

# Signals Detection Activities including Direct Patient Reporting

**Mick Foy**  
Vigilance Intelligence and Research Group  
Vigilance and Risk Management of Medicines

2<sup>nd</sup> December 2011

Safeguarding public health

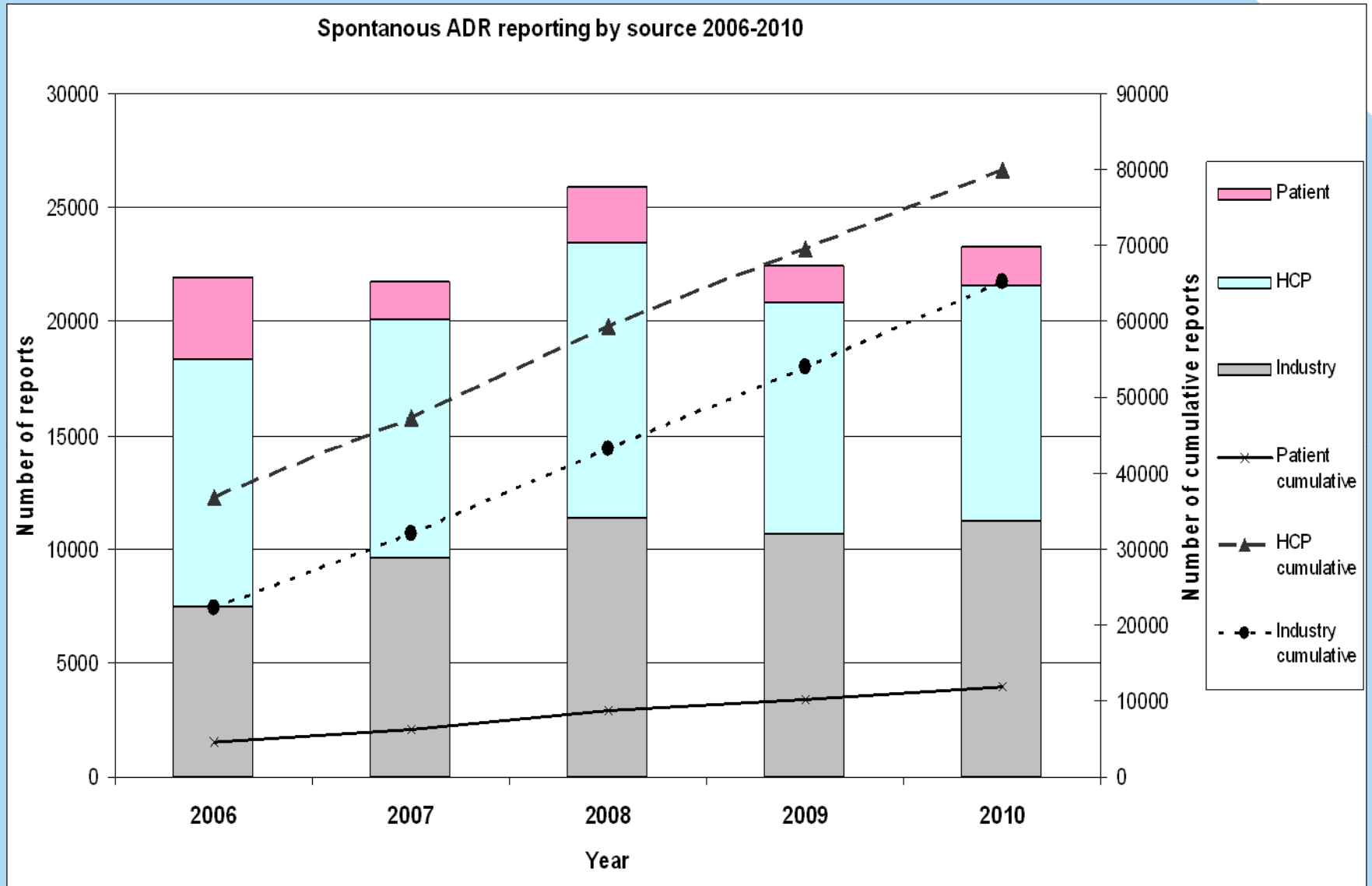
# Agenda

- ADR Reporting in the UK
- Patient ADR Reporting
- Signal detection at the MHRA
- Evaluation of the contribution of patient reporting
- Contribution of patient reports to signals
- Challenges ahead for patient reporting & signalling
- Summary

