



# **Irish Institute of Pharmacy Seminar 2015**

## **‘Supporting the Pharmacy Journey’**

### **A Healthcare Products Regulatory Perspective on the journey ahead.**

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**Almath Spooner, Pharmacovigilance and Risk Management Lead,  
HPRA and Vice Chair EMA’s PRAC**

**Irish Institute of Pharmacy, RCSI, Dublin, September 23rd 2015.**



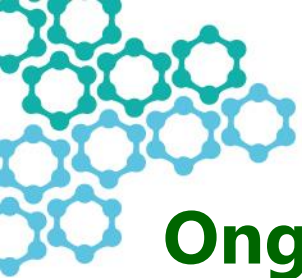
**Complex Biologics,**  
**Gene Therapy**  
**Regenerative**  
**Medicine**  
*Precision Medicine*  
**Diagnostic/device/drug**  
**combos**  
**Nanomedicine**  
*Synthetic Biology...*

# Regulatory Timeline



IMB Act – human and veterinary medicines, clinical trials		Export certification for medicines				Medical devices				Tissues and cells					Cosmetics		Human organs for transplantation		IMB becomes the Health Products Regulatory Authority
1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
IMB established					Enforcement		Controlled drugs (licensing remains with the Department of Health)			Blood and blood components					Protection of animals used for scientific purposes				Veterinary clinical field trials

The role of the Health Products Regulatory Authority (HPRA) is to protect and enhance public and animal health by regulating medicines, medical devices and other health products.



# Ongoing improvement in medicines regulation



- **50** years of EU regulation
- **20** years of EMA
- **5** years since adoption of Phvlg legislation
- **3** years of PRAC
- **1** year of HPRA



## DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

- (2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.



# The EU public health challenge

5% of all hospital admissions due to ADRs

5% of all hospital patients experience an ADR

ADRs 5<sup>th</sup> 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 Risk Assessment Committee PRAC

REGULATION (EU) No 1235/2010 the Mandate shall cover...

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

## PRAC membership

### Appointed by each Member State:



- 1 member + alternate
- 27 + EEA countries non voting members

### Appointed by the European Commission (public call for expressions of interest):



- 1 patient organisations<sup>1</sup> rep + alternate
- 1 healthcare professionals<sup>1</sup> rep + alternate



- 6 members to ensure relevant expertise available

<sup>1</sup> *Criteria for involvement in EMA activities*





EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

7 September 2015  
EMA/PRAC/596669/2015  
Procedure Management and Committees Support Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 07-10 September 2015

