EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance in Paediatric Population

The PRAC's perspective

June M Raine
Chair, PRAC

EMA Workshop
28 April 2014

An agency of the European Union

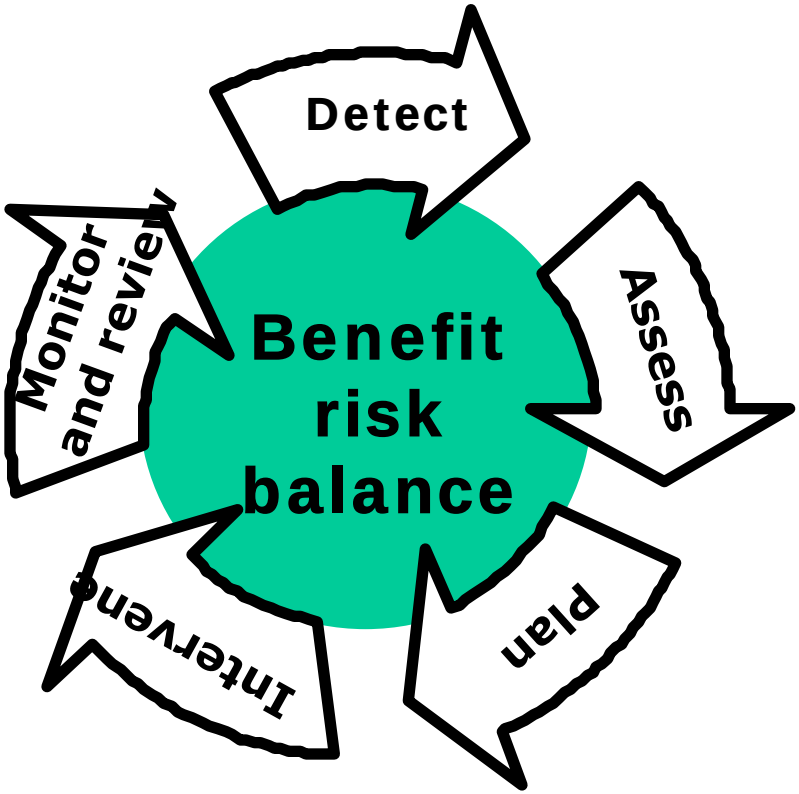
Outline of presentation

- What is **PRAC's experience** to date of pharmacovigilance in the paediatric population?
- What do we consider are **special challenges** in paediatric pharmacovigilance?
- What are the **new EU legislative tools** which can strengthen paediatric pharmacovigilance?
- What are the **current opportunities and priorities for** paediatric pharmacovigilance?

Pharmacovigilance Risk Assessment Committee

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

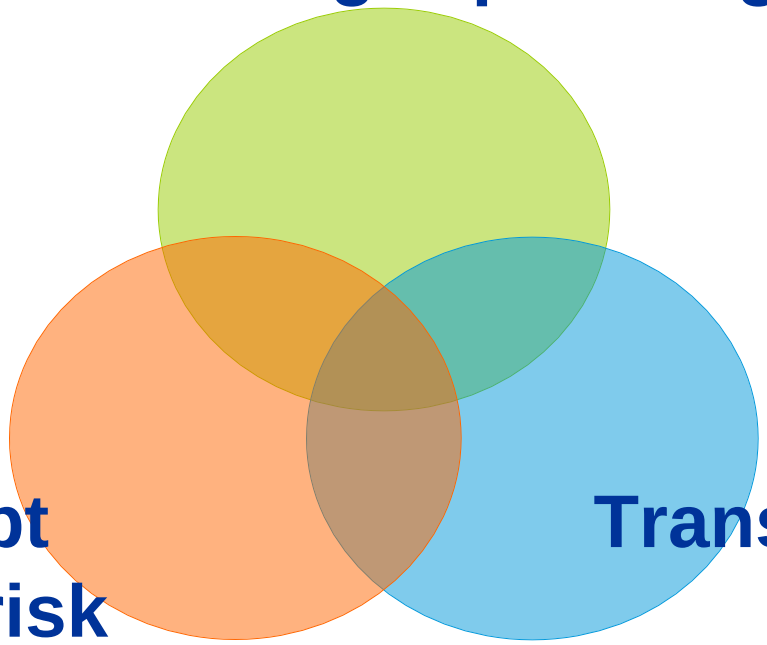
Pharmacovigilance cycle



Gaining knowledge of risks & risk management in therapeutic use

PRAC's three public health pillars

Proactive safety monitoring & planning



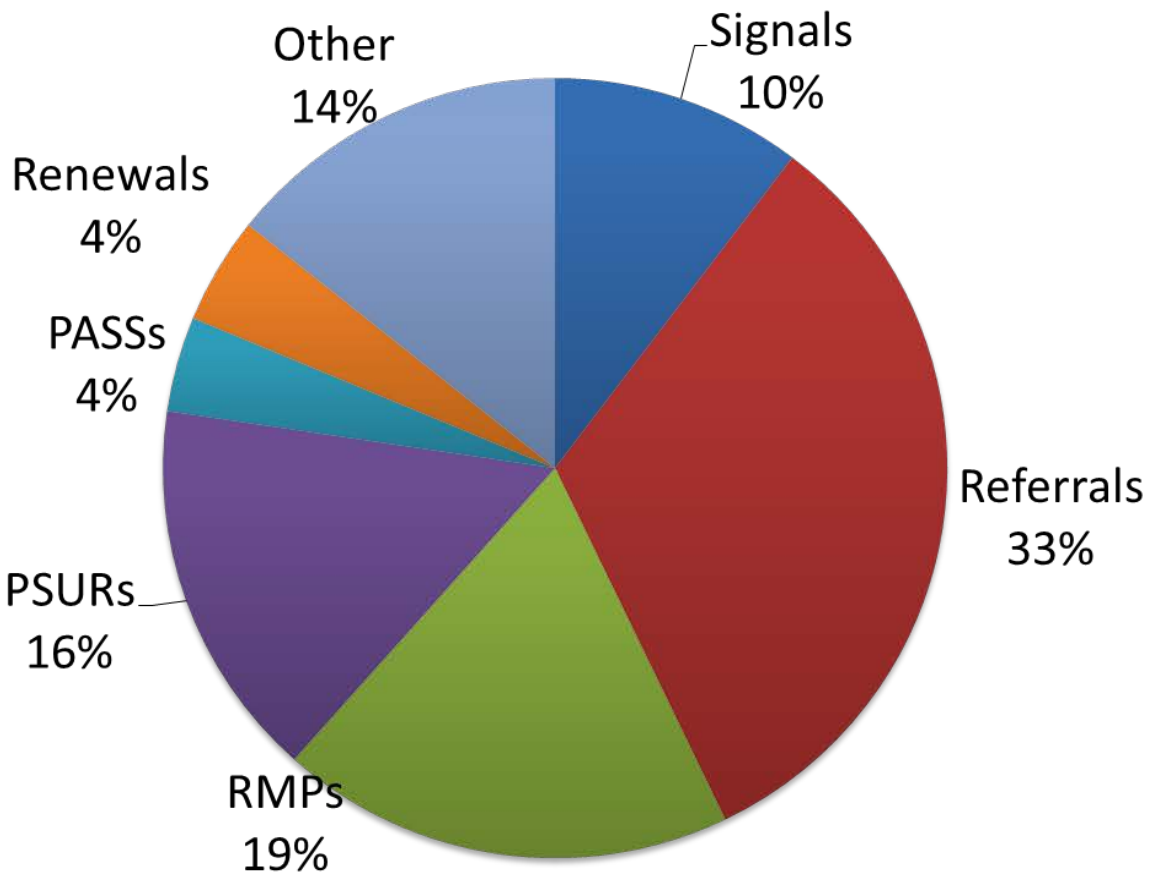
Prompt benefit risk action

Transparency and communication

PRAC's legislative tools ...

