

SIGNAL DETECTION

Nassrin Payvandi

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What will be covered?

- Signal detection
 - Definitions
 - Sources
 - Methods of detection
 - Clinical trials
 - Spontaneous data

 - Steps taken when signal is identified
-

'Definitions of SIGNAL'

WHO definition: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

CIOMS VI Definition of signal: A report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance

- Not a confirmed finding
 - Hypothesis generating
-

New Safety Information

- **A New signal**
 - **Unidentified**
 - **Unlabelled**
 - **New information about an existing signal**
 - **Change in frequency**
 - **Change in severity**
 - **Information on risk factors**
-

SOURCES OF SIGNALS

- **Pre-clinical data (animal toxicology, pharmacology)**
 - **Clinical trials (phases I - IV)**
 - **Spontaneous reports (company database, regulatory databases)**
 - **Published literature**
 - **Epidemiology/Registeries/PEM**
 - **Competitor data**
-

Sources of Signals Vary During the Product Lifecycle

Pre-clinical Development	Clinical Development	1 st years after launch	Mature Product
<u><i>In vitro</i> studies</u> Chemistry ADME* Target receptors Transporters	<u>Human studies</u> <ul style="list-style-type: none">▪ Adverse events▪ Laboratory data▪ Biometrics▪ PK <u>Animal studies</u> <u><i>In vitro</i> studies</u>	<u><i>Human studies</i></u> <ul style="list-style-type: none">▪ Phase IIIb/IV▪ New indications Spontaneous case reports Published literature Epidemiology	Published literature Epidemiology Spontaneous case reports
<u><i>In vivo</i> studies</u> Animal			

*Absorption, distribution, metabolism, excretion

Objectives of Clinical Trials

- To demonstrate efficacy
- To detect and characterise common ADRs
- To identify ADR risk factors
- To meet regulatory requirements to file

NO. OF PATIENTS REQUIRED TO BE 95% CERTAIN OF DETECTING ONE, TWO AND THREE CASES OF AN ADVERSE REACTION

INCIDENCE OF ADVERSE REACTION	NO. OF PATIENTS REQUIRED NO. OF ADVERSE REACTIONS DETECTED		
	One Case	Two Cases	Three Cases
1 IN 100	300	480	650
1 IN 200	600	960	1,300
1 IN 1,000	3,000	4,800	6,500
1 IN 2,000	6,000	9,600	13,000
1 IN 10,000	30,000	48,000	65,000

Factors that Limit the Power of Clinical Trials to Detect Rare ADRs

Number of patients

Exclusion of certain patients

Limited duration of treatment

Restricted doses

Restricted doctors

CIOMS VI Recommendations – Improving Signal Detection During Development

- Prompt medical evaluation of:
 - Individual serious cases
 - ***Regardless of attribution or expectedness***
 - *Events of special interest e.g.*
 - Stevens Johnston Syndrome
 - “Hy’s law” cases (elevated ALT and bilirubin)

 - Periodic aggregate assessment of all available clinical safety data

 - Safety evaluation of completed, unblinded studies
 - Individual studies
 - Combined data sets across studies
 - Statistical analysis (not just data summaries!)
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Signal Detection Tips - Clinical Trials

- Explore signals when they are first reported

 - Look at **all** the data
 - Clinical adverse events
 - Laboratory data
 - Biometric data e.g. blood pressure or ECGs

