Day 45	Comments from PRAC members
Day 50	Updated PRAC Rapporteur AR
Day 60	Adoption of PRAC recommendation

Communications and transparency

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- Advanced notification of signals on the PRAC agenda
- PRAC agenda
- PRAC Recommendations
- Translations of the product information
- Assessment reports
- PRAC minutes

EU - Signal management process

In 2017 the EMA signal management team reviewed in detail a total of 2,062 potential signals (Drug-event pairs from screening of the EudraVigilance database, medical literature, information received from other regulatory authorities).

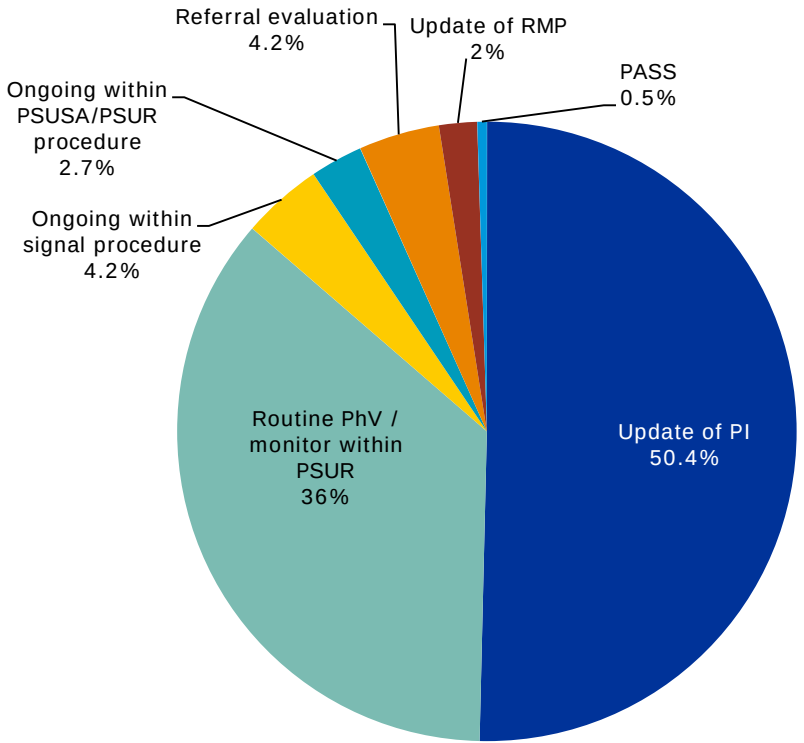
81.8% of the signals originated from EudraVigilance

43 prioritised and assessed by PRAC

Sep 2012 to Dec 2017:

PRAC evaluated 403 signals

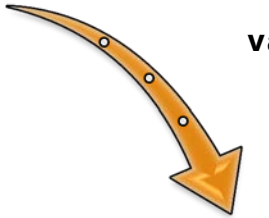
Signal outcomes (Sep 2012 to Dec 2017)



EudraVigilance monitoring by MAHs

EUROPEAN MEDICINES AGENCY

- From November 2017 MAHs have access to EudraVigilance to comply with their pharmacovigilance obligations.
- MAHs shall ensure the continuous monitoring of EudraVigilance
- Where a MAHs detects a new signal when monitoring the EV database, it shall validate it and shall forthwith inform the Agency and NCAs



Signals validated by MAHs

Conclusions

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The EU Signal Management process is implemented since 2012

Further strengthened the link between scientific assessments and regularity actions delivering public health

New access to EudraVigilance: Safety monitoring of the database will be reinforced with the access by MAHs

EMA and medicines regulatory agencies have progressed significantly in the transparency and communication aspects

Support, guidance and training

EUROPEAN MEDICINES AGENCY

- Signal Management webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac05807 27d1b
- GVP general page: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b0 1ac058058f32c
- Guideline: “Screening for adverse reactions in EudraVigilance”: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf
- Questions & answers on signal management: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150743.pdf
- EudraVigilance Access Policy Revision 3: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218300.pdf
- EudraVigilance Training Program: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a 1a1fb

Thank you for your attention

Further information

Contact me at: rodrigo.postigo@ema.europa.eu

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

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SCIENCE MEDICINES HEALTH

Periodic Safety Update Report (PSUR)

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Gaelle Bec on 9 March 2018
Procedure Management Department

What is a PSUR (=Periodic Benefit-Risk Evaluation Report (PBRER))?