- **New safety signals**
- **Urgent and non urgent union procedures** triggered due to safety concerns identified in medicinal product(s) authorised in more than one member state
- **Risk Management Plans**
- Non-interventional safety study protocols and study reports if the need for a **non-interventional post-authorisation safety study** is identified
- **Periodic Safety Update Reports**
- List of **medicines under additional monitoring**

% of PRAC plenary discussion time 2013, based on total hours



What are PRAC's achievements in first 18 months?

- **Proactive pharmacovigilance**
  756 RMPs (160 products), 202 PASS studies registered
- **Real-time signal detection & prioritisation**
  - 121 signals, leading to 57 label updates
- **Additional monitoring scheme** in place
- **Prompt action on benefit risk issues** -
  recommendations on 486 PSURs, 22 referrals started, 13 completed in average time of 6.4 months
- **New era for transparency** in EU drug safety systems
  - agenda, highlights, full committee minutes published

And for the paediatric population?

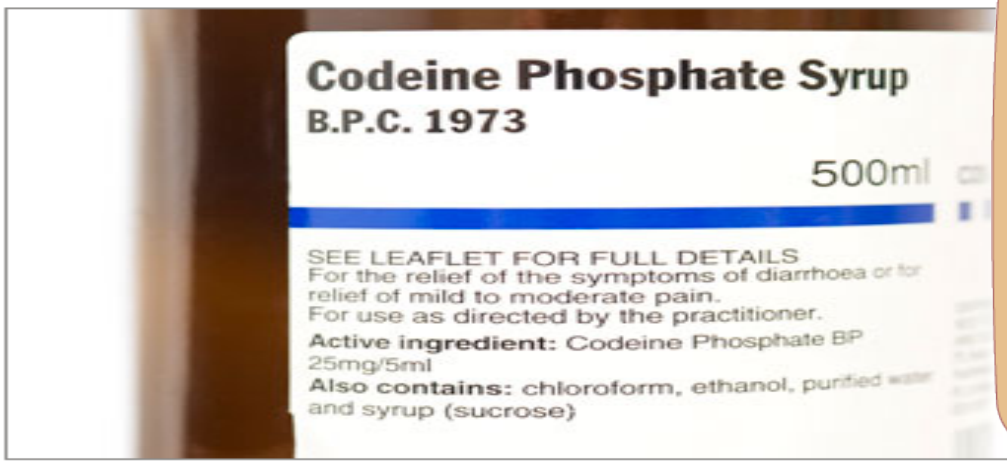
- The first Article 31 referral and first article 107i referral
- Thirteen signals
- Risk management plans – vaccines in particular
- PASS – the first to include efficacy outcomes?
- Communications – on referral outcomes

A relatively small but important and challenging proportion of PRAC's work

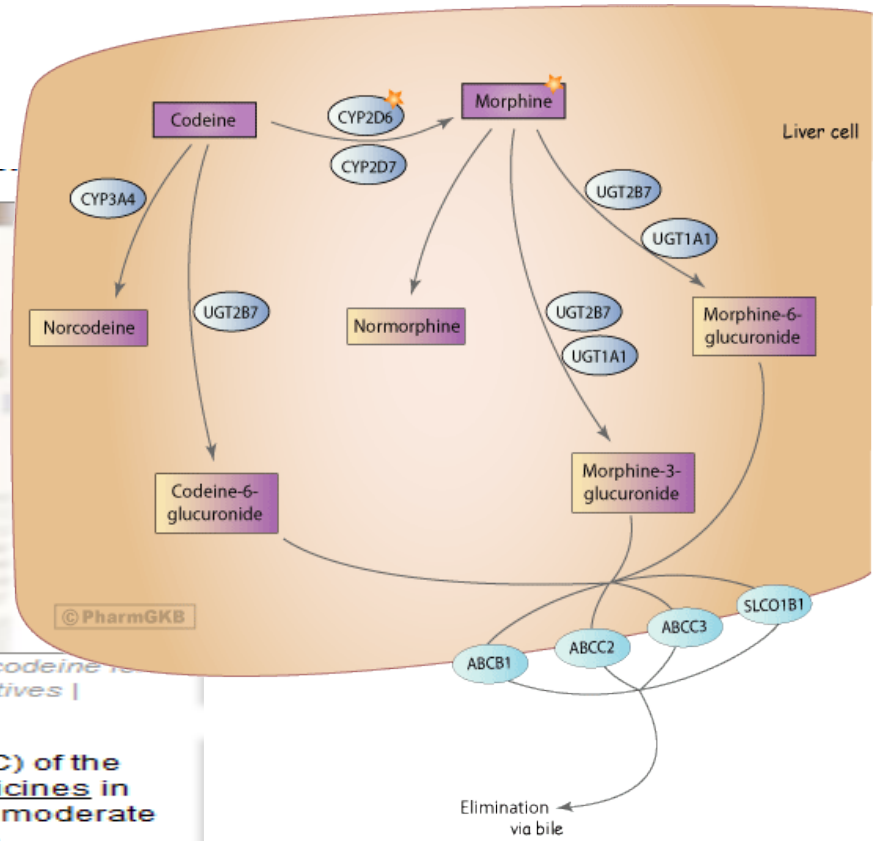
Referrals relating to medicines used in the paediatric population

- **Codeine** for analgesia and opiate toxicity in CYP2D6 ultra-rapid metabolisers
- **Numeta** for parenteral nutrition and reports of hypermagnesaemia
- **Octocog alfa** and inhibitor antibodies – Factor VIII product differences
- **Domperidone** and cardiac risk
- **Sodium valproate** and developmental disorders following use in pregnancy

Codeine for analgesia in children



The risk of respiratory depression outweighs the benefits of using codeine for moderate pain in children under 12 years as there are safer alternatives | SCIENCE PHOTO LIBRARY



The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recommended that use of codeine-containing medicines in children be restricted to those aged over 12 years with acute moderate pain that cannot be relieved by other analgesics, for example, paracetamol or ibuprofen.