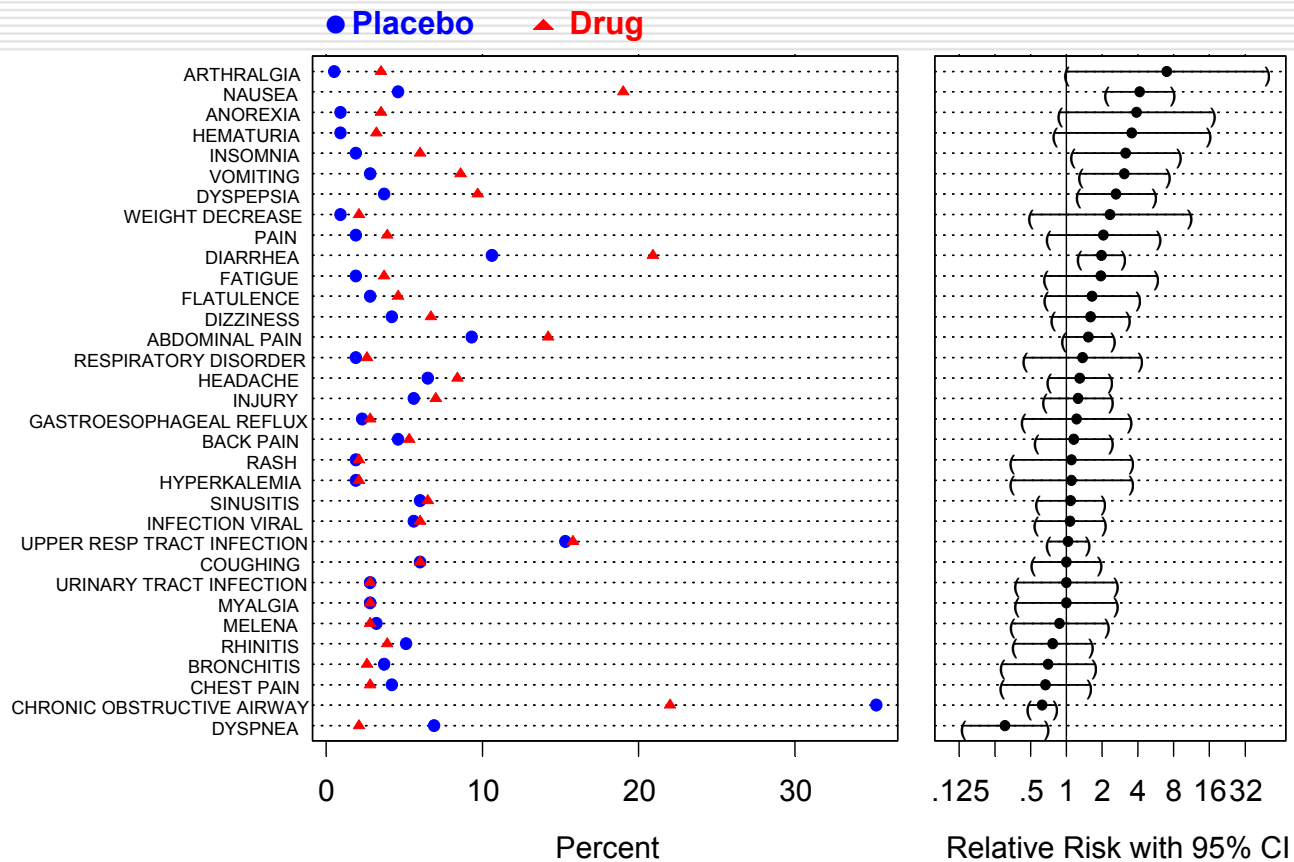
 - Use tools which facilitate review of large volume of data
 - Integration of data across studies
 - Graphics
 - Outliers, shifts in distributions
 - Tools to allow exploration of aggregate data with capability to drill down to individual patient data
-

Statistical Techniques Used for Signal Detection

- Relative risk or odds ratios (95% CIs)
- Logistic regression
- Proportional Reporting Ratio*
- Bayesian approaches
 - Multivariate Gamma-Poisson Shrinker (MGPS)

*Evans et al. Drug Safety 2001 10(6) 483-6

Relative Risk or Odds Ratio (95% CIs)



Useful for signal detection in controlled clinical studies

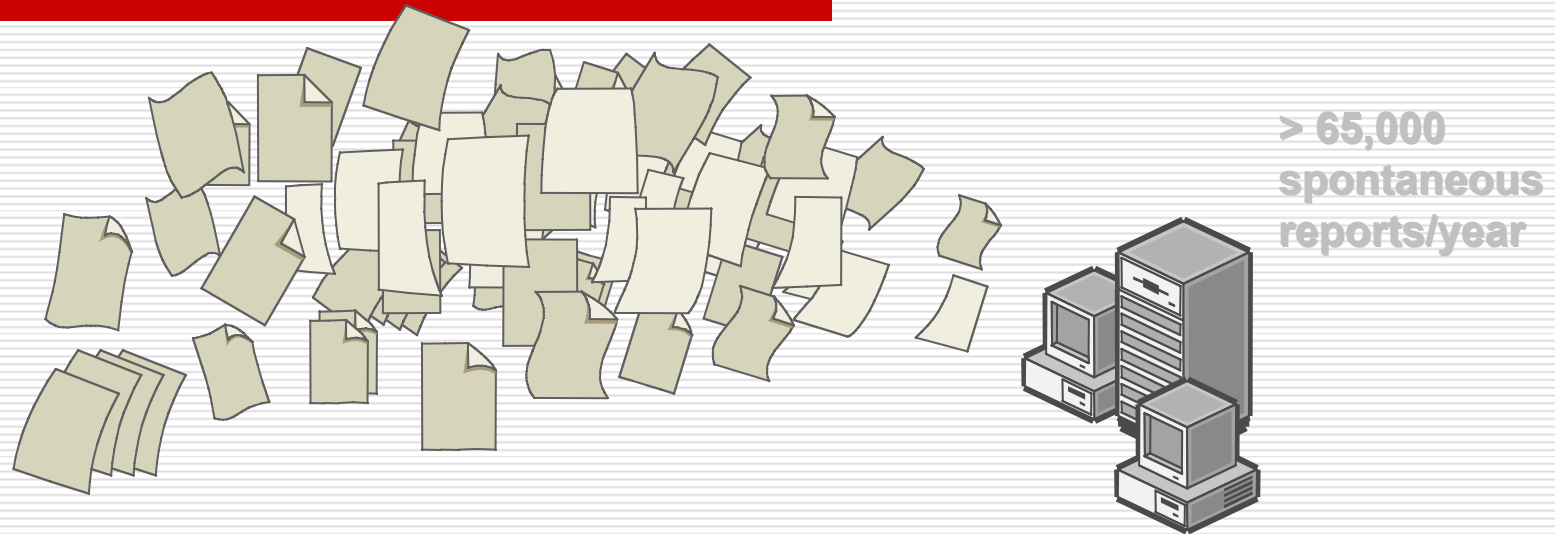
Signal Detection from Spontaneous Reporting