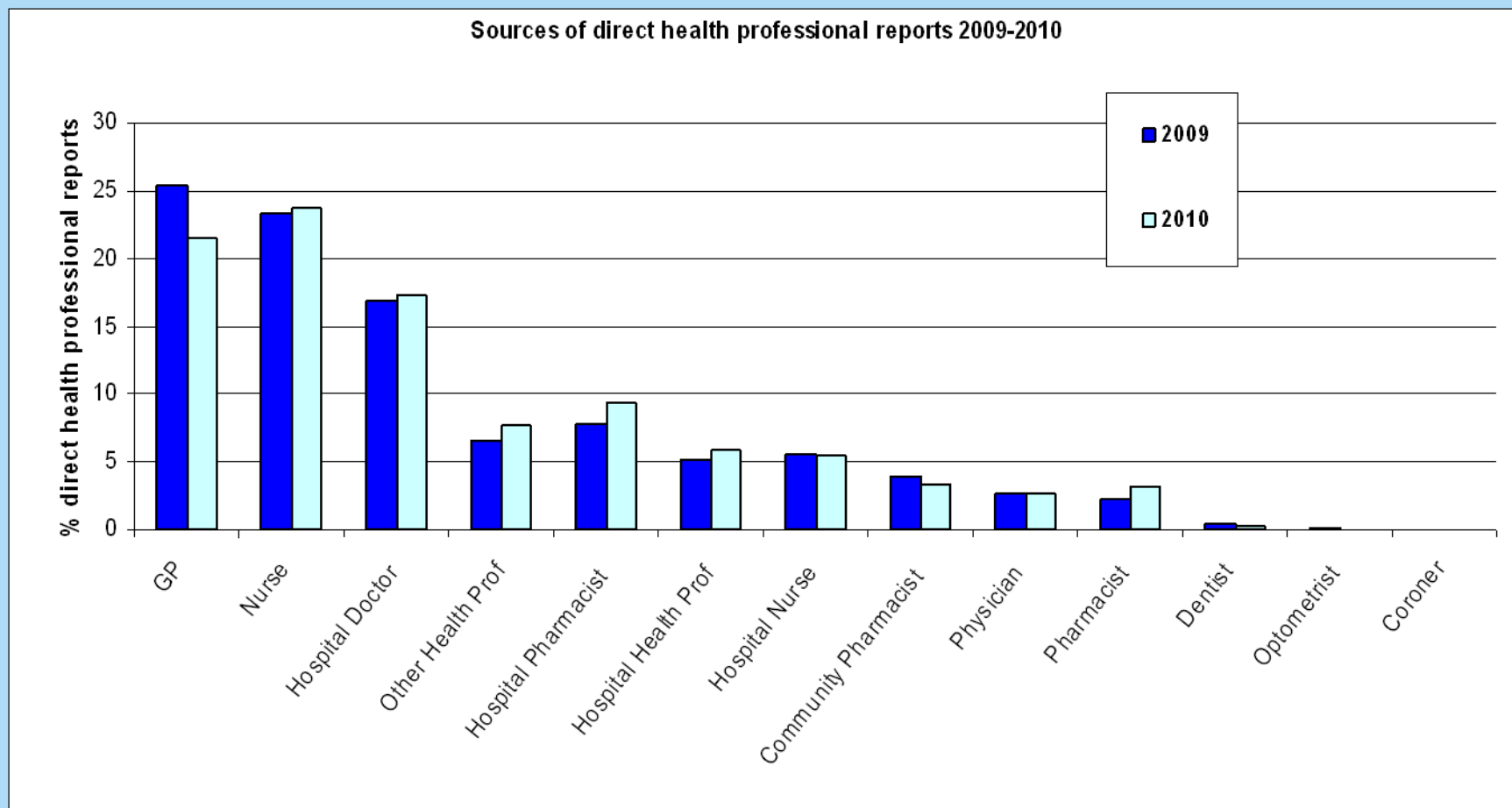
# ADR reporting: 2009 - 2010

Yellow Card Statistic	2009	2010	Trend
Total number of reports	22,444	23,273	↑
Serious reports	82%	85%	↑
Fatal reports	5%	6%	↑
Industry reports	47%	48%	↑
Patient reports	(7%)	(7%)	static
Direct reports	53%	52%	↓
Direct serious reports	67%	72%	↑
Direct electronic reports	36%	40%	↑
Most reported drug	Clozapine (10%)	Clozapine (10%)	-
Most reported vaccine	Human Papilloma Virus vaccine (65%)	Human Papilloma Virus vaccine (56%)	-
Most reported drug & reaction pair	Clozapine / neutropenia (1%)	Clozapine / neutropenia (1%)	-
Reports in <18s	15%	14%	↓
Gender: M:F:unknown	37%: 57%: 6%	39%: 55%: 6%	↑ male ↓ female - unknown
Most reported age group	50-64 years	50-64 years	static

# Overall ADR Reporting trends (2006 to 2010)



# Source of direct HCP reports



# Patient Reporting

# Patient reporting

- *Article 102*
- The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;

# Patient reporting

## *Article 107*

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study
2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.
3. Marketing authorisation holders shall submit electronically .... all serious suspected adverse reactions that occur in the Union and in third countries within 15 days ....Marketing authorisation holders shall submit electronically.. all non- serious suspected adverse reactions that occur in the Union, within 90 days..

# Patient reporting at MHRA

- Yellow Card Scheme (1964, thalidomide tragedy)
  - Voluntary reports submitted of suspicions of ADRs (in confidence) to date >700,000 reports.
- Need for consumer reporting highlighted:
  - Independent Review of access to the Yellow Card Scheme (Metters, 2004)
- Until 2005, only HCPs could report directly
- Patient Reporting Working Group and engagement with patient organisations / charities

# Patient reporting – the beginning

- **When?**

- January 2005 - Pilot scheme for patient reporting introduced

- **How?**

- paper
- internet reporting
- telephone

- **What?**

- all reports welcomed, especially for serious or unlabelled suspected side effects

# Experience from pilot scheme

By 2007 end:

- > 6,000 patient reports received
- Majority received via paper; 31% via the internet
- Evaluation: Detailed review of reports received during first 6 months of pilot scheme (CHM November 2005)

## Key findings from pilot scheme

- Similar levels of reports of serious reactions
- Fewer reactions to black triangle drugs
- Less complete reports: but no difference in causality, or proportion of unlabelled reactions
- More information on impact of ADRs on quality of life
- Low levels of consumer awareness of the YC Scheme

# Formal Launch of Patient reporting – 18<sup>th</sup> February 2008

- 6 week campaign, supported by RPSGB
- Community Pharmacies
- Information packs (leaflets, posters)
- Advice & support for patients
- Engaging with patient groups and charities to promote the scheme

## PLUS Media Coverage:

- BBC News/Radio
- Article in Pharmaceutical Journal



**YellowCard**<sup>®</sup>  
Helping to make medicines safer

**A side effect of your medicine?**

You can report it using **YellowCard**<sup>®</sup>

You can report suspected side effects:

- online at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)
- or using a Yellow Card form.

**Pick up a leaflet for more information**

**This pharmacy supports the Yellow Card Scheme.**

Medicines and Healthcare products Regulatory Agency 

© Crown Copyright 2008

# Updated internet reporting platform electronic Yellow Card

MHRA

**YellowCard**  
Helping to make medicines safer

MHRA

Home

The Yellow Card Scheme

Frequently Asked Questions

Further Information

Downloadable Information

Contact Us

MHRA Website

Welcome to the on-line reporting site for the Yellow Card Scheme

This site can be used to report suspected side effects to any medication.

Not Registered?

If you are a new visitor to the site or have not registered previously, please select one of the options below before entering the main site. This will allow us to provide you with the best possible information to help you while using this site.

I'm a member of the public

I'm a health care professional

Already Registered, Login Here

If you have already registered with this site, please login.

Fields marked with a \* are required

Email Address \*

Password \*

Login

If you have forgotten your password please complete this form.

- UAT by patient groups
- Easy to complete
- Smart fields
- Registering details (optional)
- Saveable

Reporting links on:

- NHS Choices
- EMC
- MIMS

**SWINE FLU**

**YellowCard**  
Helping to make medicines safer

MHRA

Home

Frequently Asked Questions

Further Information

MHRA Website

Welcome to the online reporting site for Flu medications and vaccines. This is a parallel site to the Yellow Card Scheme.

If you would like more information about the suspected side-effects which have been reported to Tamiflu, Relenza and the Pandemic vaccines (Celvapan and Pandemrix), please visit the Swine Flu information pages on the MHRA main website:

[www.mhra.gov.uk/swineflu](http://www.mhra.gov.uk/swineflu)

This site should be used to report suspected side effects to particular medications administered during this time period to manage influenza.

Not Registered?

If you are a new visitor to the site or have not registered previously, please select one of the options below before entering the main site. This will allow us to provide you with the best possible information to help you while using this site.

