EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Implementation of the Pharmacovigilance legislation: Building on two years of operation

8th Stakeholders forum – 15 September 2014

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In this presentation

Pharmacovigilance legislation - Building on two-years of operation:

- Key messages
- Reminders: objectives, constraints, priorities
- What has been delivered in 2013-2014
- Looking forward
- Conclusions

Pharmacovigilance legislation: Building on two years of operation - Key messages

Two-years of operation delivered:

- Proactive planning of studies and risk minimisation
- Increased patient reporting of ADRs
- Signals managed through PRAC
- Benefit risk assessment delivered through referrals and periodic safety updates
- Increased transparency
- EU coordination of safety messages

Now focus on:

- Continued delivery for public health
- Process improvement to increase effectiveness and efficiency,
  - Based on experience
  - Based on better scientific methods
  - Based on delivering IT systems and business change
- Enhanced stakeholder engagement
- Demonstrating impact

Reminders: objectives, constraints, priorities

Objectives: Promote and protect public health by reducing burden of Adverse Drug Reactions and optimising the use of medicines:

1. Clear roles and responsibilities
2. Science based and risk proportionate
3. Increased proactivity
4. Reduced duplication and increased efficiency
5. Integrate benefit and risk
6. Ensure robust EU decision-making
7. Strengthen the EU Network
8. Engage patients and healthcare professionals
9. Increase transparency
10. Provide better information on medicines

Reminders: objectives, constraints, priorities

Challenges:

- Major resource constraints
- Size of change
- Number of stakeholders impacted

Reminders: objectives, constraints, priorities

Criteria for prioritisation:

- Firstly, public health activities
- Secondly, transparency and communication activities
- Thirdly, simplification activities (primarily for pharmaceutical industry)

What has been delivered in 2013-2014

- Pharmacovigilance Risk Assessment Committee continued full operation
- New business processes operating
- Audits of the National Competent Authorities pharmacovigilance systems
- Audits of the European Medicines Agency's pharmacovigilance systems
- More and better guidance
- Process improvements

Good pharmacovigilance Practice (GVP)- Developments since October 2013

I PhV and QS		XI Participation	Consult on Public Hearings
II PSMF		XII Continuous PhV	Drafting Out:2015
III Inspections	Rev 1 published	XIV International	Referred to 2015
VI Audits		XV Communication	
V RMP	Rev 1 in preparation	XVI RMM	Published
VI ICSR	Rev 2 published Published today	P.I Vaccines	Published
VII PSUR	Rev 1 published	P.II Biologicals	Drafting Out:2015
VIII PASS	Rev 1 in preparation	P.III Pregnancy	Drafting
IX Signals	Rev planned	P.IV Geriatrics	Drafting
X Add Monitoring		Annex I Definitions	Rev published

Guidance: Next steps

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Look out for the following revisions:

- GVP Module V – Risk management systems
- GVP Module VI – Management and reporting of adverse reactions to medicinal products
- GVP Module VIII – Post-Authorisation Safety Studies
- GVP Module IX – Signal management
- ENCePP methods guide

Look out for the new modules:

- GVP Module XII – Continuous Pharmacovigilance
- GVP Product /Population-Specific Considerations II: Biologicals, pregnancy, geriatrics
- Good practice guides on medication errors
- Good practice guide on educational materials
- Efficacy studies scientific guidance