- Operates as soon as a drug is marketed
 - Covers entire population receiving drug
 - Involves all doctors
 - Includes all drugs
 - Detects common and rare reactions
 - Continues indefinitely
 - Inexpensive
-

Factors Influencing Spontaneous Reporting

- **Use/sales of drug**
 - **Time on market**
 - **ADR profile of similar drugs**
 - **Seriousness of ADR v Seriousness of disease**
 - **Publicity**
-

Post-marketing Pharmacovigilance is Challenging and Labor-intensive



- Reporting is voluntary
 - No denominator
 - No control group. Signal vs. noise?
 - Traditionally focused on individual cases.
 - No systems-based tools for signal detection
 - Nonetheless, data contain important safety information**
-



Graphical views with interactive navigations

Quarter	Value
1st Qtr	30
2nd Qtr	45
3rd Qtr	90
4th Qtr	45

Alerts to potential toxicities !

Warnings on key parameters

Outputs at predefined intervals

Now → **Future**

**Manual
Paper**

**A paradigm shift in how signals
are detected/ explored**

**Electronic
Enhanced**

Request 4: Smarter ways to review safety data

Safety Data Mining Enables Rapid and Systematic Identification of Safety Signals

- With post-marketing data, it's difficult to distinguish signals from noise.
- Safety Data Mining (SDM)/disproportionality methods identify AEs that are reported with $>$ expected frequency (statistical independence)

Frequency is assessed against the background of all other drugs and events. Results are used for hypothesis generation.



- ➔ Enhanced effectiveness of post-marketing pharmacovigilance through rapid, systematic screening of AE databases
- ➔ Enhanced benefit-risk management

Disproportionality Analysis (DPA)

Assesses the frequency of specific drug-adverse event combinations against the background of all other drugs and events

	Drug X	All other Drugs
Event of interest	A	C
All other Events	B	D

$$Is \frac{A}{A+B} > \frac{C}{C+D} ?$$

Disproportionality Analysis (DPA)

Detects reporting frequencies that are “**higher than expected**” in large adverse event databases

Interpreted as hypotheses regarding potential causal associations between drugs and events

DPA scores do not directly measure CAUSAL association between the drug and event, or provide INCIDENCE.

DPA scores may be elevated for reasons other than causal associations, such as:

- Background disease in the population using the drug
 - Publicity / litigation about the possible adverse drug reaction
 - Concurrent medication(s) often used with drug of interest
 - Infrequently used MedDRA term
-

Proportional Reporting Ratio (PRR)*

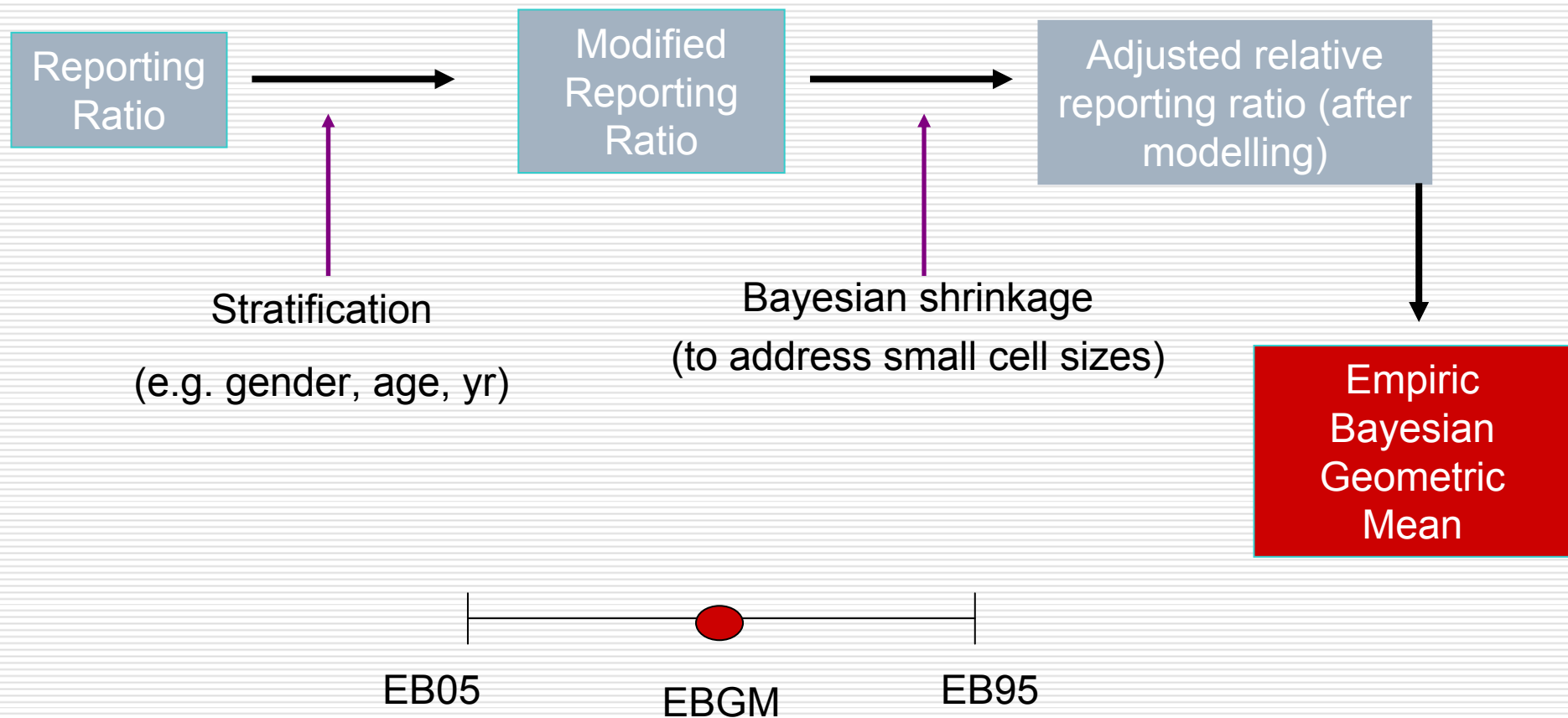
PRR is the ratio of the number of reports of:

$$\frac{\text{Event of interest for drug of interest}}{\text{All events for drug of interest}} \bigg/ \frac{\text{Event of interest for all other drugs}}{\text{All events for all other drugs}}$$

PRR > 1 - positive quantitative association between the drug and the event of interest.

*Evans et al. Drug Safety 2001 10(6) 483-6

Multi-Item Gamma Poisson Shrinker (MGPS)



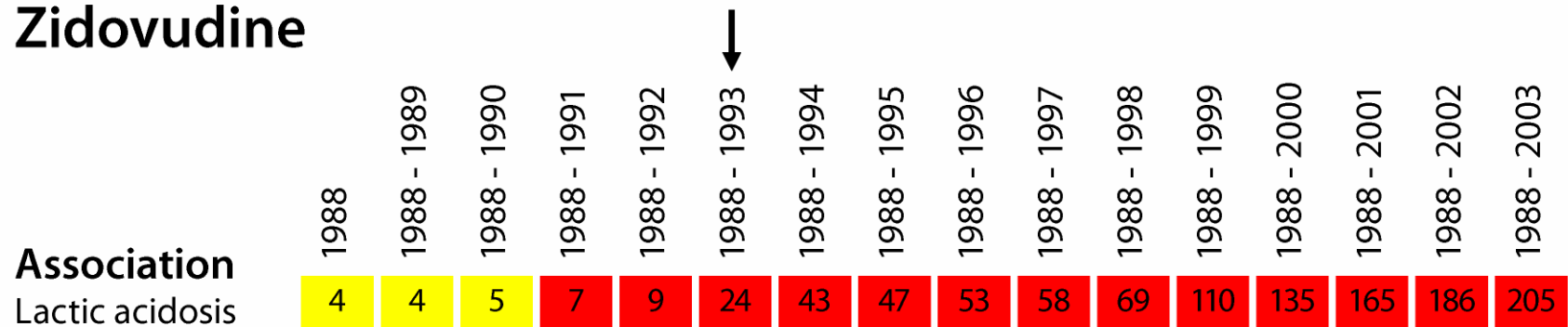
DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

Empirical Bayes Geometric Mean (EBGM)

- EBGM is an observed/expected score that is the output of the MGPS method
 - EB05 and EB95 are the lower and upper bounds of the 2-sided 90% confidence interval around EBGM
 - Interpretation:
 - If $EBGM = 7.2$ for paracetamol-hepatic failure, then this drug-event combination occurred in the data set 7.2 times more frequently than expected
 - If $EB05 = 4$, then the drug-event occurred *at least* 4 times more frequently in the data set than expected
 - Thresholds used for Data Mining :
 - $EB05 \geq 2$ will flag drug-event combinations that occur *at least* twice as often as expected
-

Example

Zidovudine



$$\begin{array}{ccccccc} 0 \leq EB05 \leq 1 & 1 < EB05 \leq 2 & 2 < EB05 \leq 4 & 4 < EB05 \leq 8 & 8 < EB05 < \infty \\ \color{blue} \blacksquare & \color{green} \blacksquare & \color{yellow} \blacksquare & \color{orange} \blacksquare & \color{red} \blacksquare \end{array}$$

A Signal Detection System

- Prior to 2002



Now

Proactive, regular signal detection

- Use aggregate data
- On-line, desk top system
- EBGM, EB05 and EB90 available for all events for all products
- Track trends over time
- Capability to drill down to individual cases
- Filter and sort
- Seriousness and listedness assessed automatically

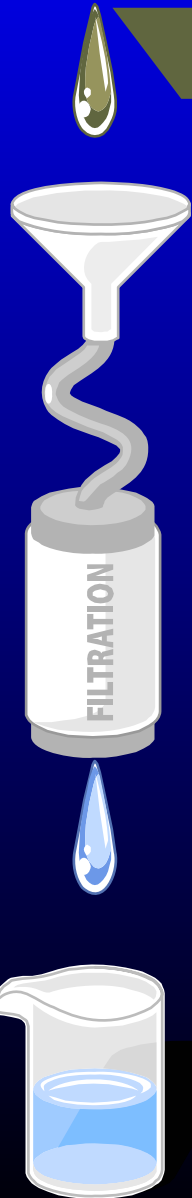
Important, serious cases flagged daily

Routine literature review

Challenges Encountered:

