AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Signal management & Eudravigilance

Laura Sottosanti

10/07/2018

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Laura Sottosanti, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

Learning objectives

By the end of this session you should have a general understanding of the:

1. Signal definition
2. GVP module IX and signal process
3. Roles and responsibilities within the EU signal management process
4. Signal management in AIFA
5. Standalone signal notification
6. Emerging Safety Issue
7. Eudravigilance (EV) and Eudravigilance Access Policy
8. Use of EV data and eRMR (electronic Reaction Monitoring Report)

- # Guidance and Legal Requirements

- Commission Implementing Regulation (EU) No 520/2012
- Directive 2010/84/EU
- Good Pharmacovigilance Practices Module IX revision 1
- Addendum of GVP IX with new methodology for Signal detection
- Guideline on screening ADRs in EudraVigilance
- User Manuals on how to use the tool in signal detection (EMA, NCAs, MAH)
- EMA Question & Answers on Signal Management

What's a Signal?

- **Signal** is an 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 event, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Report of the Council for International Organisations of Medical Sciences WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010).

Signals

Signals are generated from several sources, such as spontaneous reports of suspected adverse reactions, clinical studies and the scientific literature.

The evaluation of safety signals is a routine activity within pharmacovigilance to establish whether or not there is a causal relationship between the medicine and the reported adverse event. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary.

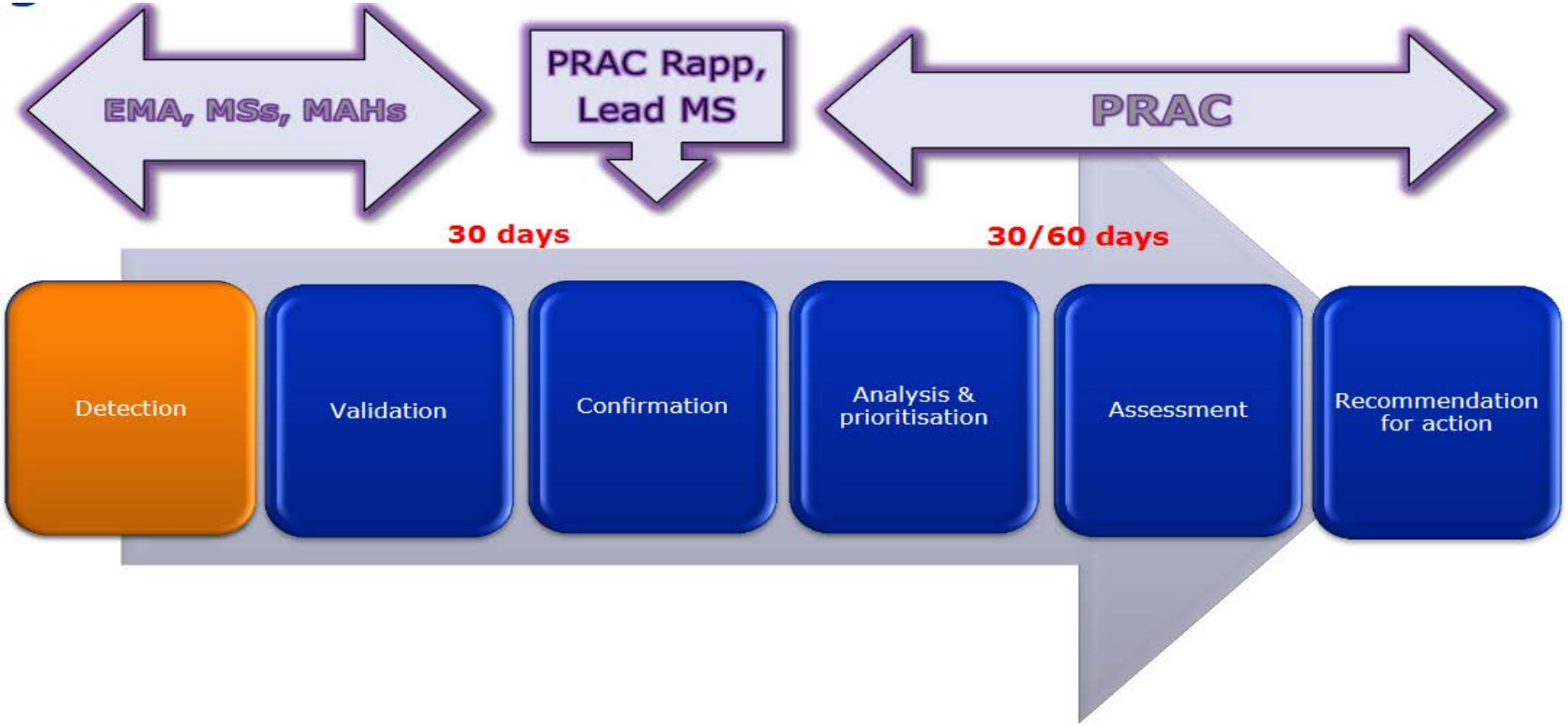
**EMA's Annual Report 2015*

Signal Management Process

- A set of activities performed to determine whether, based on an examination of
  - individual case safety reports (ICSRs),
  - aggregated data from active surveillance systems or studies,
  - scientific literature information
  - or other data sources,
- there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

Signal Management Process

- The EU signal management process includes the following activities:



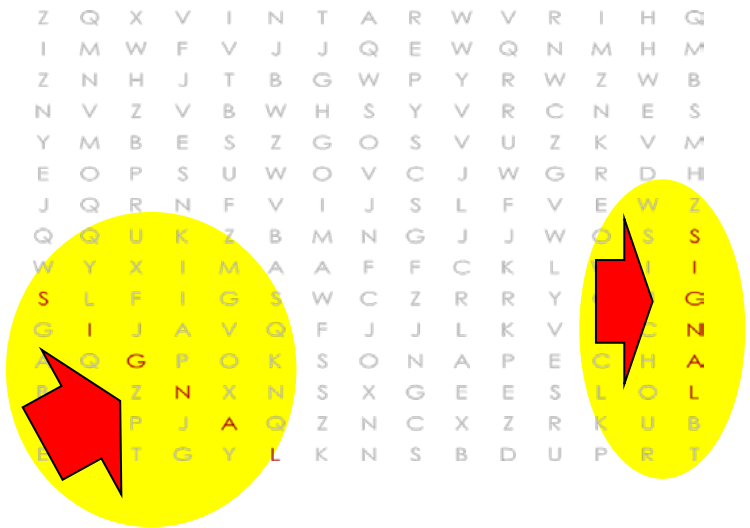
Signal detection

The act of looking for and/or identifying signals using data from any source

Detection of safety signals may be performed based on:

- from statistical analyses in large databases,
- a review of *individual case safety reports (*ICSRs),
- or from a combination of both.

Detection of signals by monitoring new and historical data in EudraVilance



Statistical criteria to generate a signal

Thresholds defining a signal of disproportionate reporting (SDR) in EudraVigilance

Implemented recommendation in EudraVigilance

The following criteria are applied in the EV system (eRMR and EVDAS) to define an SDR:

- The lower bound of the 95% confidence interval greater than one;
- The number of individual cases greater than or equal to

  3 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS);

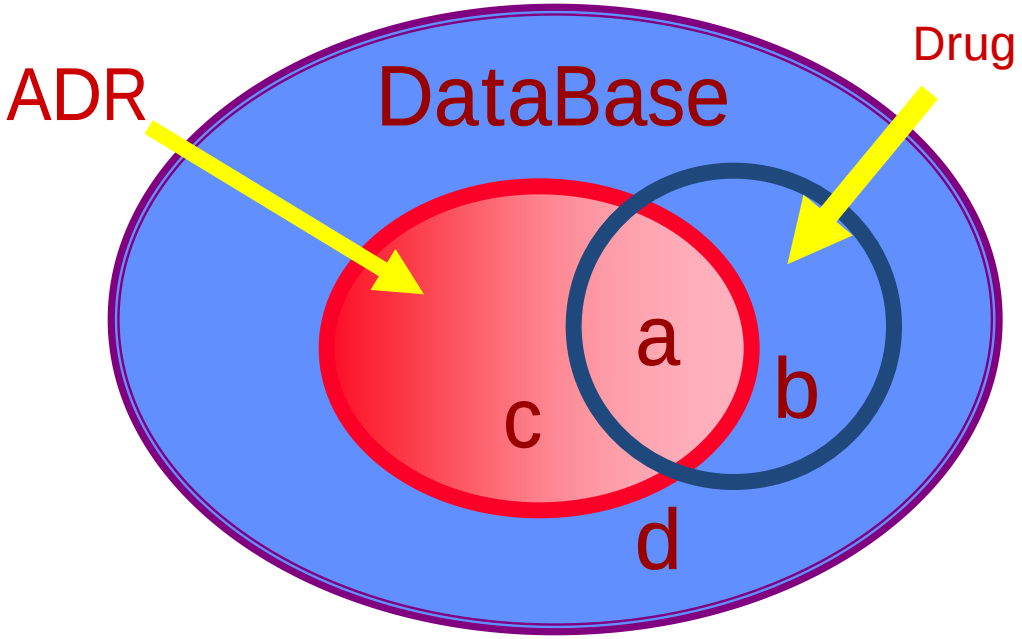
  5 for the other active substances;
- The event belongs to the IME list.

European Medicines Agency
Evaluation of Medicines for Human Use

- ROR(-) $\geq$ 1
- At least 3 cases (AM) or 5 cases (RM)

PRR and ROR

The PRR is defined as the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for all drugs in the comparison group (relative to all adverse events for drugs in the comparison group)



	ADR Sospetta	Altre ADR
Farmaco sospetto	a	b
Altri farmaci	c	d

Proportional Reporting Ratio (PRR)

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

Reporting Odds Ratio (ROR)

$$ROR = \frac{a/b}{c/d} = \frac{a*d}{c*b}$$

An example

	ADR1	Other ADRs	Tot
Farmaco-A	15	85	100
Other Drugs	5000	95000	100000
Totale	5015	95085	100100

	ADR Sospetta	Altre ADR
Farmaco sospetto	a	b
Altri farmaci	c	d

ROR= (15*95000)/(5000*85) = 3,3

Proportional Reporting Ratio (PRR)

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

Reporting Odds Ratio (ROR)

$$ROR = \frac{a/b}{c/d} = \frac{a*d}{c*b}$$

Signal validation

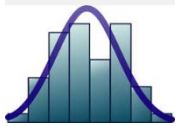
- The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal

- This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association

Evidence Based Methods

Clinical

Statistical



- **Biological plausibility**
- **Dechallenge / Rechallenge (+/-)**
- **Time to Onset: temporal association**
- **Confounders: co-suspected / concomitant drugs**
- **Underlying disease**

Review of individual case safety reports should consider

- strength of evidence for a causal effect (e.g. number of reports after exclusion of duplicates and inadequately documented cases),
- temporal association,
- plausible mechanism,
- de/re-challenge (the clinical outcome in relation to drug continuation or discontinuation),
- alternative explanation/confounders;
- the patient's demographics (e.g. age and sex), Reactions occurring in special populations
- the suspected medicinal product (e.g. dose administered) and adverse reaction (e.g. signs and symptoms),
- the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship
- Seriousness and severity of the reaction and its outcome;
- novelty of the reaction (e.g. new and serious adverse reactions);
- Drug-drug interaction
- exposure

Review of individual case safety reports should consider

...And also

- information is already included in the SmPC or patient leaflet;
- the association has already been assessed in the PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure
- literature findings regarding similar cases
- experimental findings or biological mechanisms

The detection of signals shall be based on a multidisciplinary approach

Guideline on good pharmacovigilance practices (GVP)