Chair: June Raine – Vice-Chair: Almath Spooner

07 September 2015, 13:00 – 19:00, room 3/A

08 September 2015, 08:30 – 19:00, room 3/A

09 September 2015, 08:30 – 19:00, room 3/A

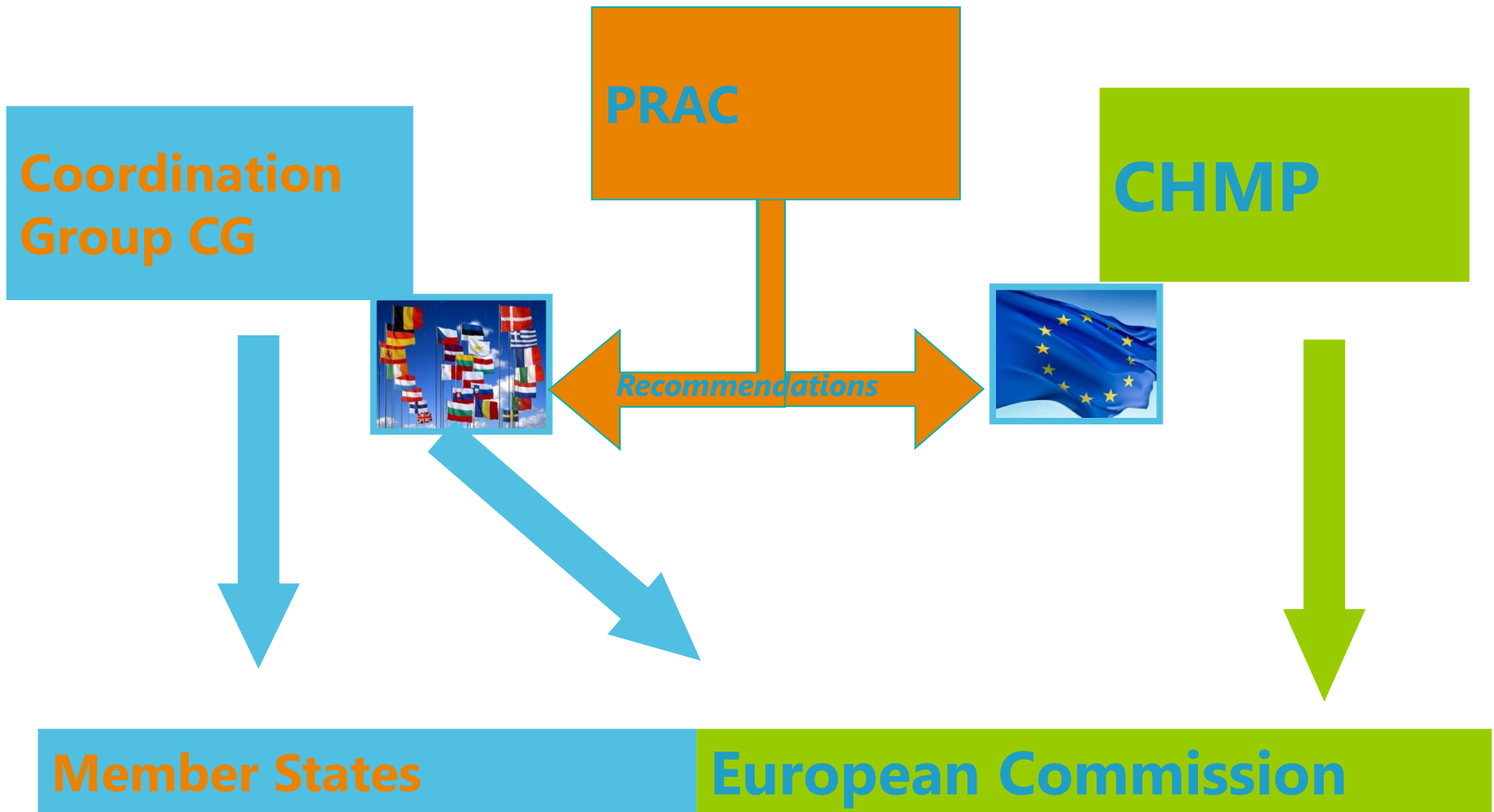
10 September 2015, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

24 September 2015, 10:00 – 12:00, room 6/B, via teleconference



**HPRA**  
An tÚdarás Rialála Táirgí Sláinte  
Health Products Regulatory Authority



# ADR reporting and Additional monitoring scheme



## OUR ADVICE ON

## Medicines and side effects

Medicines can help us live longer and healthier lives. They can help cure or treat an illness or disease and can also prevent some conditions from developing in the first place.

During the course of our lives, it is likely that

hpra.ie

We encourage people to report suspected side effects so that we have more information available about the use of medicines. This helps us to monitor their safety.

## What is a side effect?

A side effect is when something unwanted or unintended happens after taking a medicine. In many cases, side effects to medicines are mild and you can continue to take the medicine. However, for some people the side effects can



As a patient, you have the right to report unwanted side effects of medicines directly to the authorities. You can also report a side effect on behalf of someone in your care, such as a child or relative.