- ❑ Lots of data, yet little new knowledge
 - ❑ Another system had to be queried to retrieve additional information about potential signals
 - ❑ Static display of data hindered user ability to prioritize and sort through information
 - ❑ No integrated way to store results of analyses or track prior assessments
 - ❑ Lacked flexibility to serve different or user needs
-

Refining Safety Data



All Events

**AEs for each product automatically prioritized :
seriousness, listedness, signal trends, public health impact**





**User investigates and documents
assessments of safety issues**

**User “filters” known,
established issues; re-
evaluates only if new
trends emerge**

**New,
important
issues**



Signal Views with Filtering and Sorting Functions

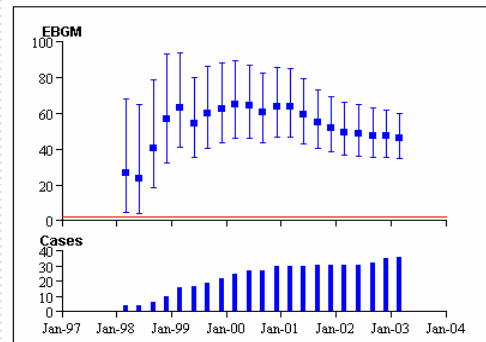
	Event	SOC	Q	Trnd1	Trnd2	Ser	Lst	Comment	N*	N	N*new	EB05	EBGM	EB05
				Jul05	Jul05				Jan06	Jan06	Jul05	Jan06	Jan06	Jul05
	Anaemia	Blood	B	NO	NO	YES	NO		<u>7</u>	<u>7</u>	<u>1</u>	0.758	1.44	0.625
	Aplasia pure red cell	Blood	B	NO	NO	YES	NO		<u>1</u>	<u>1</u>		0.284	1.381	0.285
	Pancytopenia	Blood	B	NO	NO	YES	NO		<u>3</u>	<u>3</u>		0.398	1.051	0.398
	Aplastic anaemia	Blood	B	NO	NO	YES	NO		<u>4</u>	<u>4</u>		0.642	1.498	0.64

Visualization Tools, Trend Analysis

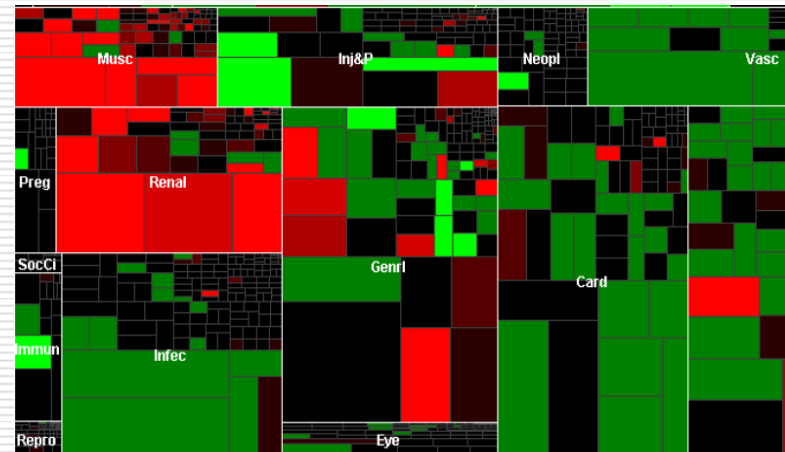
Metformin
 Anion gap increased (PT)
 Blood gas and acid base analyses (HLT)
 Inv (SOC)

Period Begin: 03/01/1998 End: 03/01/2003

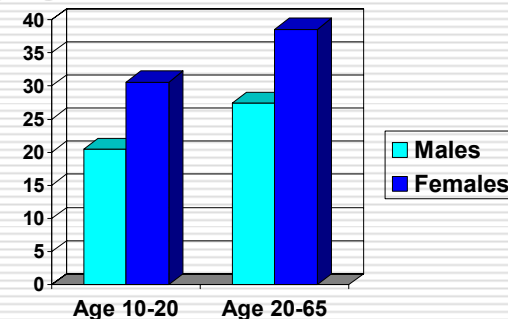
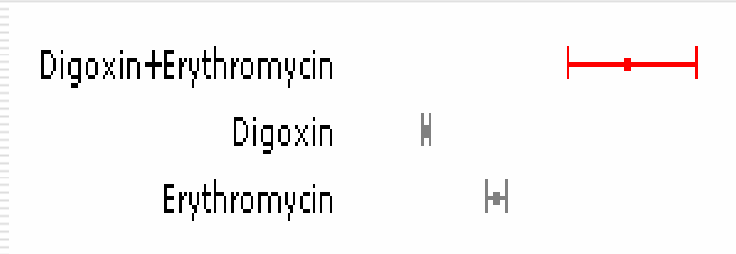
Attributes: Serious=81%, Death=41%, FDA Category=NONE, Quadrant=A