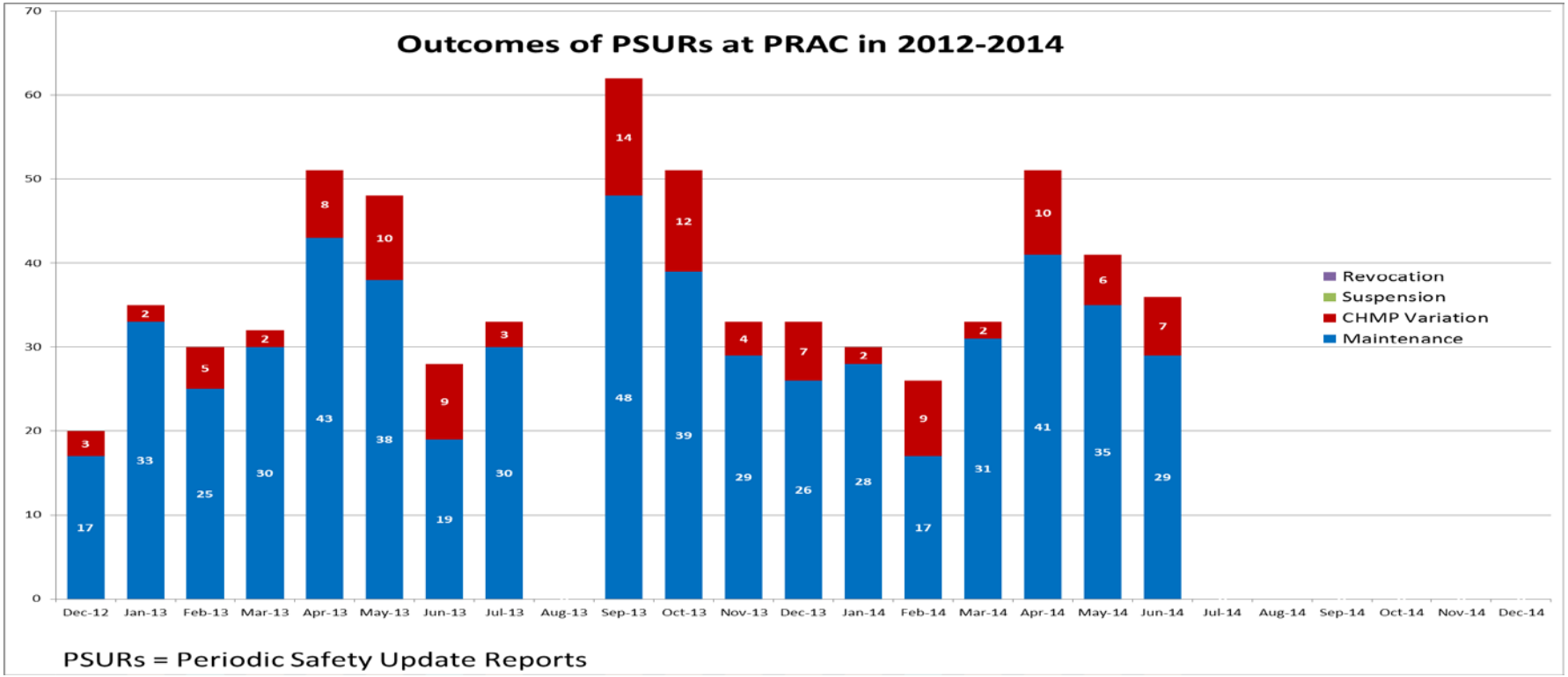
2013 – 2014: business processes

Risk management plans -submitted with applications for new medicines and when issues with medicines on the market: to plan studies and risk minimisation

RMP in the context of:	July 2012 - June 2013	July 2013 - June 2014	TOTAL
Initial application	101	120	221
Type II variation	70	194	264
PSUR	91	112	203
Renewal	18	35	53
Stand alone RMP	51	34	85

The new legislation has delivered unprecedented proactivity in pharmacovigilance

Periodic Safety Update Reports – benefit risk assessments for authorised medicines



PSURs: Observations and next steps

- Procedure for CAPs now well established with a proportion of PSUR procedures leading directly to MA variation
- Efficiency gains since no need for follow-up variation and health gains through rapid update of product information
- Mixed single assessments for CAPs and NAPs provides insight into upcoming NAPs only PSUSAs and areas for clarification:
  - For pharmaceutical industry :
    - Need to clearly list NAPs covered by a PSUR on level of national authorisation
  - For regulators:
    - requests for additional information to be more clearly phrased and tailored to the affected products
- New dedicated service for PSURs established in the procedural department with a dedicated mailbox for pre-submission queries PSURquery@ema.europa.eu

Post-Authorisation Safety Studies fill knowledge gaps: protocols and results at PRAC 2012 to June 2014

	Imposed Protocols	Non-imposed Protocols	PASS Results on Imposed Protocols	PASS Results on non-Imposed Protocols
Up to June 2014	25	48	0	20
2013	41	50	0	13
2012	5	0	0	0

EU PAS Register

Studies registered: 135
up to July 2013
345 up to Aug 2014

So:

- Increase in protocols reviewed
- Increase in results assessed
- Increase in studies registered

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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E-Register of Studies

EU PAS Register

EU PAS Register

The publicly availabe register referred to as the 'EU PAS Register' in Good Pharmacovigilance Practices (GVP) is to be maintained by the European Medicines Agency (EMA).

The E-Register of Studies *de facto* serves as the 'EU PAS Register' for all pharmacoepidemiological and pharmacovigilance studies regardless of whether they are initiated, managed or financed by a marketing authorisation holder, or whether they are conducted by a research centre that is a partner of the ENCePP network or any other research centre, including from outside the European Union.

Marketing authorisation holders should register all non-interventional post-authorisation safety studies (PASS) relating to medicines in the ENCePP E-Register of Studies.

The pharmacovigilance legislation requires the EMA to publish in a publicly available register the protocols and abstracts of results of **PASS imposed as an obligation** by a competent authority in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. It also specifies that the final report of such studies must provide the date of registration in this register.

Information about PASS which are initiated, managed or financed **voluntarily** by a MAH and which are required in the **Risk Management Plan (RMP)** to further investigate safety concerns or to evaluate the **effectiveness of risk minimisation activities**, **or any other PASS** should also be entered into this register in order to support the same level of transparency, scientific and quality standards.