*Remember to speak to your doctor or pharmacist if you are worried about any suspected side effects.*

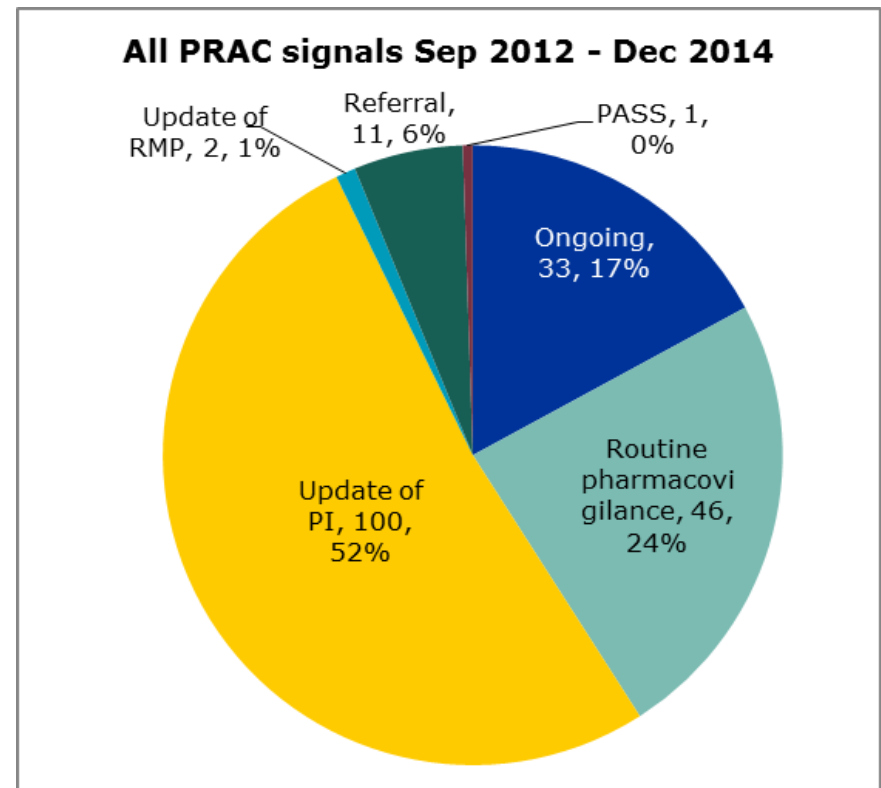
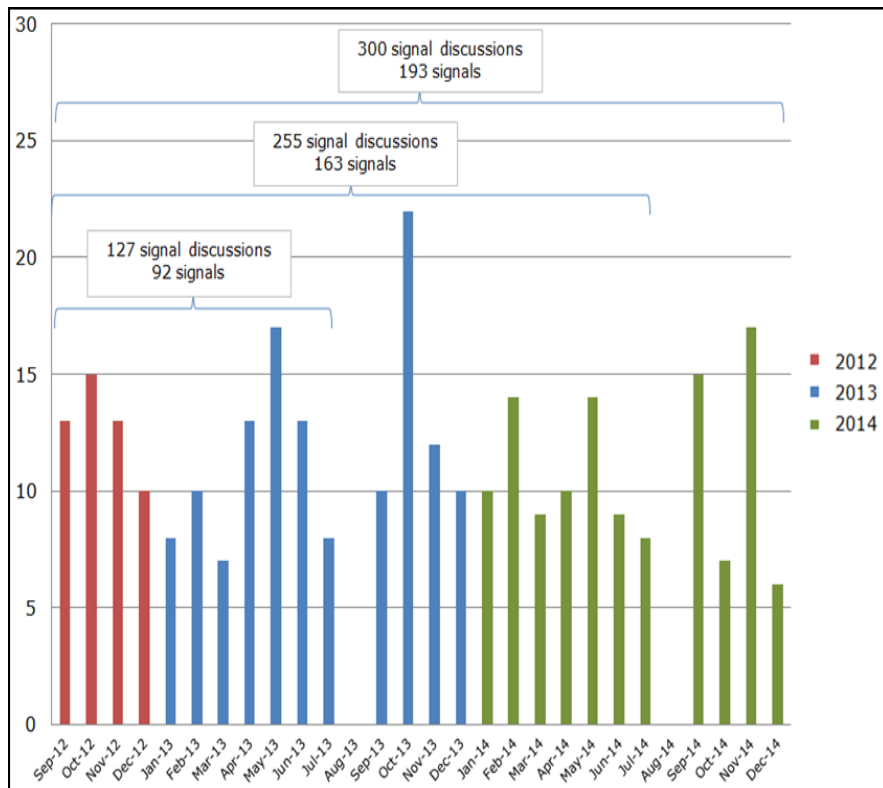
## Why report a side effect?