	Current	Prior	Diff
N	36	35	+1
EB05	34.632	35.568	-0.936
EBGM	45.993	47.435	-1.442
EB95	60.117	62.233	-2.116
PRR	55.101	56.982	-1.881
CHISQ	1455.591	1460.578	-4.987

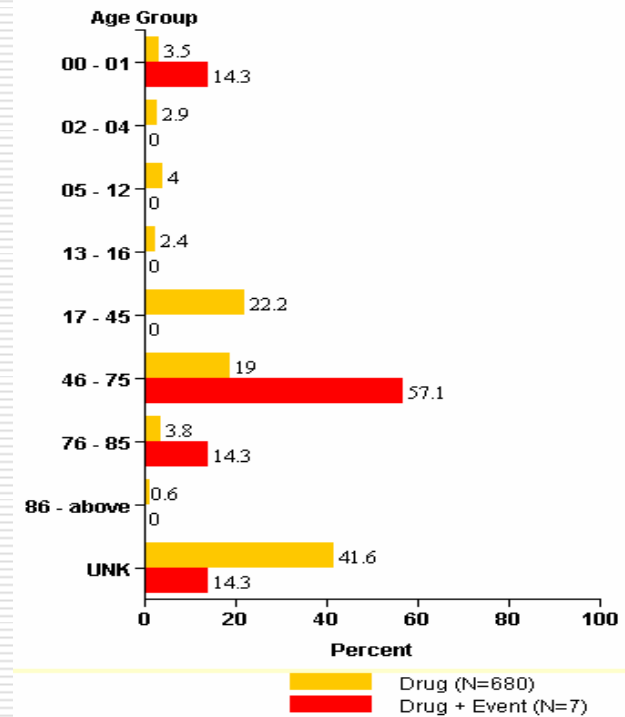
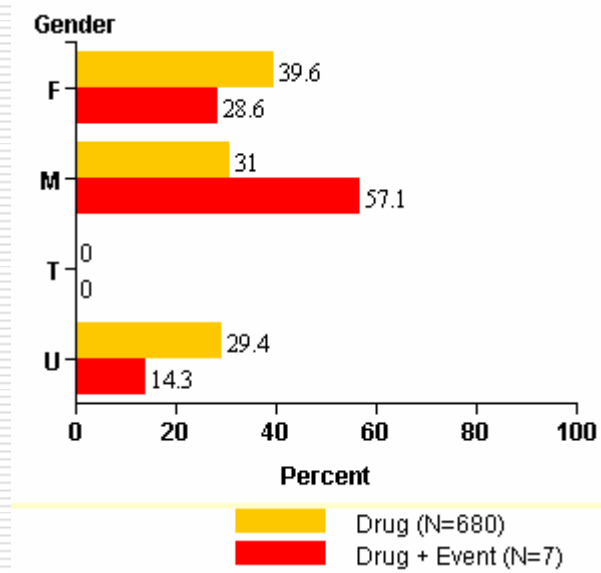


Screening for Drug Interactions or Risk Factors



Visualization tools

- [Filter Event](#)
- [Review Summary](#)
- [View Similar Combinations](#)
- [View Gender Breakdown](#)
- [View Age Group Breakdown](#)
- [View Sector Map](#)
- [View Interactions](#)



Collaboration & Documentation

	Drug	Entry Date	Listed	Monitoring	Nonspecific	Other Factors	Review Planned	Reviewed
		10/24/2005	0	0	0	0	0	0
								0
								3
								3
								0
								0
								0
								0
								0
								0
								0

The following issues were investigated:

Issue 1: <<brief description>>
Date identified: <<date>>
Brief comment (top line results of assessment, 2-3 lines): <<comment>>

The following signals need further evaluation [reminder: enter these]

Signal 1: <<brief description>>
Date identified: <<date>>

Enter Notes
View Notes

Key messages

- ❑ Safety data mining finds **associations** between drugs and events in large safety databases
- ❑ Causality is only **one** of the possible explanations for the association...
 - **Events associated with the condition treated**
 - ❑ urological signs/symptoms with drugs used to treat BPH
 - **Media coverage/publicity**
 - ❑ may also affect signals for other drugs in the same class
 - **Co-prescribing (i.e., bystander effects)**
 - ❑ lactic acidosis is signaled for some antidiabetic drugs that are frequently co-prescribed with metformin
 - **Coding practices / dictionary changes**
 - ❑ use of an infrequently used event term / synonym



Key messages

Case review and **domain knowledge*** are essential to assess the likelihood of a causal relationship between a drug and an event.