I'm a member of the public

I'm a health care professional

Already Registered, Login Here

If you have already registered with this site, please login.

Fields marked with a \* are required

Email Address \*

Password \*

Login

If you have forgotten your password please complete this form.

# Promotional material



Tear along the dotted line

Confidential

## YellowCard<sup>®</sup> report

Use blue or black ink. Complete all the lines marked with \* and give as much other information as you can

### 1 About the suspected side effect

\* What were the symptoms of the suspected side effect, and how did it happen? If there isn't enough space here, attach an extra sheet of paper.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

How bad was the suspected side effect? Tick the box that best describes how bad the symptoms were.

\*  Mild  Unpleasant, but did not affect everyday activities  Bad enough to affect everyday activities  Bad enough to see doctor  
 Bad enough to be admitted to hospital  Caused very serious illness  Caused death  Other \_\_\_\_\_

When did the side effect start?

\_\_\_\_\_

How is the person feeling now? Tick the box that best describes whether the person still has symptoms of the suspected side effect.

\*  Better (no more symptoms)  Getting better  Still has symptoms  More seriously ill  Died  Other \_\_\_\_\_

Can you give any more details? For example, did the person take or receive any other treatment for the symptoms? Did they stop taking the medicine as a result of the side effect?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

### 2 About the person who had the suspected side effect

Who had the suspected side effect?

\*  You  Your child  Someone else

Information about the person Supply as much information as you can, even if you prefer not to give a name.

First name or initials \_\_\_\_\_ Family name \_\_\_\_\_  Male  Female

\* Age \_\_\_\_\_ Weight \_\_\_\_\_  kg  stones/pounds Height \_\_\_\_\_  metres  feet/inches

Any other relevant information? For example, does the person have any medical conditions or allergies?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Make sure you have completed all the lines marked \*

Please turn over →

### What is the MHRA?

The Medicines and Healthcare products Regulatory Agency (MHRA) is a UK government body. Its principal aim is to protect the public's health. It does this by making sure that medicines and medical devices work properly and are acceptably safe.

When any possible problem is found, the MHRA takes prompt action to protect the public and reduce risk.

For more information about the MHRA:

visit [www.mhra.gov.uk](http://www.mhra.gov.uk)

or telephone 020 7084 2000

© Crown Copyright 2008

### A side effect of your medicine?

If you have a symptom which you think may be a side effect of your medicine...

- 1 Check the patient information leaflet supplied with the medicine. This lists the known side effects, and advises you what to do.
- 2 Ask your doctor or pharmacist for advice.
- 3 You can report the side effect using Yellow Card, especially if it is not mentioned in the patient information leaflet.

Always talk to your doctor if you have any symptom that worries you.



### How to report a suspected side effect

There are three ways to use the Yellow Card Scheme:

- use the online Yellow Card at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)  
This is the easiest way to make a report, if you have access to the Internet.
- ask your pharmacist for a Yellow Card form which you can complete and post
- call the Yellow Card hotline on 0808 100 3352

You can report suspected side effects of any medicine or herbal remedy, whether it was prescribed by your doctor or bought without a prescription.

### What happens to Yellow Card reports?

The MHRA (*see overleaf*) collects Yellow Card reports from people taking medicines, as well as from healthcare professionals such as doctors, pharmacists and nurses.

These reports are used to identify side effects and other problems which might not have been known about before. If a new side effect is found, the MHRA will review the way that the medicine can be used, and the warnings that are given to people taking or using it.

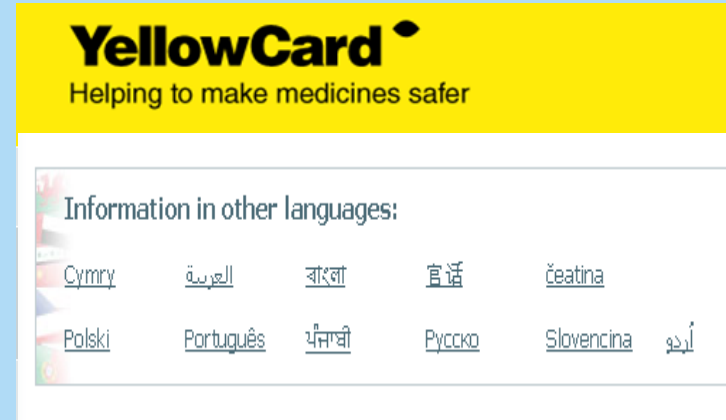
The information you provide will be kept safe, secure and confidential. No details that could identify you will be passed on without your permission.

# YellowCard<sup>®</sup>

Helping to make medicines safer

# Increased accessibility to Patients

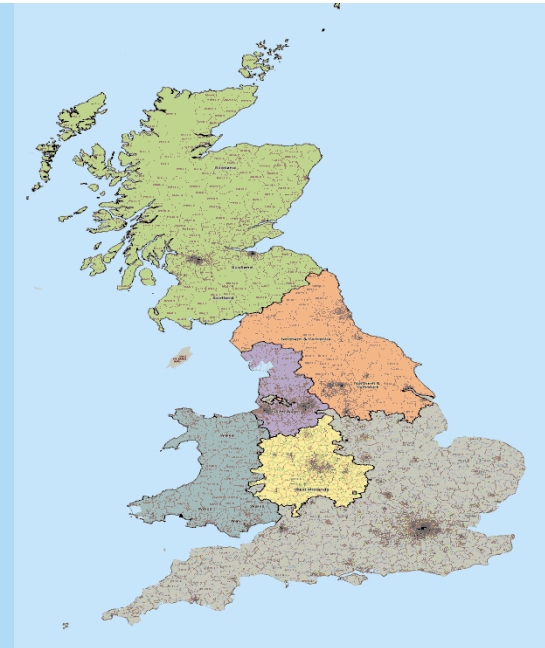
- TV advert for some GP surgeries
- Poster campaign
- Nationwide Leaflet Distribution
- Translation into 10 languages