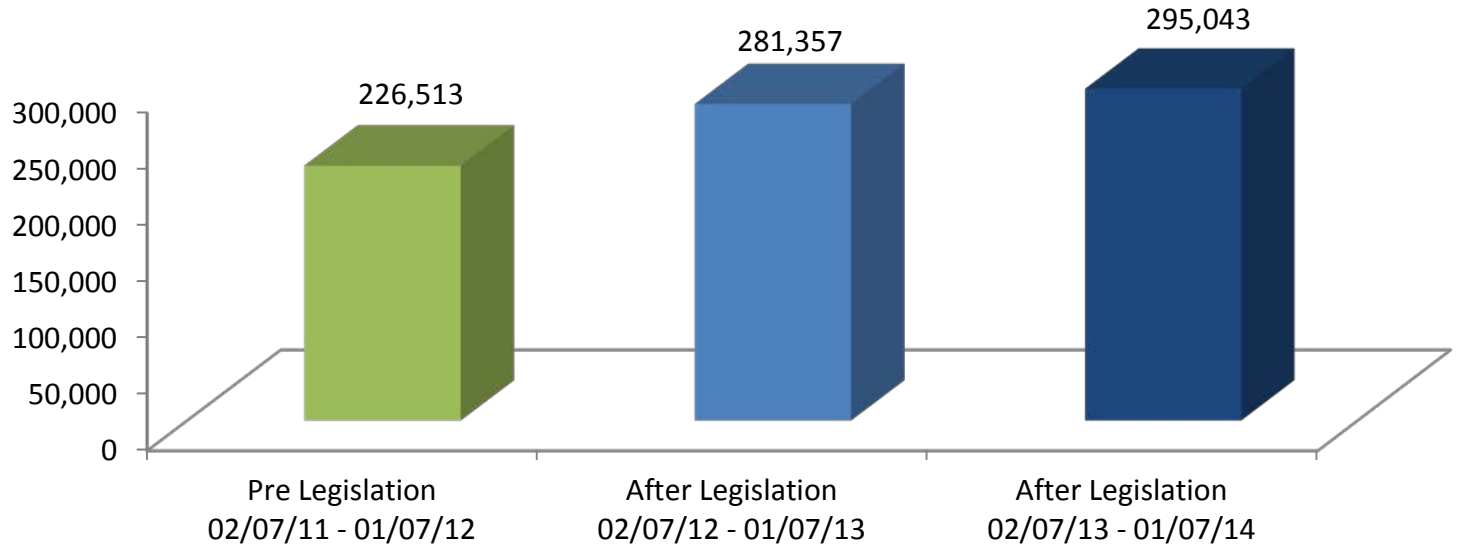
Further information about the requirements for the registration of PASS is available in the guideline on Good Pharmacovigilance Practices (GVP) module VIII, chapter VIII.B.4.

To register a study, go to the ENCePP E-Register of Studies.

Post authorisation efficacy studies

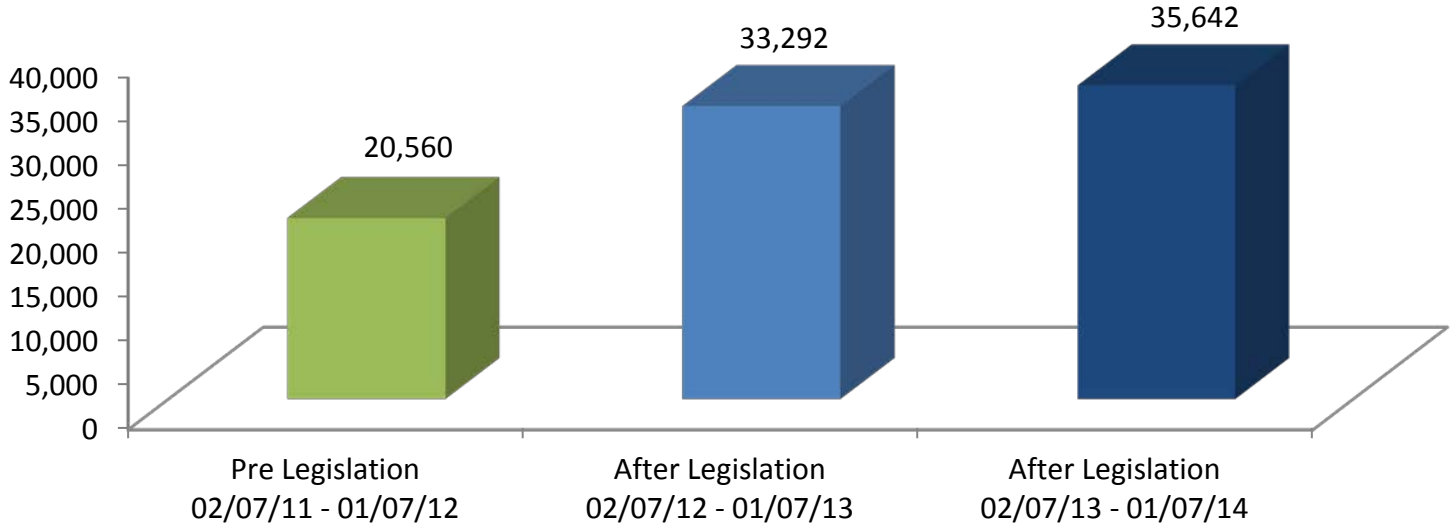
- PAES Delegated Regulation (EU) No 357/2014 adopted in Feb 2014, entry into force May 2014.
- PAES scientific guidance: in preparation, public consultation Q1 2015, publish Q3 2015