In addition, codeine should never be used for children under 18 years undergoing tonsillectomy or adenoidectomy to treat obstructive sleep apnoea. The prescribing information will also be updated to contraindicate codeine in conditions associated with impaired breathing.

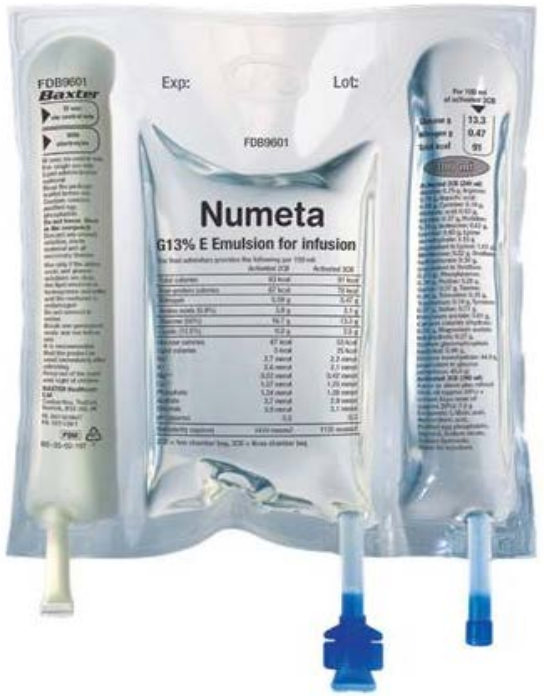
Numeta 13% and hypermagnesaemia

Numeta 13% parenteral nutrition for preterm babies

Signal of 14 reports from MAH of hypermagnesaemia – July 2013

Voluntary recall of Numeta 13%

PRAC concluded advice in September 2013 to suspend Numeta 13%, introduce risk management for Numeta 16%



Kogenate and Helixate & inhibitor development

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

Samantha C. Gouw, M.D., Ph.D., Johanna G. van der B
Rolf Ljung, M.D., Ph.D., Carmen Escuriola, M.D., An
Ségolène Claeyssens-Donadel, M.D., Christel van Ge
Gili Kenet, M.D., Anne Mäkipernaa, M.D., Ph.D., Angelo Cl
Wolfgang Muntean, M.D., Rainer Kobelt, M.D., Georg
Elena Santagostino, M.D., Ph.D., Angela Thomas,
and H. Marijke van den Berg, M.D., Ph.D
for the PedNet and RODIN Study Group

ABSTRACT

BACKGROUND

For previously untreated children with severe hemophilia A, the type of factor VIII product administered and switching a sociated with the development of clinically relevant inhibitor development).

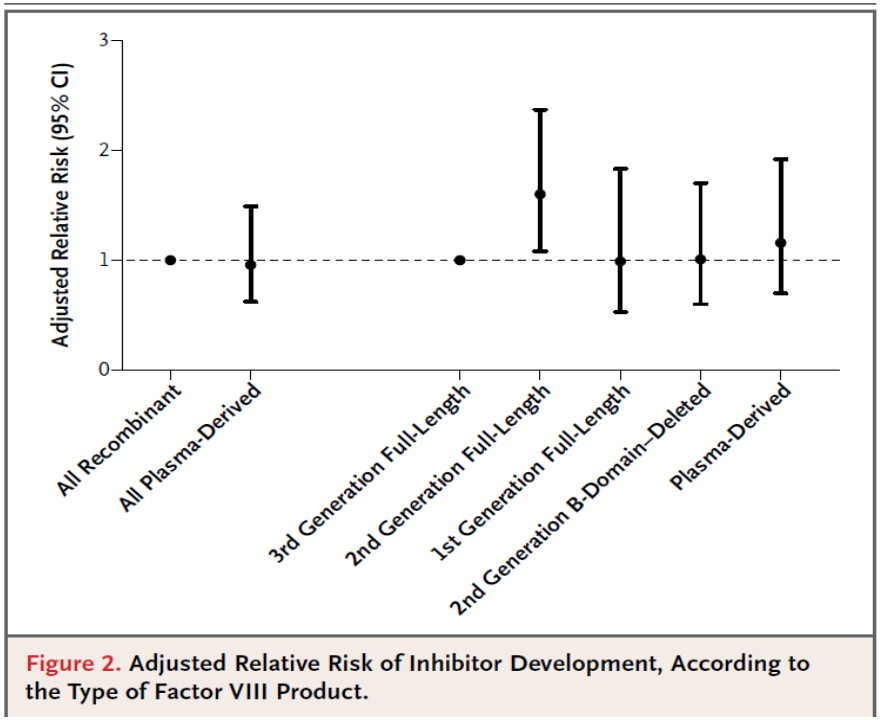
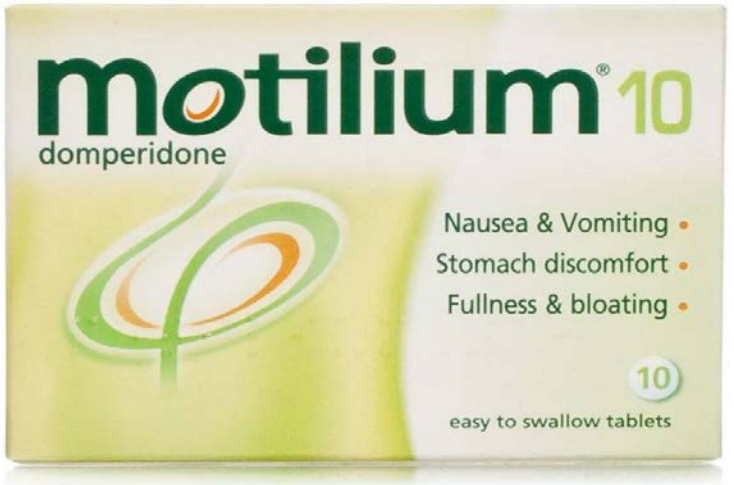


Figure 2. Adjusted Relative Risk of Inhibitor Development, According to the Type of Factor VIII Product.