* epidemiology & natural history of disease, medical practice, pharmacology of drug

Relative reporting rate \neq incidence or risk

Key messages

□ Data mining addresses only **reporting frequency**

- Domain knowledge & clinical judgement are needed to recognize non-signaled events warranting further evaluation (e.g., agranulocytosis, torsade de pointes)

□ Absolute signal thresholds can be dangerous, particularly if used to filter data for display

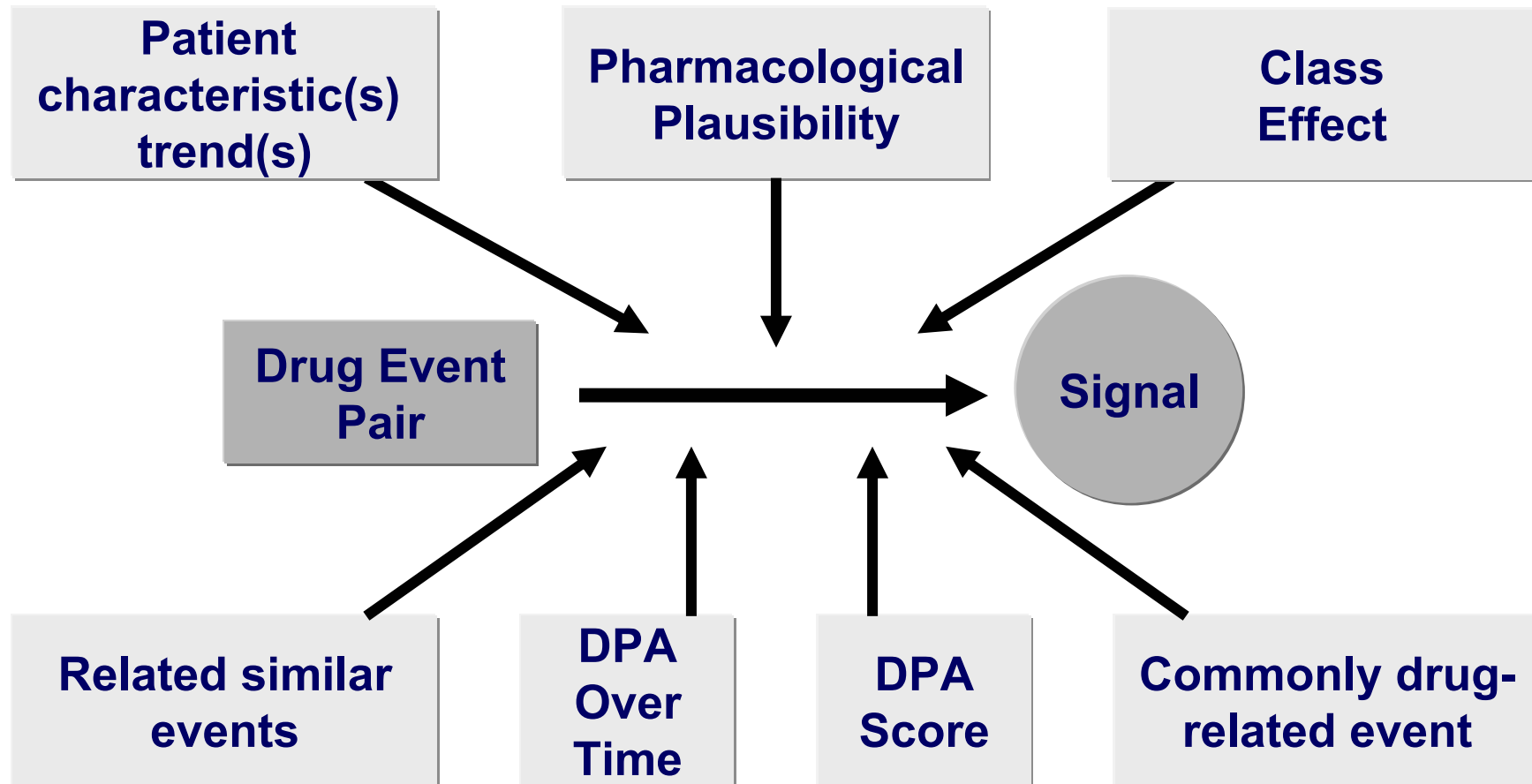
- A drug-event pair that does not meet the threshold may be of great interest (e.g., a medically important event).
-

Key messages

- Follow-up of positive signals should include related events
 - Comparing relative reporting rates between drugs
 - should be considered hypothesis-generating, requiring further evaluation to confirm differences
 - subject to reporting bias
-

Factors to Consider in Signal Detection

Considerations for when a drug event pair is a signal



Signals Relating to Manufacturing Defects

- Need to be alert for possibility and liaise with appropriate manufacturing site
- Characteristics of a signal that might indicate a manufacturing issue (e.g. lack of efficacy, change in taste)
- Points to consider when evaluating possibility (e.g. batch specificity, changes in manufacturing process, device failure)
- Monitor reports of ‘pharmaceutical product complaint’

Steps taken following identification of signal

Signal Evaluation

Holistic approach and not simply a review of spontaneous data

▪The sources of data consulted and their value will depend on many factors - e.g. drug itself, length of time on market, event, number of markets, indication(s)