Spontaneous reporting in EEA*



* Number of ICSRs received in EudraVigilance before de-duplication

Spontaneous reporting by patients in EEA*



* Number of ICSRs received in EudraVigilance before de-duplication

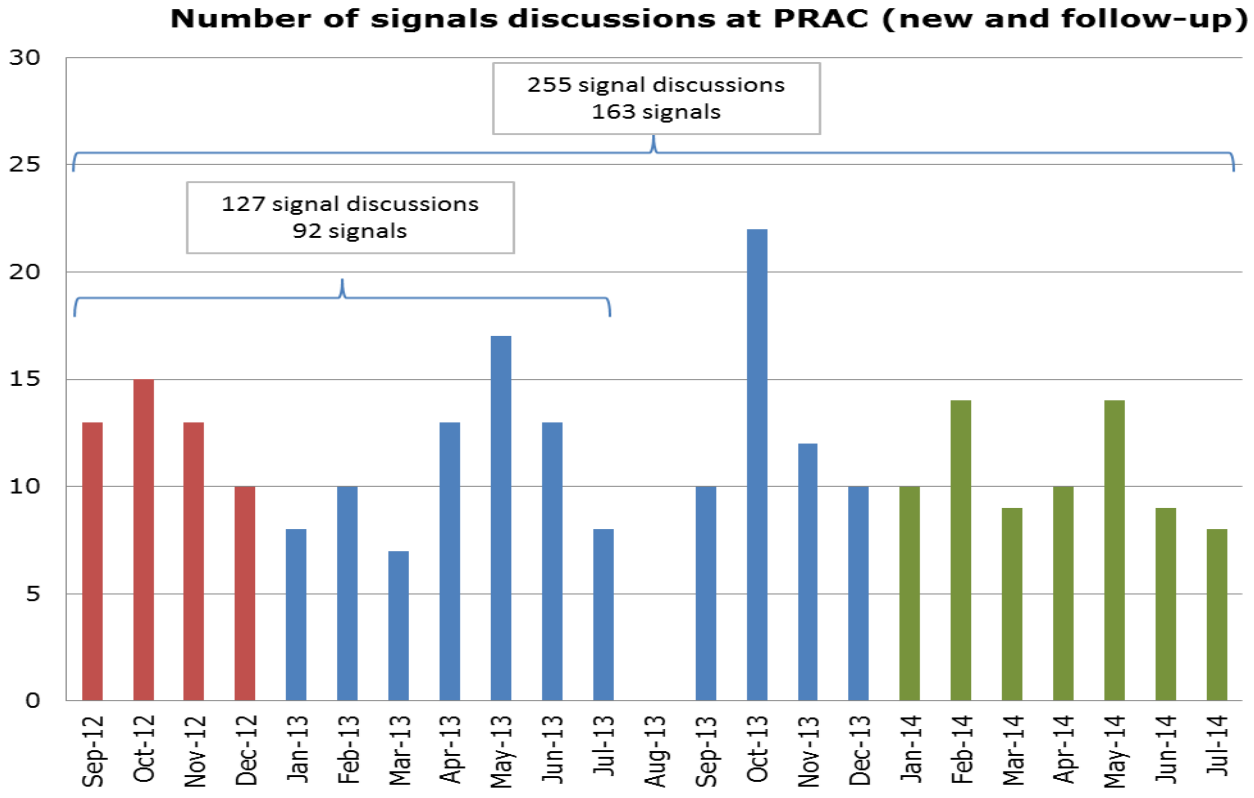
Eudravigilance Data Quality management 07/2013 – 07/2014