Module IX – Signal management

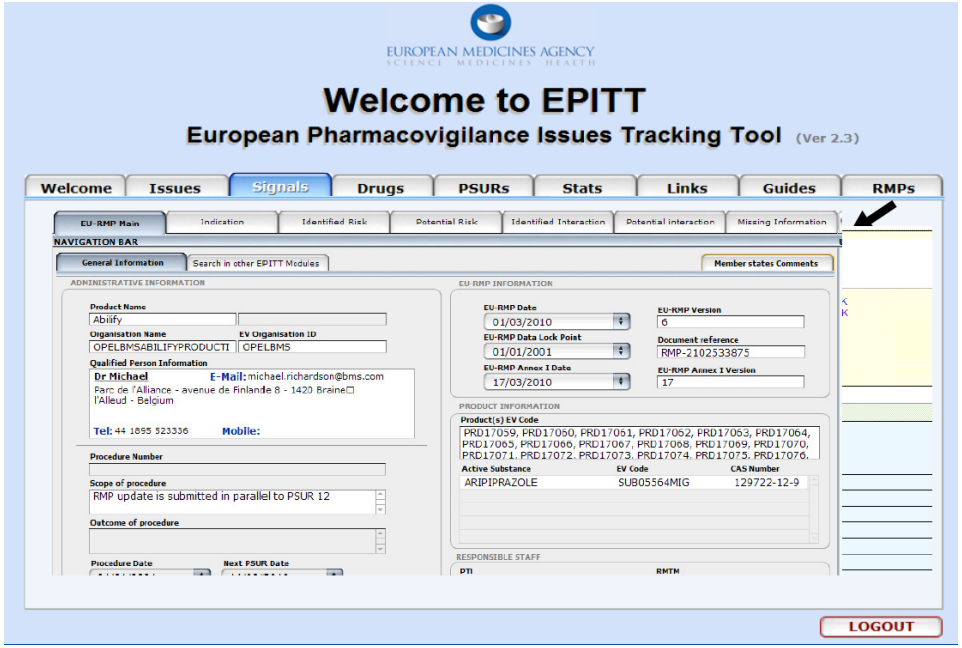
Signal validation

- Validated signal: A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

- Non-validated signal: A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted.

Tracking

All signals validated should be recorded and tracked systematically for each step: detection, validation, confirmation, prioritisation, assessment, timelines, decisions, actions, etc..



Signal confirmation

- The process during which the competent authority of a Member State (where the signal concerns a medicinal product authorised in accordance with DIR), or the Rapporteur appointed by the Pharmacovigilance Risk Assessment Committee (PRAC) (where the signal concerns a product authorised in accordance with REG), decides whether or not a validated signal should be analysed and prioritised by the PRAC.

- This should be done within 30 days from receipt of the validated signal.

- Signal confirmation is not intended to be a full assessment of the signal. The fact that a signal is confirmed does not imply that a causal relationship has been established, but that the signal should be discussed at EU level and further investigated by PRAC

Signal analysis and prioritisation by the PRAC

- The process by which the PRAC determines whether a confirmed signal requires further evaluation, and if required, to what timeframe and in which procedural framework.

- This is based on an initial analysis of the potential impact of the signal on patient and public health and the risk-benefit balance of the concerned medicinal product(s)

Signal analysis and prioritisation by the PRAC

When prioritising signals, the PRAC may take into account several factors, including:

- any potential impact on the benefit-risk profile of the product,
- strength of evidence supporting a causal association,
- severity and seriousness of the reaction
- estimated frequency of occurrence,
- preventability, the consequences of discontinuing treatment
- the availability of alternative therapeutic options,
- extent of utilisation of the medicinal product in the general population or in particular patient groups,
- complexity of the issue
- the expected volume of data.

Signal analysis and prioritisation

- A key element of the signal management process is to promptly identify signals with important public health impact or that may affect the benefit-risk balance of the medicinal product in treated patients.

- Which signals require urgent attention and need to be evaluated without delay.

Signal analysis and prioritisation by the PRAC

- When the PRAC requests additional data from MAHs, these timelines usually encompass 2 months for submission of responses by the MAHs and 60 days for assessment by the PRAC.

- However where appropriate, shorter or longer timelines may apply.

Signal assessment by the PRAC

- Following PRAC initial analysis and prioritisation, the process of evaluating all available data relevant to a signal to determine the need for any regulatory action

PRAC recommendations for action

- No need for further evaluation or action at this point in time
- Request for additional data to be submitted:
  - Monitor any relevant emerging information on the signal as it becomes available
  - Address the signal in the following PSUR or submit an ad-hoc PSUR
  - Submit additional data (such as cumulative review)
  - Collect further information or perform additional analyses in EudraVigilance or other data sources
  - Conduct a post-authorisation safety study
- Need for regulatory action:
  - The product information and/or RMP should be updated through a variation
  - The Member States or the Commission, should initiate a referral procedure
  - Urgent safety restrictions should be imposed
- A Pharmacovigilance inspection should take place

PRAC recommendations for update PI

PRAC recommendations for update of the product information following assessment of a signal usually include the wording to be implemented in the summary of product characteristics (SmPC) and/or package leaflet (PL) as well as the timeline for submission of the variation

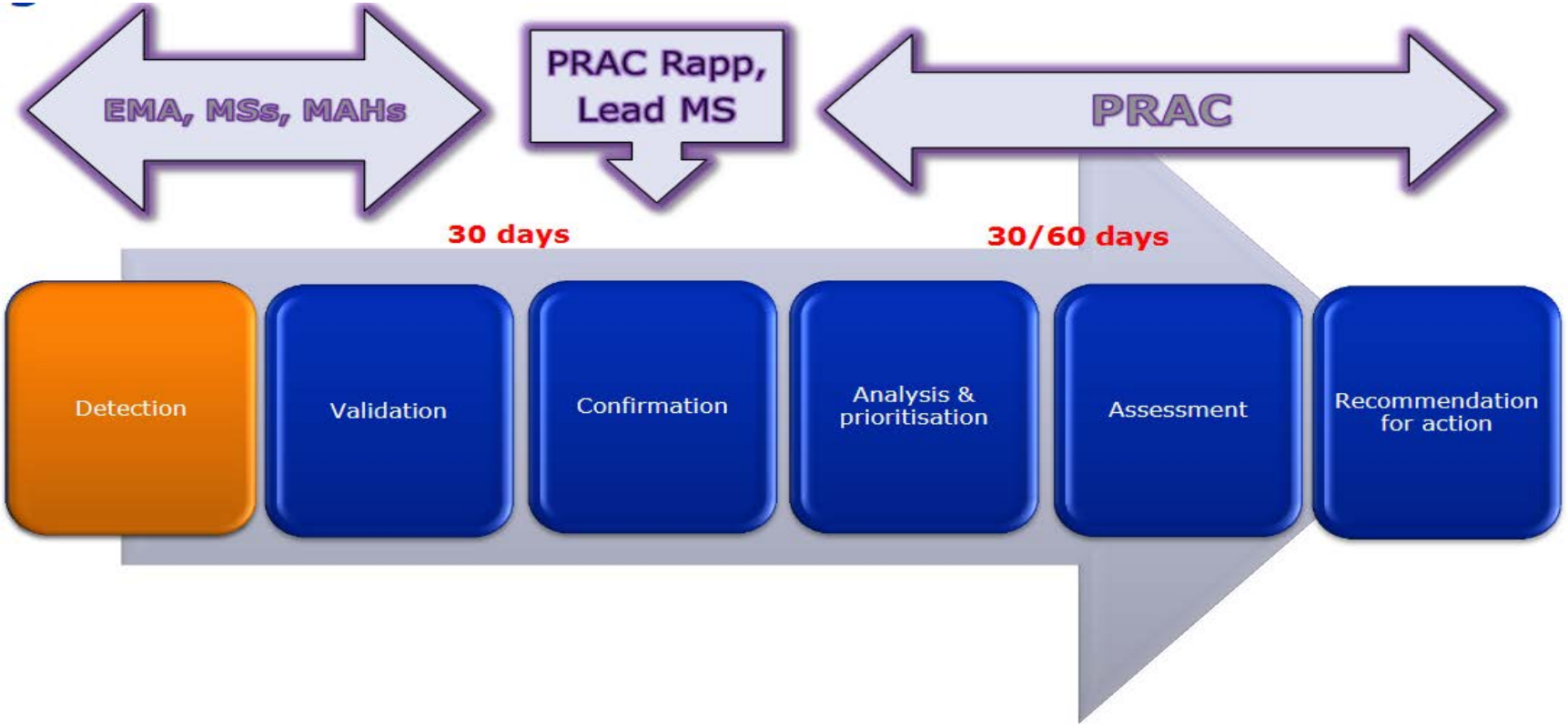
The implementation of the published wording and translations can generally be handled through a type IA^{IN} variation.

PRAC recommendations to update the product information are applicable to all medicinal products containing the concerned substance, unless otherwise specified

MAHs are expected to submit the requested variation according to the timeline specified in the PRAC recommendation. This timeline is calculated from the date of publication of the PRAC recommendation. For instance, recommendations for update of the product information adopted by PRAC in September 2014 were expected to be submitted within 1 or 2 months of 30 September 2014 (publication date), as applicable.

Signal Management Process

- The EU signal management process includes the following activities:



Roles and responsibilities within the EU signal management process

The continuous monitoring of EudraVigilance is a legal requirement in the EU

All Member States shall be responsible for monitoring the data in the EudraVigilance database

Within the EU regulatory network, the Agency takes the lead for EudraVigilance monitoring, signal detection and signal validation for active substances contained in at least one centrally authorised product. Signals validated by the Agency should be confirmed (or not) by the PRAC rapporteur for the concerned centrally authorised product.

For active substances only contained in nationally authorised products, Member States take the lead (Lead Member State) for EudraVigilance monitoring, signal detection, validation and confirmation.

Roles and responsibilities within the EU signal management process

- Lead Member State for signal management: The Member State responsible for monitoring the EudraVigilance database for an active substance or combination of active substances contained in medicinal products authorised in more than one Member State through the national, mutual recognition or decentralised procedures. The lead Member State shall validate and confirm signals on behalf of the other Member States

- If the active substance is authorised in only one Member State, that Member State automatically assumes the responsibilities of the Lead Member State.

Roles and responsibilities within the EU signal management process

- PRAC Rapporteur: Rapporteur appointed by the PRAC in the context of the centralised procedure. Within the EU signal management process, the PRAC Rapporteur is responsible for the confirmation of signals concerning centrally authorised medicinal products.