Labelling for related drugs

Clinical trial data

Epidemiologic or PMS studies

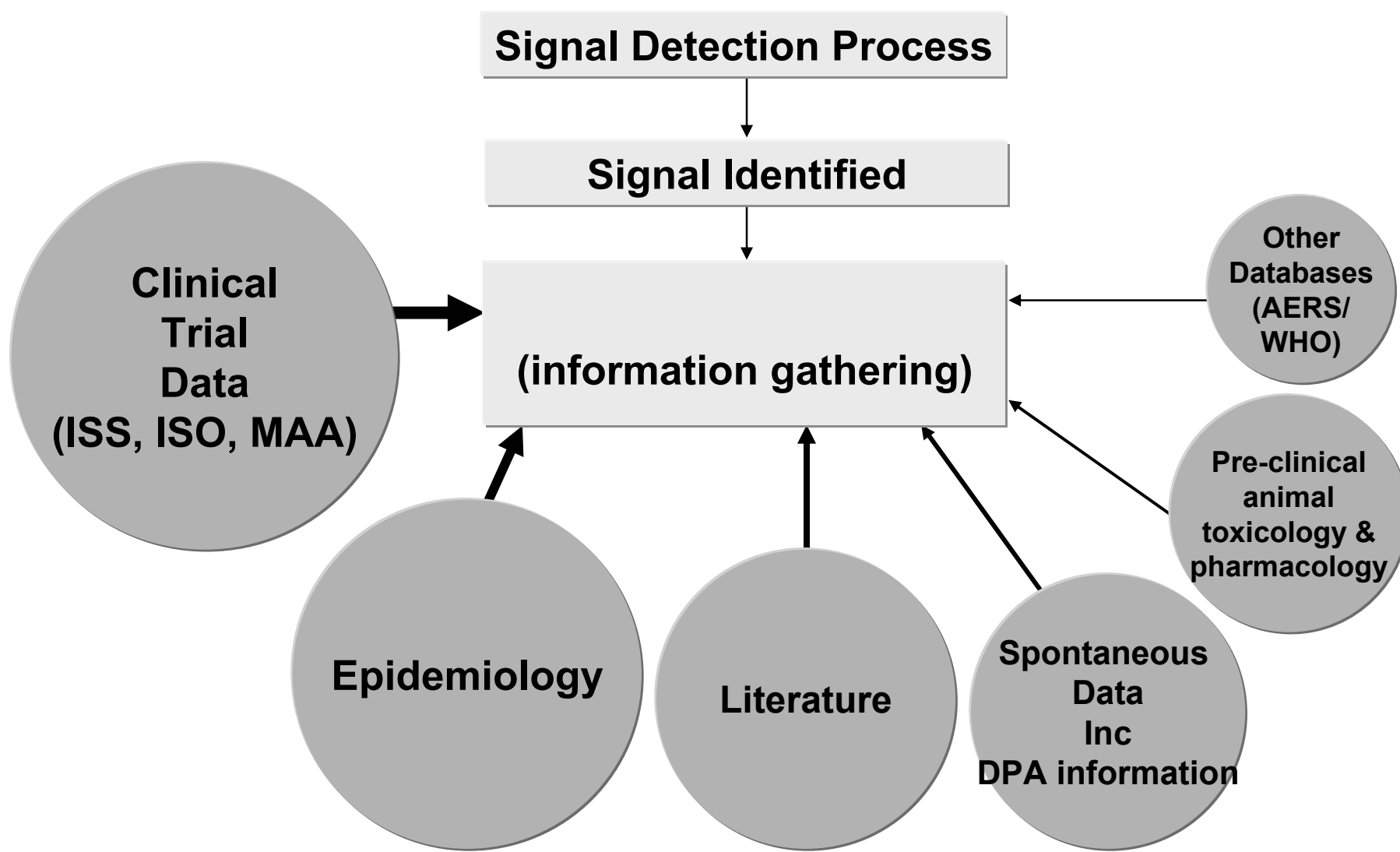
Literature

Spontaneous reports (including DPA)

Pre-clinical pharmacology/toxicology studies

Other

Evaluating Signals Using Evidence Hierarchy



* Size of circles indicates robustness of the data

Overall Evaluation

- ❑ A brief, **critical appraisal** of evidence of causal relationship
 - ❑ Comment on whether evidence is consistent between data sources
 - ❑ Other considerations (e.g. identifiable subgroup at risk)
-

Is There Anything New?

Is this a Public Health Issue?

- Unidentified/unlabeled
 - Change of frequency
 - Change of severity
 - New risk factors
 - Serious, severe, or sustained?
 - Who, and therefore how many will be affected?
-

Possible Actions Resulting from Signal Evaluation – Risk Management Activities

- No evidence of a causal relationship
 - No action, document
 - Insufficient information: Need to continue to monitor and revisit
 - Plan to gather more information
 - Targeted follow up questions for spontaneous reports
 - Design studies (Pharmacoepidemiological studies, clinical studies, drug interaction studies)
 - Milestone reviews- when significant information available
-

Risk Minimisation Activities

- If a safety issue identified, identify risk minimisation activities, examples could include:
 - Communicate the risk
 - Include in datasheet
 - Expedited warning (e.g. Dear Healthcare Professional letters)
 - Patient education programmes
 - Introduce patient cards
 - Restrict population for treatment
 - Introduce certification and consent for prescribers and patients
 - Measure impact of risk minimisation activities
 - In rare circumstances, withdraw drug from market
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Acknowledgements

- June Almenoff
 - Nancy Yuen
 - Karol Lacroix
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