Achievements of EV Data Quality management

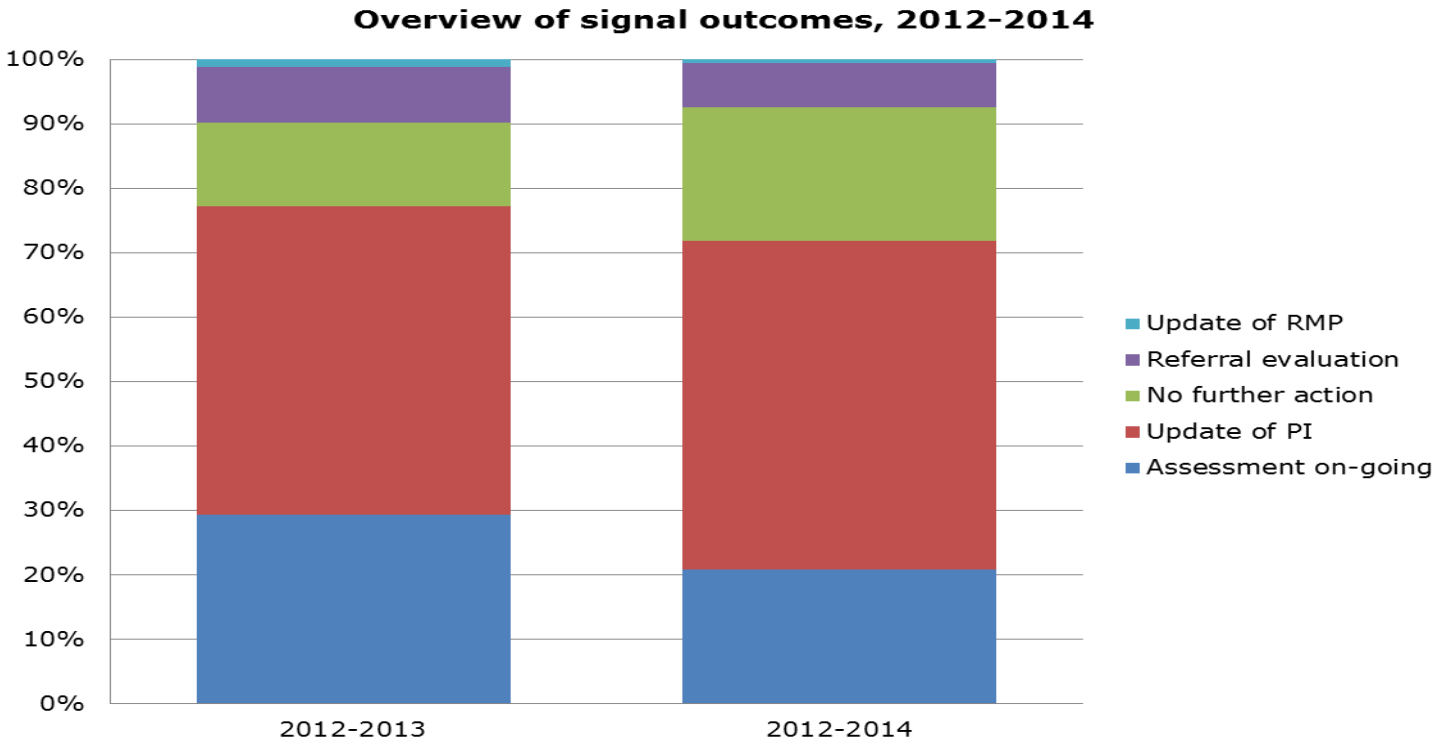
- Recoding of medicinal product terms reported in safety reports: 84,288 terms recoded
- Duplicate detection & management of individual safety reports: 85,677 duplicate cases removed from the system
- EudraVigilance Data Quality Assessments: 136 assessments performed and senders (MAHs/Sponsors/NCAs) provided feedback

Signals: new potential safety issues or changes to known safety issues

- 163 signals (255 signal discussions) managed by PRAC in the first two years
- Unprecedented transparency for stakeholders
- Delivers rapid assessments to that product information can be updated to support safety and effective use of products