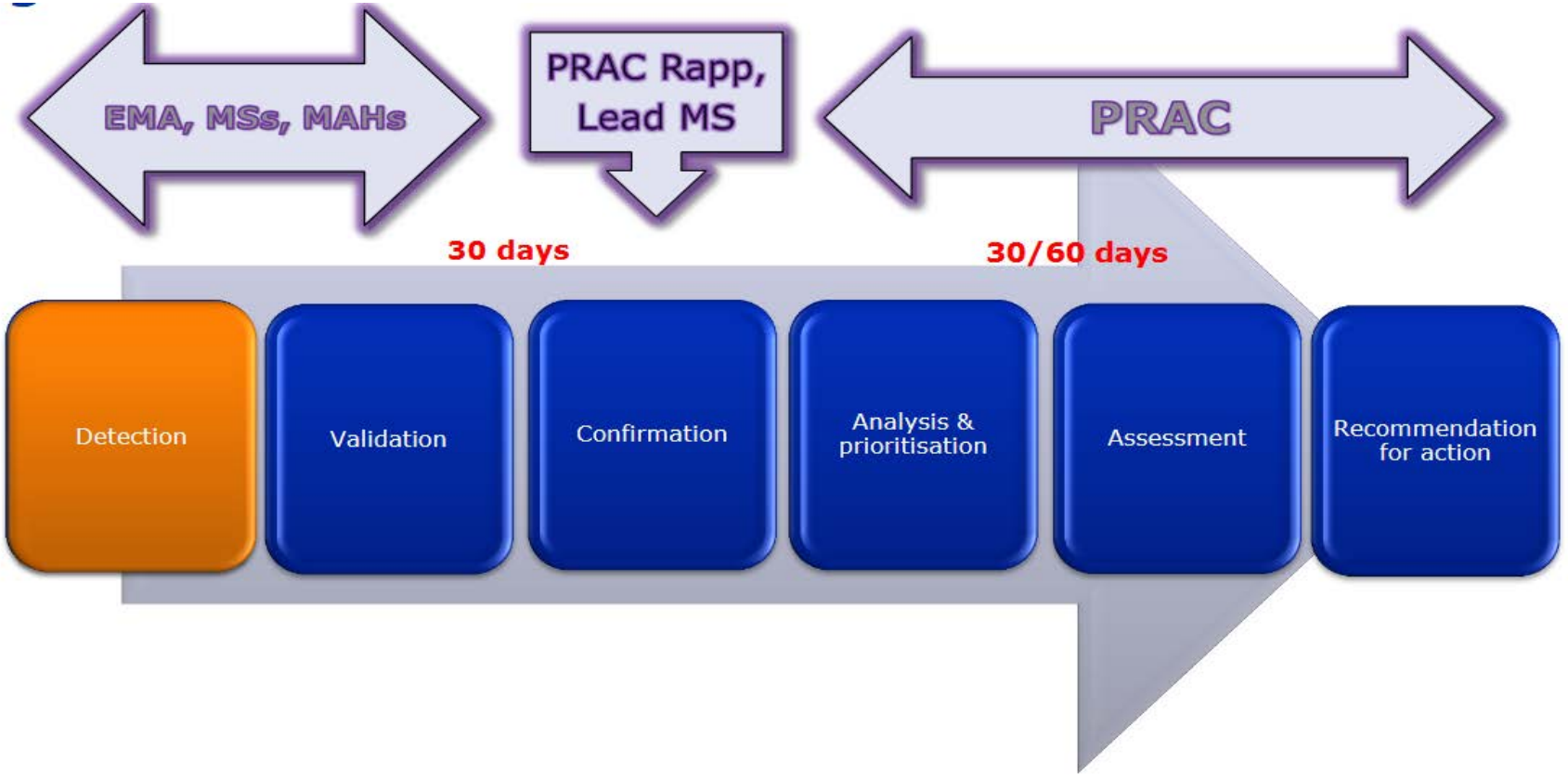
- Signal confirmation by the PRAC Rapporteur or (lead) Member State: The process of deciding whether or not a validated signal entered in the European Pharmacovigilance Issues Tracking Tool (EPITT) requires further analysis and prioritisation by the PRAC.

  This should be done by the PRAC Rapporteur or the (lead) Member State within 30 days from receipt of the validated signal.

Roles and responsibilities within the EU signal management process

	MAH (their products)	Agency (for CAPs)	Lead MS State (allocated NAPs)	PRAC rapporteur of CAP	Member States (unallocated NAPs)	PRAC and rapporteur appointed to assess the signal (for CAPs and NAPs)
EudraVigilance monitoring, signal detection, validation	✓	✓	✓		✓	
Signal confirmation			✓	✓	✓	
Signal analysis and prioritisation, assessment, recommendation						✓

European signal process



ABSENCE OF EVIDENCE IS NOT EVIDENCE OF ABSENCE

If no signal is produced at the end of the analysis it is not possible to tell whether this is because the signal does not exist or because insufficient data are being analysed

Signal Management by MAHs

Commission Implementing Regulation (EU) No 520/2012 (article 18) requires EMA, national competent authorities and marketing authorisation holders (MAHs) to continuously monitor the data available in EudraVigilance.

22 February 2018

Signal Detection in EVDAS by MAH: Transitional arrangements for MAHs

- Pilot period of 1year
- MAHs of the active substances included in the additional monitoring list
- Three-month 'grace period‘ to familiarise

Monitoring EV – Signal Management

- All other MAHs also have access to EudraVigilance data and can integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EudraVigilance and inform the regulatory authorities of validated signals.

- After one year, EMA will base the next phase of implementation on experience gained through the pilot.

- It also requires MAHs to inform EMA and national competent authorities of validated signals detected when monitoring the database.

Standalone signal notification

Within 30 days of receipt of a signal validated by the Agency or a Member State, or a standalone signal notification from a marketing authorisation holder, the PRAC rapporteur or (lead) Member State, as applicable, should confirm or not the signal.

Emerging Safety Issue

- A safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

- An ESI is in addition to the ICSR submission requirements, when the emerging safety issue refers to a single case of suspected adverse reactions

Emerging Safety Issue

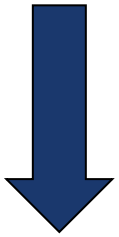
- When the MAH in the EU becomes aware of an emerging safety issue from any source, they should notify it in writing to the competent authority(ies) of Member State(s) where the medicinal product is authorised and to the Agency to the mailbox P-PV-emerging-safety-issue@ema.europa.eu".

- This should be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

- For AIFA: esi@aifa.gov.it

Emerging Safety Issue

MAHs



as soon as possible and no later than 3 working days

- Agency to the mailbox
  P-PV-emerging-safety-issue@ema.europa.eu

- Competent authority(ies) of MSs where the medicinal product is authorised

  (AIFA to the mailbox esi@aifa.gov.it)

Emerging Safety Issue

- When notifying an emerging safety issue, the marketing authorisation holder should describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and should provide any relevant documentation available at the time of initial notification.

- Upon being notified of an emerging safety issue, the national competent authorities and/or the Agency as appropriate should promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised. This may involve the consultation of the Incident Review Network, if warranted

Emerging Safety Issue and possible actions

Should the MAH decide as a result of the emerging safety issue to take any of the following actions:

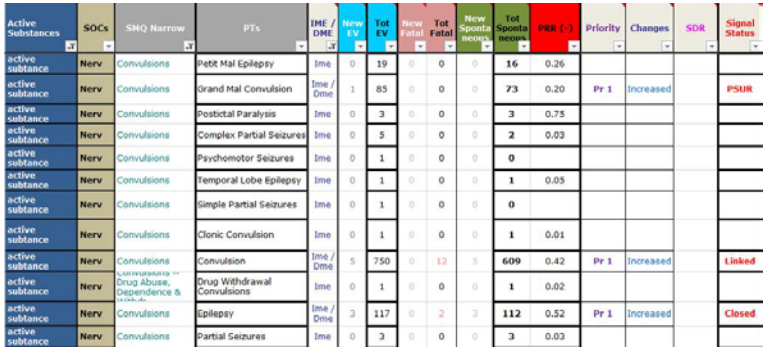
- temporary or permanent cessation or suspension of marketing of a medicinal product,
- withdrawal of a medicinal product from the market,
- request for the withdrawal of a marketing authorisation
- or non-application for the renewal of a marketing authorisation,

Signals

The safety information contained in EudraVigilance is continuously screened using statistical reports called electronic Reaction Monitoring Reports (eRMRs). In 2017, a total of 21,496 such outputs were produced and provided to the EU network for review.

- NAP: Lead member State
- CAP: EMA & PRAC Rapporteur (of 2,062 potential signals which were reviewed by the Agency in 2017, around 82% originated from EudraVigilance, highlighting its central role for ADR data monitoring).

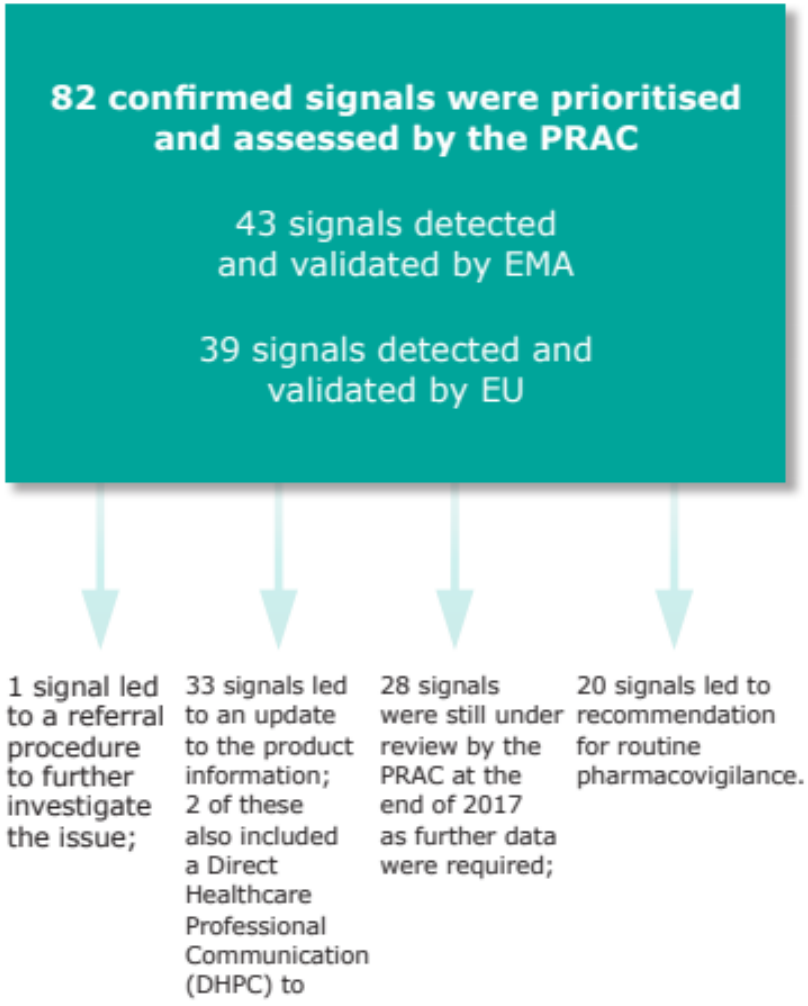
electronic
Reaction Monitoring Reports
(eRMR)



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 [illegible] Drug Abuse, Dependence & [illegible]	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				

Signals

In 2017, the PRAC assessed 82 signals of new or changing safety issues and about two thirds of these were detected in full or part from EudraVigilance.



eRMR

- The eRMR is a tool to perform signal detection in EV.
- This tool provides aggregated data related to the ICSRs submitted to EudraVigilance stratified by different parameters and incorporates the Reporting Odds Ratio (ROR) as a statistical measure.
- Valid cases transmitted to the EVPM module only (ICSRs transmitted retrospectively to EVPM)
- Identified duplicates are excluded by default

eRMR for screening EudraVigilance
Tools Used in Signal Detection

Electronic Reaction Monitoring Report (eRMR) is a formatted Excel file used as a tool for monitoring the safety of drug use, facilitating prioritisation, detection, evaluation and documentation of suspected adverse drug reactions (ADR) in EudraVigilance EV

- Manage the workload
- Early identification of very serious ADRs

eRMR – structure and content

eRMR

Active Substances	SOCs	HLGTs	HLTs	SMQ Narrow	PTs
Active substance	Renal	Renal Disorders (Excl Nephropathies)	Renal Disorders Nec		Renal Disorder

Active Substances	SOCs	HLGTs	HLTs	SMQ Narrow	PTs	IME / DME

Active Substance	SOC	PT	IME/DME	SDR All	Changes
Substance1	Gastr	Abdominal Discomfort			Increased
Substance1	Gastr	Abdominal Mass			
Substance1	Infec	Abdominal Sepsis			