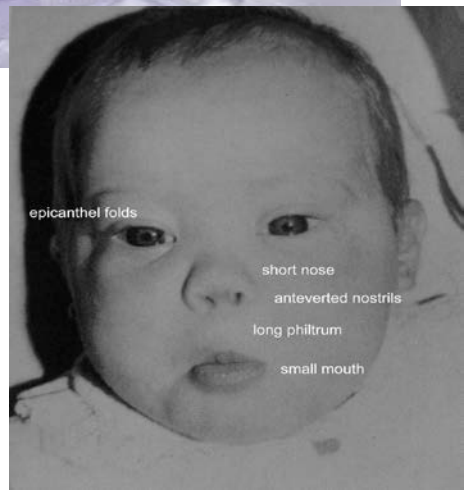
Domperidone and CVS risk

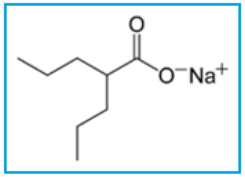
- Cardiac safety reviewed by PRAC after data accrued
- Large pharmepi study confirmed increased risk of sudden cardiac death in over 60s
- Restriction of indication to nausea and vomiting, dose restriction and duration limit
- Data on efficacy in children to be generated



Sodium valproate in pregnancy & persistent developmental delay

- Indications include epilepsy, bipolar disorder & migraine
- Use in women of child bearing potential varies across Europe
- Nature and magnitude of risk needs to be better understood
- Effectiveness of risk minimisation





SODIUM VALPROATE A COVER UP THAT IS THE NEW THALIDOMIDE

Conclusions from PRAC referrals in paediatric population

- Need for specialist paediatric input to interpret data on benefits and harms, need for perspective of children and parents/carers
- Need for early planning for stakeholder involvement when referral notified
- Where robust data are lacking, may need to require studies to be done
- Special challenge of interpreting potential harms in child from pregnancy exposure

Newly started PRAC referrals

- **Codeine for cough / cold** and risk of toxicity in CYP 2D6 ultra-rapid metabolisers

- **Ambroxol / bromhexine** and risk of serious skin reactions

- **Testosterone** and cardiovascular risk
- **Hydroxyzine** and cardiovascular risk

Signals in paediatric population

Safety Issue	Data source
Paracetamol – pregnancy use	• Published study
Cinacalcet - hypocalcemia	• Clinical study
Dexmedetomidine –apnoea	• EudraVigilance
Somatropin – convulsions	• EudraVigilance
Sertraline - growth retardation	• Published study
Fentanyl patches: accidental exposure	• FDA communication

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

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For Consumers

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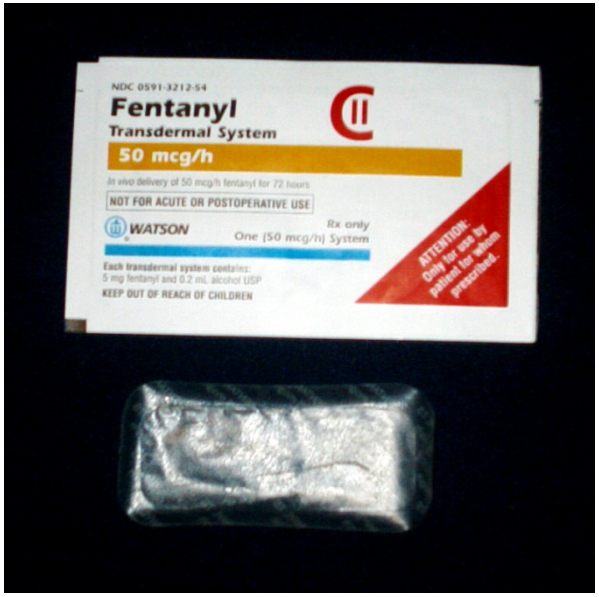
Consumer Updates

Fentanyl Patch Can Be Deadly to Children



Mother enters plea in connection with death of son

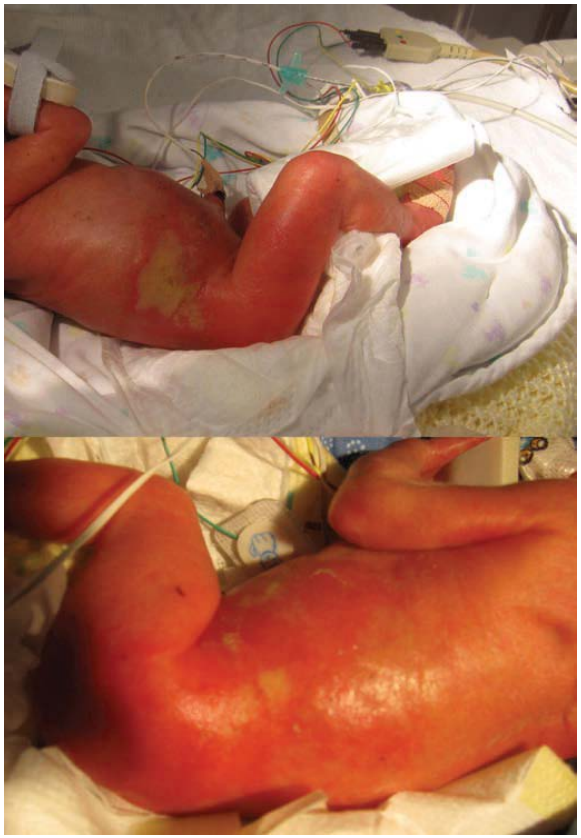
WMUR Manchester - 2 days ago

... that Davis failed to properly secure a **fentanyl patch** that was accidentally transferred from her body to her 7-month-old **child** in July 2011.

Vaccine signals in paediatric population

• **Pandemrix** and risk of narcolepsy	• PASS
• **HPV vaccine** [types 16, 18] - signal of complex regional pain syndrome	• Spontaneous ADRs
• **HPV vaccine** [type 16, 18]- signal of primary premature ovarian failure	• Spontaneous ADRs
• **HPV vaccine** [type 6, 11, 16, 18] – signal postural orthostatic tachycardia	• Spontaneous ADRs
• **HPV vaccine** [types 6, 11, 16, 18] - Bronchospasm in patients with or without asthma	• Spontaneous ADRs

Incoming PRAC signal in paediatric population



Images in neonatal medicine

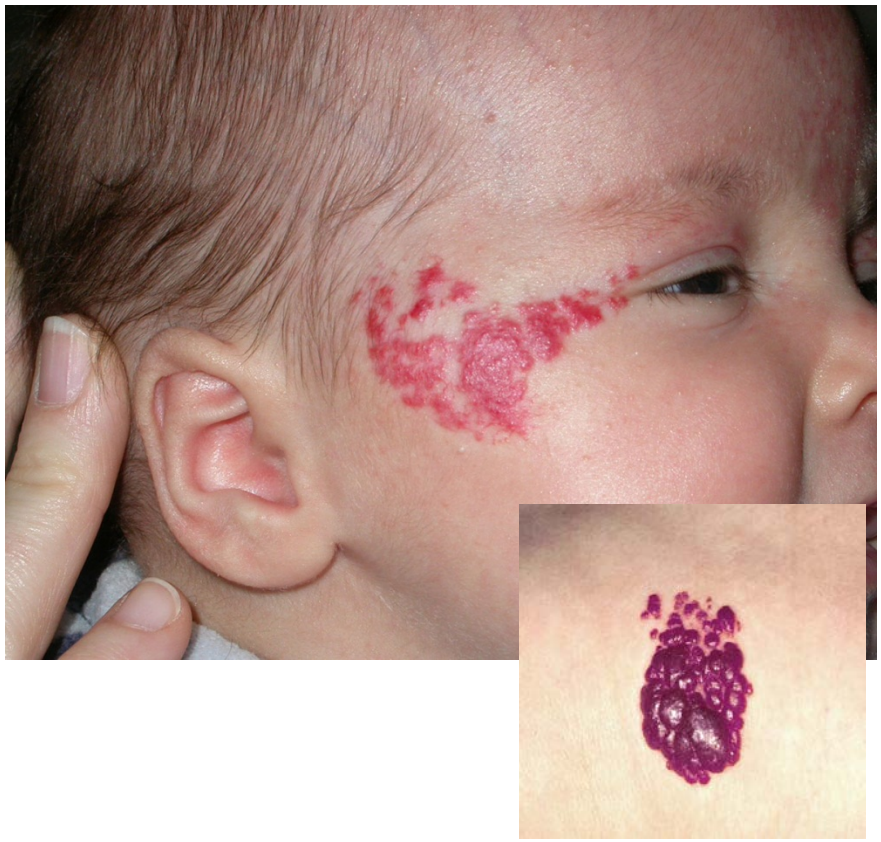
Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant

Arch Dis Child Fetal Neonatal Ed: F64 January 2012

Conclusions from PRAC signals in paediatric population

- Different ADR patterns
  - *Need for case definitions*
  - *Need for accurate age in ICSRs*
- Importance of literature monitoring as specialists tend to publish rather than report ADRs
- Long term effects including developmental disorders
- Pregnancy exposure
- Importance of published literature as resource
- Adapted approaches for vaccines to support rapid signal validation

Risk management plans in paediatric population



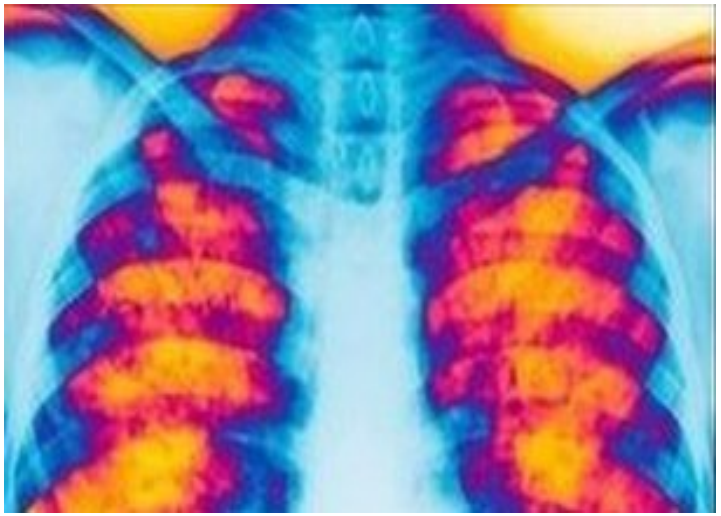
- Example – Haemangiol (propranolol 3.75 mg/ml) for treatment of proliferating infantile haemangioma
- PRAC advised on RMP and considered recruitment into PASS study

Post authorisation safety studies in paediatric population

Example – Ivacaftor

PRAC advised on a long-term observational study

To include microbiological and clinical endpoints (e.g. exacerbations



http://clinicaltrials.gov/ct2/show/NCT01117012?term=ivacaftor&rank=22

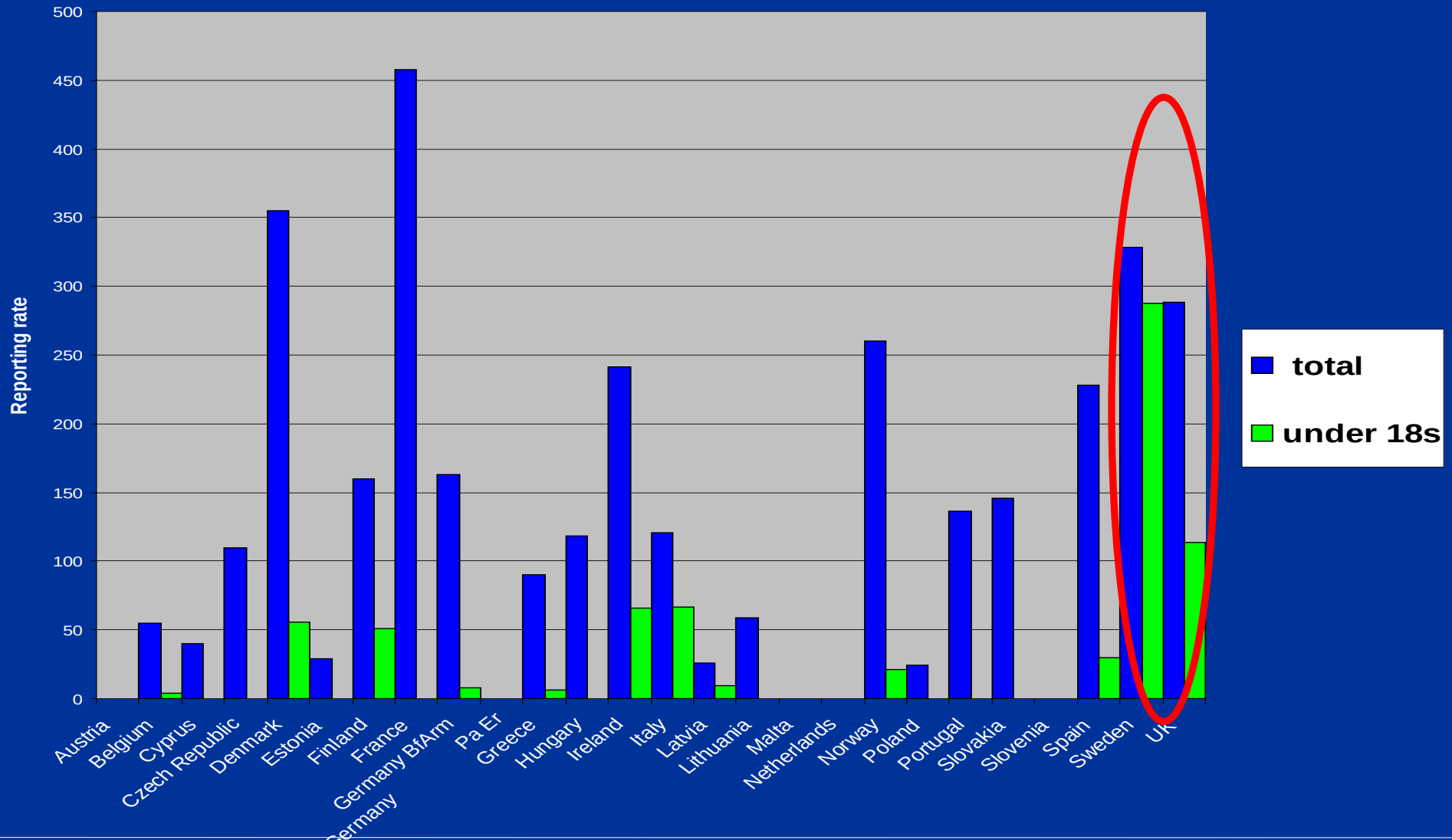
PRAC's conclusions from proactive pharmacovigilance in paed population