## 5 Regional Centres for promotion (MI hospital based)

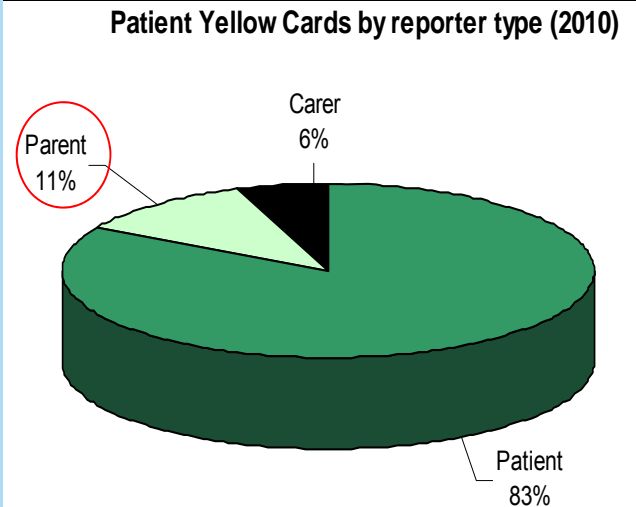
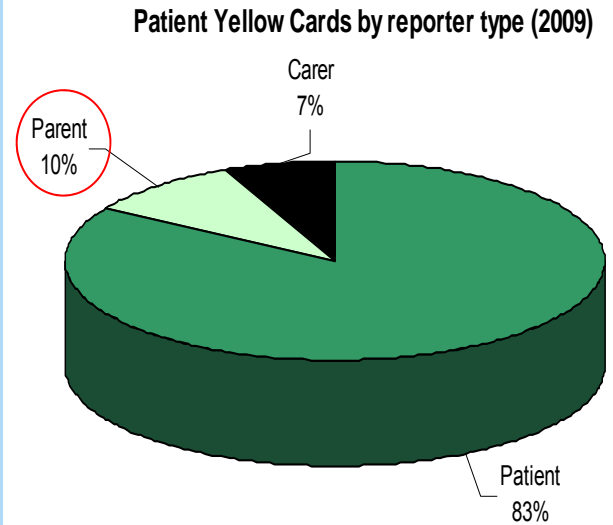
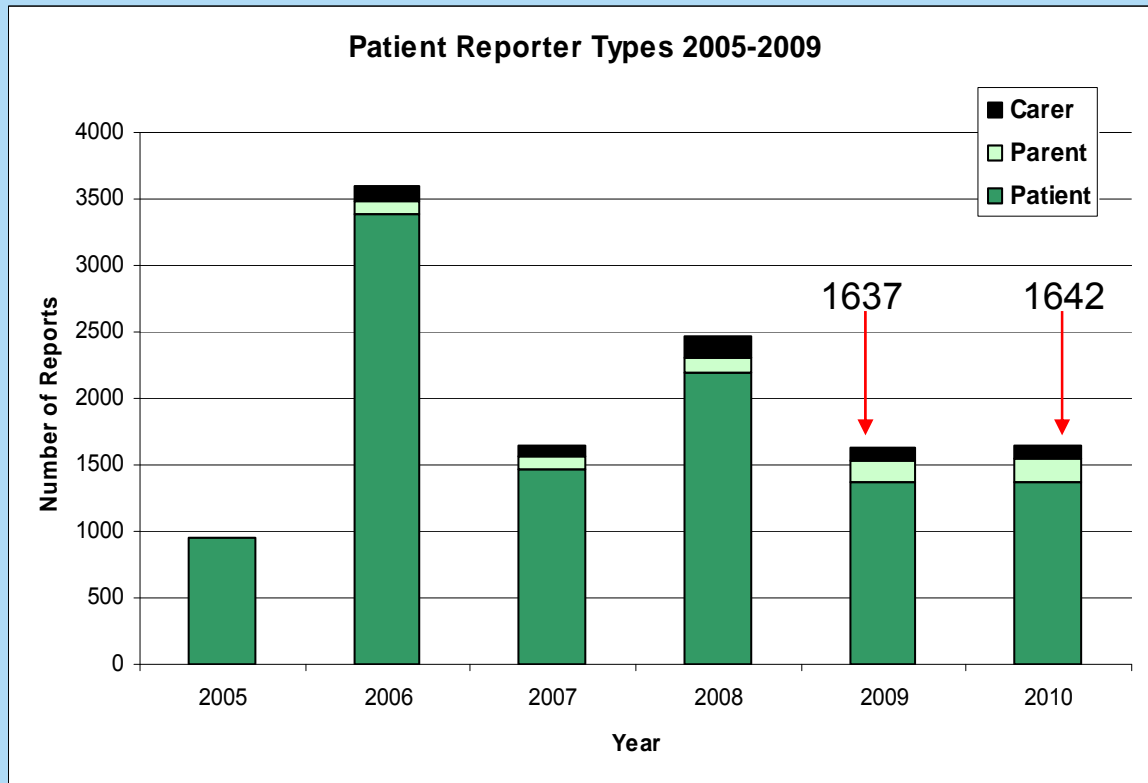
- Scotland (Edinburgh)
- Wales (Cardiff)
- West Midlands (Birmingham)
- Northern and Yorkshire (Newcastle)
- North West (Liverpool)

Education / awareness - patient groups  
Conferences



# Patient reporting

- Proportion of total reports: 7.3% (2009) & 7.0% (2010)
- Proportion of serious reports: 86.7% (2009) & 88.3% (2010)