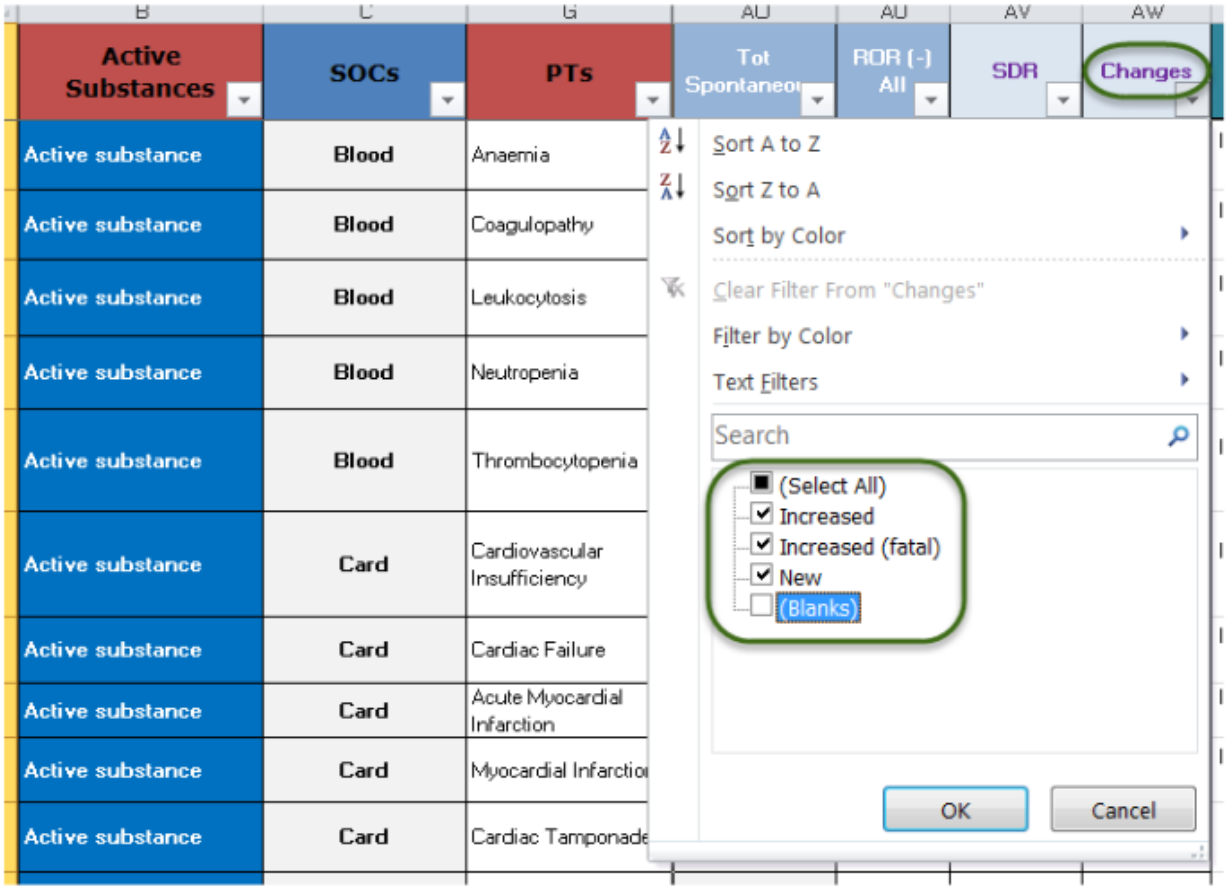
Sort A to Z
Sort Z to A
Sort by Color
Clear Filter From "SDR All"
Filter by Color
Text Filters

New EVPM	To EV
0	1
0	1
0	2
0	3
0	1

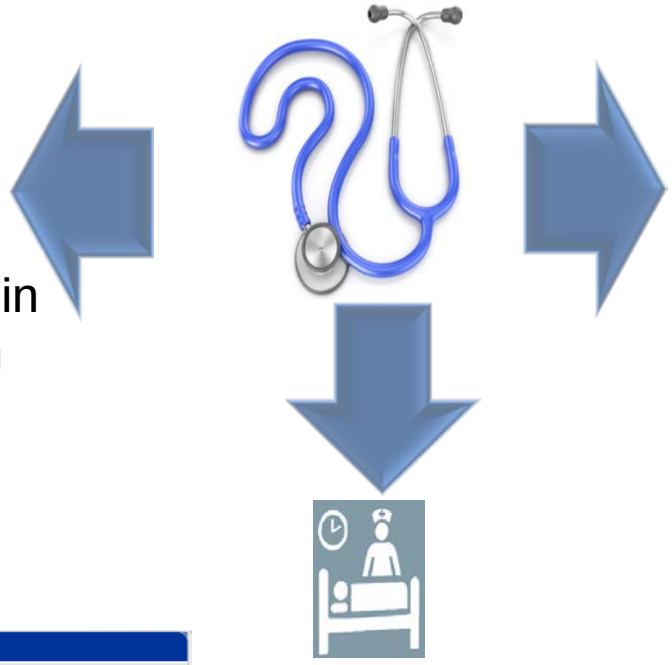
Tot Spont Europe	Tot Spont N America	Tot Spont Japan	Tot Spont Asia	Tot Spont Rest	Tot Spont	ROR (-) Europe	ROR (-) N America	ROR (-) Japan	ROR (-) Asia	ROR (-) Rest	ROR (-) All
15	19	4	2	3	44	1.2476	1.641375	0.5342	0.62163	0.69038	1.47041
0	1	0	0	0	1		0.729339				0.21484
1	0	0	0	0	1	1.5412					0.76376
0	3	0	1	0	5		1.6717		0.53986		0.98992

How to select the eRMR

- Column “Changes”: to display only the DECs received during the period of interest, in the column ‘Changes’ filter out the ‘Blanks’ option:



Clinical Methods



Designated Medical Events (DMEs)

- Events known to arise in causal association with medicinal products

Targeted Medical events (TMEs)

- The TMEs are ADRs more frequently associated with a more serious outcome in children

Designated Medical Event (DME) List		
Acute hepatic failure	Dermatitis exfoliative generalised	Pancreatitis acute
Acute kidney injury	Drug reaction with eosinophilia and systemic symptoms	Pancytopenia
Agranulocytosis	Drug-induced liver injury	Product contamination microbial
Anaphylactic reaction	Erythema multiforme	Progressive multifocal eukoencephalopathy
Anaphylactic shock	Febrile neutropenia	Pulmonary arterial hypertension
Anaphylactoid reaction	Granulocytopenia	Pulmonary fibrosis
Anaphylactoid shock	Haemolysis	Pulmonary hypertension
Angioedema	Haemolytic anaemia	Renal failure
Aplasia pure red cell	Hepatic failure	Reye's syndrome
Aplastic anaemia	Hepatic infarction	Rhabdomyolysis
Autoimmune haemolytic anaemia	Hepatic necrosis	Stevens-Johnson syndrome
Autoimmune hepatitis	Hepatitis fulminant	Sudden cardiac death
Autoimmune pancreatitis	Immune thrombocytopenic purpura	Sudden hearing loss

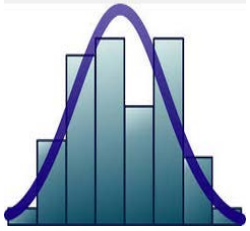
Fatal Events

1. Events reported with a fatal outcome
2. May have strong impact on public health

Paediatric Targeted Medical Events	
Cardiac arrest	Apnoea
Overdose	Drug Abuse
Drug ineffective	Neutropenia
Respiratory arrest	Haemorrhage intracranial
Dyspnoea	Pulmonary embolism
Brain oedema	Hypertension
Cardiac failure	Anaemia
Respiratory distress	Medication error
Off label use	Arrhythmia
Accidental overdose	Accidental exposure to product
Intentional overdose	Intentional product misuse
Pulmonary oedema	Renal Impairment
Pulmonary haemorrhage	Asthma
Septic shock	Drug interaction
Thrombocytopenia	Drug administration error

PRIORITISATION in the TOTAL Population

1. (DMEs)



2. SDR - IME (not DME) by subgroups

3. All remaining events with a fatal outcome

Flagging **Priorities**

- ❑ Priorities Total population
- ❑ Priorities Paediatrics
- ❑ Priorities Geriatrics

1.DME

Priority all

Active Substances	SOCs	SMQ Narrow	PTs	Priority Paed	Priority Geriatr	Priority All
Active Substances	Resp	Convulsions - - Gen-Conv-Seiz Following Immunisatio	Dyspnoea	1. TMEs		
Active Substances	Immun	Depress & Suicide/Self-Inj	Anaphilactic shock		2-IME SDR	1. DME
Active Substances	Immun		Transplant Rejection	2 - IME SDR		3. IME Fatal
Active Substances	Inj&p		Transplant Dysfunction			2-IME SDR
Active Substances	Blood	Haematopoietic Cytopenias	Leukopenia			

- Positive Re-challenge
- Literature Reports
- Most reported Route of Administration (RoA)
- Most reported Indicat. (HLGT)

Tot + RC	Tot Lit	Roa 1	Tot Roa (n/a)	Indic.1 (HLGT)	Tot Indic. (n/a)
0	5	Oral Use	18	Seizures (Incl Subtypes)	13
0	0	Oral Use	8	Seizures (Incl Subtypes)	1
1	33	Intravenous Use	34	Therapeutic Procedures And Supportive Care Nec	6
0	3	Intravenous Use	9	Therapeutic Procedures And Supportive Care Nec	5
8	3	Oral Use	55	Demyelinating Disorders	159

A M O M O

Rational

- No imposed prioritisation: they are a contributory factor in the assessment
- Enhanced visual presentation in the eRMR
- No statistical detection of risk related to AMOMO (no SDR) but view in conjunction with a potential ADR

AMOMO

Active Substances	PTs	New EV	Tot EV	New Abuse - Misuse - Over	Tot Abuse - Misuse - Over	New Med Err	Tot Med Err	New Occup Exp	Tot Occup Exp	AMOMO
Fingolimod	Abortion Spontaneous	3	155	1	5	0	0	0	0	+--
Fingolimod	Urinary Retention	5	111	0	1	0	3	1	1	---
Fingolimod	Neurogenic Bladder	2	60	0	1	0	1	0	0	---
Fingolimod	Renal Failure	1	34	0	2	1	10	0	0	-+-
Fingolimod	Angioedema	1	17	1	3	1	9	0	0	++-
Peginterferon Beta-1a	Pancytopenia	1	3	0	0	0	0	0	0	---

Most relevant columns of the eRMR which allow interaction with the Validators for tracking reviews and previous awareness.
The labels used to assigned the signal status are provided in a drop-list and in the legend worksheet.

