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SCIENCE MEDICINES HEALTH

Pharmacovigilance Risk Assessment Committee

Five years of operation

Eleventh Stakeholder Forum on the Pharmacovigilance Legislation

21 September 2017

Presented by June M Raine Chair PRAC

PRAC – 5 years of operation

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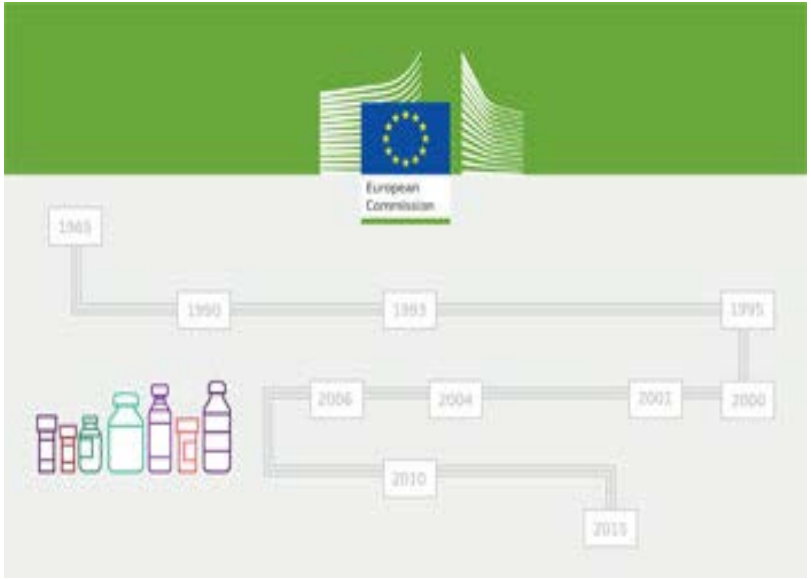
Where have we come from – challenges of operating new systems

How have we operated - opportunities of using new regulatory tools

What have we achieved – and PRAC's areas of current focus



50 years of medicines regulation

22 years of EMA

7 years of PhVig legislation

5 years of PRAC

A time of rapid change

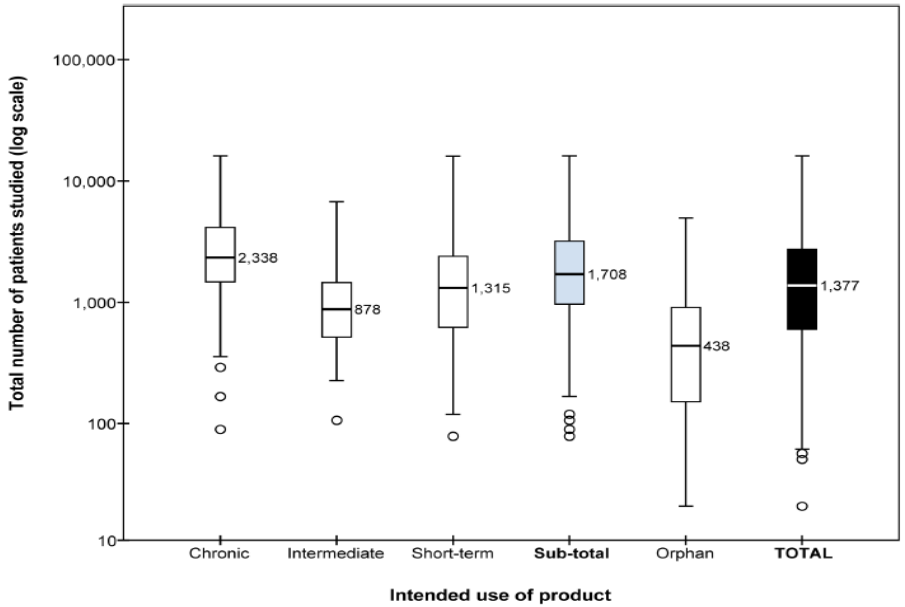
Growing public and patient expectations

Changing demographics and disease patterns

Digital transformation

New science and advanced therapies

Patients studied before approval



Duijnhoven et al

PLoS March 2013

Patients studied prior to approval of new medicine

For **200** new “standard” medicines between 2000 -2010

median total no patients= **1708**, for orphan drugs = **438** patients

For 84 medicines for chronic use **79.8%** met guidelines for 12 months (at least 100 participants)

Filling the knowledge gaps

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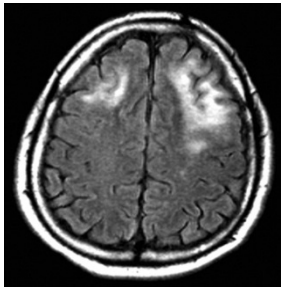
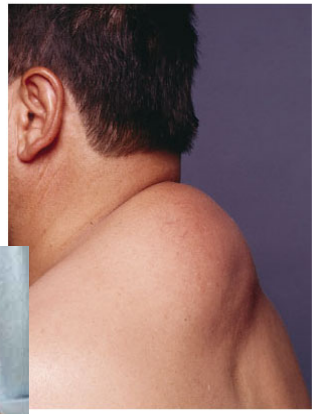
Unidentified ADRs

Long term safety

Special populations

At risk groups





Impact of ADRs – preventable harm

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PDS Pharmacoepidemiology & Drug Safety

Official Journal of the International Society for Pharmacoepidemiology

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2011; **20**: 626–634
Published online 8 March 2011 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2118

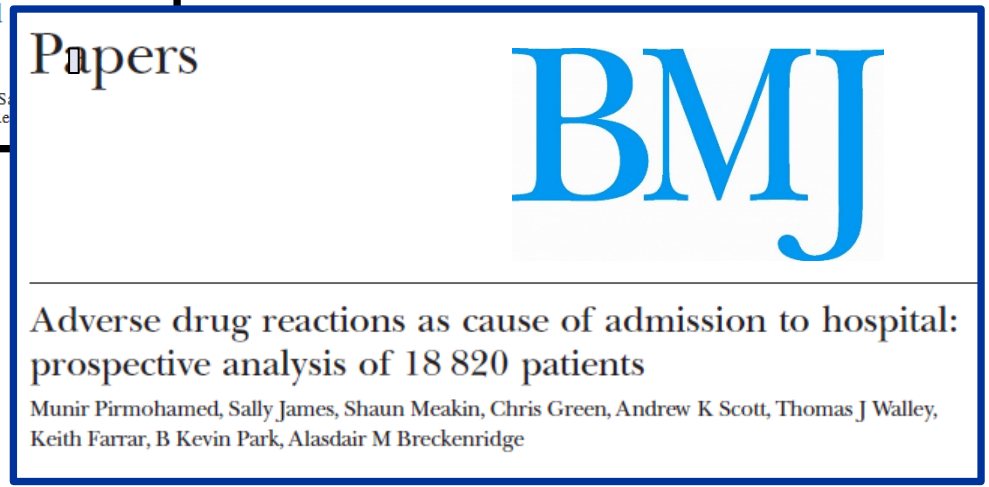
ORIGINAL REPORT

Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations

Dominik Rottenkolber[1,2]*, Sven Schmiedl[3], Marietta Rottenkolber[4], Katrin Farker[5], Karen S... Silke Mueller[7], Marion Hippius[8], Petra A. Thuermann[3] and Joerg Hasford[4] for the Net of Re... Pharmacovigilance Centers

Rottenkolber 2011, Pharmacoepi & Drug Safety; 20: 626–634

Pirmohamed et al 2004
BMJ 329; 15-19



Papers

BMJ

Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

Munir Pirmohamed, Sally James, Shaun Meakin, Chris Green, Andrew K Scott, Thomas J Walley, Keith Farrar, B Kevin Park, Alasdair M Breckenridge

European Commission estimate of harm burden from ADRs

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5% of all hospital admissions due to ADRs

5% of all hospital patients experience an ADR

ADRs 5th most common cause of hospital death

197,000 deaths per year in EU caused by ADRs

Total societal cost €79 billion

5910 lives per year and €237m could be saved

Pharmacovigilance legislative aims

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1. **Clarity** on roles and responsibilities

2. **Proactive** & proportionate safety monitoring

3. **Robust and timely** decision-making leading to consistent action on safety issues

4. **Greater inclusiveness** for patients, healthcare professionals

5. **High levels** of **transparency**

6. **Best use of resources** – avoid duplication

Pharmacovigilance Risk Assessment Committee

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All aspects of risk management of use of medicines including detection, assessment, minimisation and communication relating to risk of adverse reactions, having due regard to the therapeutic effect of the medicine, design & evaluation of post-authorisation safety studies & pharmacovigilance audit

Membership of PRAC

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Appointed by each Member State:

1 member + alternate

28 + EEA countries non voting members

Appointed by European Commission:

6 members - relevant expertise including clinical pharmacology and pharmacoepidemiology

1 member / alternate representing patient organisations

1 member / alternate representing healthcare professionals

Incorporating patients and HCPs

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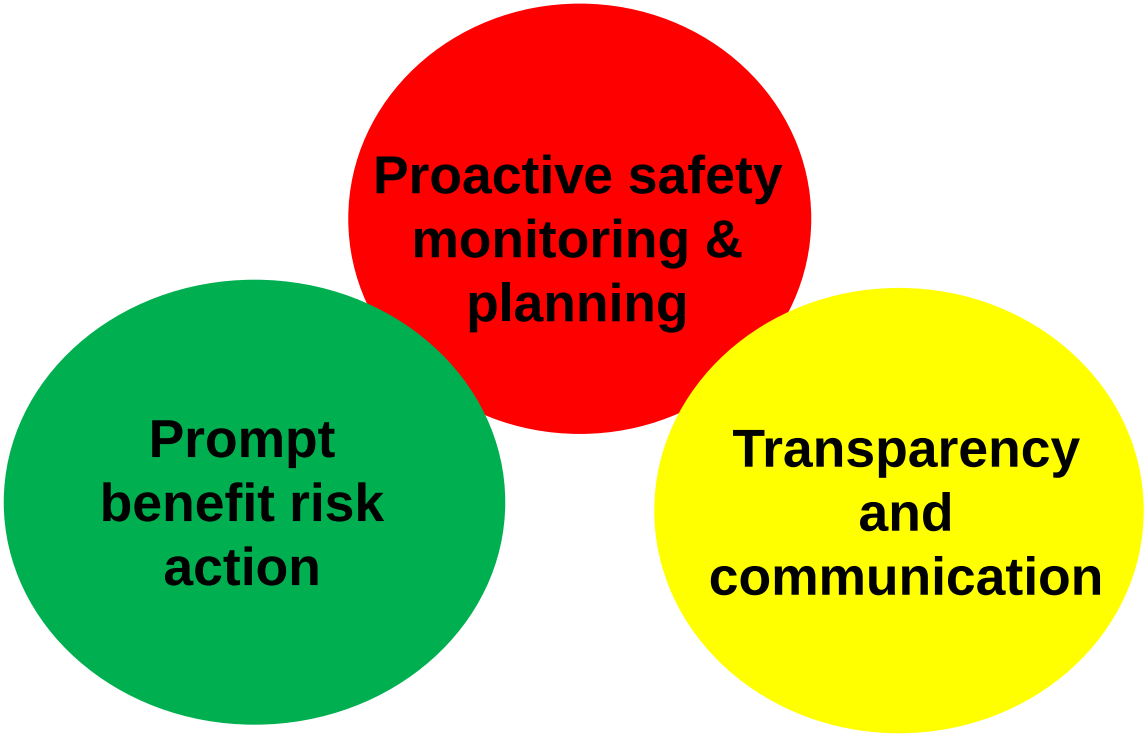
Kirsten Myhr