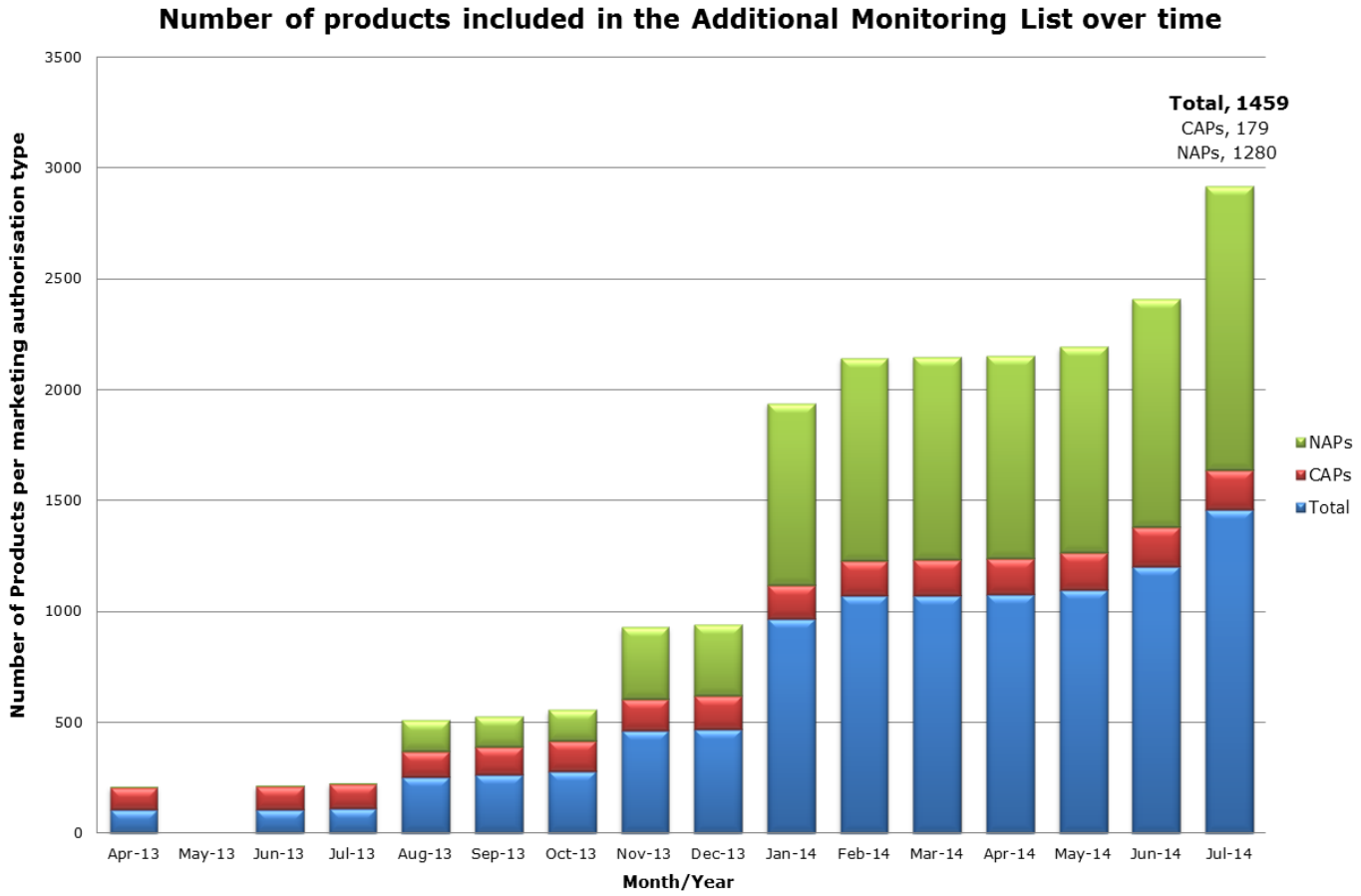


Median:
10 signals
per month

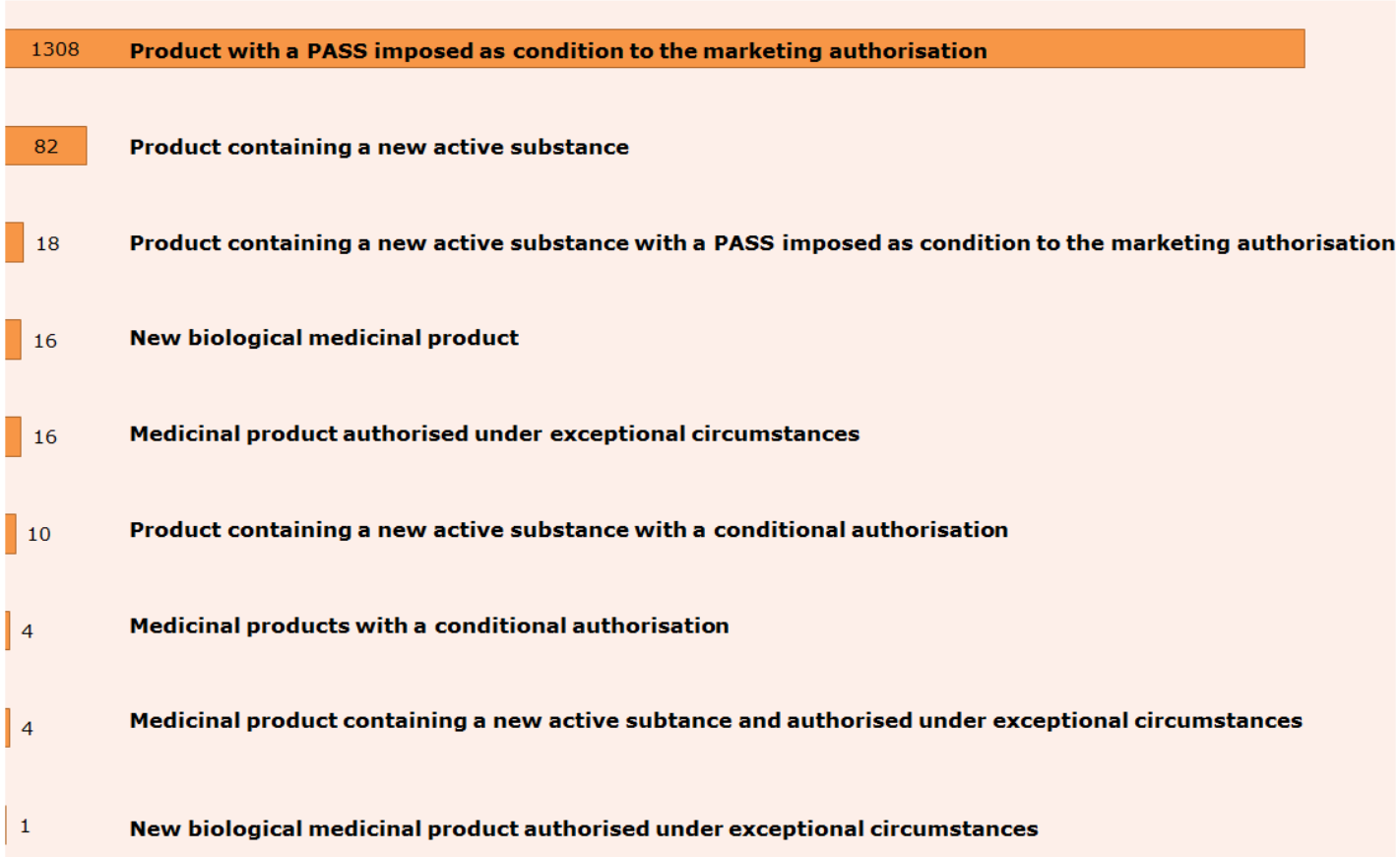

Overview of signal outcomes, 2012-2014
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2012-2013
2012-2014
Update of RMP
Referral evaluation
No further action
Update of PI
Assessment on-going

Additional monitoring

- Mandatory for following some products e.g. Medicines containing a new active substance / biological medicinal products and medicines with obligation for post authorisation safety studies
- Optional for other products at the request of the EC or a national agency, following consultation with the PRAC
- Additional monitoring list published every months by EMA
  - Currently 1459 products (as of 31 July 2014 compared to 105 in April 2013)
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852


Number of products included in the Additional Monitoring List over time
Total, 1459
CAPs, 179
NAPs, 1280
Number of Products per marketing authorisation type
3500
3000
2500
2000
1500
1000
500
0
Apr-13
May-13
Jun-13
Jul-13
Aug-13
Sep-13
Oct-13
Nov-13
Dec-13
Jan-14
Feb-14
Mar-14
Apr-14
May-14
Jun-14
Jul-14
Month/Year
NAPs
CAPs
Total

Distribution of products included in the additional monitoring list



Referrals: safety or benefit risk reviews of medicines

- Number of referrals (July 2012 – July 2014[1]):

Referral type	Started	Finalised
Art. 20	7	5
Art. 107i	6	6
Art. 31	18	11
Total	**31**[2]	**22**[3]

[1] Also includes procedures started and finalised by PRAC in July 2014

[2] In 8 procedures (26%) an ad-hoc expert meeting has been organised

[3] Finalised means final outcome obtained at either CHMP or CMDh

Pharmacovigilance inspection procedures

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Pharmacovigilance inspection procedures: human

European Union pharmacovigilance inspectors have developed Union procedures and guidance on pharmacovigilance inspections of marketing-authorisation holders of human medicines.

The Union procedures support harmonisation for the mutual recognition of pharmacovigilance inspections and to facilitate administrative collaboration and the exchange of inspection-related information. They apply to inspections conducted following adoption by the Committee for Medicinal Products for Human Use (CHMP) or under the national inspection programmes of concerned Member States.

