EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Signal management process

Eleventh Stakeholder forum on the Pharmacovigilance legislation
21 September 2017

Presented by Georgy Genov
Head of Signal & Incident Management Service
Acting Head of Pharmacovigilance & Epidemiology Department

Where we are 5 years after the implementation of the Signal Management process

Working together for continuous improvement of health promotion and protection

- Clear roles and responsibilities
- Faster safety issue detection and faster warnings to users
- Key safety issues addressed at EU level by PRAC
- Increased transparency
- Increasing use of validated scientific methods and Real world data
- Focus on simplification and efficiencies

EU signal management process: who did what until now

1,600+ NAP substances subject to worksharing

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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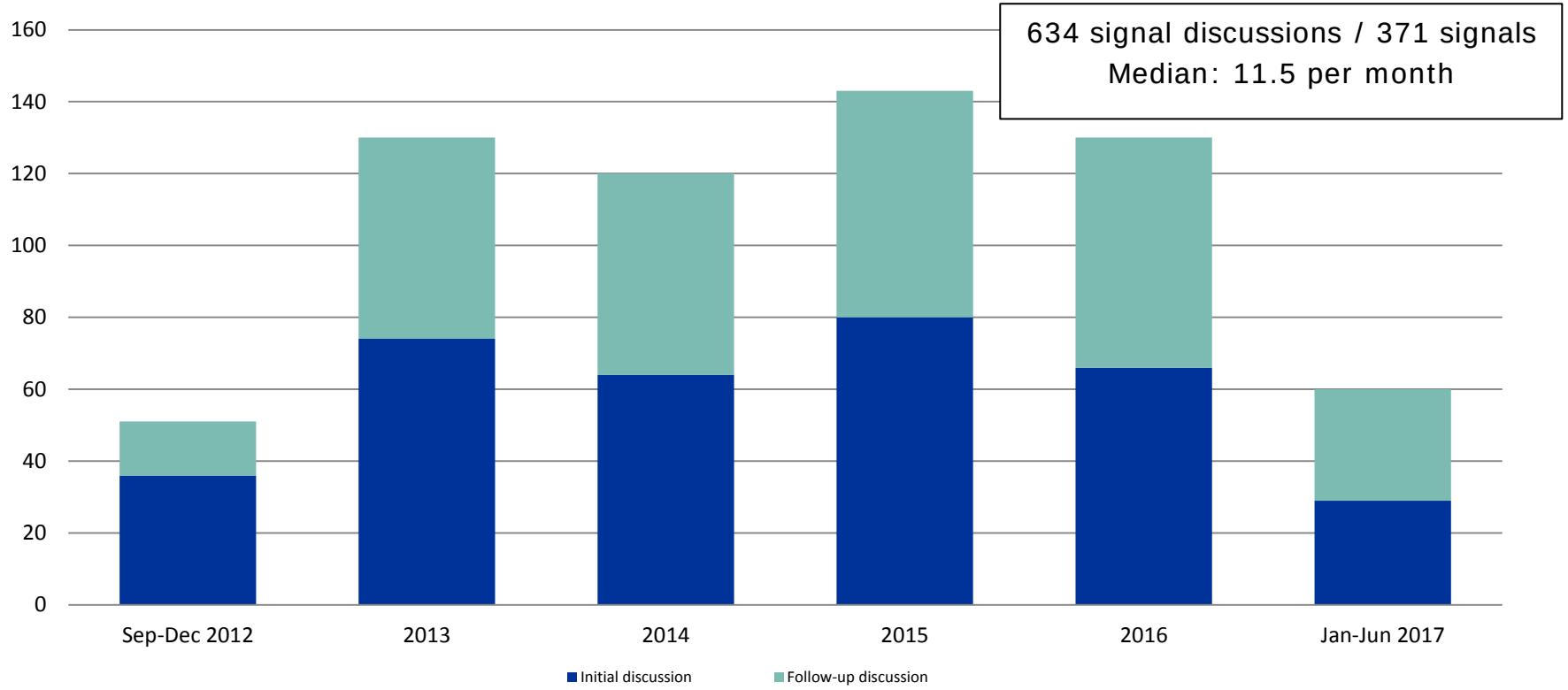
EMA/563056/2014 Rev. 4
Inspections & Human Medicines Pharmacovigilance Division

List of substances and products subject to worksharing for signal management

For medicinal products authorised through the national, mutual recognition or decentralised procedures in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation was obtained through the above-mentioned procedures, the legislation foresees that a lead Member State, and where appropriate a co-leader, may be appointed to monitor data in EudraVigilance, and to validate and confirm signals on behalf of the other Member States.
The Agency provides appointed Lead Member States with reaction monitoring reports from EudraVigilance for the substances allocated to them. For substances with no Lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised.

