Signal Detection – Quantitative Analysis of Safety Data

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Regulatory Background

- Signal management is a core safety process to determine new/changed risk associated with the use of a drug, ultimately to protect patients and support healthcare providers.
- Signal detection is one step in signal management.
- Highly regulated process with quality requirements, which is frequently inspected and audited. Every decision needs to be documented.
- Any pharmaceutical company developing a medicinal product for human use or holding a marketing authorization for a given compound is obliged to continuously perform medical surveillance.

• International Conference on Harmonization (ICH E2C, E2E and E6)	
• GVP Module IX • Regulation (EU) No 520/2012 Regulation (EU) No 1235/2010 Regulation (EC) No 726/2004 • Directive 2010/84/EU Directive 2001/83/EC	• United States (US) 21 Code of Federal Regulation (CFR) 312 and 314 • FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Definition

Signal [*zɪŋˈnaːl*]

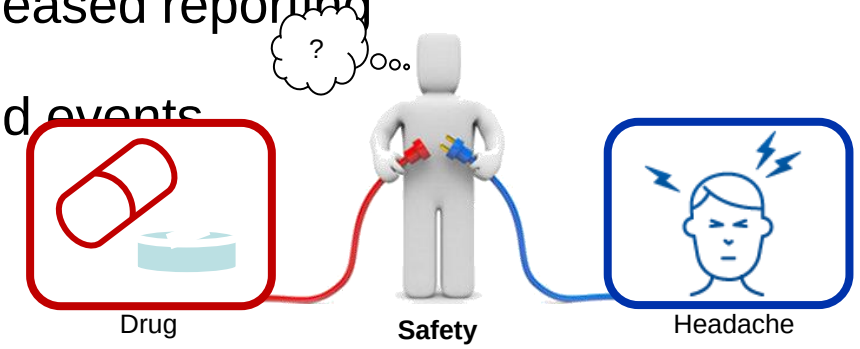
Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

*CIOMS Working Group VIII, Report 2010**

*Council for International Organizations of Medical Sciences

Goals of Signal Detection

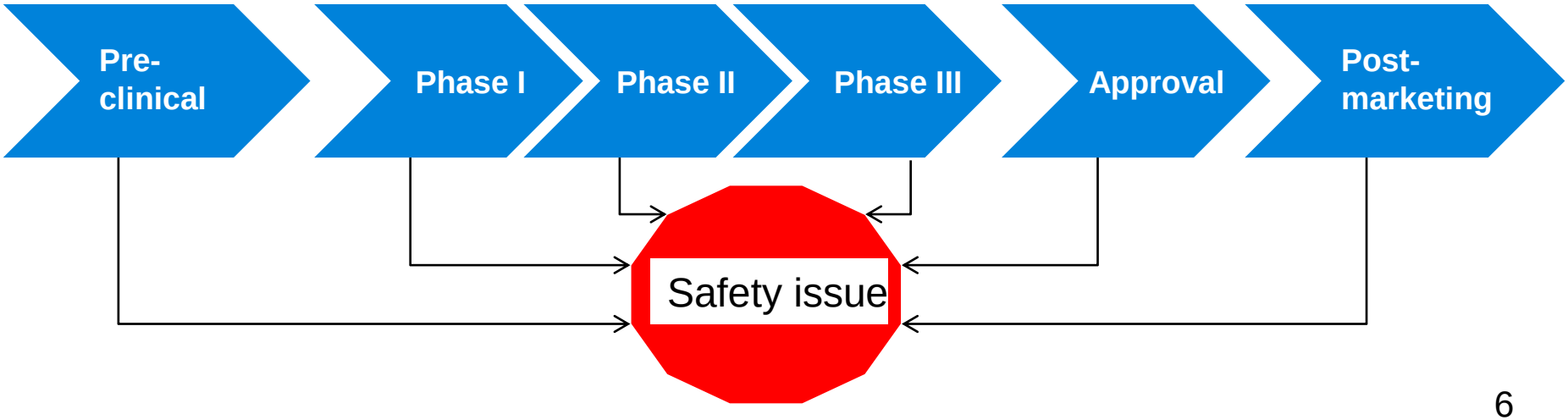
- **Ensure safe use of drugs**
- Early identification of associations between compounds and adverse events
- Highlight disproportionate and increased reporting
- Highlight important and unexpected events
- Support scientific decision-making
- Enable creation of hypothesis