A report prepared by the Marketing Authorisation Holder (MAH) describing the worldwide safety experience with a medicine at a defined time after its authorisation.

Part of the lifecycle benefit-risk management of a medicine.

The legal requirements are established in the Regulation (EC) No 726/2004 and the Directive 2001/83/EC.

PSUR format

- Commission implementing Regulation (EU) No 520/2012
- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic Safety Update Report
- ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2))

1. Introduction	2. Worldwide marketing approval status	3. Actions taken in the reporting interval for safety reasons	4. Changes to reference safety information
5. Estimated exposure and use patterns	6. Data in summary tabulations	7. Summaries of significant findings from clinical trials during the reporting interval	8. Findings from non-interventional studies
9. Information from other clinical trials and sources	10. Non-clinical data	11. Literature	12. Other periodic reports
13. Lack of efficacy in controlled clinical trials	14. Late-breaking information	15. Overview on signals: New, ongoing or closed	16. Signal and risk evaluation
17. Benefit evaluation	18. Integrated benefit-risk analysis for authorised indications	19. Conclusions and actions	20. Appendices to the PSUR

PSUR cycle and submission

- PSURs are submitted after approval of a medicine
- Submission requirements are set out in **the list of Union reference dates** (**EURD list**) (published on the EMA web-portal)

General principle:

- 1st PSUR should cover 6-month period from date of marketing authorisation in EU
- Subsequent PSURs submissions frequency as set in EURD list (e.g. 6-monthly, yearly, 3-yearly)

EURD list

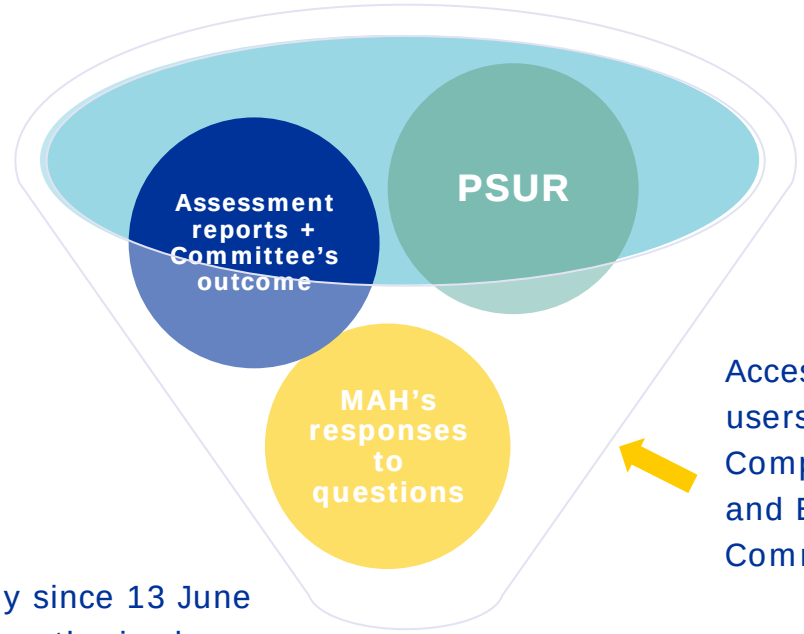
List of **active substances (AS)** and **combinations of AS authorised in EU** for which a PSUR shall be submitted (does not include Art 58 products)