- PRAC needs better knowledge of PDCO recommendations of risk management systems
- PIPs and RMPs need to be integrated as a continuum
- Facilitate involvement of ENCePP paediatric network
- Better awareness of work of Enpr-EMA network

Challenges in paediatric pharmacovigilance

- **Likely extensive underreporting** of suspected adverse reaction reports in children
- Concern that risk of **ADRs greater in off-label** use in children
- **Medication errors** more frequent and more serious in paediatric population
- As new medicines become available for paediatric population, must **shift from reactive to proactive**, demonstrate effectiveness of risk minimisation
- **Adapting pharmacovigilance communications** to paediatric population's needs

Survey of ADR reporting rates 2002



Evidence on ADRs in off-label and unlicensed use in children

Eur J Clin Pharmacol (2012) 68:21–28
DOI 10.1007/s00228-011-1097-1

REVIEW ARTICLE

Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature

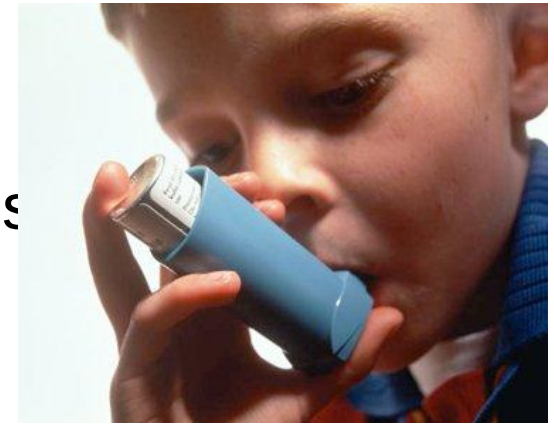
Jennifer Mason · Munir Pirmohamed · Tony Nunn

Received: 20 April 2011 / Accepted: 29 June 2011 / Published online: 22 July 2011
© Springer-Verlag 2011

Abstract The use of unlicensed and off-label medicines in children is common because trials in children have not usually been performed during the drug development process. Consequently, the information available to paediatricians may not always be as detailed or as robust as that available when prescribing a medicine that is licensed for that has received some attention in this population is the use of off-label and unlicensed medicines [3]. The necessity of using off-label and unlicensed medicines in children is a consequence of how, historically, medicines have been developed and regulated.

PRAC approach to addressing challenges of pharmacovigilance in paediatric population

- Using “tools” of Pharmacovigilance legislation to fullest potential for paediatric population
- Operating an effective interface between paediatric and pharmacovigilance systems, PDCO and PRAC
- Better science - building relationships and interactions with academia and research networks
- Optimising the contribution and value-added of public and patients



PhVig legislative tools relevant to the paediatric population

- Expanded definition of ADR including off-label, unlicensed, error and misuse
- Member states to encourage ADR reporting
- Additional monitoring system
- Signal detection systems
- Urgent decision-making referrals
- Risk management plans for all new MAs
- PASS and PAES studies
- Transparency and communication
- Stakeholder involvement

How well are PhVig legislative tools being used for paediatric population?

- Ad hoc consideration by PRAC of benefit risk in paediatric population rather than systematically
- Usually later in referral procedures or after completion – getting earlier
- Guideline on pharmacovigilance in paediatric population requires updating to reflect new legislation

Current opportunities to strengthen pharmacovigilance in paediatric population

- Getting messages across about importance of ADR reporting – additional monitoring and patient reporting
- Adapting signal detection to paediatric population, especially in area of vaccines
- Incorporating patient and public views in referrals
- Focus on better science – supporting research in paediatric population - involving ENCePP paediatric network and Enpr-EMA

EUROPEAN MEDICINES AGENCY

Did you know?

You can report side effects yourself

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.

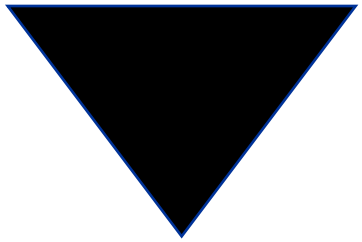
Why report a side effect?

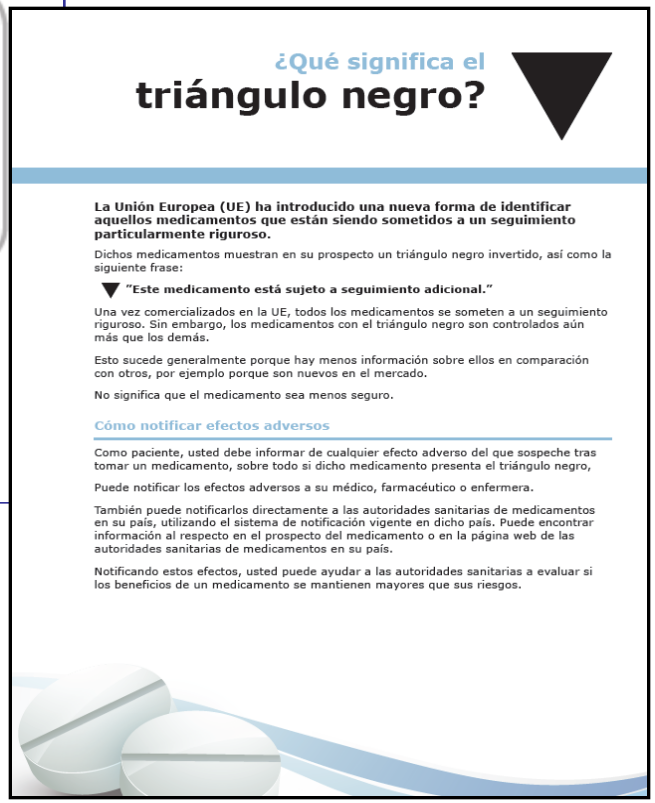
We are always learning more about medicines.

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.





¿Qué significa el

triángulo negro?

La Unión Europea (UE) ha introducido una nueva forma de identificar aquellos medicamentos que están siendo sometidos a un seguimiento particularmente riguroso.

Dichos medicamentos muestran en su prospecto un triángulo negro invertido, así como la siguiente frase:

▼ **"Este medicamento está sujeto a seguimiento adicional."**

Una vez comercializados en la UE, todos los medicamentos se someten a un seguimiento riguroso. Sin embargo, los medicamentos con el triángulo negro son controlados aún más que los demás.

Esto sucede generalmente porque hay menos información sobre ellos en comparación con otros, por ejemplo porque son nuevos en el mercado.

No significa que el medicamento sea menos seguro.