Signal Status	Comments
Listed	*SmPC 4.8/4.4*
Linked	*Synonymous or related medical concept*
Validated	*Signal Entered in EPITT*
PSUR/RMP	*Signal Assessed in PSUR*
Disease	*Indication/Symptoms*
Other	*Review unlikely useful*
Closed	*Alternative explanations*
Ongoing	*Signal under review*
Monitor	*Signal under monitoring*
Check	*Case review warranted*

In AIFA 2 signal management processes in cooperation with Regional Pharmacovigilance Centers

**All national data*
(Rete Nazionale di FV)**

- For all substances
- Every 6 months

All Eudravigilance data

- Only on some substances (153 con IT LMS)
- 26 substances every month
- 69 substances every 3 months
- 58 substances every 6months

* The competent authority of each Member State shall be responsible for monitoring the data originating in the territory of that Member State

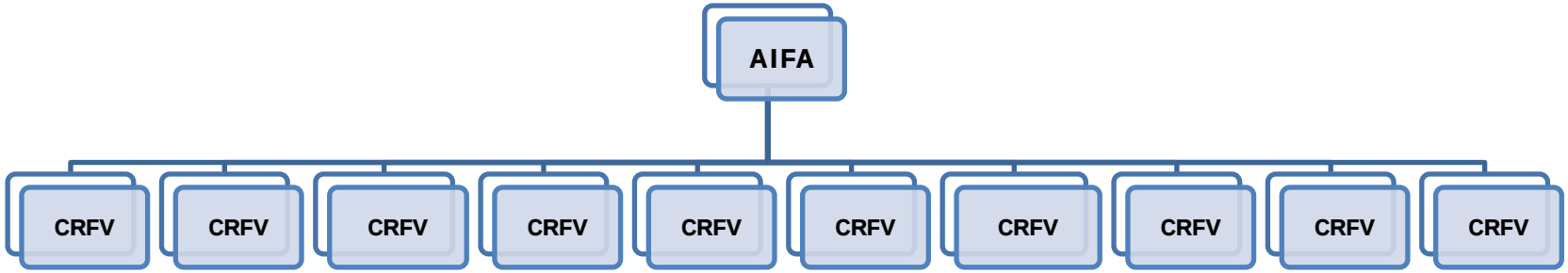
Signal Management Process and Quality System

We have two different Standard Operative Procedures

- SOP 067 - Gestione dei segnali dalla Rete Nazionale di Farmacovigilanza

- SOP 401 - Signal Management in Eudravigilance

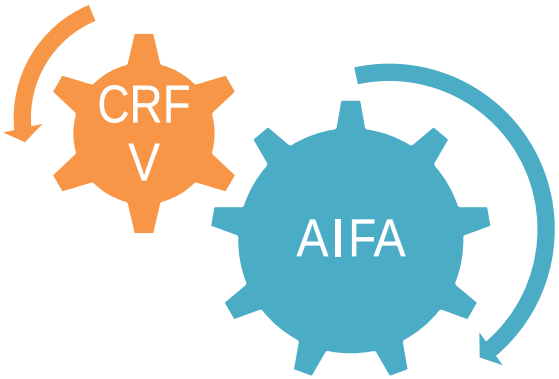
The activity of signal management in AIFA is carried out in collaboration with Regional Pharmacovigilance Centers



The activity is organized by category ATC

D.M. 30.04.2015 - Farmacovigilanza, procedure operative e soluzioni tecniche

Signal detection



Art. 31.

Identificazione del segnale

1. Nei confronti dei medicinali autorizzati ai sensi del presente decreto, l'AIFA, in collaborazione con l'EMA, adotta le seguenti misure:

a) monitora i risultati delle misure di minimizzazione del rischio previsti dai piani di gestione del rischio e delle condizioni di cui agli articoli 5 o 6 del presente decreto, o dell'art. 33 del decreto legislativo 24 aprile 2006, n. 219 e successive modificazioni;

b) valuta gli aggiornamenti del sistema di gestione del rischio;

c) monitora i dati della banca Eudravigilance per stabilire se vi siano rischi nuovi o che si sono modificati o se tali rischi abbiano un impatto sul rapporto rischio/beneficio.

2. L'AIFA per l'attività di identificazione del segnale su rischi nuovi o su rischi che si sono modificati e su modifiche del rapporto rischio/beneficio e per l'adozione delle misure di cui al comma 1, si avvale della collaborazione dei Centri regionali di farmacovigilanza in accordo con le linee guida di cui all'art. 15, comma 2.

Categoria ATC	CRFV
M - Musculoskeletal system B - Blood and blood forming organs	Lombardia - Piemonte
C - Cardiovascular system	E Romagna - Calabria - Puglia
J - Antiinfectives for systemic use S - Sensory organs V- Various ATC structures	Sicilia - Veneto
L - Antineoplastic and immunomodulating agents	Toscana - Lazio – Umbria – Abruzzo
A - Alimentary tract and metabolisma H - Systemic hormonal preparations, excluding reproductive hormones and insulins	Veneto - Friuli VG - PA Bolzano
N - Nervous system P - Antiparasitic products, insecticides and repellents	Campania - Molise - Sardegna
R - Respiratory system	Liguria - Valle D'Aosta
D - Dermatological drugs	Basilicata - Marche
G - Genitourinary system and reproductive hormones	Lazio – Umbria

Signal management process in AIFA

STEP 1 – the eRMR files are generated by EMA and saved in the European Medicines Agency Meeting documents system (MMD). One eRMR for each substance

STEP 2 – the eRMR files (with Italy as LMS) are downloaded by AIFA signal coordinator and saved in a common area of the Office

STEP 3 - the eRMR files are updated with the results of previous evaluations and forwarded by AIFA to all Regional PhV Centers (an e-mail is sent to CRFVs by the AIFA signal coordinator)

STEP 4 – the CRFV carry out the screening of eRMR following the priority and statistical criteria. In the eRMR the CRFV fill the “signal status field” with their evaluation and comments. At the end of this activity the CRFVs generate the files “comments” for each eRMR

Signal management process in AIFA

STEP 5 – The “comments “ containing the results of screening by the CRFV are sent to AIFA

STEP 6 – AIFA carry out the review of ICSRs in Eudravigilance for each drug-event combination flagged with “check” by CRFV.

STEP 7 – for potential signal the review of literatureit is requested to CRFV

STEP 8 - if the signal is validated, AIFA and CRFV cooperate to prepare the signal AR to upload in EPITT

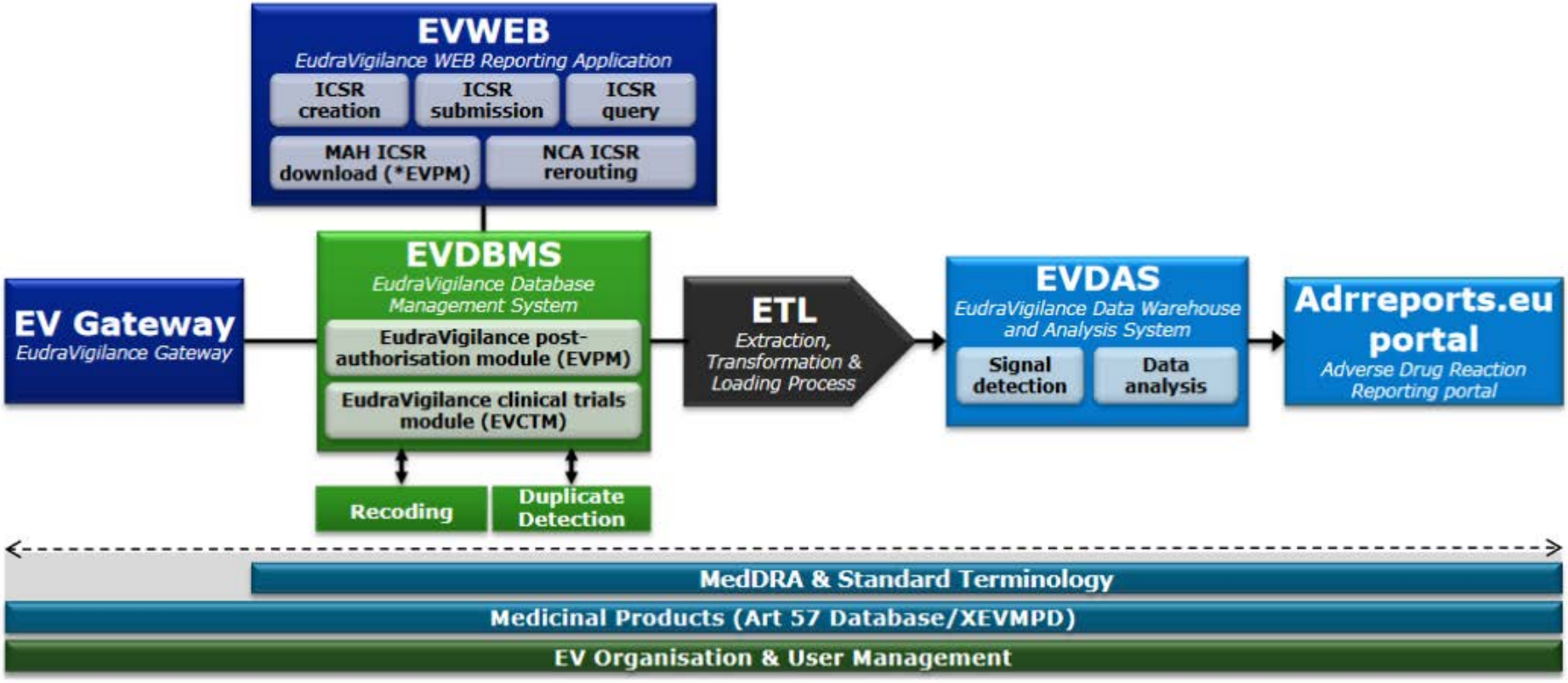
Signal management process in AIFA

- CRFV:
  - Screening eRMR (statistical criteria)
  - Literature review
  - Check RCP (ADR is listed or unlisted)
  - Review of cases in national database

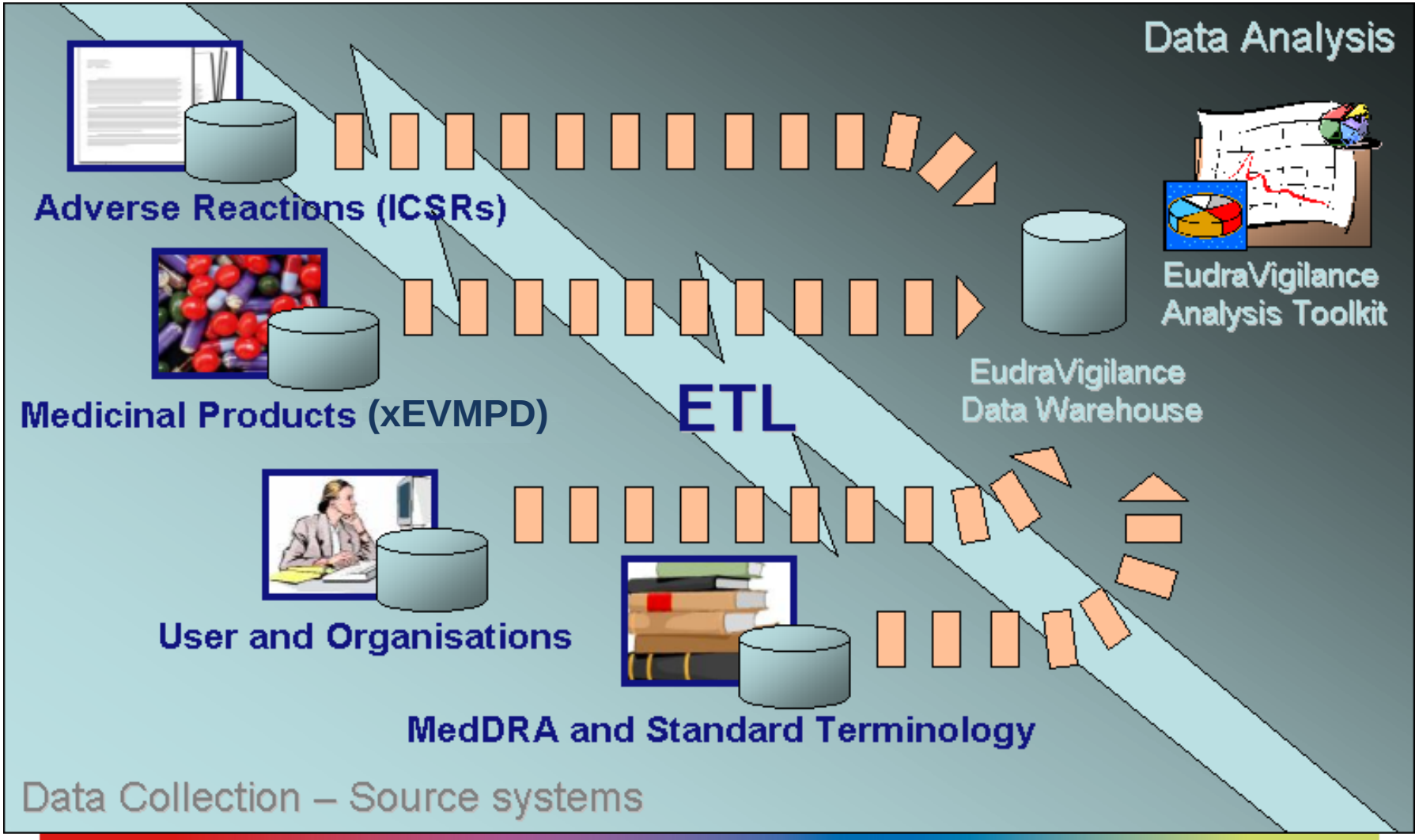
- AIFA:
  - Review of cases in Eudravigilance and signal validation

- AIFA + CRFV:
  - Signal Assessment Report (signal description (including recommended actions and summary of the relevant case narratives))

The new EudraVigilance System



Data Origins



Data Origins

The data stored in the EV Data Warehouse (EV DWH) carry the same information as the ones stored in the Source Systems.