Albert van der Zeijden

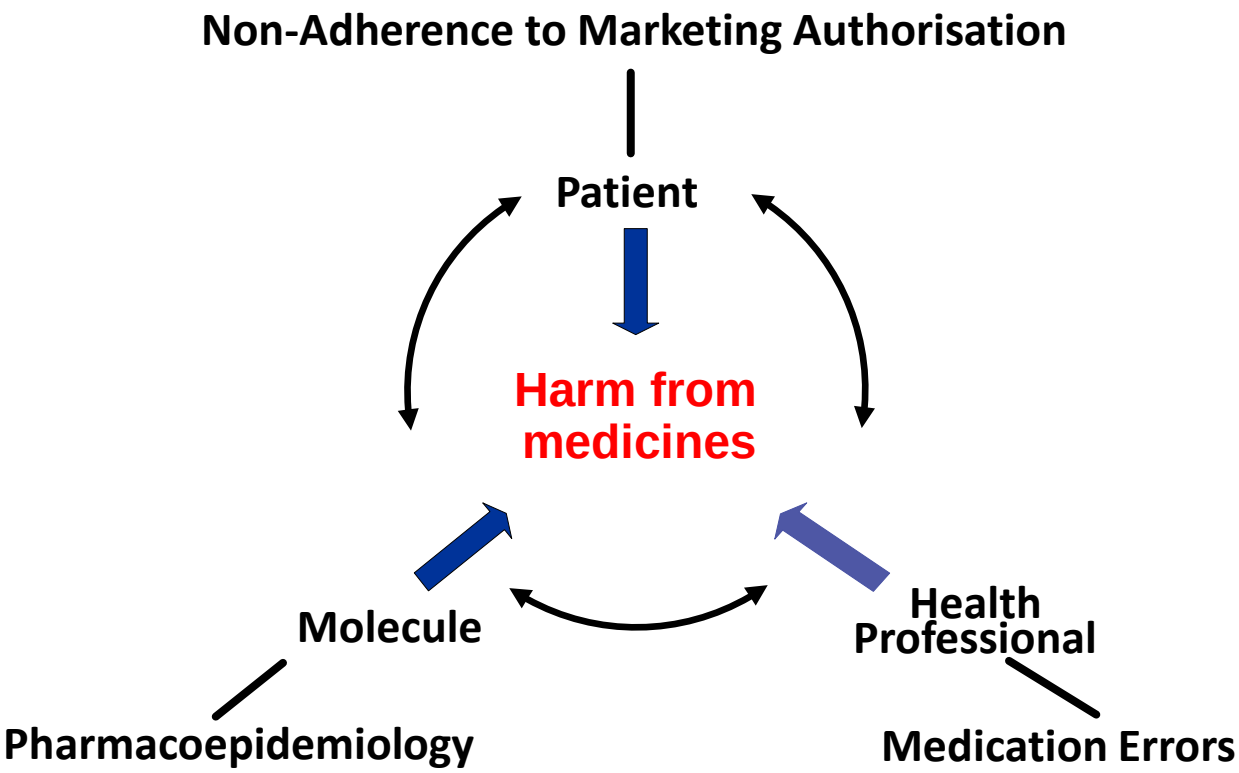
Raymond Anderson

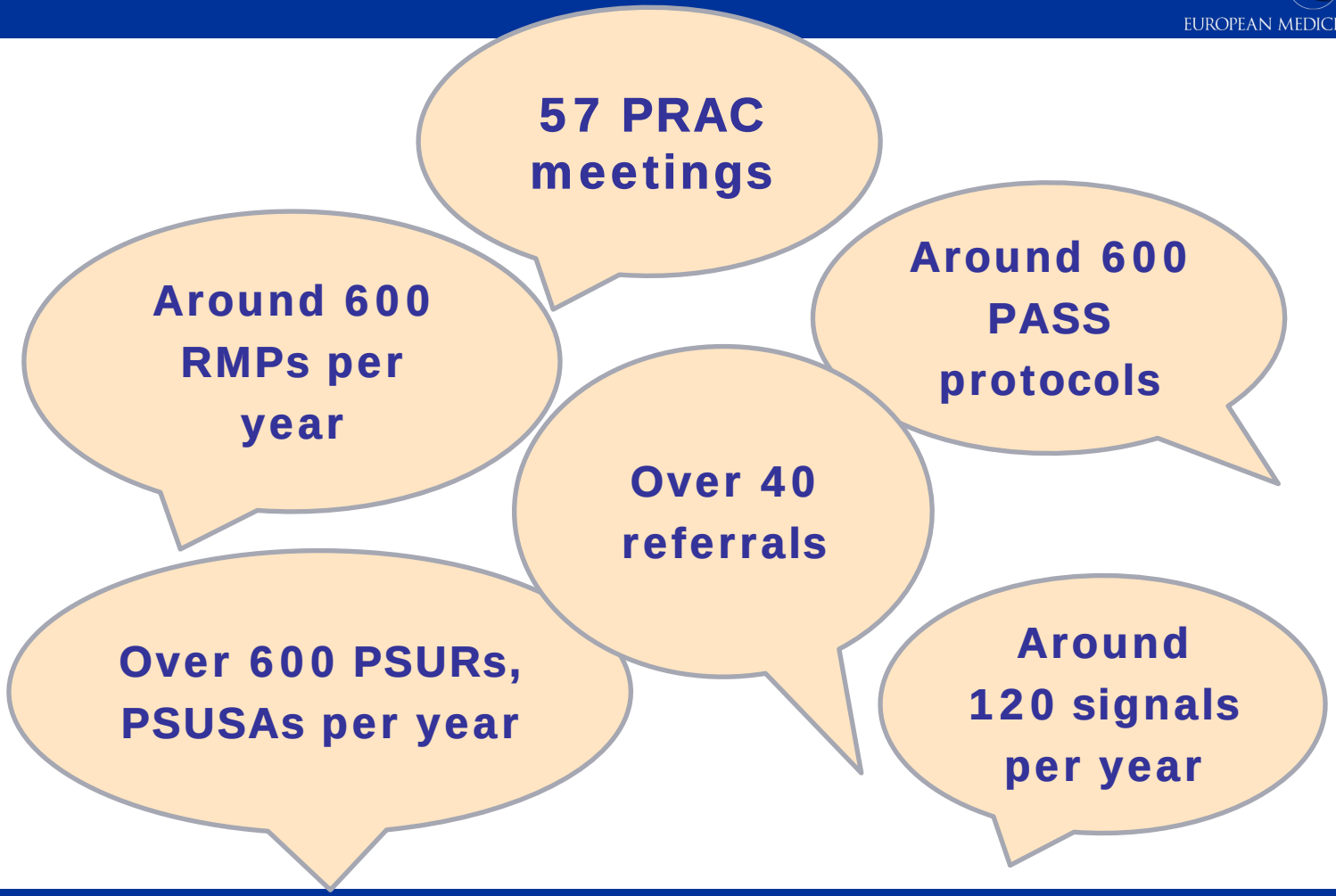
Marco Greco

PRAC's three public health "pillars"