Active substances and combinations of active substances	European Union reference date (EURD)	PSUR Submission Frequency	DLP	Submission date	Next DLP	Next Submission date	Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended? Yes/No	Publication Date	Notes	Procedure number of the PSUR single assessment (DLP)	Procedure number of the PSUR single assessment procedure (Next DLP)	PRAC representative of the PSUR single assessment procedure	(Lead) Member State of the PSUR single assessment procedure	CAP	NAP
(18)Fludeoxyglucose	14/11/1994	3 years	30/11/2017	28/02/2018			No	31/07/2015	PRAC Rapporteur name was amended on 23/07/2018 PRAC Rapporteur name updated on 07/04/2016 PRAC Rapporteur name updated on 04/02/2016 Lead MS was added on 22/12/2014	PSUSA/00001437/201711		Claire Férard	France		NAP
1,3-butanediol / cinchocaine hydrochloride / dexamethasone	23/09/1983	13 years	15/05/2025	13/08/2025			No	01/10/2012		PSUSA/00000753/202505					NAP
125I-human serum albumin	15/12/1988	13 years	15/12/2025	15/03/2026			No	01/10/2012		PSUSA/00000003/202512					NAP
131I-6-iodo-norcholesterol	21/06/1990	13 years	21/06/2025	19/09/2025			No	01/10/2012		PSUSA/00000004/202506					NAP
14C-urea	14/08/1997	5 years	15/07/2019	15/04/2019			No	01/10/2012	PRAC Rapporteur name updated on 12/05/2015	PSUSA/00000006/201801		Jan Neuhauser	Austria	CAP	
1-propanol / 2-propanol / 2-biphenylol	23/10/1980	5 years	23/10/2019	21/01/2020			No	27/11/2015	New substance added on 27/11/2015	PSUSA/00010409/201910					NAP
1-propanol / 2-propanol / lactic acid	07/09/1981	5 years	07/09/2019	06/12/2019			No	27/11/2015	Procedure number was corrected on 18/11/2015 New substance added on 27/11/2015	PSUSA/00010414/201909					NAP

- Contain the EURD, PSUR submission frequency, DLP, submission date …
- The frequency of PSURs submission for the same AS and combination of AS is harmonised
- The management and assessment of PSURs within the EU is optimised
- The predictability of PSURs submission is increased
- The list is updated monthly

PSUR repository

(Common storage)



Accessible by authorised users (EMA, National Competent Authorities (NCA) and EMA's scientific Committee Members)

The use of the repository is mandatory since 13 June 2016 for both centrally and nationally authorised medicines.

PSUR single assessment (PSUSA) process

Single evaluation of PSURs of medicines containing the **same AS** or **same combination of AS**

Assessment by PRAC Rapporteur (CAP or CAP/NAP) or Lead Member State (NAP only)

Adoption of outcome: Maintenance, variation, suspension, revocation of marketing authorisation(s)

Timelines: 120 days (PRAC assessment) (+ 14 days CHMP/CMDh + 67 days of EC decision making process)

CAP: centrally authorised product
NAP: Nationally authorised product

Scope of the PSUSA

Evaluation of new or emerging information on the **risks**

Evaluation of any new **efficacy / effectiveness** information

Gain **cumulative knowledge** on the product while retaining a **focus on new information**

Conduct an **integrated benefit-risk evaluation** for approved indications

Outcomes of PSUSA are published on:

European Public Assessment Report (EPAR) (centrally authorised medicinal products)

Community Register (for centrally and nationally authorised products)

EMA web page under 'Home/Find medicine/Human medicines/Periodic safety update report single assessments' (for nationally authorised products)

Continued improvement of PSUR single assessment

PSUR Road map activities:

- Identifying key issues encountered by Industry and Regulators in the preparation of PSURS, sharing Best Practice on ways to address these key issues to achieve a common understanding of the quality standards needed to facilitate the EU PSUR single assessment
- Explanatory note to GVP module VII
- PSUR Q&A for assessors

Useful links

Guideline on good pharmacovigilance practices Module VII – Periodic safety update report
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142468.pdf

Periodic safety update reports – EMA webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp&mid=WC0b01ac058066f910

Periodic safety update reports: questions and answers
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000041.jsp&mid=WC0b01ac0580023e7d

EURD list - Introductory cover note
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133157.pdf

Thank you, any questions?

Further information

Contact me at Gaelle.Bec@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Abbreviations

AS: Active substance

CAP: Centrally Authorised Product

CHMP: Committee for Medicinal Products for Human Use

DLP: Data Lock Point

EC: European Commission

EMA: European Medicines Agency

EPAR: European Public Assessment Report

EU: European Union

EURD : European Union Reference Date

GVP: Good Pharmacovigilance Practices

MA: Marketing Authorisation

MAH: Marketing Authorisation Holder

MS: Member State

NAP: Nationally Authorised Product

NCA: National Competent Authority

PSUR: Periodic Safety Update Report

PSUSA: PSUR single assessment