We are always learning more about medicines. Although they are tested extensively in clinical trials before they are authorised, not everything can be known about their side

## How do I report a side effect?

If you think a medicine has caused a side effect, please check the package leaflet that comes with the medicine for information on how to report it.

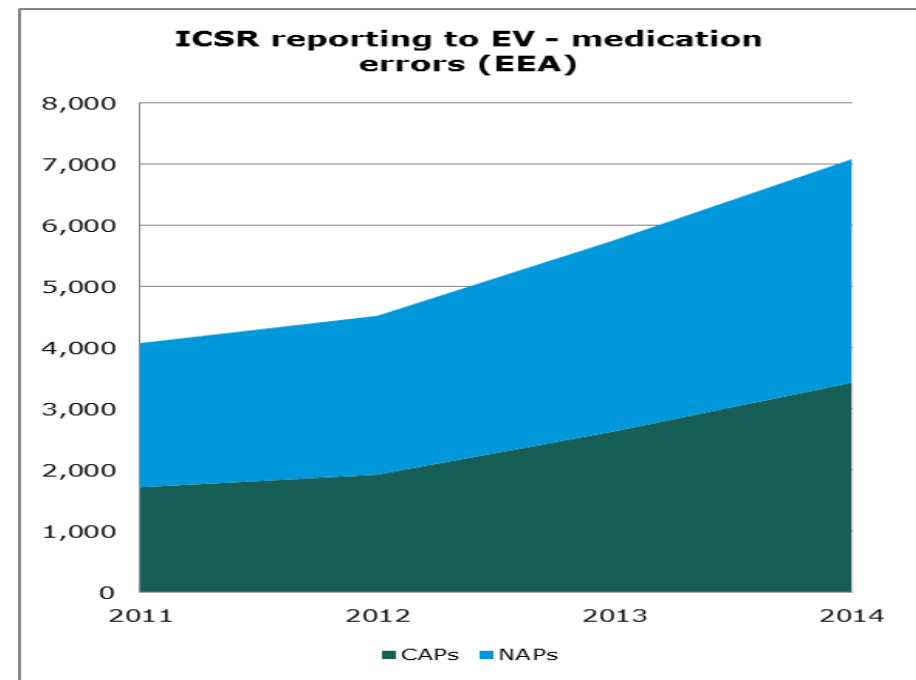
# Safety signals: Faster detection and management of new and changing safety issues



# Medication errors: improvements to reduce the burden of harm

## HMA Medication Errors Action Plan 2014-2015

Deliverable ▶					
Framework ▼					
	Good Practice Guide Coding & Reporting	Good Practice Guide Risk Minimisation & Prevention	Concept Paper Working Group	Awareness Campaign Reporting	Communication Toolbox
<b>SCOPE</b> (Strengthening Collaboration for Operating Pharmacovigilance in Europe )	Consultation/Input			Lead Development	Lead Development
<b>EMA / EU-Regulatory Network</b> (PhV Legislation Implementation)	Lead Development	Lead Development	Consultation/Input	Consultation/Input	Consultation/Input
<b>MedDRA Points to Consider</b> Working Group	Consultation/Input		Lead Development		
<b>Patient Safety &amp; Quality of Care</b> Working Group	Consultation/Input	Consultation/Input	Consultation/Input	Consultation/Input	Consultation/Input