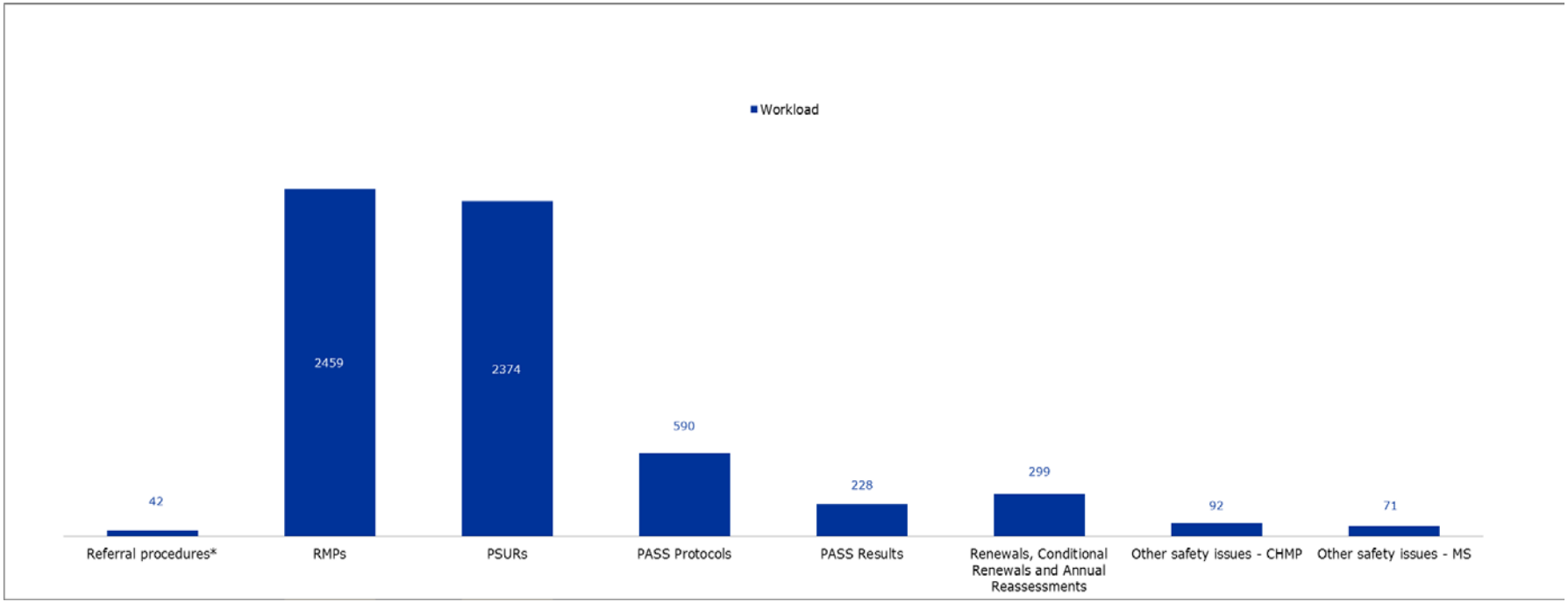


Holistic view of harms from medicines



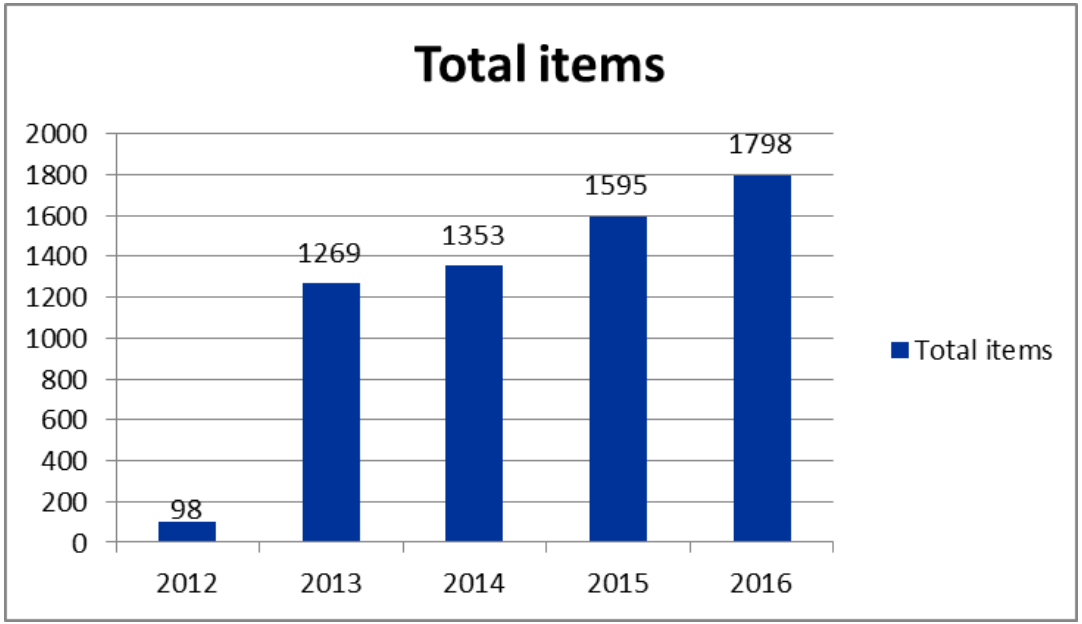

57 PRAC meetings
Around 600 RMPs per year
Around 600 PASS protocols
Over 40 referrals
Over 600 PSURs, PSUSAs per year
Around 120 signals per year

Selected PRAC agenda items - 2012-2016

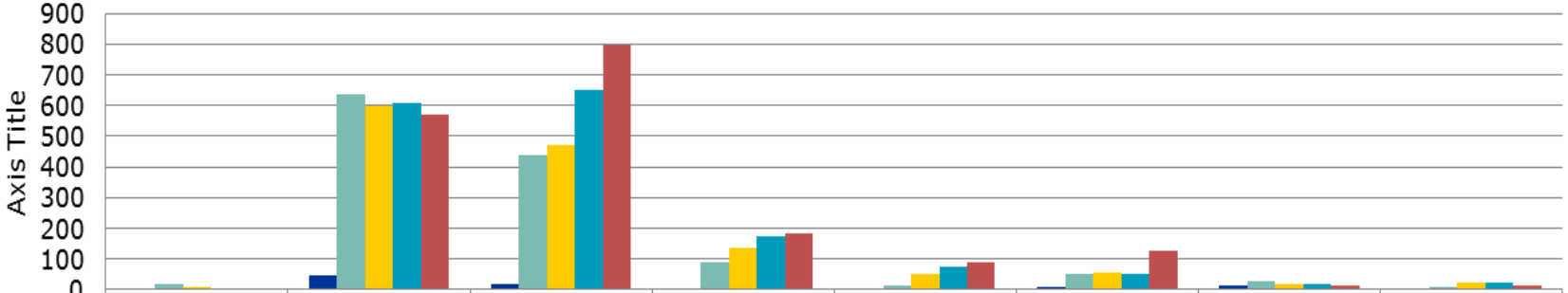


*Referrals figures relate to actual procedures as per the referral team's tracking

Total items per year for Referrals, RMPs, PSUSAs, PASSs, Renewals, Other safety issues



Yearly delta of selected agenda items



	Referral procedures*	RMPs	PSURs	PASS Protocols	PASS Results	Renewals, Conditional Renewals and Annual Reassessments	Other safety issues - CHMP	Other safety issues - MS
2012	6	48	20	5		8	12	5
2013	18	637	438	91	13	53	29	8
2014	7	597	470	137	51	56	19	23
2015	5	607	650	173	73	53	17	22
2016	6	570	796	184	91	129	15	13

*Referrals figures relate to actual procedures as per the referral team's tracking

Proactive & planned pharmacovigilance

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Major PRAC focus on signal detection –Signal Management Review Team (SMART)

- Tools and processes

- Methodological guidance

- Signal detection methods

Implementing Regulation 520/2012 "the Pharmacovigilance Risk Assessment Committee shall regularly review the methodology(ies) used and publish recommendations, as appropriate" [Art 20(3)]

Eudravigilance

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Around 50% signals derive from Eudravigilance ICSRs

If EV used in addition to other resources >54% serious safety issues detected earlier (*Alvarez et al 2010 **)

After audit report PRAC advised in May 2017 that EV meets functional requirements

Go-live November 2017

**Drug Safety 33(6) 475-487*

Receiving ADR reports from patients and HCPs

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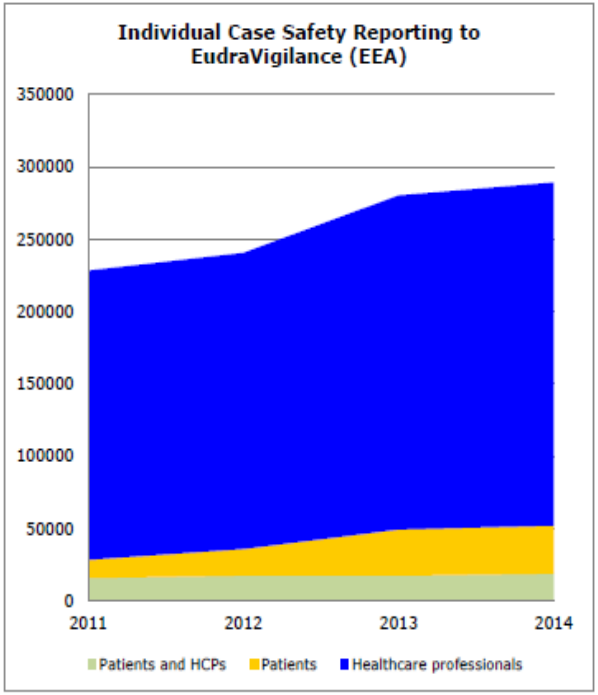
EUROPEAN
COMMISSION

Brussels, 8.8.2016
SWD(2016) 284 final

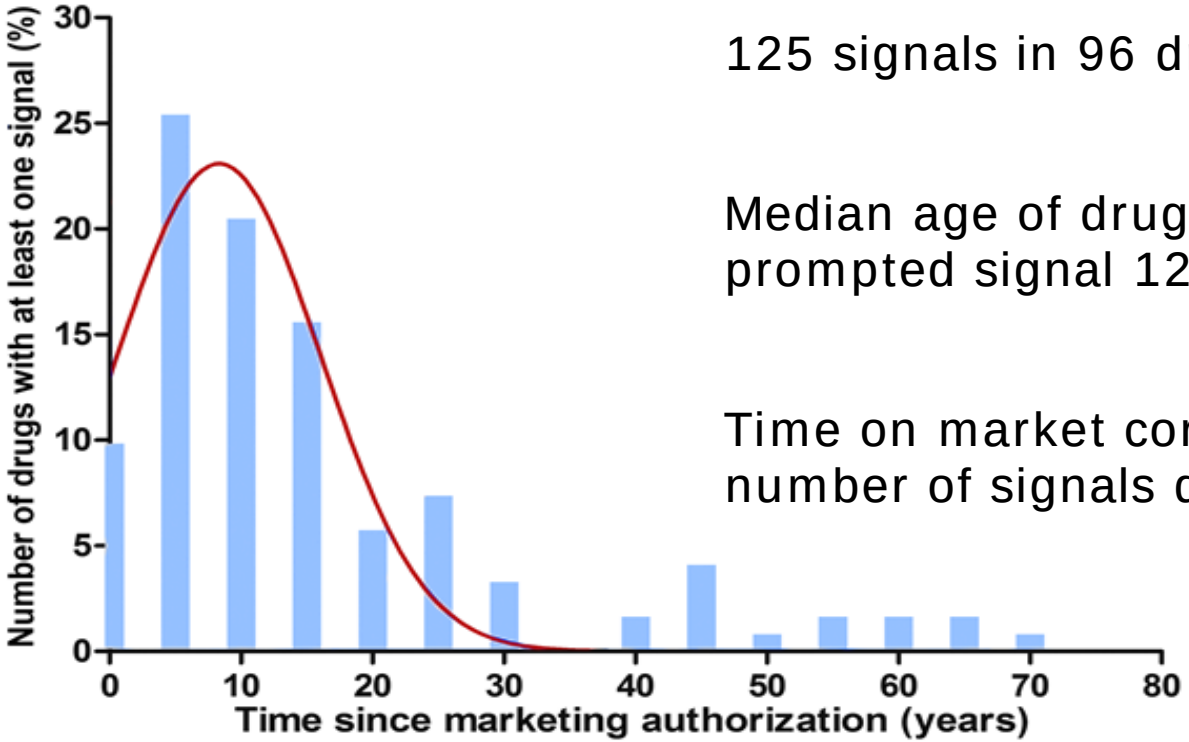
COMMISSION STAFF WORKING DOCUMENT
Accompanying the document

Commission Report

Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012 – 2014)