There is a procedure called EudraVigilance ETL that:

- Extracts the data from the source systems,
- Transforms the data in order to structure the information in a way more useful to the data analysis, &
- Loads the re-structured data in the EV DWH

ETL process

The *extraction, transfer, and loading (ETL)* process is the means by which data are transferred from source systems and loaded into the EudraVigilance Data Warehouse. Specifically, the ETL process does the following:

- Stores information about the structure and contents of source systems and the Data Warehouse;
- Correlates the source systems structure and contents to the structure and contents of the Data Warehouse;
- Provides information to the data extraction tools that physically execute the transfer of data from source systems to the Data Warehouse.

!! The ETL process is performed NIGHTLY so that every day the EudraVigilance Data Warehouse is populated with data updated to the day before

The new and improved EudraVigilance to simplify reporting and data analysis

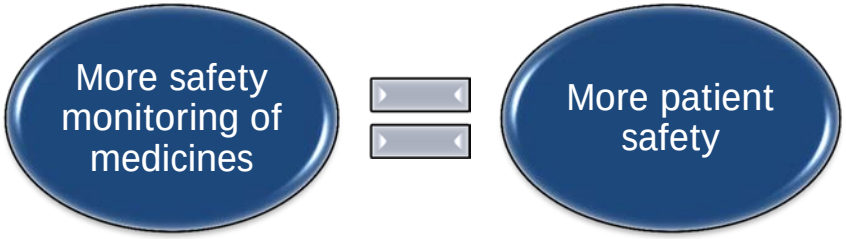
On 22 November 2017, EMA launched the new and improved version of EudraVigilance, the European database and analytical system that holds reports of suspected adverse reactions to human medicines that are authorised or being studied in clinical trials in the European Economic Area.

The enhancements and expected benefits of the new EudraVigilance are:

- simplifed reporting of ICSR and reduced duplication of efforts. Marketing authorisation holders now report directly to EudraVigilance rather than individual NCAs, who instead access the ICSRs from EudraVigilance;
- better detection of new or changing safety issues, enabling rapid action by regulators to protect public health;
- better searchability and more efficient data analysis based on the use of the ISO/ICH agreed standard for ICSRs and new query functions;

The enhancements and expected benefits of the new EudraVigilance are:

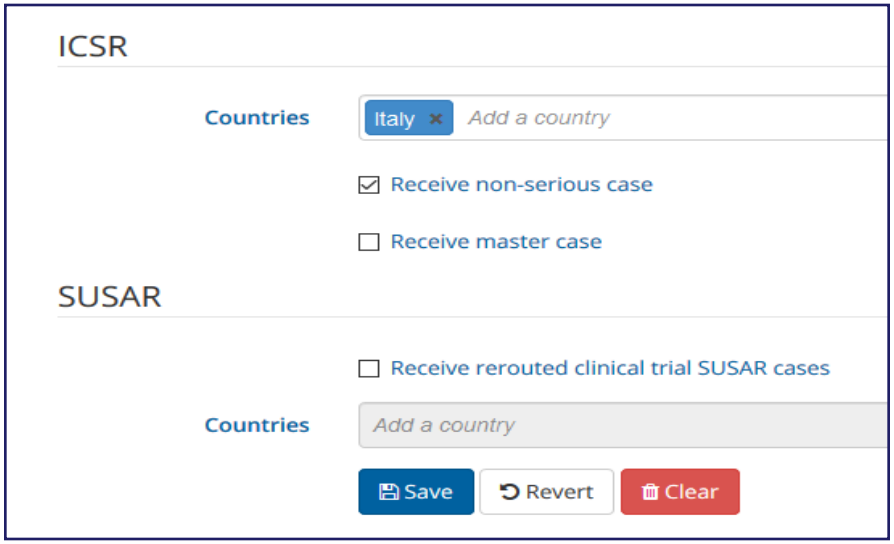
- increased system capacity to support large volumes of users and reports;
- greater transparency in safety monitoring and much greater access to data and information for patients and healthcare professionals (adrreports.eu);
- more efficient collaboration with the WHO, with EMA making all ICSRs originating in the EEA directly available from EudraVigilance to the WHO Uppsala Monitoring Centre (UMC).



Rerouting for NCAs

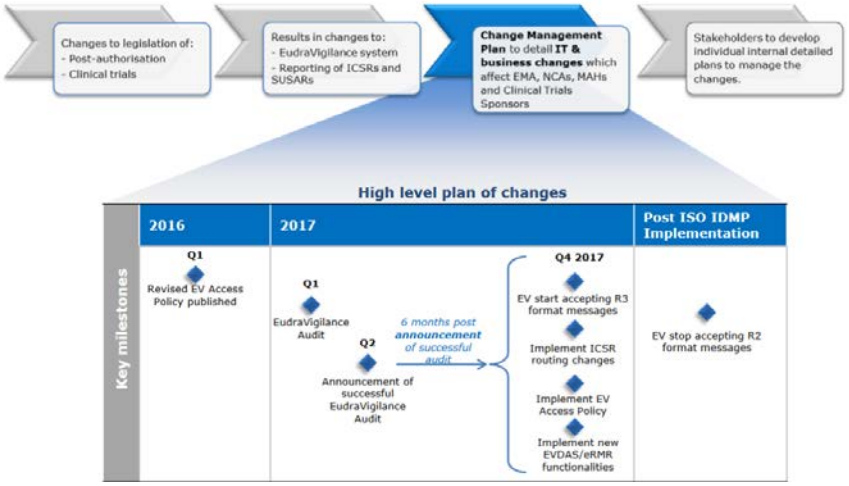
- NCAs are able to update the rerouting parameters at any time
- Automatic forwarding of ICSRs to the applicable NCA in a Member State
- ICH E2B(R3) format (ICSRs are rerouted in the format received i.e. no conversions between ICH E2B(R2) and ICH E2B(R3) is applied)

Rerouting parameters for Italy



Recoding process

- The rerouting of ICSRs with recoded medicinal product information will be put in place following implementation of the ISO IDMP terminologies



- The current recoding process is only for use by EMA.
- XEVMPD is used to support recoding of medicinal product information in ICSRs until ISO IDMP terminologies are available and implemented

Download for MAHs

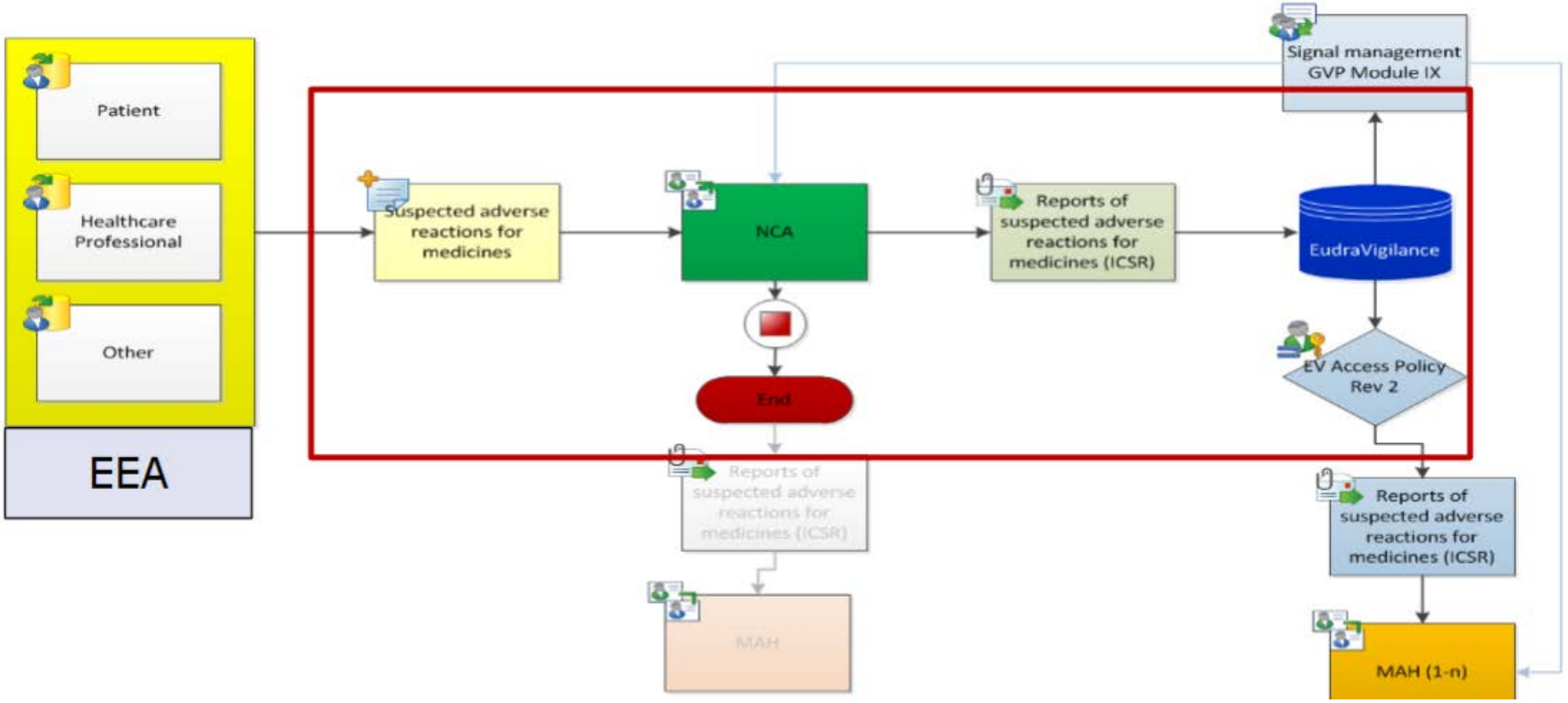
- MAHs no longer have to receive ICSRs directly from NCAs
- A download function is available to MAHs to obtain access to these ICSRs
- MAHs are able to download ICSRs for active substances of medicinal products, for which the MAHs hold a marketing authorisation in the EEA
- Access to ICSRs is based on the medicinal product information submitted by MAHs to the XEVMPD (Article 57 product submissions) (Access Level 2A of the revised EudraVigilance Access Policy)
- ICSRs are made available in ICH E2B(R3) format only