# Sources of evidence: expansion of data streams

## **‘Hierarchy’ of evidence and regulatory decision making**

Ia: systematic review or meta-analysis of RCT's

Ib: at least one RCT

IIa: at least one well-designed controlled study without randomisation

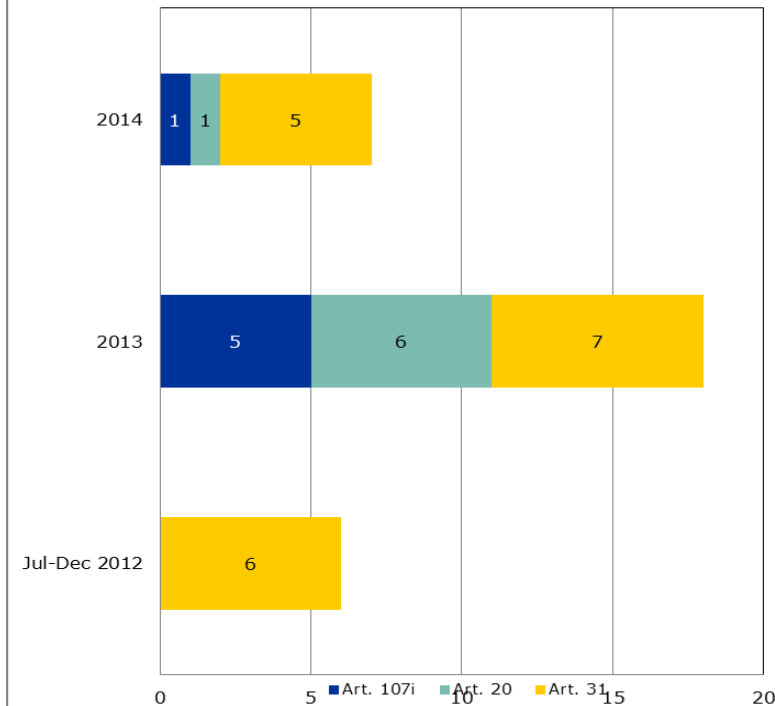
IIb: at least one well-designed quasi-experimental study, such as a cohort study

III: non-experimental descriptive studies, e.g. comparative studies, correlation studies, case–control studies and case series

IV: expert committee reports, opinions and/or clinical experience of respected authorities

# Referrals to PRAC: major assessments delivering labelling for safe and effective use of medicines

Pharmacovigilance related referrals started per year



Valproate related substances	31PhV	Oct-13	neurodevelopmental effects following exposure in utero
Ponatinib	20PhV	Dec-13	vascular occlusive events
Testosterone	31PhV	Apr-14	cardiovascular events
Codeine for cough in paediatric population	31PhV	Apr-14	respiratory depression
Ambroxol/Bromhexine	31PhV	Apr-14	hypersensitivity reactions in children
Hydroxyzine	31PhV	May-14	pro-arrhythmogenic potential
Ivabradine	20PhV	May-14	CV death + non-fatal MI in symptomatic angina patients
Ibuprofen and dexibuprofen	31PhV	Jun-14	thrombotic risk potential as of COX-2 inhibitors and of low-dose aspirin

*Example* - Sodium valproate in pregnancy

Indications in EU include epilepsy, bipolar disorder & migraine

Use in women of child bearing potential varies across Europe

Nature and magnitude of developmental risk needs to be better understood

## Patient representatives contributing to decision





### In this Edition

- 1 Health Products Regulatory Authority (HPRA)
- 2 Transdermal fentanyl: Reminder about the potential for life-threatening harm from accidental exposure to transdermal fentanyl
- 3 Denosumab (Prolia): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia
- 5 Ferumoxytol (Riasol): New important advice to mitigate the risk of serious hypersensitivity reactions.
- 6 Beta interferons: Risk of thrombotic microangiopathy and nephrotic syndrome
- 7 Adverse Reaction Reporting during 2013
- 8 Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

## Health Products Regulatory Authority (HPRA)



As highlighted in the 62nd edition of the Drug Safety Newsletter (DSN) published in June 2014, the link

To continue to receive the DSN, please register on the HPRA website [www.hpra.ie](http://www.hpra.ie) to receive an alert



National Cancer Control Programme Toolkits



Upcoming CPD Opportunities



HPRA Drug Safety Newsletter



Right-click here to

book prevented automatic download of some pictures in this message.

substitution of medicines not included in the HPRA List of Interchangeable Medicines. Further information on interchangeable medicines can be found on the [HPRA website](http://www.hpra.ie).