Signals reviewed by PRAC in first 18 months



125 signals in 96 drugs

Median age of drugs which prompted signal 12 years

Time on market correlated with number of signals detected

Pacurariu et al Drug Safety 15 Nov 2014

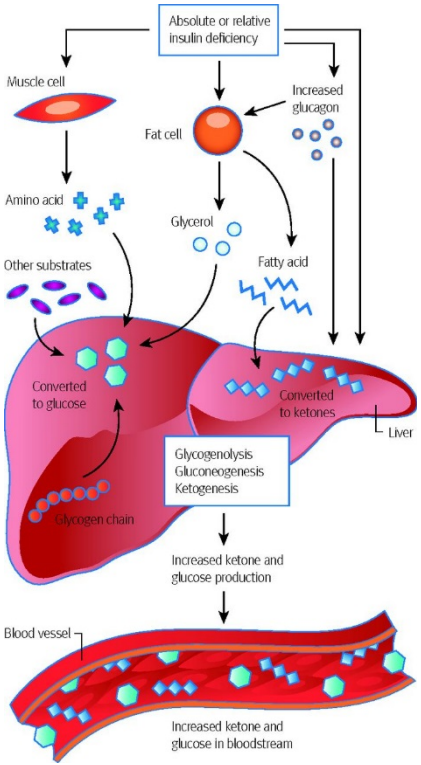
Signal detection algorithm performance

IMI PROTECT project – Research to address limitations of current methods in pharmacoepidemiology & pharmacovigilance

- Compared 15 signal detection algorithms across 7 databases
- Algorithms based on PRR, ROR, MGPS, BCPNN etc
- Key results & conclusions: all disproportionality methods can achieve similar overall performance by choice of algorithm

Candore G et al Drug Safety 2015; 38(6):577-87

Signal - SGLT2 inhibitors & diabetic ketoacidosis

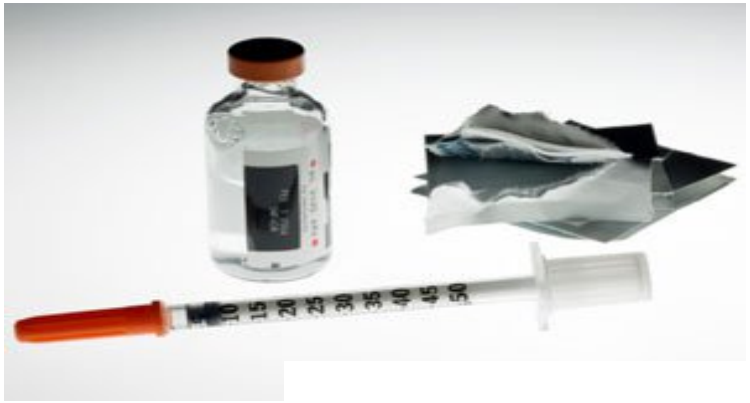


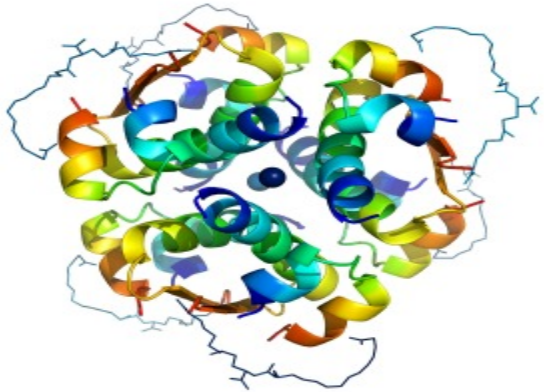
Case reports of diabetic ketoacidosis associated with SGLT2 inhibitors in Type II diabetes

Prompt communication to HCPs in view of particular characteristic of signal – eugycaemia – related to mechanism of action of SGLT2s

Product information for HCPs and patients updated to include serious and occasionally fatal outcome

Medication error - insulins





New generation of insulins

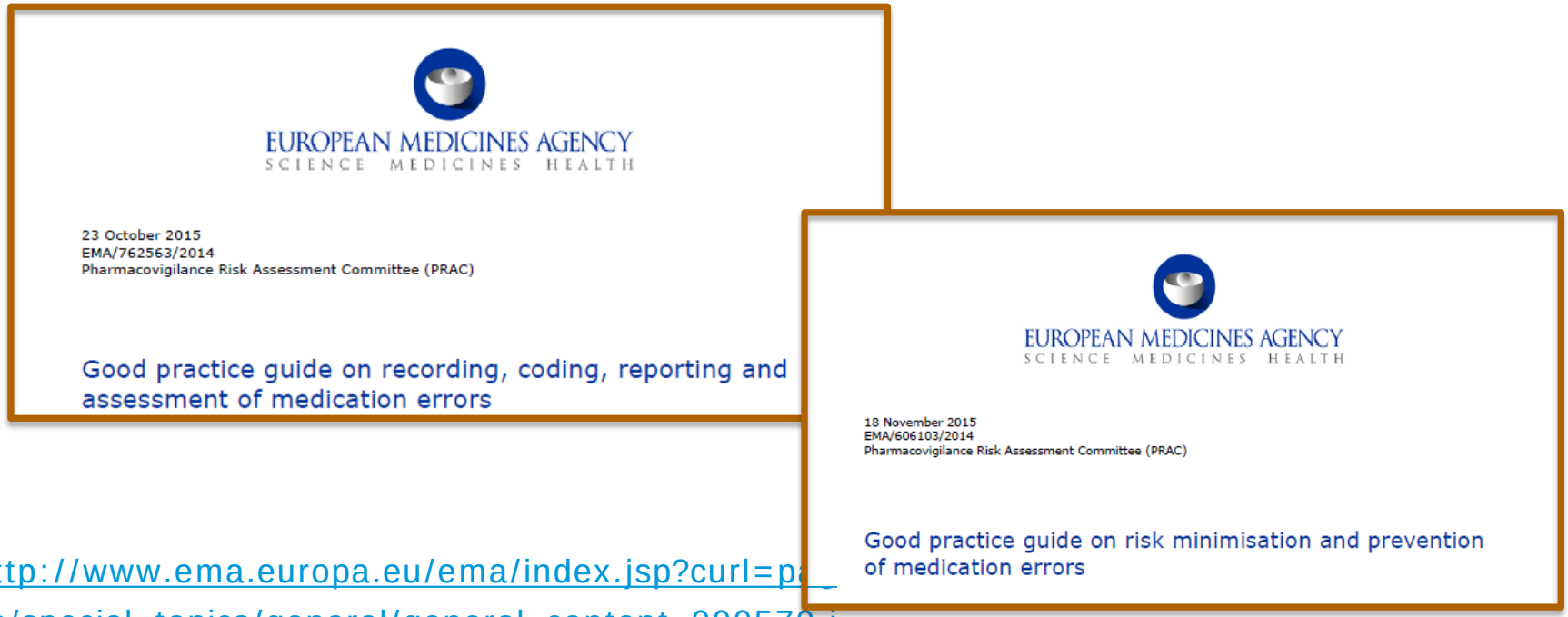
Potential risk of error

- higher strengths

- new combinations

Addendum to GPG supports consistent approach

Medication Errors Good Practice Guides



http://www.ema.europa.eu/ema/index.jsp?curl=pa_
es/special_topics/general/general_content_000570.j
sp

New methodologies for investigating ME error

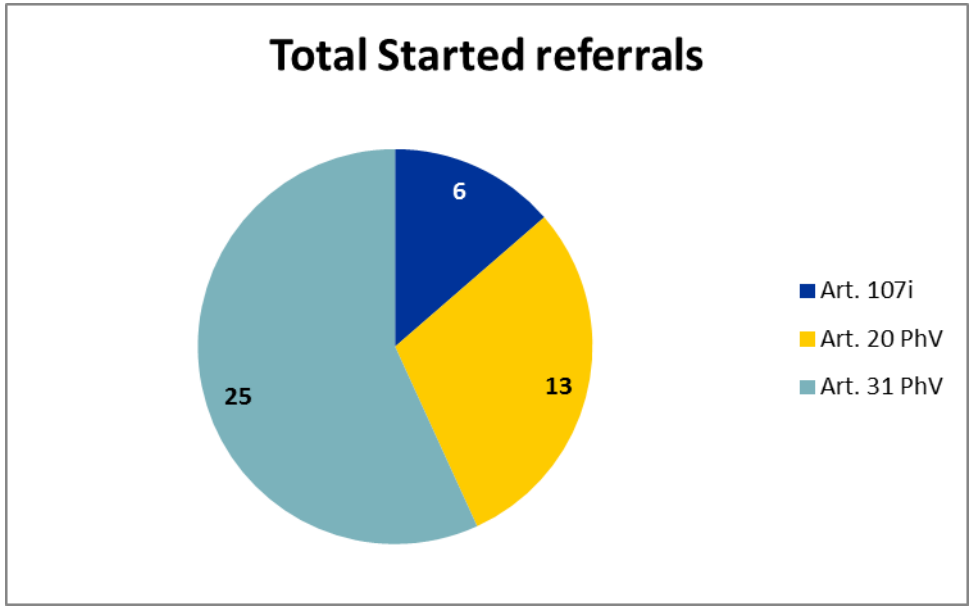
Systematic approach to evaluation making best use of latest available guidance and methodologies

ME Signal evaluation to include Root Cause Analysis

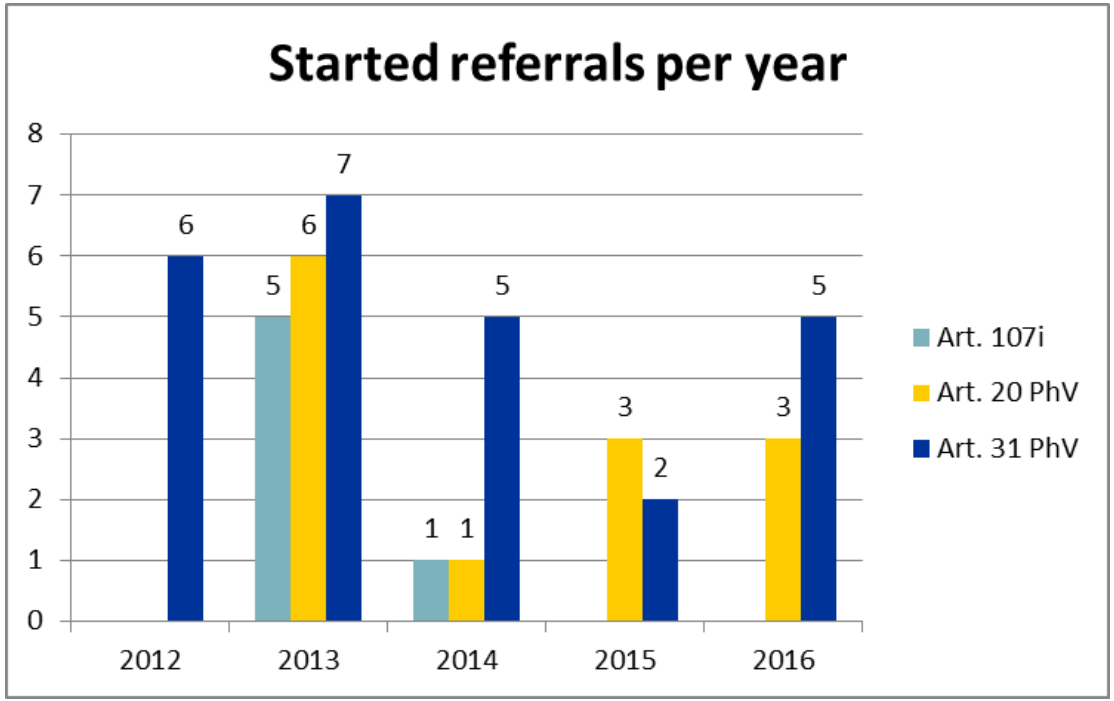
Use of Failure Mode and Effects Analysis Framework