Cómo notificar efectos adversos

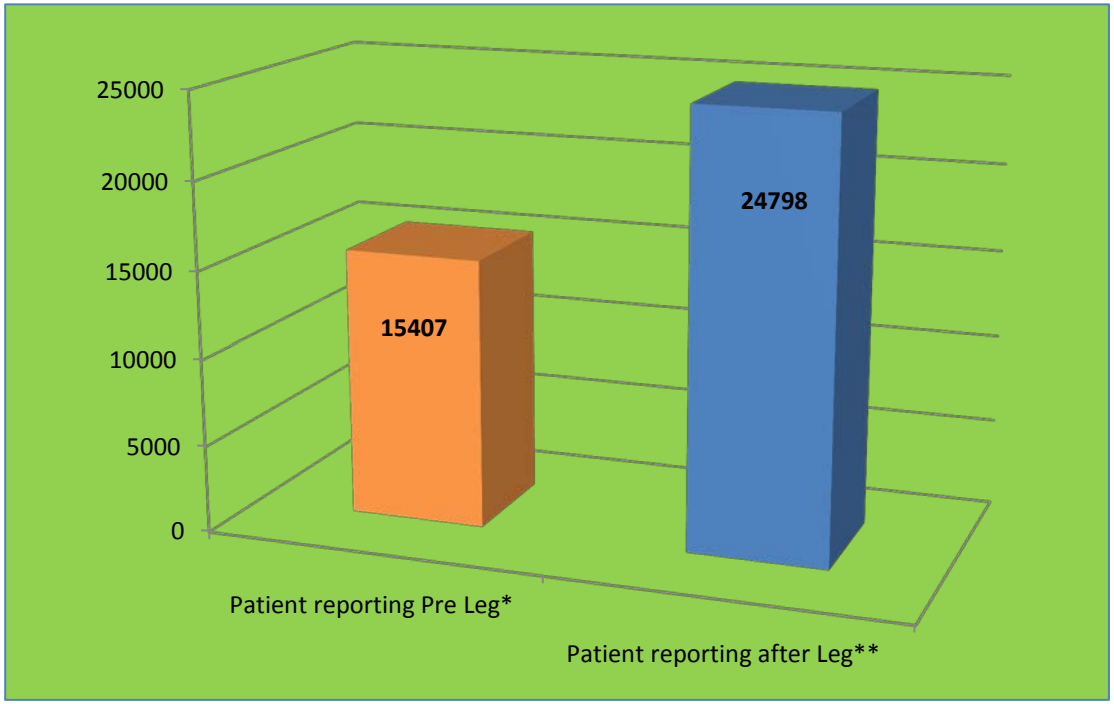
Como paciente, usted debe informar de cualquier efecto adverso del que sospeche tras tomar un medicamento, sobre todo si dicho medicamento presenta el triángulo negro,

Puede notificar los efectos adversos a su médico, farmacéutico o enfermera.

También puede notificarlos directamente a las autoridades sanitarias de medicamentos en su país, utilizando el sistema de notificación vigente en dicho país. Puede encontrar información al respecto en el prospecto del medicamento o en la página web de las autoridades sanitarias de medicamentos en su país.

Notificando estos efectos, usted puede ayudar a las autoridades sanitarias a evaluar si los beneficios de un medicamento se mantienen mayores que sus riesgos.

Patients' contribution to ADR reporting



* Pre legislation data period - 02/07/2011 - 01/07/2012

** Post legislation data period -02/07/2012 - 01/07/2013

New signal detection methodologies in vaccine vigilance

ELSEVIER

Vaccine

Volume 31, Issue 43, 9 October 2013, Pages 4961–4967

14273||

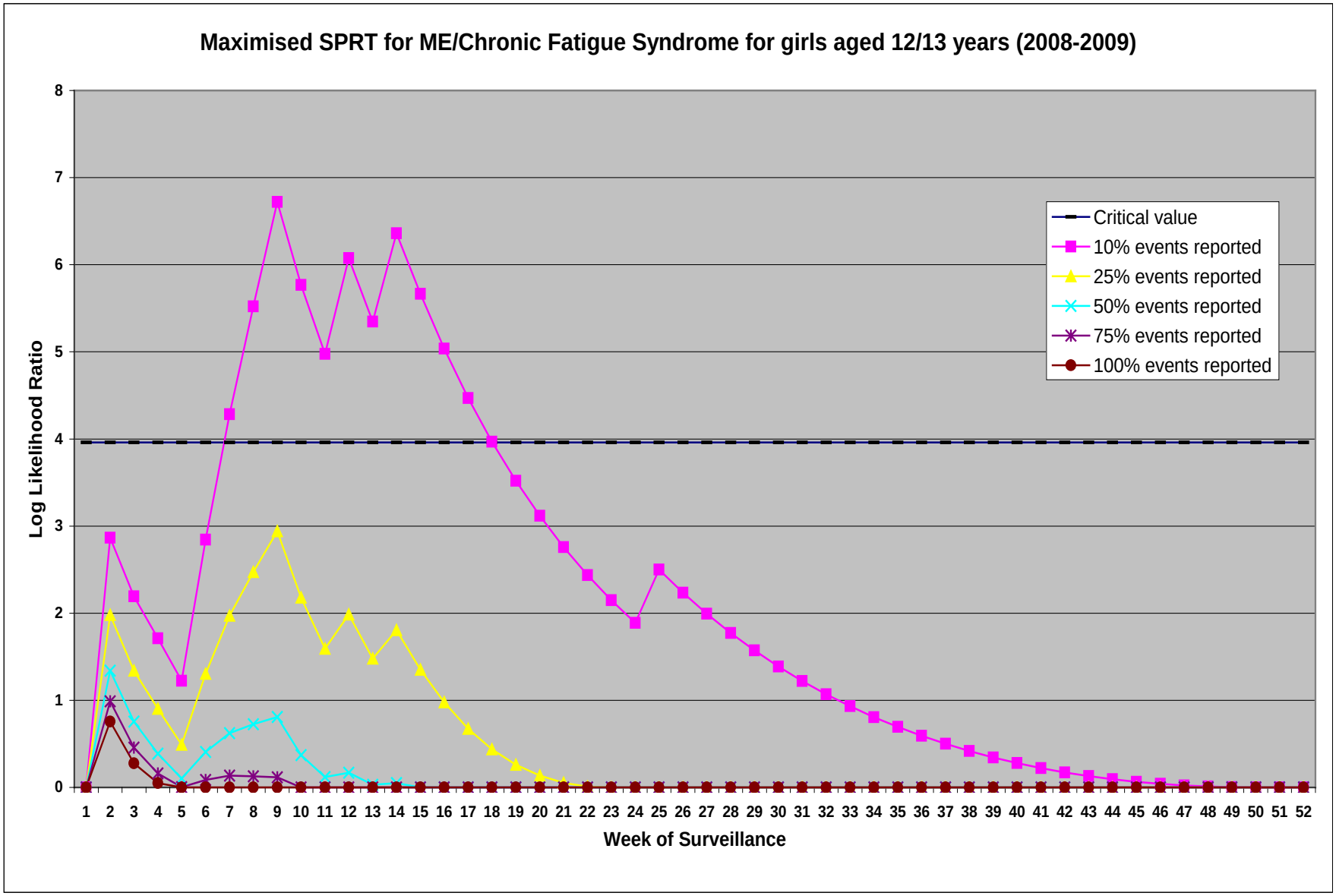
Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK

Katherine Donegan, Raphaelle Beau-Lejdstrom, Bridget King, Suzie Seabroke, Andrew Thomson, Philip Bryan

Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London, UK

Maximised sequential probability ratio testing for observed vs expected signals

Donegan et al 2013, Vaccine 31, 43, 4961-7

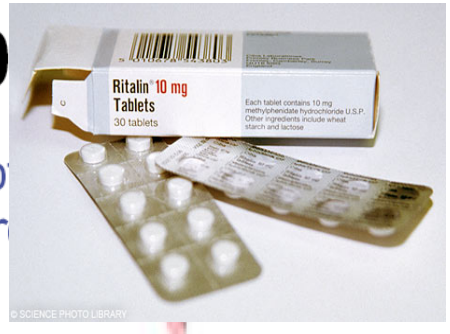

Maximised SPRT for ME/Chronic Fatigue Syndrome for girls aged 12/13 years (2008-2009)
Log Likelihood Ratio
Week of Surveillance
Critical value
10% events reported
25% events reported
50% events reported
75% events reported
100% events reported

Long term safety - EU Funding

- Long term effects methylphenidate in ADHD
- Medicines use in pregnancy
- Long term adverse effects of immunomodulators
- Suicidal behaviour and various drugs/classes

Medicines information for children and young people — a forward step

In this article, **Nicola Gray** and colleagues describe the development o
patient information leaflet that contains specific information for childr



This info is to help you learn the main things about your medicine called [product].

If you don't enjoy reading, someone like your mum, dad or carer (sometimes called "your guardian") can read it to you and answer any questions.

It may help if you read small bits at a time.

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opportunity was
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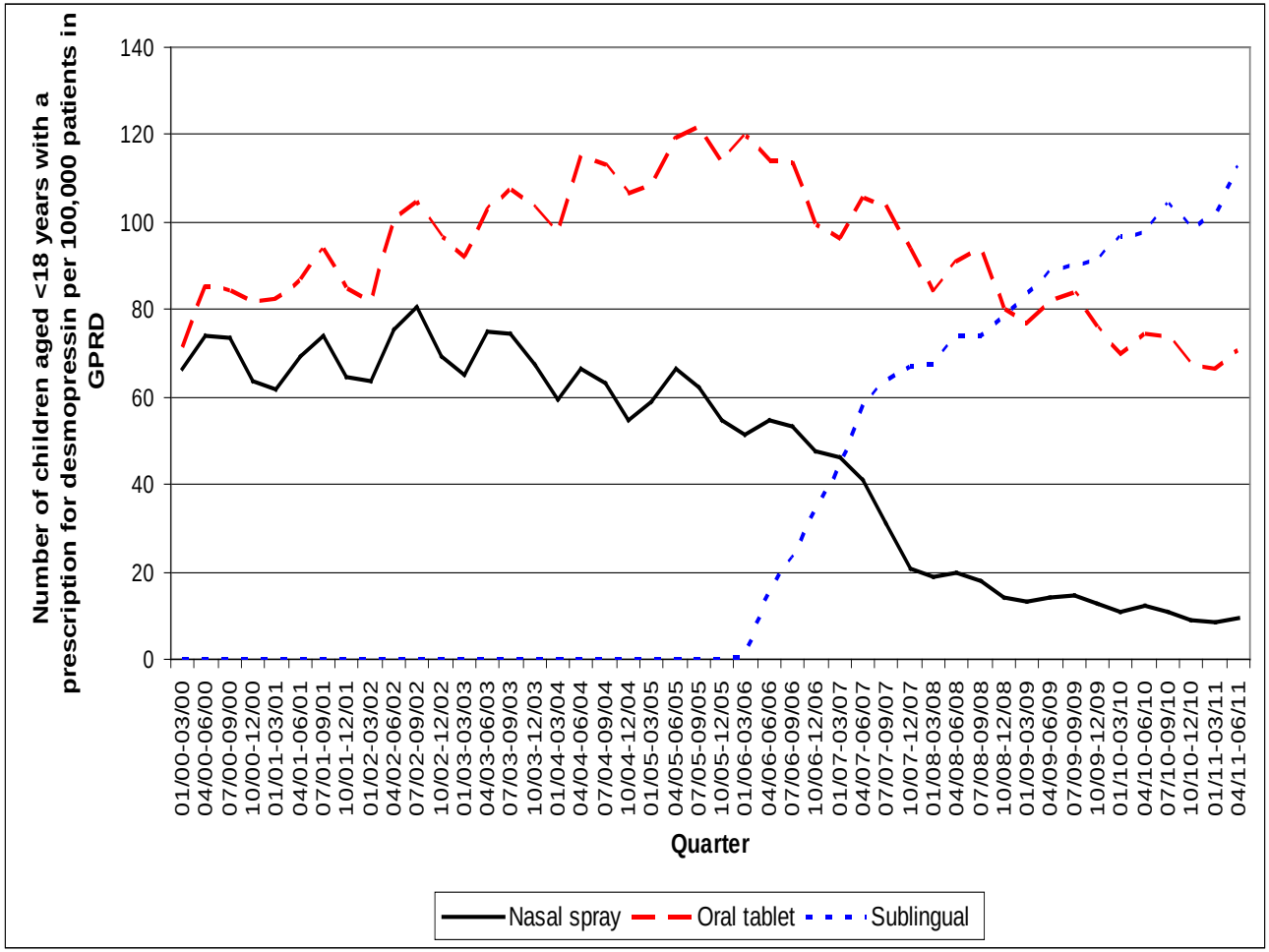
about med ecially regarding side effects.[2] The in as the potential to increase access to m ines for these groups,

medicine had agreed to work together to produce a common leaflet text that would then be

GELPI/DREAMSTIME.COM

Effectiveness of risk minimisation *example - desmopressin*

Impact of action to remove indication of nocturnal enuresis for desmopressin nasal spray



Summary of PRAC perspective

- Some progress in addressing the special challenges for pharmacovigilance in paediatric populations
- Mismatch between CT population and real life use in paediatrics means a significant knowledge gap
- Pharmacovigilance legislative tools create significant potential to minimise harms in paediatric population from strengthened systems
- Paediatric population issues need to be considered in all phases of the pharmacovigilance cycle

Priorities for Paediatric Pharmacovigilance

- Promote reporting ADRs in children - networks of paediatric centres?
- Pilot new approaches to strengthen signal detection
- Press ahead with work on medication error
- Promote research networks – including pregnancy
- PRAC/PDCO collaborative working on benefit risk throughout product lifecycle