### 2. Risk of Abnormal Pregnancies in Women taking Valproate Containing Medicines

In December 2014, the HPRA highlighted important [Safety Information on Medicines containing Valproate and the Risk of Abnormal Pregnancy Outcomes](#).

The HPRA and Epilepsy Ireland have brought to our attention that many women of child bearing age who take medicines containing valproate (generally prescribed for the treatment of epilepsy or bipolar disorder) have not been informed by their healthcare professional that they are at an increased risk of abnormal pregnancy outcomes. Pharmacists should ensure that female patients, of child bearing age, are informed of and understand:

- the risks associated with valproate during pregnancy;
- the need to use effective contraception;
- the need for regular review of treatment;
- the need to rapidly consult a healthcare professional if they are planning a pregnancy or if they become pregnant.

Further information and educational materials, available to healthcare professionals and patients, can be found in this HPRA notice on [Medicines Containing Sodium Valproate](#). Pharmacists are encouraged to bring these, and any other appropriate educational materials, to the attention of relevant patients presenting in the pharmacy.



# Life-cycle pharmacovigilance - What we are trying to achieve: Protect and promote – two sides of the same coin



## **Protect 'safety'**

- Through detection and management of side effects

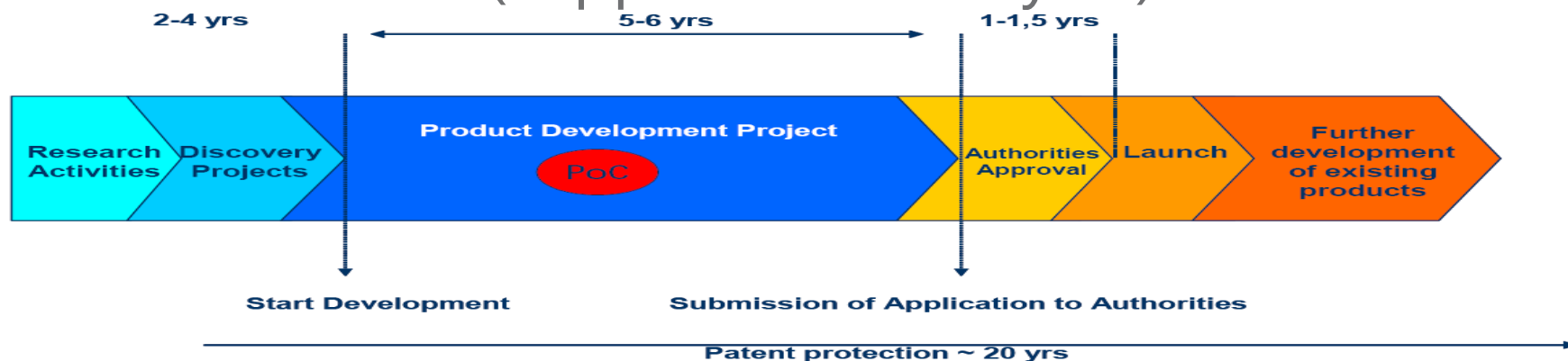
## **Promote 'efficacy'**

- Fulfil unmet medical needs

Support product lifecycle and innovation through better data collection

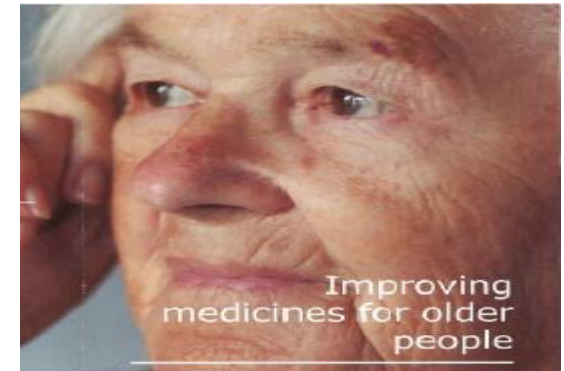
# How does pharmacovigilance support safe innovation?