PRAC safety referrals

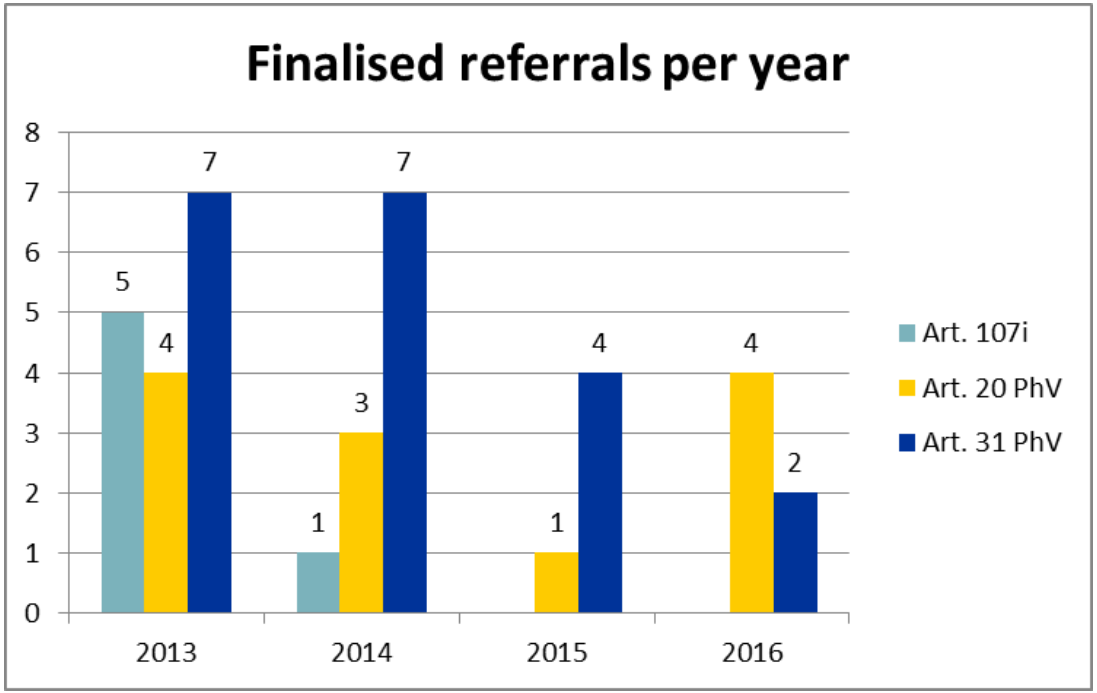
Total procedures started at PRAC per article – 2012-2016



Started referral procedures per year per article – 2012-2016



Finalised referral procedures per year per article – 2012-2016



Benefit Risk review - Gadolinium contrast agents

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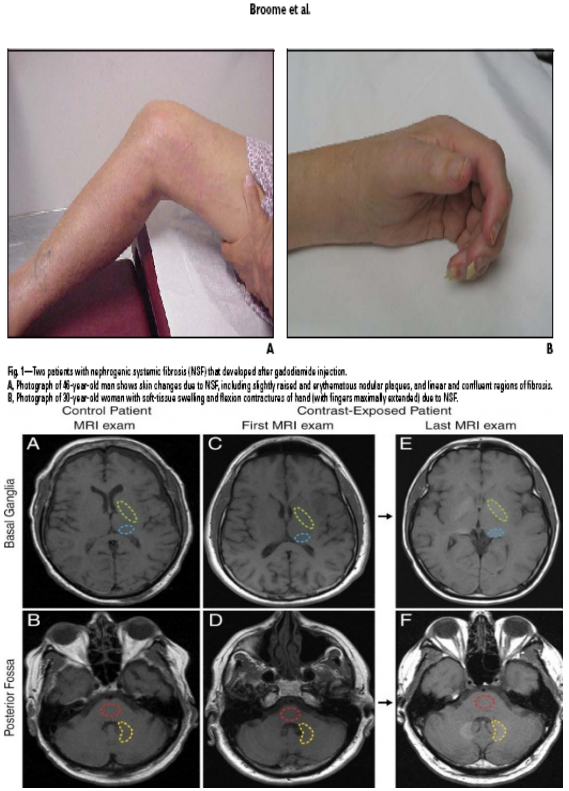
Regulatory action in 2007 on nephrogenic systemic fibrosis

Risk of tissue accumulation appears greater with linear than macrocyclic agents

Benefit risk for some linear agents no longer considered favourable



Benefit risk review - fluoroquinolones

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Drugs

Home > Drugs > Drug Safety and Availability

Drug Safety and Availability

FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together

According to a July 26 FDA Drug Safety Communication (www.fda.gov), these medications have been associated with disabling and potentially permanent side effects involving tendons, muscles and/or joints, as well as peripheral nerves and the central nervous system. Some patients may even experience more than one such adverse effect.

Sodium valproate - risk minimisation effectiveness

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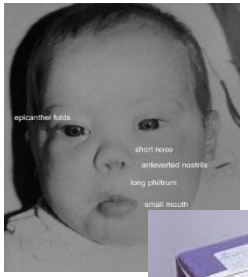
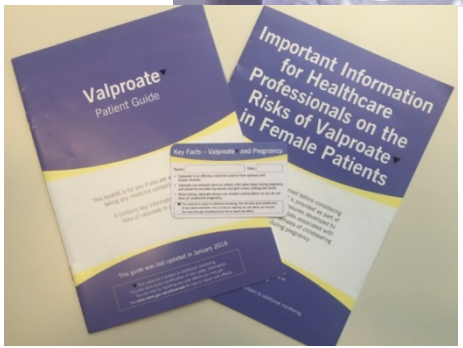
Developmental disorders up to 30 -40% of pre-school children exposed in utero

In addition to 11% risk of birth defects

Further restrictions & strengthened warnings in product information

Ongoing concerns about effectiveness of risk minimisation





Prompt benefit risk action

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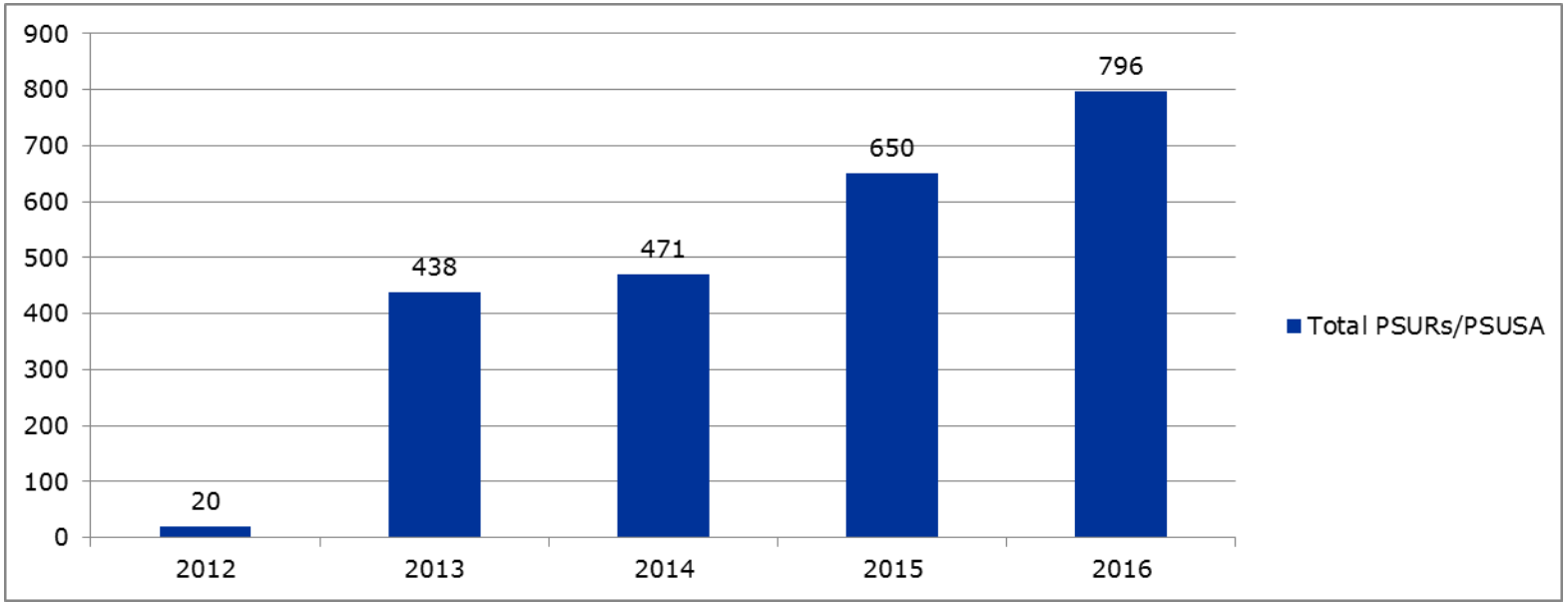
Binding outcomes from referrals, plus rigorous adherence to legal timeframes

PSURs also an important benefit risk decision-making tool in life-cycle

PSUSAs now established and work ongoing via PSUR “Road Map” initiative is optimising procedure

Total PSURs/PSUSA - 2012-2016



PRAC workload statistics 2012-2016

Pharmacogenomics in pharmacovigilance

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SCIENCE MEDICINES HEALTH

January 2014
V/281371/2013
mittee for Medicinal Products for Human Use (CHMP)

4 Guideline on key aspects for the use of pharmacogenomic
5 methodologies in the pharmacovigilance evaluation of
6 medicinal products
7 Draft

Draft Agreed by Pharmacogenomics Working Party	April 2013
Adoption by CHMP for release for consultation	20 December 2013
Start of public consultation	30 January 2014
End of consultation (deadline for comments)	30 July 2014

8

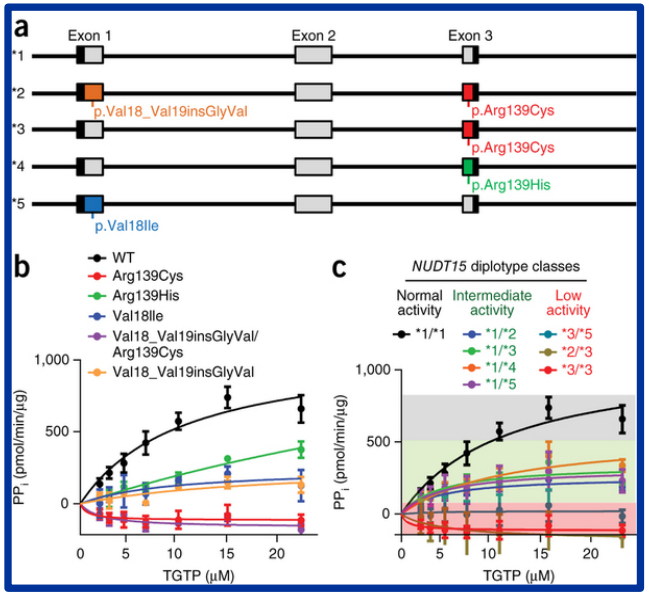
Risk management – 6-mercaptopurine

Mutations in NUDT15 gene result in increased thiopurine-related toxicity - leukopenia, alopecia

Ethnic variability in frequency of NUDT15.415 C>T

- ~ 10 % in E Asians
- 4 % in Hispanics
- 0.2 % in Europeans
- 0 % in Africans

Consider dose reduction in patients positive for NUDT15R139 C variant?