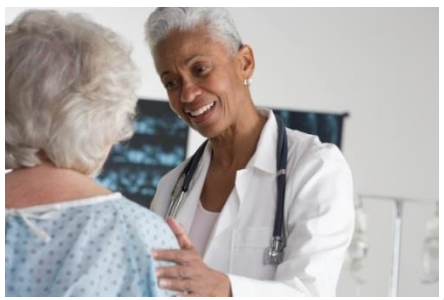
- **Don't**:
  - Make medical judgment obsolete

Surveillance throughout Lifecycle of a Drug

- Medical surveillance does not start only after product launch.
- Safety issues can arise anywhere in the drug development pipeline.
- In fact, safety is one of the main reasons for attrition of drug projects.
- Signal detection is applied to identify problems as early as possible, because with every achieved drug development phase, patient exposure grows.



Data Sources



Any Competent Authorities

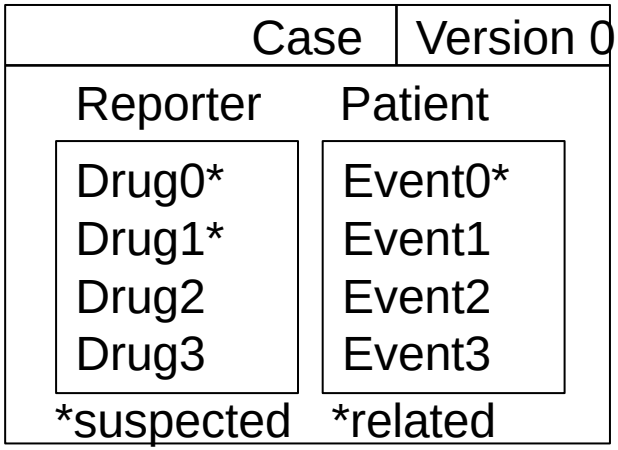
Preclinical data, clinical trials, observational studies, spontaneous reports, patient support programs, registries, social media, literature, etc.

Manufacturing and quality

- **Regulatory database usually**
  - Embrace lots of products
  - Are big
  - Only post-marketing drugs
  - Spontaneous cases only

- **Company databases can be**
  - Relatively small, more accurate (?)
  - Biased towards few products
  - Include development drugs
  - Include solicited and spontaneous data

Case Structure and Data Fields

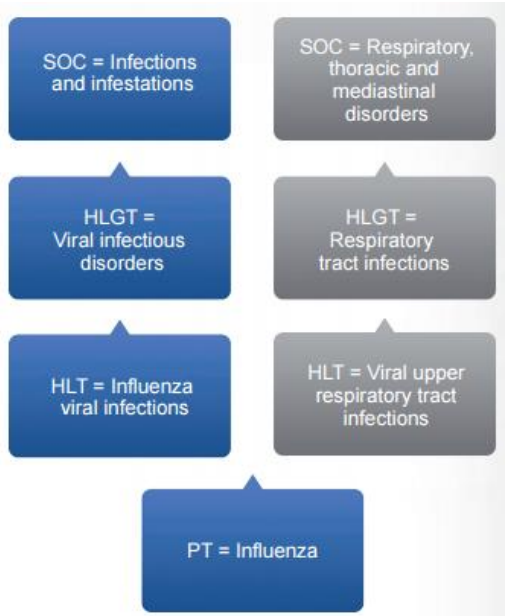


- Minimum set for a valid case:
  - Reporter
  - Patient
  - Drug
  - Event (MedDRA coded)
- Cases with less information are regarded as incomplete cases. Signal detection still must occur!
- Some additional helpful fields
  - Concomitant treatment
  - Medical history of patient
  - Diagnosis
  - Course of lab values before, during and after therapy
- Availability of data fields varies

MedDRA*

Medical Dictionary for Regulatory Activities

- Standardized ontology of adverse events
- Created in October 1994 by ICH
- Organized by system organ class on five levels, multi-axial dependencies, codes and multi-language decodes
- Updated bi-annually, managed by the Maintenance and Support Services Organization (MSSO)
- Simplifies reporting and enables statistical analysis