- **Proactive enabler:** planning for data collection, management of risk and monitoring of use.
- **Reactive responder:** analysis and integration of various data streams – updated advice to optimise use.
- Provides: **assurance that data will be available once a product** is on the market to allow actions for risk minimisation and benefits optimisation
- **Enabler: product development and authorisation** (supports the lifecycle)



# Lifecycle benefit risk management and risk proportionality in practice

- **Timely access** to medicines.
- **Managing risk.**
- Improving access to **high quality patient information.**
- Collecting and evaluating safety data – **establishing safety in use.**
- Responsive to **public health challenges** and **changes in health care delivery.**
- Expanding the parameters of OTC medicines – **patient empowerment facilitated by the enhanced role of pharmacy.**



## Update on Domperidone

October 2014:

Subsequent to the below, the PSI issued [Guidance on the safe supply of products containing domperidone](#). See related

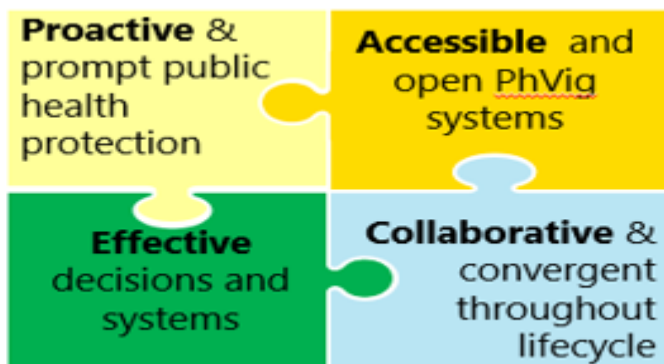
## Guidance for Pharmacists on the Safe Supply of Non-Prescription Levonorgestrel 1500mcg for Emergency Hormonal Contraception

Pharmaceutical Society of Ireland

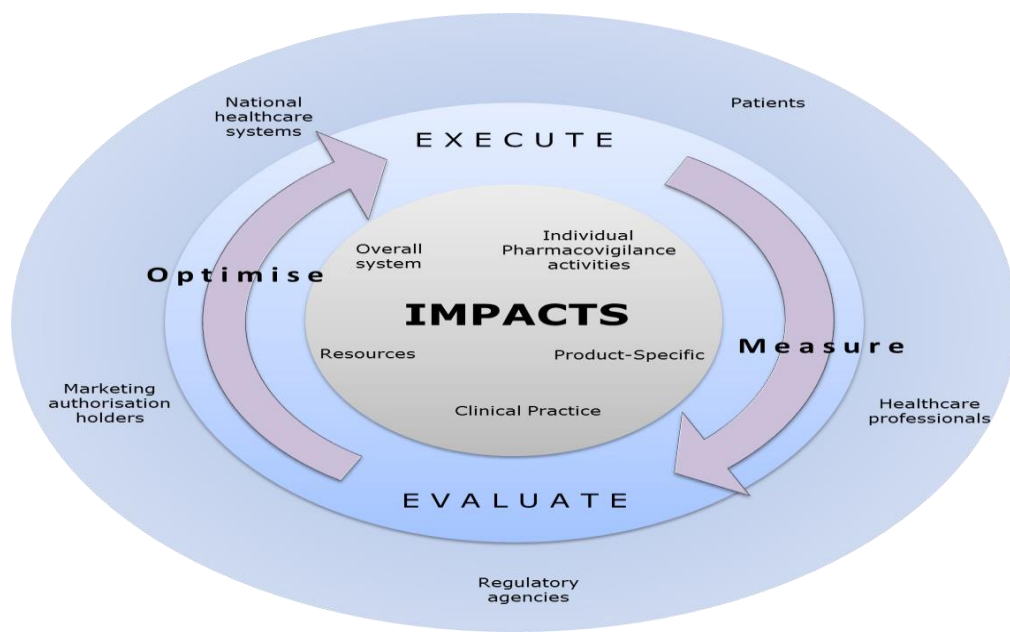
Version 3 January 2015

# PRAC improvement themes

## Keeping up the PACE – advancing regulatory science



**Making a difference – outcomes.**





# Use of pharmacogenomic evidence



Using pharmacogenomics to define populations at risk of ADRs



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 10 January 2014  
2 EMA/281371/2013  
3 Committee 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

o





# Incorporating new methodologies & building on the best practices





# Building on the strengthened pharmacovigilance system – now piloting adaptive pathways



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 March 2014  
EMA/254350/2012  
Senior Medical Officer