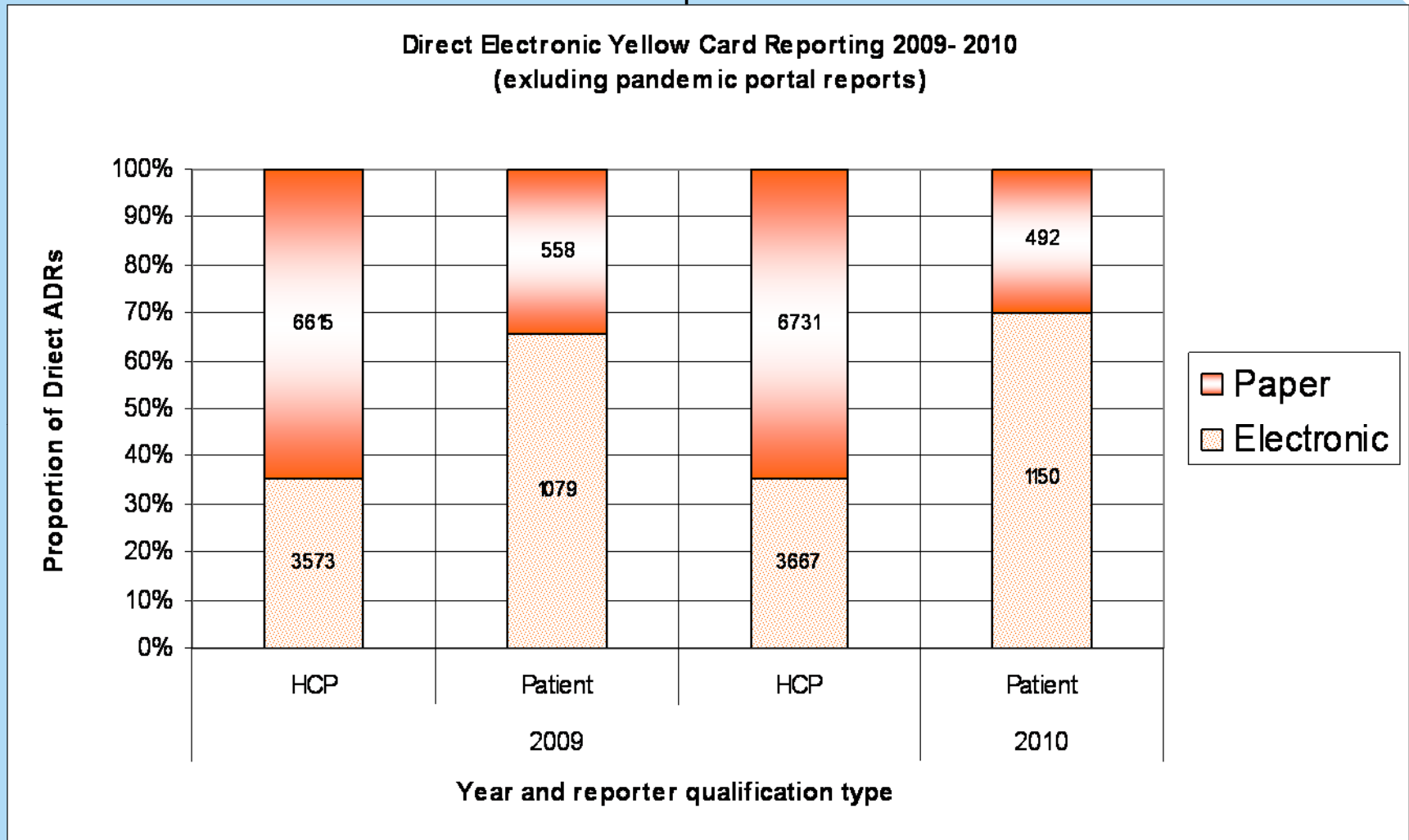


> 80% report themselves

# Electronic reporting



- 70% eYC patient reports in 2010; 4% ↑      Direct HCP – constant 35%



# Drug-Reaction Combinations 2010

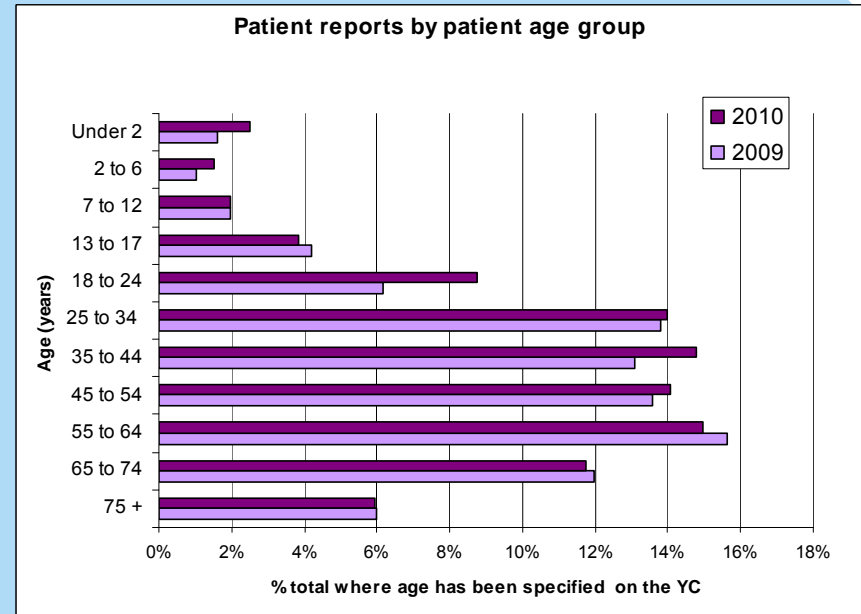
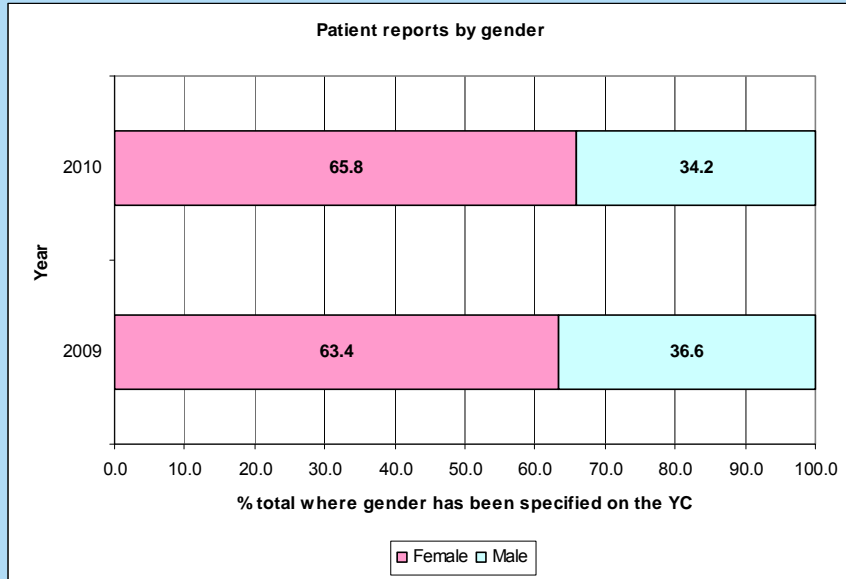


HCP Drug-Reaction combinations				Patient Drug-Reaction combinations			
Drug substance	ADR term (*Serious PT)	No. reports	% Total HCP reports	Drug substance	ADR term (*Serious PT)	No. reports	% Total patient reports
HPV ▼	Dizziness	354	3.4	Simvastatin	Myalgia *	25	1.5
HPV ▼	Nausea	292	2.8	HPV ▼	Headache	25	1.5
HPV ▼	Headache	277	2.7	Simvastatin ▼	Arthralgia *	19	1.1
HPV ▼	Pain in extremity	229	2.2	Paroxetine	Withdrawal syndrome *	18	1.1
HPV ▼	Fatigue	124	1.2	HPV ▼	Nausea	18	1.1
HPV ▼	Malaise	116	1.1	Paroxetine	Paraesthesia	15	0.9
HPV ▼	Vomiting	112	1.1	HPV ▼	Dizziness	15	0.9
Varenicline ▼	Nausea	105	1	Simvastatin ▼	Pain in extremity	14	0.8
Varenicline ▼	Depressed mood *	104	1	HPV ▼	Fatigue	14	0.8
HPV ▼	Syncope *	103	1	Desogestrel	Depression **	13	0.8

\* - serious PT; \*\*Signal – RMS - Sweden

- HCP all BT, patients - 40% in 2009 to 60% in 2010
- Vaccines make up 15.9% patient reports