New Business Rules

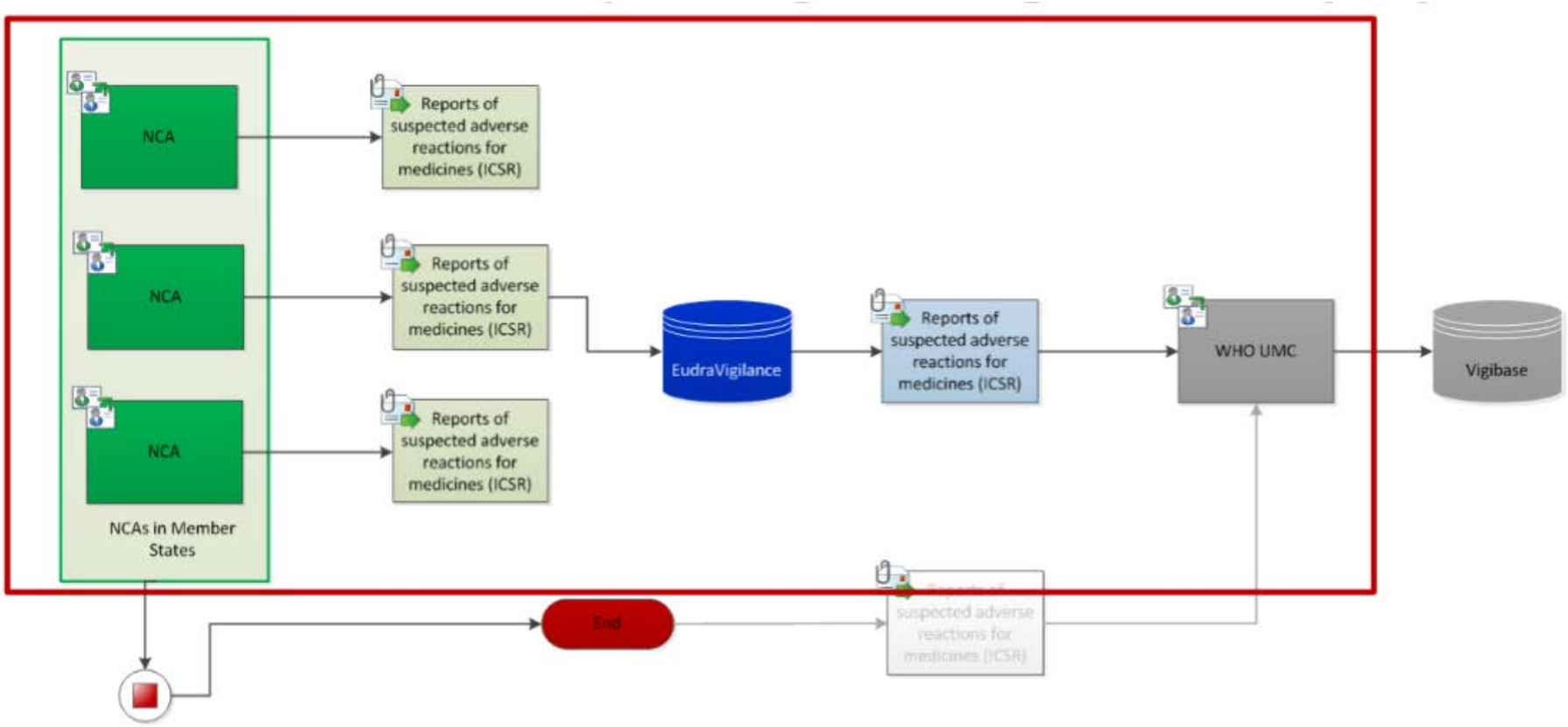
22 November 2017

- Eudravigilance Access Policy – Rev 2
- MAH access to the EV system
- GVP Module VI – Rev 2
- Simplified Electronic Reporting
- GVP Module IX – Rev 1

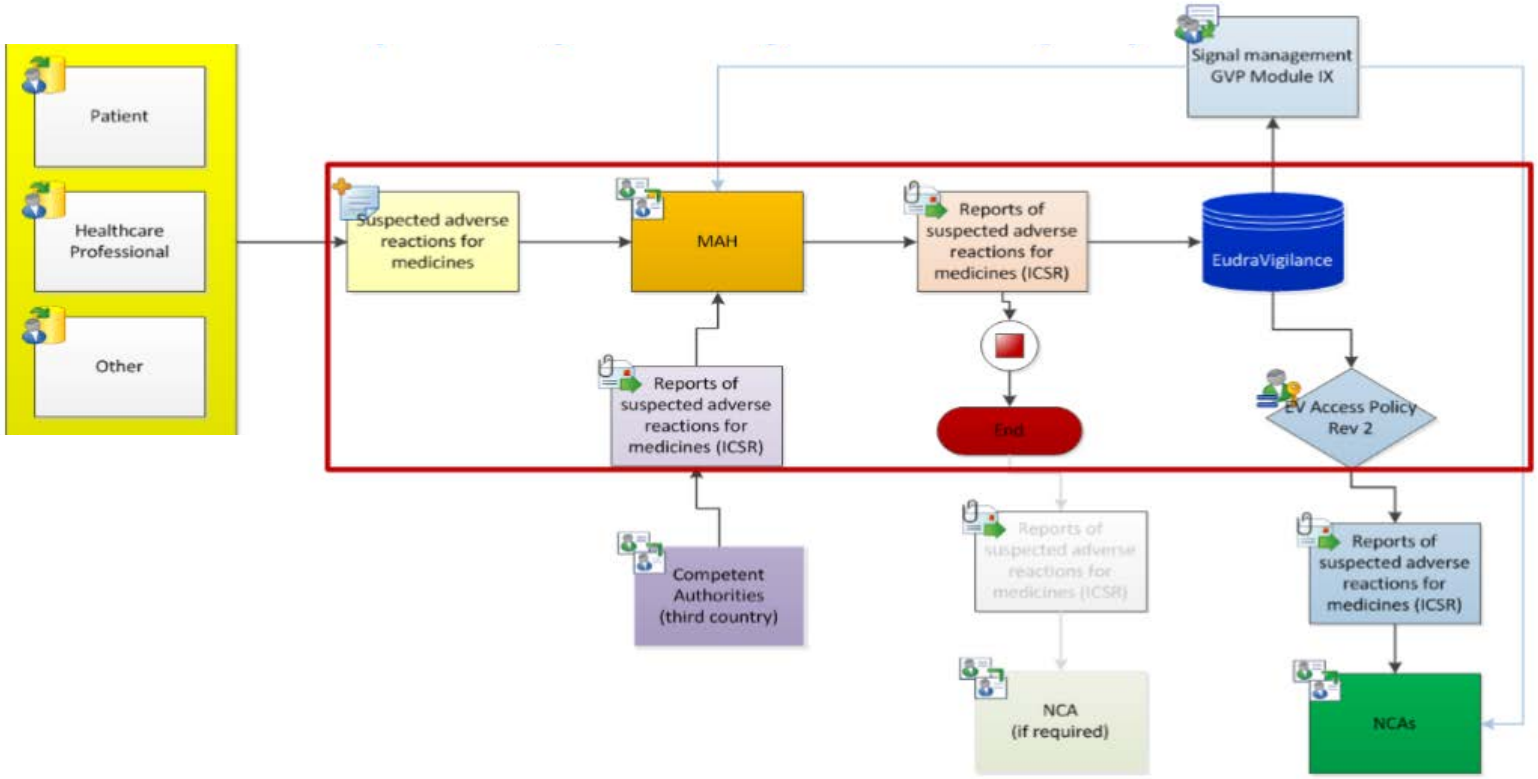
Simplified reporting of suspected adverse reactions in the EU - NCAs



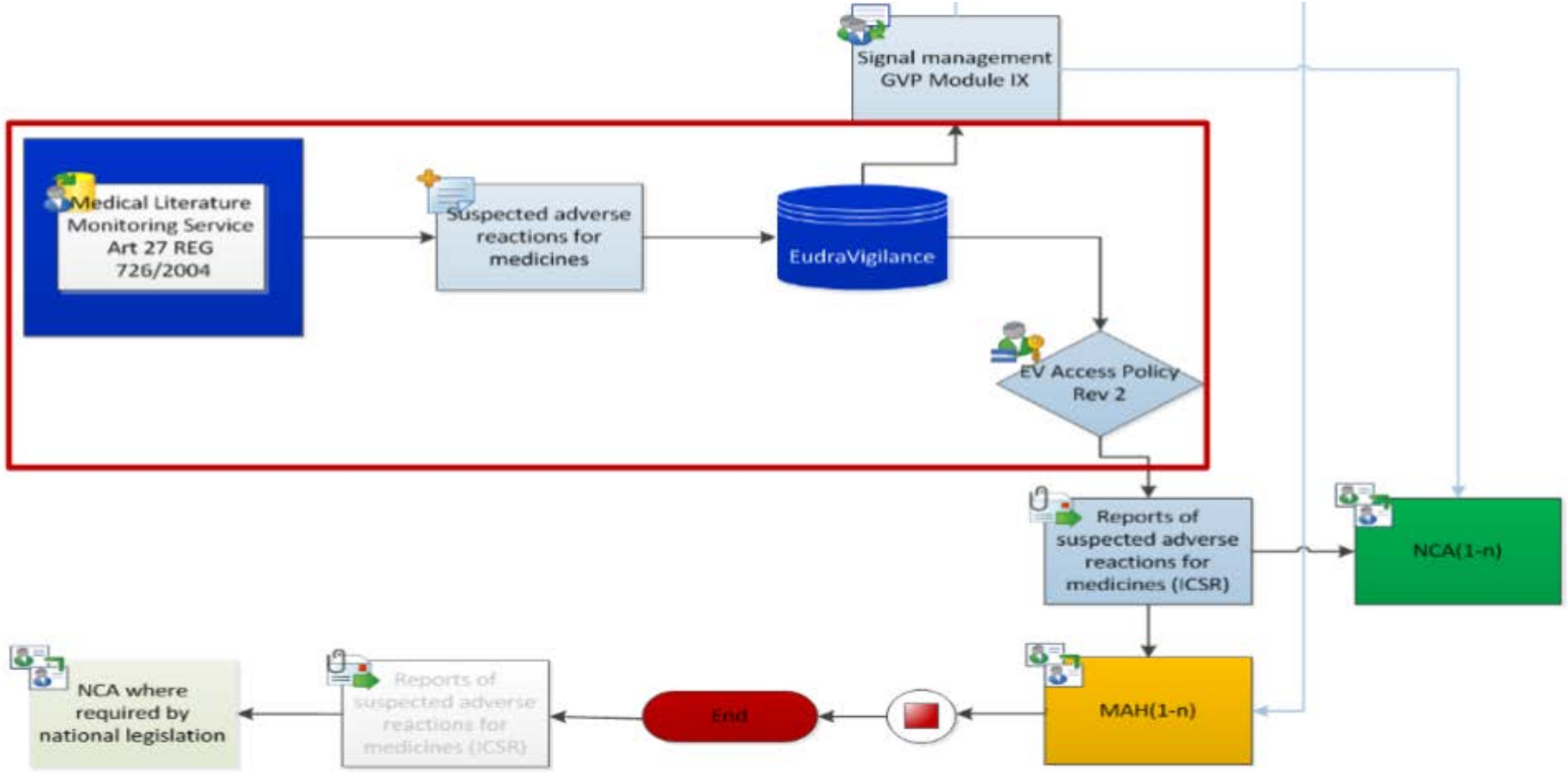
Simplified reporting of suspected adverse reactions in the EU – WHO-UMC