Active substance(s) / product name(s)	Lead Member Stat
(18f) fludeoxyglucose	France
1,3-butanediol / cinchocaine hydrochloride / dexamethasone	Slovakia
125i-human serum albumin	France
5 fluorouracil	Germany (BfArM)

PRAC signal activity (Sep 2012 – Jun 2017)



Few examples of signals discussed at PRAC and leading to update of information

- Adalimumab – **Dermatomyositis**
- Aflibercept – **Blindness**
- Agomelatine – **Angioedema**
- Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin – **Immune mediated necrotizing myopathy**
- Capecitabine – **Acute renal failure**
- Clopidogrel – **Eosinophilic pneumonia**
- Domperidone – **Cardiotoxicity**

Fluoroquinolones – **Retinal detachment**

- Ipilimumab – **Anaphylactic reaction**
- Mirtazapine – **Pancreatitis**
- Paracetamol – **Drug-induced Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis**
- Roxithromycin – **Hearing disorders**
- Thalidomide – **Posterior reversible encephalopathy syndrome**
- Riociguat - **Signal of increased mortality and serious adverse events (SAEs)**

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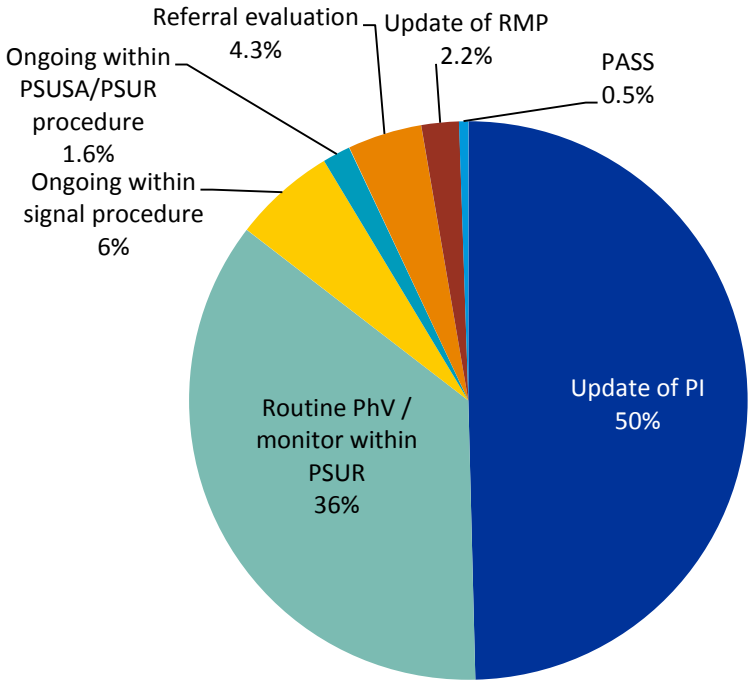
Outcomes of PRAC signal assessment (Sep 2012 – Jun 2017)



Transparency

INN	Signal	PRAC meeting	Update of product information recommended by PRAC
Amoxicillin	Drug reaction with eosinophilia and systemic symptoms (DRESS)	09-12 January 2017 PRACmeeting minutes	No
Amoxicillin	Drug reaction with eosinophilia and systemic symptoms (DRESS)	2-5 May 2017 PRAC meeting minutes	No
Amoxicillin	Drug reaction with eosinophilia and systemic symptoms (DRESS)	3-6 July 2017 PRAC minutes	Yes

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PRAC recommendations on safety signals: monthly overv

Document(s)	Language	Status
PRAC recommendations on signals adopted at the 3-6 July 2017 PRAC meeting	(English only)	adopted
New product information wording: extracts from PRAC recommendations on signals adopted at the 3-6 July 2017 PRAC	EN = English GO	

1.1. Amoxicillin; amoxicillin, clavulanic acid – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	18802
PRAC rapporteur(s)	Jan Neuhauser (AT)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of amoxicillin-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Amoxicillin

Summary of product characteristics

4.4. Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.