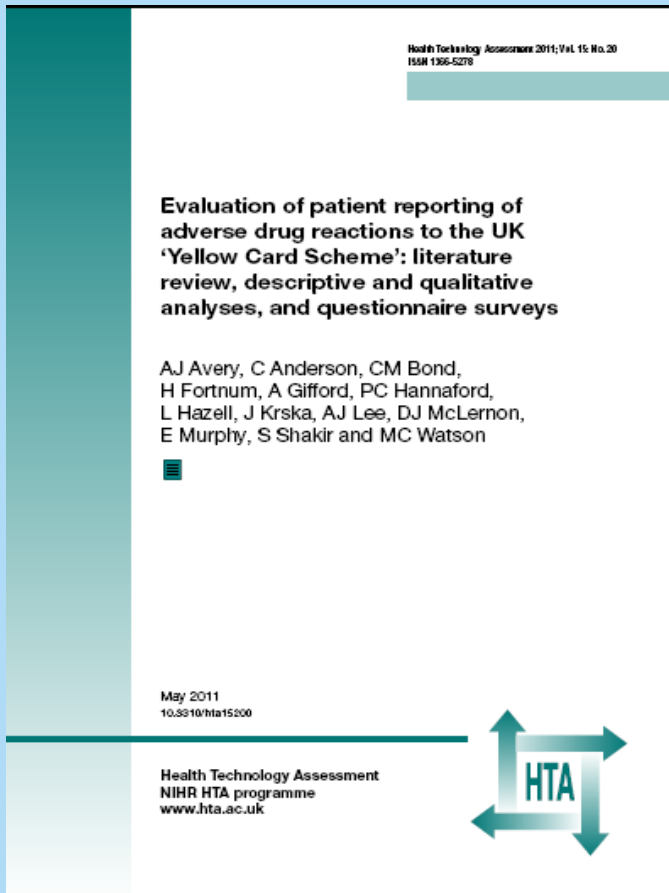
# Age and gender reporting



## Summary for gender breakdown:

- (male): simvastatin (2009 4.1%, 2010 3.0%)
- (female): HPV vaccine (2009 5.2%, 2010 4.1%)
- (male): fatigue (2009) and headache (2010)
- (female): dizziness (2009) and nausea (2010)
- serious (male): depression (2009), arthralgia (2010)
- serious (female): depression (2009 & 2010)

# Evaluation of patient ADR reporting to Yellow Card Scheme

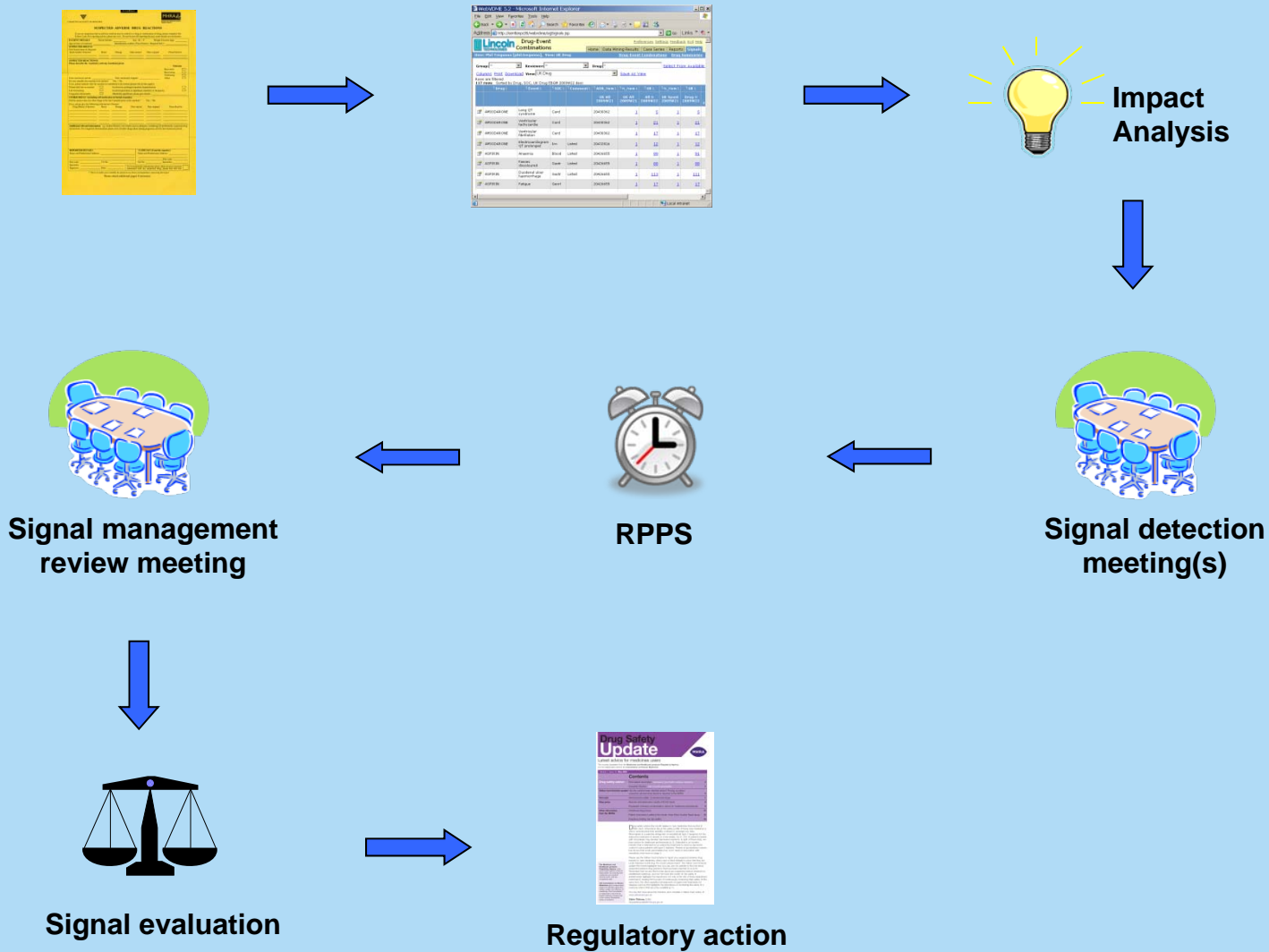


- Higher median number of ADRs per patient report than HCPs and more detailed description
- Similar proportion of “serious” reports
- More signals when combined HCP and patient reports - 47 new serious Some signals in HCP only set were lost but fewer than those gained
- Different patterns of drugs and reactions reported by patients