Moriyama et al 2016

Nature Genetics

PRAC: Agendas, minutes and highlights

The European Medicines Agency (EMA) publishes the agendas, minutes and highlights of the plenary meetings of its Pharmacovigilance Risk Assessment Committee (PRAC).

EMA has published the list of acronyms and abbreviations commonly used in the PRAC agendas and minutes:

List of acronyms and abbreviations commonly used in PRAC agenda and minutes.

The table below lists the different types of publications EMA publishes in relation to PRAC plenaries.

Publication type	Publication time
Meeting highlights	Friday after Committee plenary
Agendas	Before start of Committee plenary
Minutes	After Committee plenary where minutes are adopted

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-6 July 2017

News

07/07/2017

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-6 July 2017

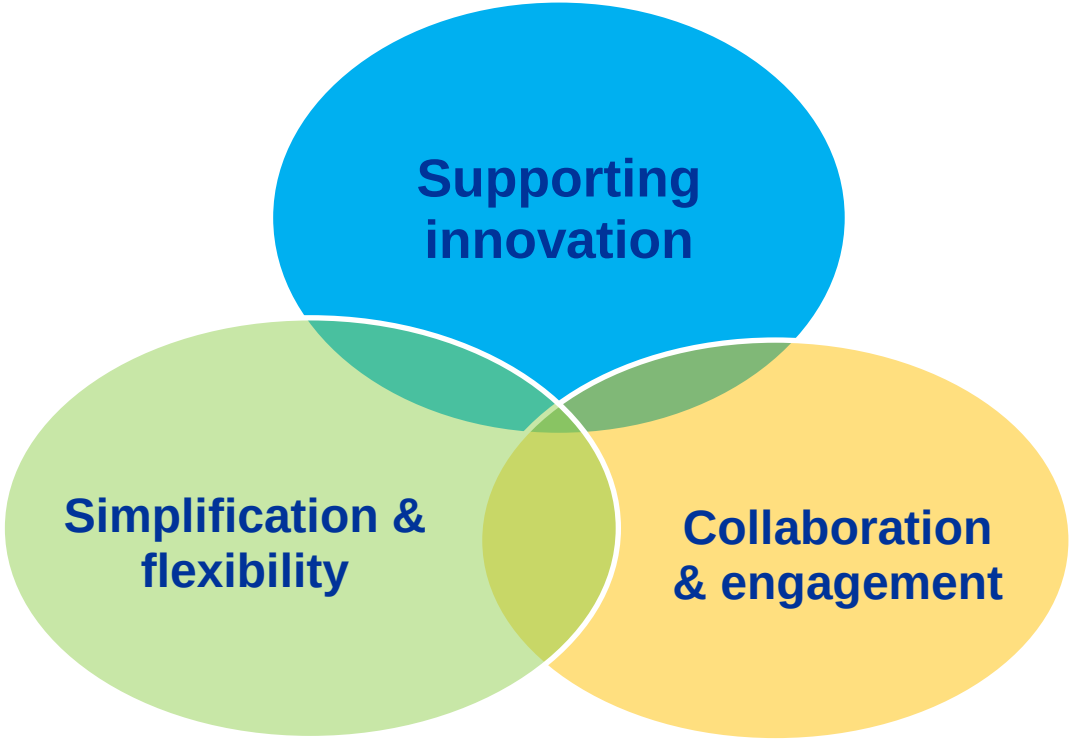
PRAC concluded two referrals and issued provisional measures for treatment of multiple sclerosis; PRAC aware of contraindication for valproate in France

Injectable methylprednisolone products containing lactose must not be given to patients allergic to cow's milk proteins

Related information

- Zinbryta: EPAR
- Medicinal products containing lactose of bovine origin for IV/IM use in acute allergic reactions: Article 31 referrals
- Zinbryta: Article 20 procedures
- Valproate and related substances: Article 31 referrals
- Gadolinium-containing contrast agents: Article 31 referrals

Where are we now?



Enabling access to innovative medicines

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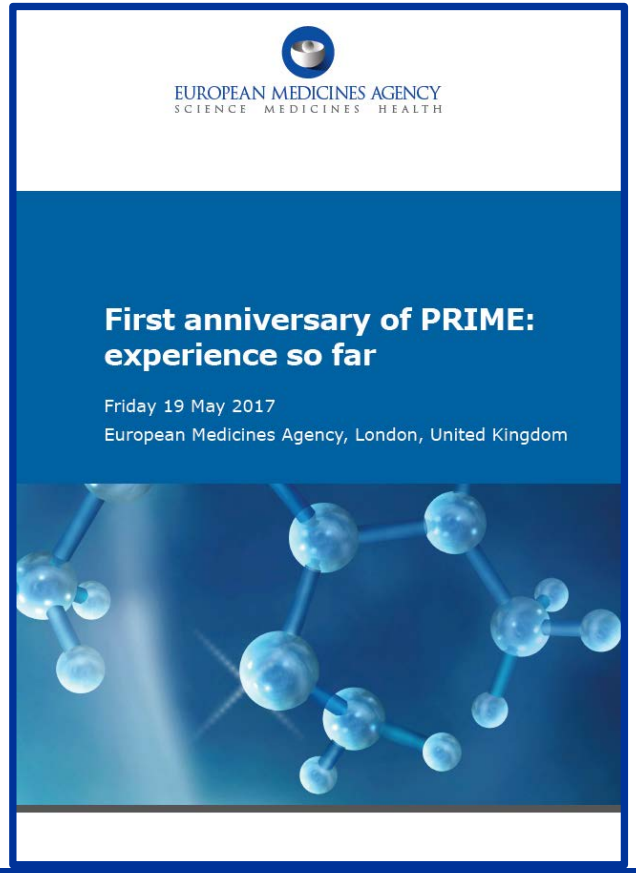

"Many patients with serious diseases have no or only unsatisfactory therapeutic options and should be able to benefit from scientific advancement and cutting edge medicines as early as possible"

Pharmacovigilance as an enabler of innovation

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Access provided to Medicines and Healthcare Products Regulatory Agency by Information Services

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NATURE REVIEWS DRUG DISCOVERY | CORRESPONDENCE

Associated links

CORRESPONDENCE

LINK TO ORIGINAL ARTICLE

Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee

Peter Arlett, Geraldine Portier, Roberto de Lisa, Kevin Blake, Noel Wathion, Jean-Michel Dogne, Almath Spooner, June Raine and Guido Rasi

challenges in the optimization of their safe and effective use.

In the first 18 months of its operation, the PRAC has considered risk management plans for 160 medicinal products. In this work the PRAC has focused on ensuring feasible, evidence-based and risk-proportionate planning[4].

The collection of individual reports of suspected adverse drug reactions (ADRs) is one of the foundations of drug surveillance, and the reporting rules have been strengthened. These now include the formal

"We suggest more safe & effective drugs can be made available

Through planning, engagement and transparency, as well as rapid assessment"

Arlett P et al 2014 Nat Rev Drug Disc

Risk Management Plans 2012-2016

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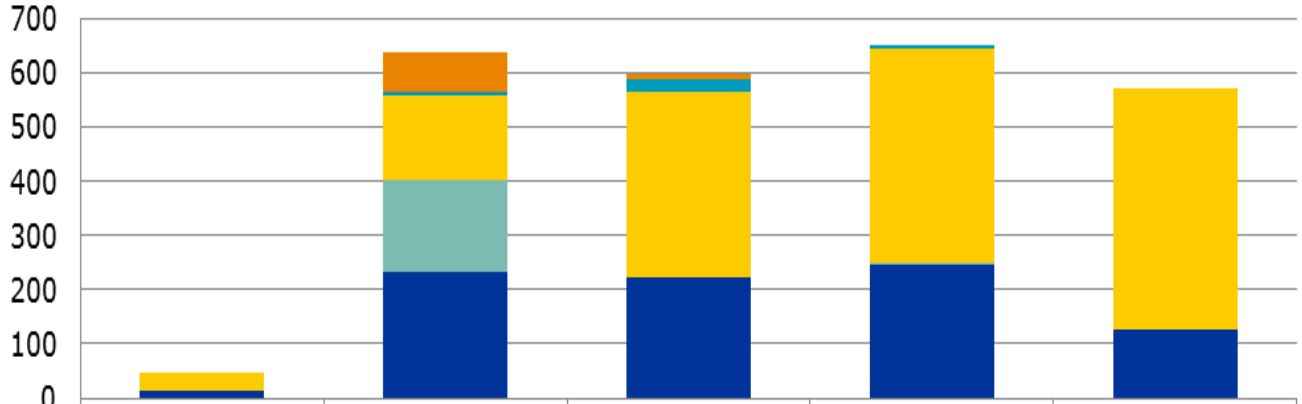
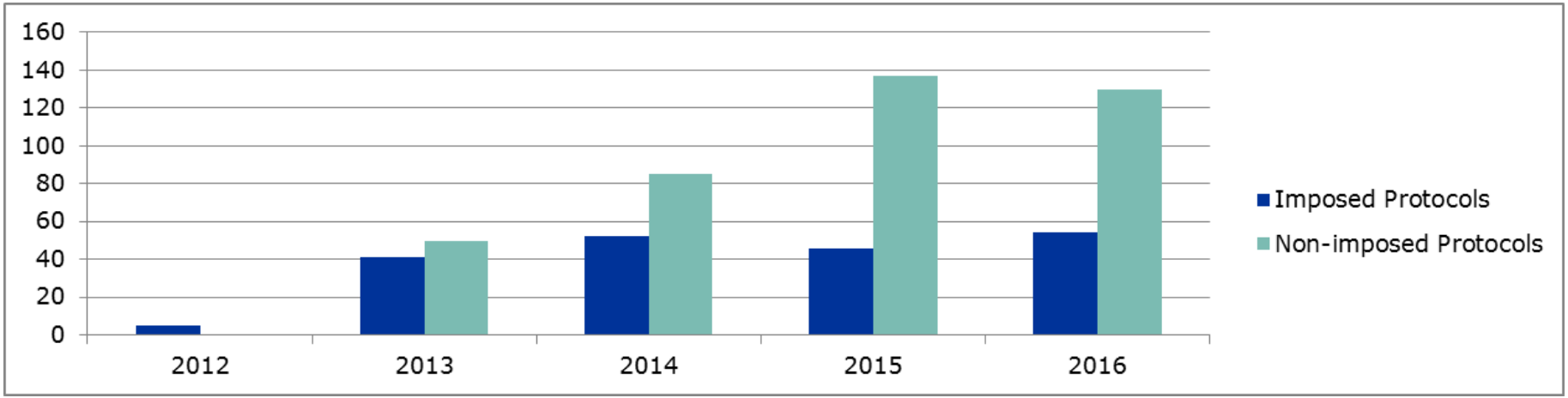
Origins of RMPs on PRAC Agenda 2012-2016