Preferred Term Code	English	Spanish	Japanese
10022000	Influenza	Influenza	インフルエンザ
10047470	Viral myocarditis	Miocarditis vírica	ウイルス性心筋炎
10027599	Migraine	Migraña	片頭痛

*https://www.meddra.org/sites/default/files/main_page_slideshow/meddra2013.pdf

Signal Detection Strategies

Review by

- Medical events (important, special interest, designated, targeted)
- Drug class
- Event severity and outcome, e.g. fatal
- Population (paediatric, geriatric, elderly)
- Type of administration
- Time period
- Other, e.g. literature, batches, lots

Method

a) Manually review each reported case qualitatively

b) Establish frequency overviews

c) With growing data size, use of statistical methods to aid quantitative review

d) Employ disproportionality data mining algorithms

Disproportionality Was event E reported more often with a particular drug D, compared to all other drugs in the database and/or compared to all other events reported with that drug?

Disproportionality Data Mining Algorithms

- Disproportionality algorithms were created due to lack of exposure data
  - In an ideal world, one would know how many patients have received a drug and compare to the ratio of patients experiencing adverse events, in order to help deciding if there really is an issue.
  - As exposure is usually not available for spontaneous reports, alternatives were generated based on observed and expected case counts.
  - Companies and Health Authorities use arbitrary methods or many at the same time (heterogeneous use is considered a benefit)

- Algorithms make use of **contingency table** of pharmacovigilance databases and respective counts of Individual Case Safety Reports (ICSRs)

Number of ICSR	Includind Event E	Not including E	Total
Including Drug D	a	b	a+b
Not including D	c	d	c+d
Total	a+c	b+d	n

Frequentist Methods

1. Relative Rate (RR) simply compares case counts **observed** (***a***) versus **expected** (***e***), with ***e*** determined from independent frequencies of drug and event.
2. Proportional Reporting Ratio (PRR) denotes if the frequency of an **event** is higher for a particular drug compared to all other drugs having the same event (proportional between drugs)
3. Reporting Odds Ratio (ROR) introduces probability of event not being reported.

$$RR = \frac{a}{e} \qquad e = \frac{(a+b)*(a+c)}{n}$$

$$PRR = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}$$

Frequency of E of all reports of drug D

Frequency of E in **all other drugs** D

$$ROR = \frac{\left(\frac{a}{c}\right)}{\left(\frac{b}{d}\right)}$$

Ratio of D and E compared to all drugs with same event

Ratio of D **without** E vs. to all drugs **without** event

Number of ICSR	Includind Event E	Not including E	Total
Including Drug D	a	b	a+b
Not including D	c	d	c+d
Total	a+c	b+d	n

Selection of algorithm is not really important,
as long as at least one data mining strategy is used

Significance Test

- Frequentist methods sensitive on small case counts
- Significance tests, e.g. Pearson‘s χ^2, can be applied to correct for that $\chi^2 = \frac{(a-e)^2}{e}$
- **Example:**

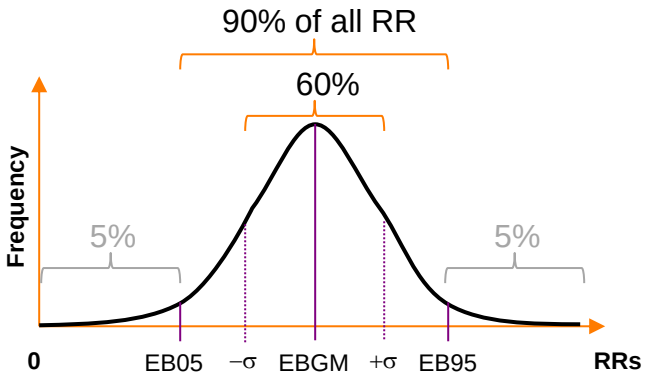
Observed D-E count	**a**	2	4	6	8	10	*Total counts increase*
Expected D-E count	**e**	1	2	3	4	5	
	RR	2.0	2.0	2.0	2.0	2.0	→ *But RR stays the same?!*
	χ^2	1.0	2.0	3.0	4.0	5.0	→ χ^2 *corrects this!*

- **Rule of Thumb:**
  Start trusting RR if corresponding χ^2 is above 4.0
  (because this ensures that there are more than 3 cases in the database)