National competent authorities of all Member States are expected to take account of the Union procedures and use them as the basis for standard operating procedures on the quality systems established within the inspectorates themselves.

The European Medicines Agency is responsible for maintaining and publishing the Union procedures.

Send all queries regarding this content to gcp@ema.europa.eu.

Union procedures

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Document(s)	Language	Status	First published	Last updated	Effective Date
Union procedure on the coordination of EU pharmacovigilance inspections	(English only)	adopted	20/06/2014		01/06/2014
Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections	(English only)	adopted	20/06/2014		01/06/2014
Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products	(English only)	adopted	20/06/2014		01/06/2014
Union procedure on sharing of pharmacovigilance inspection information	(English only)	adopted	20/06/2014		01/06/2014
Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections	(English only)	adopted	20/06/2014		01/06/2014

Publication of RMP summaries

- In March 2014, the Agency began publishing summaries of RMPs for centrally authorised medicines.
- Analysis of experience acquired during pilot phase (and way forward) to be made public in 2015
- 31 RMP summaries published as of 31st August 2014

For further information on RMP summaries and their role, see:
Questions and answers on the RMP summary

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp&mid=WC0b01ac058067a113

EMA/319729/2014

Summary of the risk management plan (RMP) for Gazyvaro (obinutuzumab)

This is a summary of the risk management plan (RMP) for Gazyvaro, which details the measures to be taken in order to ensure that Gazyvaro is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Gazyvaro, which can be found on Gazyvaro's EPAR page.

Overview of disease epidemiology

Gazyvaro is a medicine used for the treatment of chronic lymphocytic leukaemia (CLL). CLL is a rare cancer of B-lymphocytes, a type of white blood cell. Gazyvaro is used in combination with chlorambucil (another cancer medicine), in previously untreated patients who have other medical conditions that make them ineligible for a fludarabine-based cancer treatment.

In the European Union, Gazyvaro has been designated an orphan medicine due to the rarity of the condition. In Europe, in 2013, the estimated prevalence of CLL was approximately 3 per 10,000 people. CLL is almost twice as common in men as in women, and its incidence increases with age.