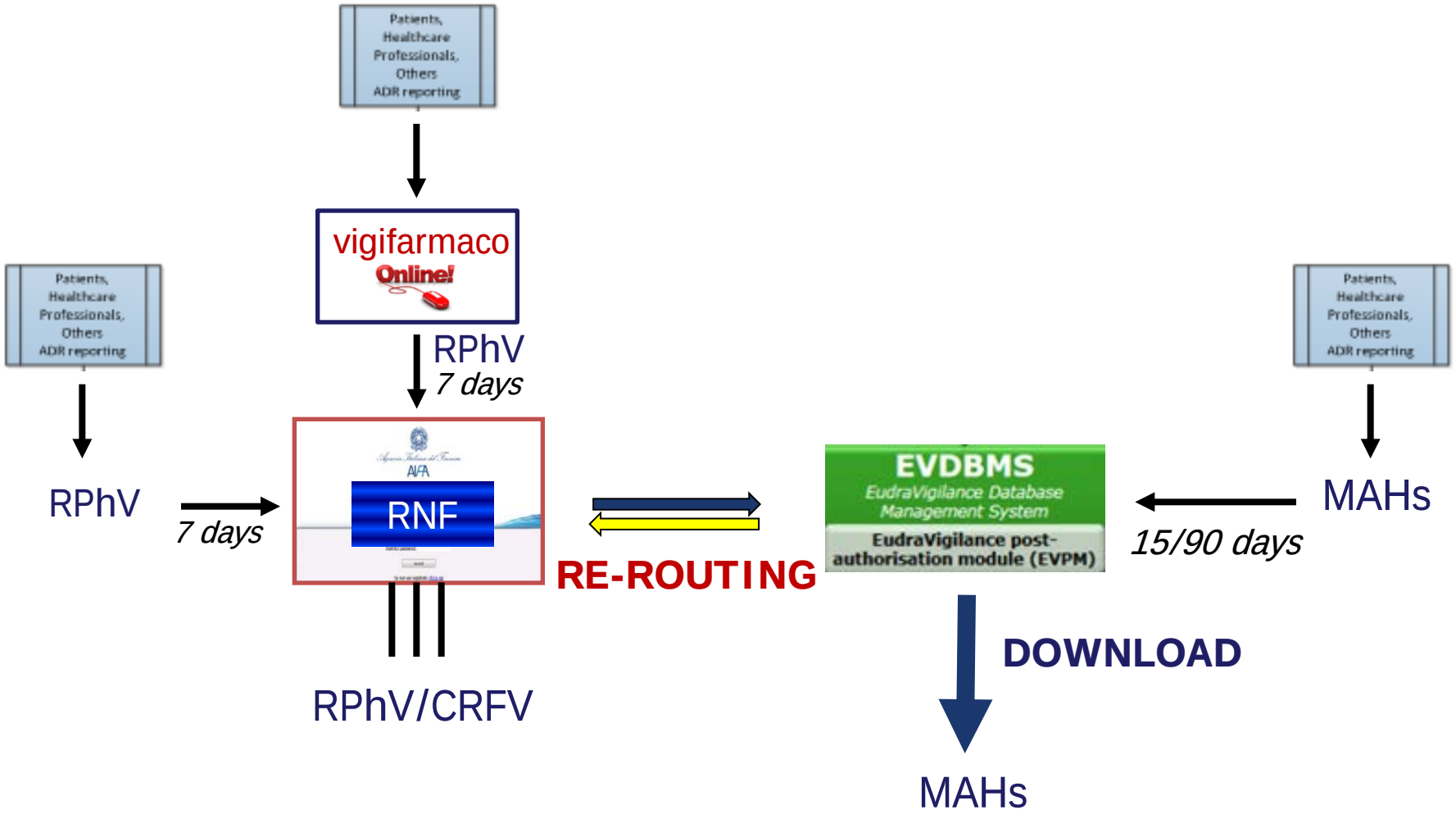
Simplified reporting of suspected adverse reactions in the EU - MAHs



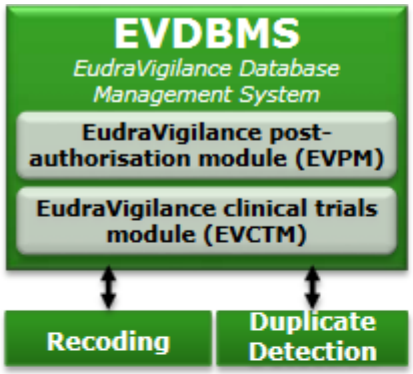
Simplified reporting of suspected adverse reactions in the EU - MAHs



Il Sistema di segnalazione italiano



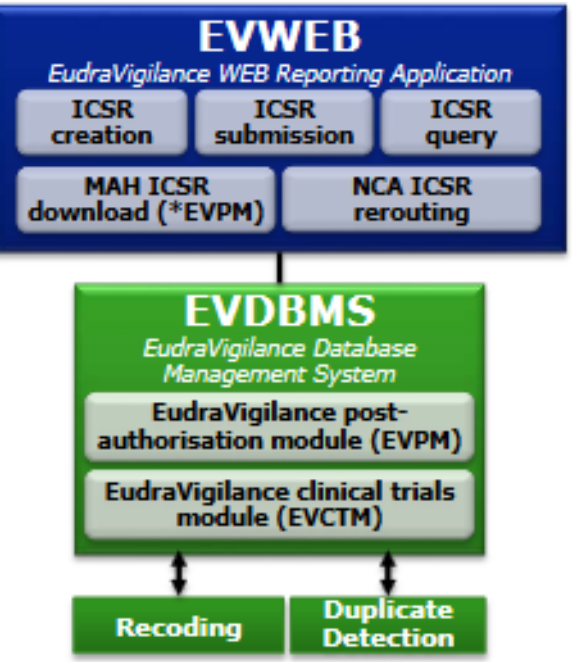
The Eudravigilance Database



The EudraVigilance Database is divided into two parts:

- The EudraVigilance Post-Authorisation Module (EVPM),
  - For ICSRs related to spontaneous reports and reports from non-interventional studies
- The EudraVigilance Clinical Trial Module (EVCTM),
  - For ICSRs related to reports on suspected unexpected serious adverse reactions (SUSARs) that occur in the frame of interventional studies

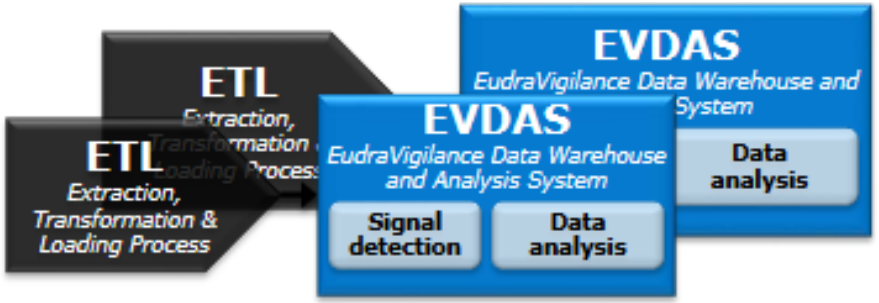
The Eudravigilance Database Management System



- The Re-routing component allows National Competent Authorities to choose which ICSRs should be re-routed to them following the implementation of simplified reporting
- The ICSR Download component allows Marketing Authorisation Holders to download ICSRs in accordance with the EudraVigilance Access policy
- The Duplication Detection component allows the EMA to manage duplicated ICSRs within EudraVigilance through the creation of master cases
- The Recoding component allows the EMA to recode verbatim drug and substance information reported in ICSRs against Art57 medicinal product information

The Eudravigilance Data Analysis System

- The EudraVigilance Data Analysis System has been designed to allow users to analyse safety data collected in EudraVigilance
- It enables better-informed decisions about the safety profile of medicinal products
- It provides a range of analytical tools: from measuring reporting compliance for regulatory purposes, to pharmacovigilance analyses (such as signal detection tools)

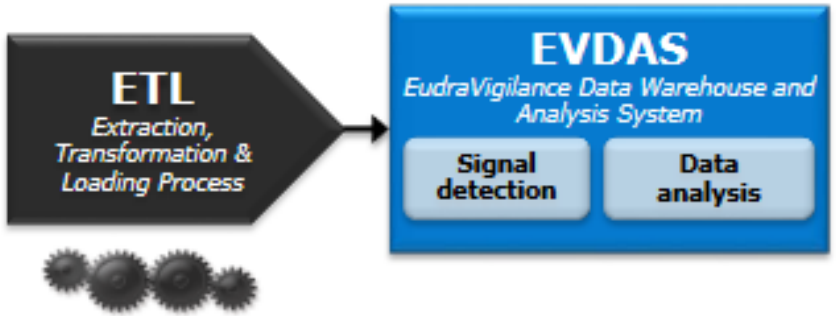


EudraVigilance Data Analysis System

ICSR Data

Organisations & Users

xEVMPD



Art 57 Database / XEVMPD

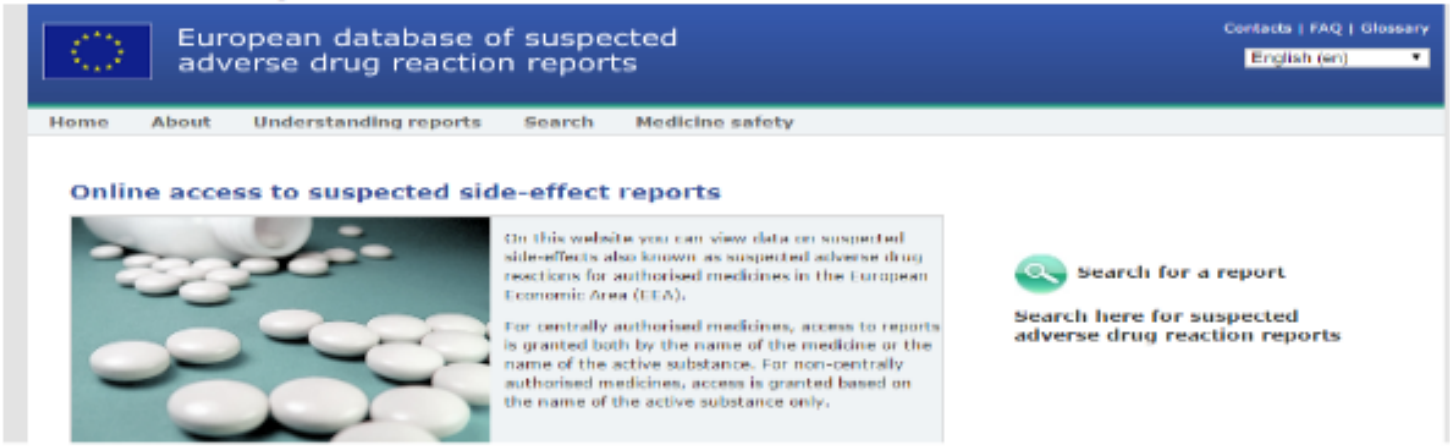
All holders of marketing authorisations for medicines in the European Union (EU) and the European Economic Area (EEA) must submit information to the European Medicines Agency (EMA) on authorised medicines and keep this information up-to-date.

This is a legally binding requirement from the EU pharmaceutical legislation.

A training course on XEVMPD is available. See details on the Agency's website

Medicinal Products (Art 57 Database/XEVMPD)

ADR Reports Portal (http://www.adrreports.eu/)



Adrreports.eu portal
Adverse Drug Reaction Reporting portal

This website was launched by the European Medicines Agency in 2012 to provide public access to reports of suspected side effects inline with the EudraVigilance access policy.

l.sottosanti@aifa.gov.it