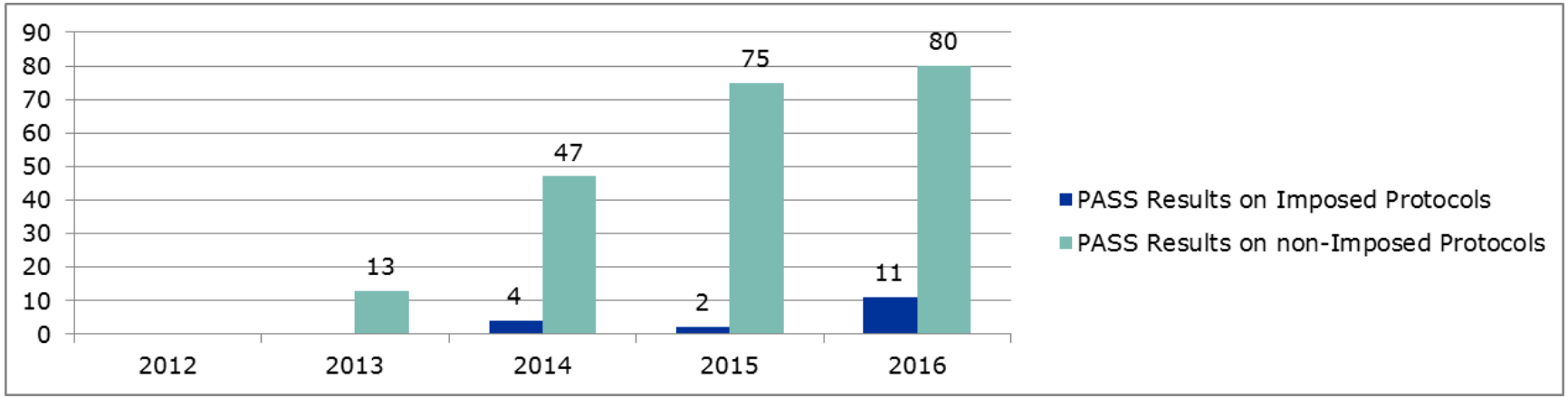


	2012	2013	2014	2015	2016
Post-auth Standalone		72	11	0	0
Post-auth with Renewal		8	21	4	0
Post-auth with Variation	34	154	343	396	444
Post-auth with PSUR		169	0	3	0
Pre-authorisation phase	14	234	222	246	126

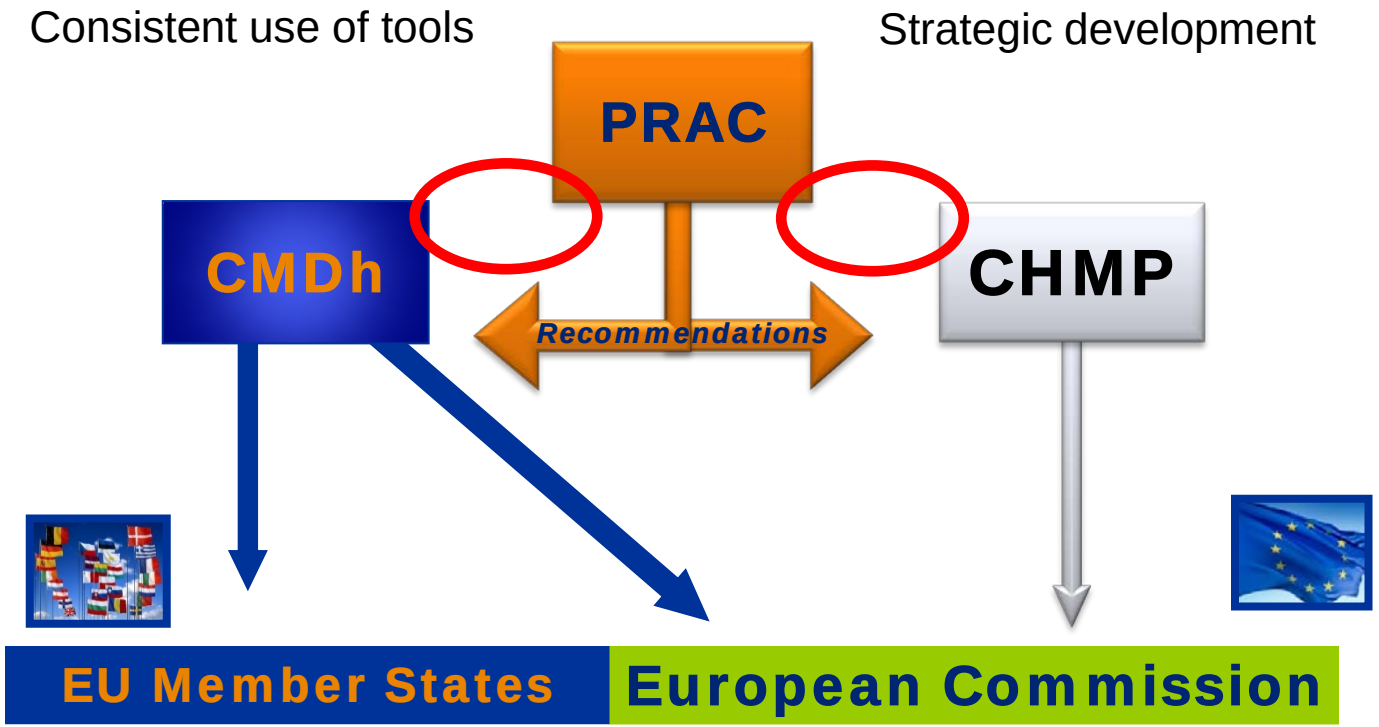
Imposed vs Non-imposed protocols - 2012-2016



PASS results by type - 2012-2016



Collaboration between committees



Engagement with patients & public

Interaction with patient and healthcare professional organisations during referrals via stakeholder groups

First PRAC public hearing
26 September 2017

Understanding patients' risk tolerance

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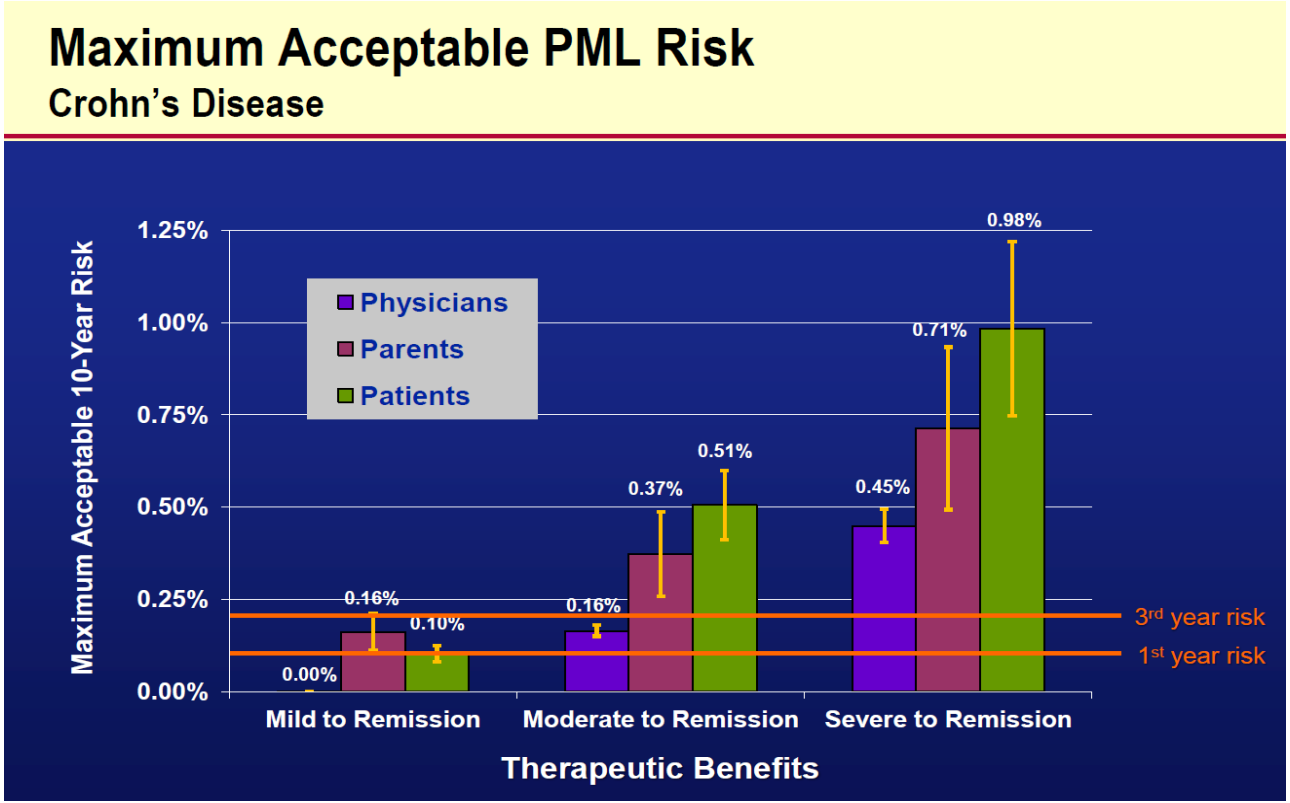