Summary of treatment benefits

Looking forward

- Continued delivery for public health
- Process improvement to increase effectiveness and efficiency
  - Based on experience
  - Based on better scientific methods
  - Based on delivering IT systems and business change
- Enhanced stakeholder engagement
- Demonstrating impact

Process improvement to increase effectiveness and efficiency

Better IT systems to support stakeholders – see session 3

Topics	Activities
Literature monitoring	EMA service to industry for population of EudraVigilance with case reports of old substances.
EudraVigilance	Delivery of enhanced functionalities and IT system audit results in centralised reporting for industry
Article 57(2) data submission and handling	Updates (variations) to the data can be submitted by industry and data fully used to support regulation, safety and stakeholder needs.
Periodic Safety Update Reports	Delivery of PSUR repository and single PSUR assessment process for NAPs allowing centralised reporting for industry and faster warnings for NAPs
Risk Management System	Implement risk-based system for measuring the effectiveness of risk minimisation
Transparency and communication	Delivery of EU Medicines web-portal and public hearings.

Process improvement and simplification, based on experience and better science

Translating regulatory science into practice

Best Evidence to support assessments

- EMA studies : in house, commissioned
- ENCePP contribution
- FP7 studies to date

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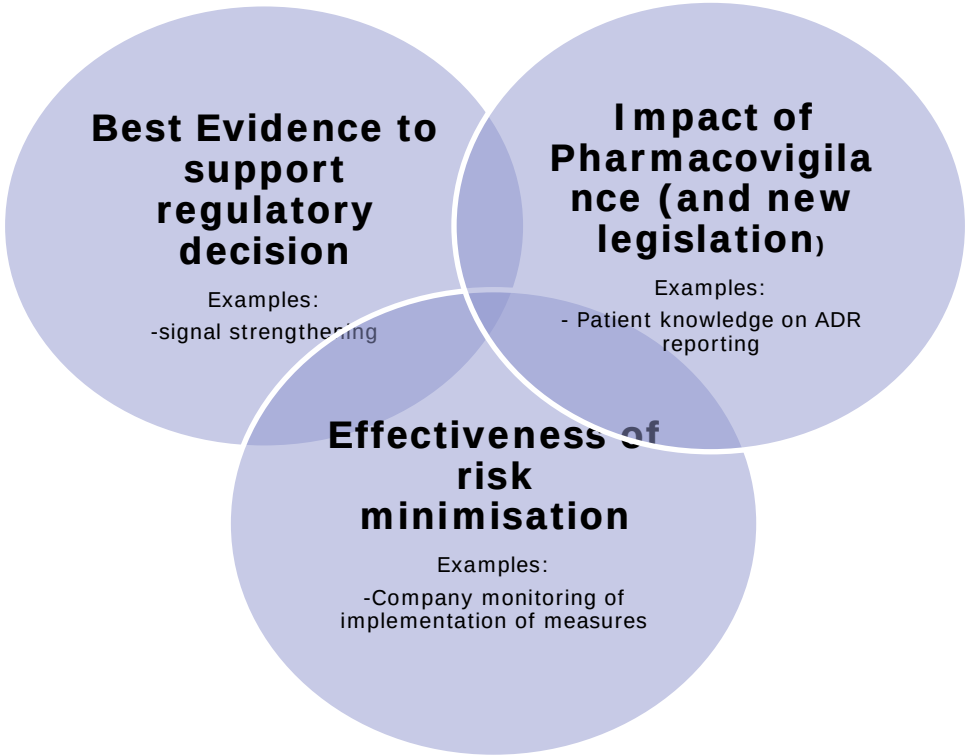
Building capacity

- SCOPE Joint Action (Strengthening Collaborations for Operating Pharmacoepidemiology and Pharmacovigilance)
- ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)

Data, information and knowledge for excellent pharmacovigilance: complementary strategies



Engaging stakeholders: Public hearings

European Medicines Agency launches public consultation on rules of procedures for public hearings

Citizens are invited to review the proposed draft rules and send their comments to the Agency by 15 October 2014.

Measuring **performance*** and **impact**** – types of measures

1. **Performance*:** Structure and process measures of implementation of activities in new PhV legislation (i.e., 'outputs', e.g., implementation milestones and process measures)
2. **Impacts**:**

- Behavioural change
- Outcomes (impacts on health system and industry)

Important because:

- Make process more effective and efficient
- Demonstrate added value
- Justify activity and spending
- Support for future reviews

Conclusions Pharmacovigilance legislation: Building on two years of operation

Delivered:

- Proactive planning of studies and risk minimisation
- Increased patient reporting of ADRs
- Signals managed through PRAC
- Benefit risk assessment delivered through referrals and periodic safety updates
- Increased transparency
- EU coordination of safety messages

Conclusions Pharmacovigilance legislation: Building on two years of operation

Focus on:

- Continued delivery for public health
- Process improvement to increase effectiveness and efficient,
  - Based on experience
  - Based on better scientific methods
  - Based on delivering IT systems and business change
- Enhanced stakeholder engagement
- Demonstrating impact

Thank you for your attention

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