*Avery et al 2011 HTA; vol 15; no 20*

# Signal Detection

# Signal detection & prioritisation process



# Methodologies & Processes (1)

Empirica Signal used for analysis and data provision:

- Empirical Bayes Geometric Mean (EBGM) routine statistic of disproportionate reporting (SDR) since 2006. PRR used since 1996, and still computed alongside EBGM.
- Statistic calculated and analysed weekly for all products
- Drugs/ Vaccines analysed separately
- Patient & HCP reports analysed together

# Methodologies & Processes (2)

Empirica Signal – essential features for signal analysis:

- Different 'views' of the data enable different thresholds for groups of products
- Only DEC's which meet thresholds in the given week are displayed for review
- Products allocated to named assessors each week; minimal manual intervention

# MHRA Thresholds

- UK reports (Black Triangle Products):
  - All DECAs reviewed
- UK reports (Established Medicines):
  - Non-listed DECAs with  $N \geq 3$ ,  $EBGM \geq 2.5$ ,  $EB05 \geq 1.8$
  - All fatal, paediatric, parent-child reports, all Alert Terms
  - Frequency change ( $\geq 8\%$  reports received in last quarter)
- Non-UK reports (Black Triangle Products):
  - Serious unlisted reactions (excluding 1<sup>st</sup> cases with no UK cases)
    - All serious reactions from fatal reports
    - All unlisted alert term reactions
- Non-UK reports (Established Medicines):
  - Serious unlisted reactions with non-UK  $n \geq 7$ ,  $EBGM \geq 2.5$  &  $EB05 \geq 1.8$ 
    - All serious reactions from fatal reports (excluding 1st cases with no UK cases)
    - All serious unlisted paediatric, parent-child, alert term reactions (excluding 1st cases with no UK cases)

# Signal detection at the MHRA

## For established drugs (Non-black triangle)

- Approximately 2000 drug – event combinations are assessed for UK & Foreign reports each week.
- 80 signals of which are discussed at the weekly signal generation meeting.

## For new drugs (Black triangle)

- Approximately 4000 drug – event combinations are assessed for UK & foreign reports each week.
- 190 signals of which are discussed at the weekly signal generation meeting.

# Timelines for signal review

## **2011/2012 Agency Signal target:**

- Ensure all potential UK signals (relating to medicines and vaccines) from whatever source are acted on promptly: 80% initially evaluated within 5 working days
- For potential signals identified by Empirica target measured by addition of comments to DECAs
- All Black Triangle product must have a deputy assessor

Group:  Reviewer:  Drug:  [Select Drug](#) SOC:

View:  [Filter By Comments](#) [Save As View](#) [Manage Views](#)

[Columns and Rows](#) [Print](#) [Download](#) [Select Rows](#)

Rows are filtered

115 rows Sorted by Drug, SOC, UK Drug EBMG 2011W46 desc

Rows Per Page:  Page  of 1

	Drug	Event	SOC	Comment	ADR_New	Signal	N_New	UK	N_New	UK	UK	UK	UK
					UK All 2011W45	Reason	UK All 2011W45	All N 2011W46	UK Spont 2011W45	Drug N 2011W46	Drug EB05 2011W46	Drug EBMG 2011W46	Drug EB95 2011W46
	CYCLOPHOSPHAMIDE	Haematopoietic leukopenia (SMQ) [narrow]			21054032	DC	1	826		170	7.92	9.00	10.2
	CYCLOPHOSPHAMIDE	Haematopoietic leukopenia (SMQ) [broad]			21054032	DC	1	827		171	7.86	8.93	10.1
	CYCLOPHOSPHAMIDE	Haematopoietic cytopenias (SMQ) [narrow]			21054032	DC	1	893		215	5.91	6.62	7.39
	CYCLOPHOSPHAMIDE	Haematopoietic cytopenias (SMQ) [broad]			21054032	DC	1	929		221	5.52	6.17	6.89
	CYTARABINE	Thrombocytopenia	Blood	Listed	21240893	A	1	33		5	0.877	1.95	3.89
	CYTARABINE	Haematopoietic leukopenia (SMQ) [broad]			21240893	D	1	152		33	3.77	5.06	6.69
	CYTARABINE	Haematopoietic leukopenia (SMQ) [narrow]			21240893	D	1	148		32	3.70	4.99	6.62
	CYTARABINE	Haematopoietic cytopenias (SMQ) [narrow]			21240893	D	1	183		39	3.03	3.97	5.13
	CYTARABINE	Haematopoietic cytopenias (SMQ) [broad]			21240893	D	1	189		40	2.87	3.75	4.84
	DEXAMETHASONE	Thrombocytopenia	Blood	Listed co-suspect	21240893	A	1	12		3	0.251	0.727	1.74
	ETHANOL	Drug interaction	Genrl	Cannot assess cumul	21054031	DA	1	8		8	2.83	5.28	9.15
	ETHANOL	Loss of consciousness	Nerv	Listed co-suspect	21054031	D	1	8		8	3.33	6.19	10.7
	ETHANOL	Fatal (Special PT Group)	PTGrp	No immediate action	21054031	DA	1	29		24	1.94	2.74	3.80
	ETHANOL	Torsade de pointes/QT prolongation (SMQ) [broad]			21054031	D	1	18		17	2.86	4.34	6.37
	ETHANOL	Noninfectious meningitis (SMQ) [broad]			21054031	D	1	44		43	2.28	2.94	3.76
	ETHANOL	Noninfectious encephalitis (SMQ) [broad]			21054031	D	1	58		56	2.27	2.84	3.52
	ETHANOL	Noninfectious encephalopathy/delirium (SMQ) [broad]			21054031	D	1	58		56	2.07	2.60	3.22
	ETHANOL	Cardiac arrhythmias (SMQ) [broad]			21054031	D	1	30		28	1.82	2.52	3.40
	FLUDARABINE	Agranulocytosis	Blood	Listed co-suspect	21054032	AC	1	5		5	1.43	3.19	6.35
	FLUDARABINE	Agranulocytosis (SMQ) [narrow]			21054032	DC	1	117		44	8.04	10.4	13.2



# RPPS & Impact Analysis

Evidence based tools for further evaluation of signals:

## Impact Analysis

- This is a tool to prioritise possible signals and decide the next step that should be taken. This takes into consideration the strength of evidence as well as the public health implications of the signal.

## RPPS

- The Regulatory Pharmacovigilance Prioritisation System. This is further signal prioritisation also taking into account public perception of the ADR and Agency obligations.