Johnson et al 2010 J Manag Care Pharm

innovative medicines initiative

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ADVANCE

Media Monitoring of the HPV Vaccines Debate – What the public wants to know and experts should address

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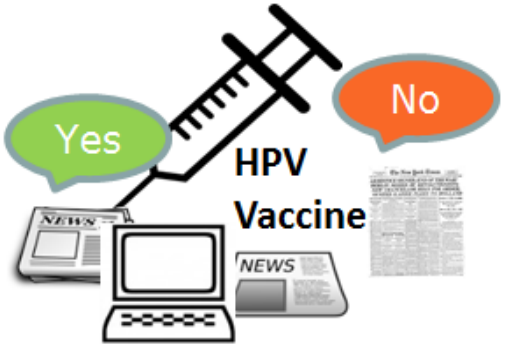
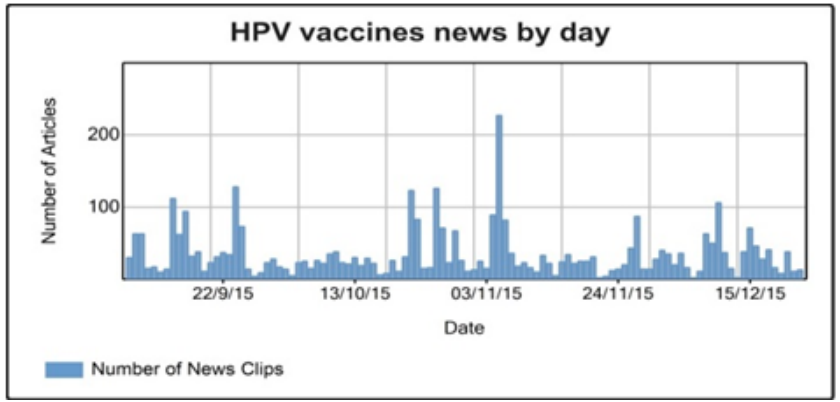




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2015
EMA/762033/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

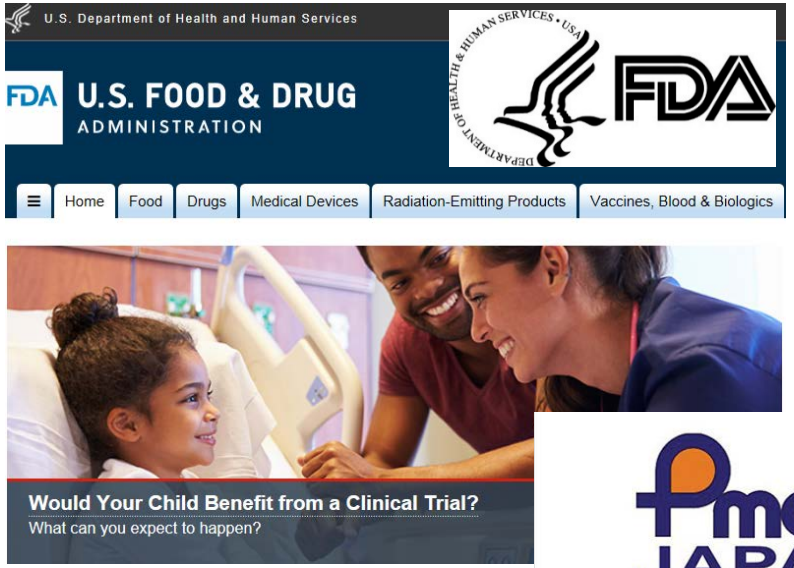
Review under Article 20 of Regulation (EC) No 726/2004

Human papillomavirus (HPV) vaccines

Procedure numbers:
Cervarix: EMEA/H/A20/1421/C/0721/0071
Gardasil: EMEA/H/A20/1421/C/0703/0060
Gardasil 9: EMEA/H/A20/1421/C/3852/0001
Silgard: EMEA/H/A20/1421/C/0732/0054

Communication and engagement following referral on HPV vaccine

International collaboration by PRAC



Regular bilateral pharmacovigilance teleconferences

Bilateral agreements with FDA, Health Canada & Japan PMDA

Health Canada

PRAC Impact Strategy

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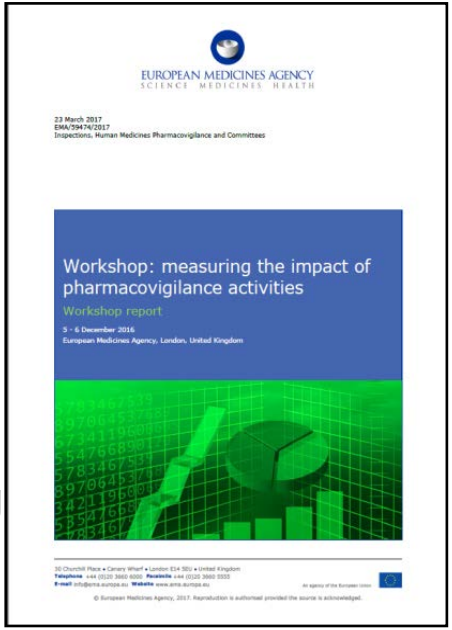
International Workshop 5-6 December 2016

Attendance >150 participants from regulatory &public bodies, healthcare professional & patient organisations, academia and pharmaceutical industry

Main objective: to explore methodologies for measuring impact of product-specific regulatory actions in terms of public health outcomes and impact of individual pharmacovigilance processes

Secondary objectives: to identify enablers & barriers to measuring impact of pharmacovigilance (patient & HCP engagement)

Recommendations reflected in adopted **PRAC Work Plan 2017**



Joint EMA/DIA Information Day

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Information Day on Impact of Pharmacovigilance 14th November

Objectives: progress of implementation of the strategy, reviewing methodologies for measuring impact and case studies, fostering collaboration and sharing of information amongst stakeholders (see EMA events calendar);

1 – *The regulatory framework for impact evaluation of pharmacovigilance activities*

2 – *Getting it right: systematic collection of impact data throughout life-cycle*

3 – *Methodologies for impact evaluation*

4 – *What do to with results of impact evaluations – are we ready for the change?*

PRAC 5 years of operation

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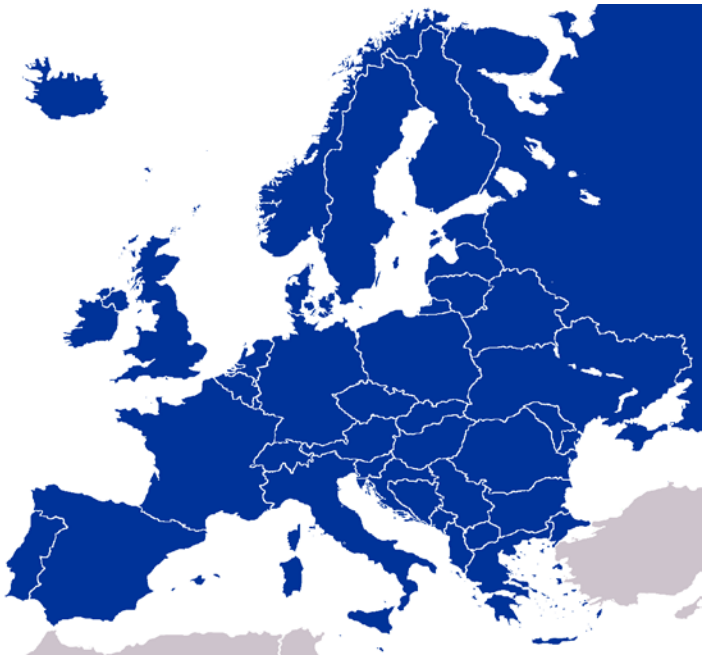
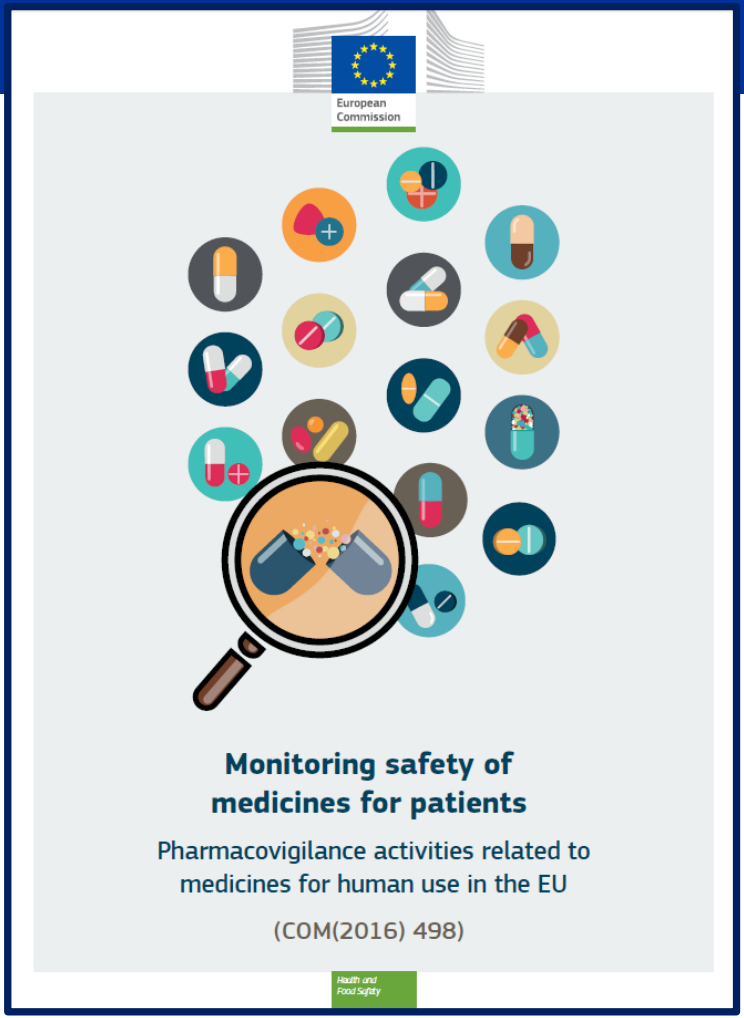
Monitoring benefit risk throughout product lifecycle in near real-time

Timely decision-making as evidence accrues

Using all available evidence supported by suitable methodologies

Patients & **healthcare professionals'** views integrated throughout





With thanks to PRAC members, PRAC Secretariat and EMA colleagues for unstinting support and dedication

Thank you for your attention

Further information

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