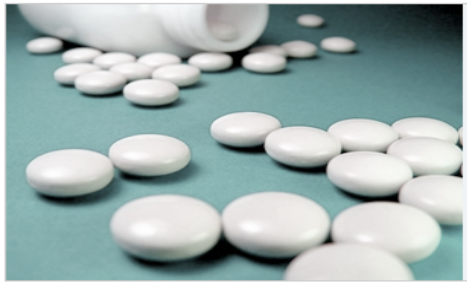
European database of suspected adverse drug reaction reports

Contacts | FAQ | Glossary

English (en)

Home | About | Understanding reports | Search | Medicine safety

Online access to suspected side-effect reports



On this website you can view data on suspected side-effects also known as suspected adverse drug reactions for authorised medicines in the European Economic Area (EEA).

For centrally authorised medicines, access to reports is granted both by the name of the medicine or the name of the active substance. For non-centrally authorised medicines, access is granted based on the name of the active substance only.

Search for a report

Search here for suspected adverse drug reaction reports

How to report a side-effect

Key information

- The information on this website relates to ***suspected* side effects**, i.e. medical events that have been observed following the use of a medicine, but which are **not necessarily related to or caused by the medicine**.
- Information on suspected side effects **should not be interpreted** as meaning that the medicine or the active substance causes the observed effect or is **unsafe to use**. Only a detailed evaluation and scientific assessment of all available data allows for robust conclusions to be drawn on the benefits and risks of a medicine.
- The European Medicines Agency publishes this data so that its stakeholders, including the general public, can access information that European regulatory authorities use to review the safety of a medicine or active substance. **Transparency** is a key guiding principle of the Agency.

Signal management: what is coming?

Legal provisions to be implemented in November

After the entry into force of the revised EV Access Policy, the legal provisions related to EV monitoring by MAHs will have to be implemented:

- The EV database shall also be accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations. *[REG Art 24(2)]*
- **MAHs shall monitor the data available in the EV database** to the extent that they have access to that database. *[IR Art 18(2)]*
- MAHs, NCAs and EMA shall ensure the **continuous monitoring** of the EV database with a frequency proportionate to the identified risk, the potential risks and the need for additional information. *[IR Art 18(3)]*
- Where a MAH detects a new signal when monitoring the EV database, it shall **validate** it and shall forthwith **inform EMA and NCAs**. *[IR Art 21(2)]*

GVP IX – Signal management – Draft revision 1

- Process for signals detected by **MAHs** based on EV monitoring
- Terminology, including **emerging safety issues** (previously GVP VI)
- Monitoring **periodicity** and analysis of EV data
- Roles and responsibilities within EU process, flowcharts
- Addendum: *"Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions"*
- Finalisation in **October 2017**

Transitional arrangements for MAHs

- EMA/EC have agreed that the requirement for MAHs to monitor EV data and inform EMA/NCAs of validated signals:
  - ✓ will start on **22 February 2018**, i.e. 3 months after go-live of the new system.
  - ✓ will only apply, for a pilot period of **1 year**, to **active substances on the additional monitoring list**.
- Between 22 November 2017 and 22 February 2018, concerned MAHs should familiarise themselves with the EV tools and the new process outlined in GVP.
- For other substances, MAHs will still have EV access and will be able to use the data as an additional data source for their existing signal management activities.

EudraVigilance as an opportunity in signal management

- ✓ One of the largest spontaneous reporting systems worldwide: over 6 million cases in in the post-authorisation module!
- ✓ Data subject to quality control and duplicate detection
- ✓ Provided to all stakeholders in real time
- ✓ Evidence-based statistical methods and extended access to individual case information to support robust data evaluation
- ✓ Let’s make the most of the system, in a pragmatic, efficient and collaborative way !

Any questions?

Further information

EMA webpages on Good pharmacovigilance practices and Signal management

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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