## Pilot project on adaptive licensing

There is currently much debate about adaptive pathways for new medicinal products to come to the market. The terms 'staggered approval', 'progressive licensing', and 'adaptive licensing' have been used, often interchangeably, to describe the same broad concept. More recently, the term 'Medicines Adaptive Pathways' (MAPs) or 'Medicines Adaptive Pathways to Patients' (MAPPs) is discussed as potentially more appropriate terminology. For the time being, and in the interest of internal consistency, the term 'adaptive licensing' (AL) is used throughout this document.

# Transformative medicines

**Risk Management Plans** to facilitate early access to medicines in areas of high unmet need

**PRIME** medicines procedures under development – new supported pathways.

**Enhance systems for real-world real-time evaluation:**

Characterising safety

Evaluating effectiveness

Informing patient stratification

Evolution of the product label

Informing use of medicines and better patient outcomes.



*ADA-SCID gene therapy*

## Conclusions

- Last three years have seen **great progress** in realising potential of EU Pharmacovigilance legislation & role of PRAC.
- Experience has demonstrated areas where a **strengthened, clarified** or **simplified** approach needed
- This will be the basis for developing a **focussed work plan** for 2016
- Ongoing **collaboration between all stakeholders** essential to achieve highest standards of public health protection in EU.

‘The best way to predict the future is to create it’.

***Anyone who stops learning is old,  
whether at twenty or eighty. Anyone who  
keeps learning stays young.***

Henry Ford



**IIOP**

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**IRISH INSTITUTE OF PHARMACY**



## Links to some key initiatives and web-resources

### Regulatory science:

- [www.ema.europa.eu](http://www.ema.europa.eu)
- [www.hpra.ie](http://www.hpra.ie)
- PROTECT signals, epidemiological studies, benefit risk assessment, data in pregnancy:  
<http://www.imi-protect.eu/>
- ADVANCE – establish framework for vaccine studies  
<http://www.advance-vaccines.eu/?page=home>
- WebRADR – apps for reporting and social media for signals  
<http://web-radr.eu/>
- Impact of pharmacovigilance
- Registries

### Capacity building:

- EC Joint Action – Collaboration among Member States:  
<http://www.scopejointaction.eu/>
  - ENCePP – networking and guidance for s <http://www.encepp.eu/>
  - Good Pharmacovigilance Practices  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000345.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp)
  - EU Network Training Centre
- Other:
- Increase proactivity – pilot of scientific advice [www.ema.europa.eu](http://www.ema.europa.eu)

[nature.com](#) ▶ [journal home](#) ▶ [current issue](#) ▶ [correspondence](#) ▶ [full text](#)

NATURE REVIEWS DRUG DISCOVERY | CORRESPONDENCE



# 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 & Guido Rasi

[Affiliations](#) | [Corresponding author](#)

*Nature Reviews Drug Discovery* **13**, 395–397 (2014) | doi:10.1038/nrd3713-c1

Published online 22 April 2014



PDF



Citation



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Article metrics

This journal has previously reported on initiatives to increase proactivity in the surveillance and management of drugs on the market and considered how this might influence drug (medicinal product) development programmes (*Nature Rev. Drug Discov.* **11**, 255 (2012))<sup>1</sup>. We now report on the implementation of a new European Union (EU) initiative to improve the promotion and

# Lifecycle benefit-risk management

EU Pharmacovigilance and Risk Management  
as enablers for:

- Transition from magic moment to life-span management.
- Toolkit development for evidence generation - safety and efficacy.
- Managed utilisation.
- Stakeholder collaboration.
- Better information for patients and their health professionals.



## Adaptive Licensing

....."The adaptive licencing process is based on a prospectively-planned process. It starts with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence-gathering and the adaptation of the marketing authorisation to allow broader patient populations to access medicine..."

...early multi-stakeholder dialogue