# Impact Analysis

- Interim step between signal detection & detailed signal evaluation
- Summarises impact of a signal through two scores:
  - Evidence (strength of evidence for causality)
    - Mean of EBGM/EB05
    - Strength of evidence from spontaneous reports
    - Biological plausibility
  - Public health (public health implications)
    - Number of cases reported per year
    - Health consequences of the ADR
    - Reporting rate over last year

# RPPS



- System of issue prioritisation which follows on from Impact Analysis and uses some of the same principles:
  - Strength of evidence for a causal effect
  - Potential public health implications
  - Public perceptions
  - Agency obligations
- Aid to the management of multiple dynamic issues in the allocation of resources
- Ensures that appropriate timescales are defined to meet MHRA's public health and other obligations
- Aid to pharmacovigilance audit
- Overall priority linked to timescales

# Signal Management

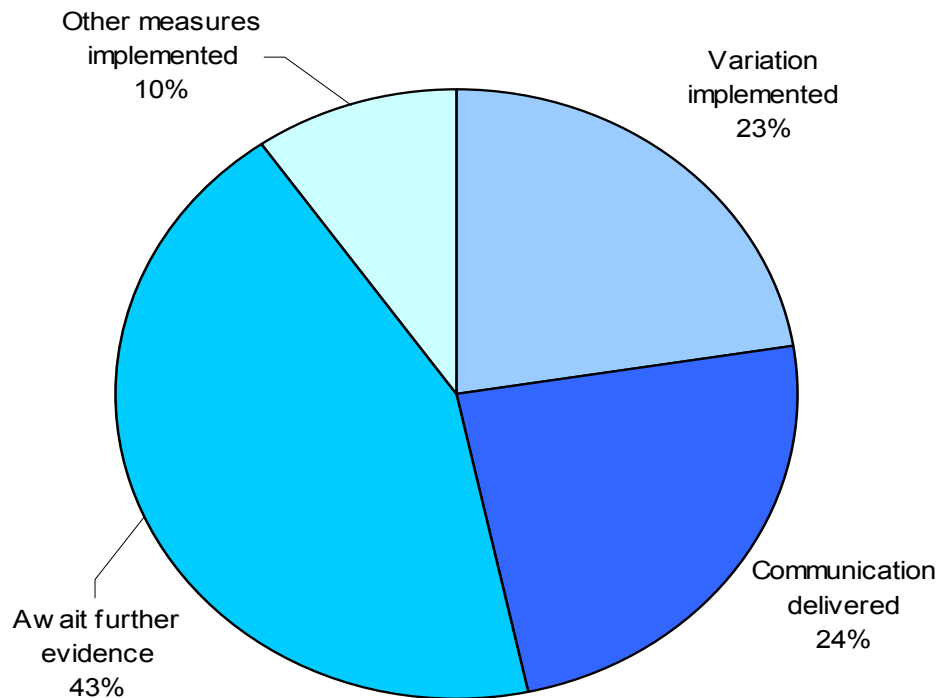


- All signals that warrant further action are discussed at our Signal Management Review Meeting
- Brings together expertise across the Agency including Assessors, Medics and Epidemiologists
- Signals are fully evaluated including assessment of biological plausibility and potential class effects
- Action are discussed and endorsed (including further expert advice required) the priority of the signal is agreed and team allocation is decided

# Signals investigated in 2009 & 2010

- 277 signals - **detailed review (53 contributing signals)**
- **15 index cases**
- 16 signals from Yellow Card data contributed to DSU articles

Outcomes of signals investigated in 2010



- **19% of signals in 2009 & 2010 had contributing reports from members of the public**

# Patient signals in 2009 & 2010

154 signals investigated **2009** - 24 contributing

123 signals investigated **2010** - 29 contributing

- orlistat and device interaction - MAH review
- amlodipine and food interaction grapefruit juice - update to SPC/PIL.
- hyoscine and visual hallucinations
- spironolactone and drug hypersensitivity - further evidence for strength
- cyproterone and hepatic failure – update to SPC/PIL
- nitrofurantoin and alveolitis fibrosing – update to SPC/PIL
- desogestrel and suicidal ideation - PSUR
- levonorgestrel and suicidal depression – PSUR
- simvastatin and epistaxis – PSUR

Others include:

- pandemic – condition aggravated e.g. convulsions
- internet– investigated by enforcement team e.g. slimming pills.
- herbals– St John's Wort

# Regulatory Action & Communication



- Updating product information (SPC/PIL)
  - Restrict indications / introduce new contra-indications / reduce the recommended dose
  - Warnings in Drug Safety Update
  - Inform rapporteur/RMS
  - Raise in PSURs
- 
- Most importantly: Who should receive any communications?
  - Proactive communication?

**Drug Safety Update**

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 3, Issue 12 July 2010

Contents		Click on text to go to page
<b>Drug safety advice</b>	Intravenous paracetamol (Perfalgan ▼): risk of accidental overdose, especially in infants and neonates	2
<b>Yellow Card Scheme update</b>	Information is now available in a number of languages	4
<b>Stop press</b>	Orciprenaline sulphate (Alupent): reminder of withdrawal from the market on Sept 30, 2010	5
<b>Other information from the MHRA</b>	Patient Information Leaflet of the month: medicines used in mental health	5

# Next steps...



Article 102:

*'The Member States shall: (1) take all appropriate measures.....To encourage **patients**, doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority'*

Article 107h:

*'....national competent authorities in collaboration with the Agency, shall take the following measures...(c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.'*

# Summary



- Every Yellow Card submitted is important to us
- Numbers of patient reports very encouraging– 75% increase since 05
- Promotion +ve impact on reporting; commitment & contribution
- Excellent move towards electronic reporting (70%)
- High quality – descriptive reporting, impact on patient QoL
- Positive contribution to signal detection and drug safety signals increased from 15.6% in 2009 to 23.6% in 2010 from patients.
- Capable of supporting real time pharmacovigilance
- Future system needs to continue to support signal detection from all ADR reports

# Crown copyright 2011



The materials featured within these MHRA presentation notes and delegate pack are subject to Crown copyright protection for this event. Any other copy or use of Crown copyright materials featured in this presentation, in any form or medium, is subject to prior approval of the MHRA which has Delegated Authority from Her Majesty's Stationery Office (HMSO) to administer Crown copyright for MHRA originated material. Applications should be in writing, clearly stating the proposed use/reuse of the information, and should be sent to the MHRA at the following address:

Conference and Education Function  
MHRA, 4th Floor, 151 Buckingham Palace Road  
London. SW1 9SZ  
e-mail: [speakers@mhra.gsi.gov.uk](mailto:speakers@mhra.gsi.gov.uk)

You may not sell or resell any information reproduced to any third party without prior agreement. The permission to reproduce Crown copyright protected material does not extend to any material in this pack which is subject to a separate licence or is the copyright of a third party. Authorisation to reproduce such material must be obtained from the copyright holders concerned.