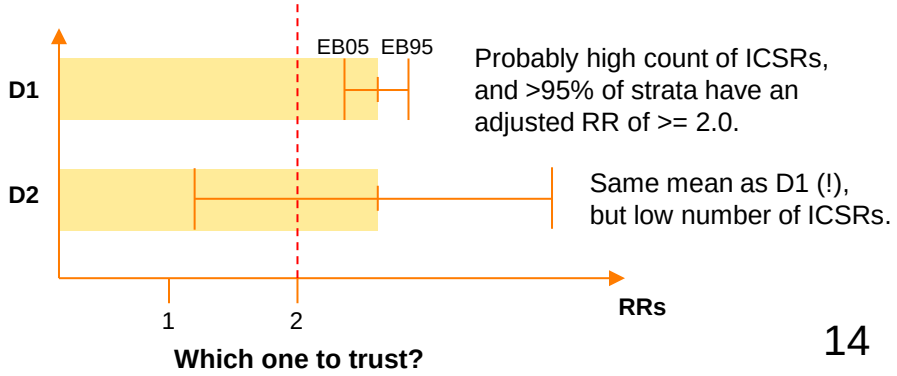
Empirical Bayesian Geometric Mean (EBGM)

- RR with adjusted sampling variability (read „more accurate“)
- Includes stratification for: age, gender, reported year, multi-drug/multi-event reports
- Calculates RR for each strata separately
- Computes RR distribution based on Poisson events
- Allows to learn expected rate and for confidence intervals:

- EBGM is actually a measurement
- The real algorithm is called: *MGPS Multi-Item Gamma Poisson Shrinker*
- EB05 >= 2.0 means: In majority of strata, cases are observed two-fold more often than it was expected
- Threshold was suggested by *Szarfman et al. (FDA, Drug Safety, 2002)*

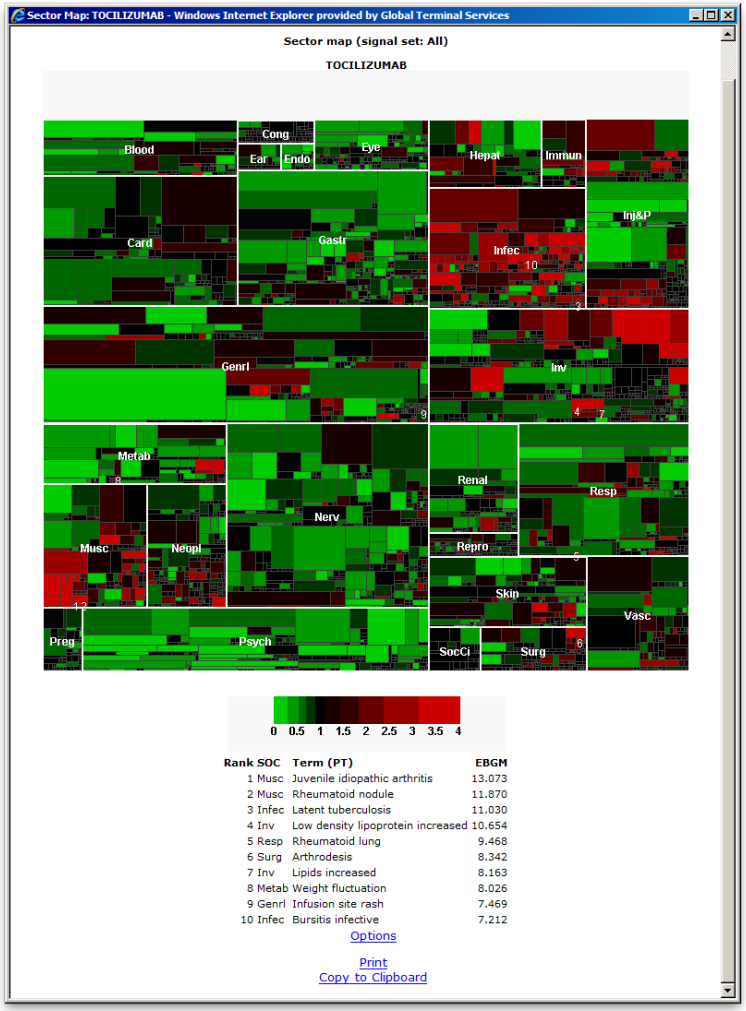


Examples:

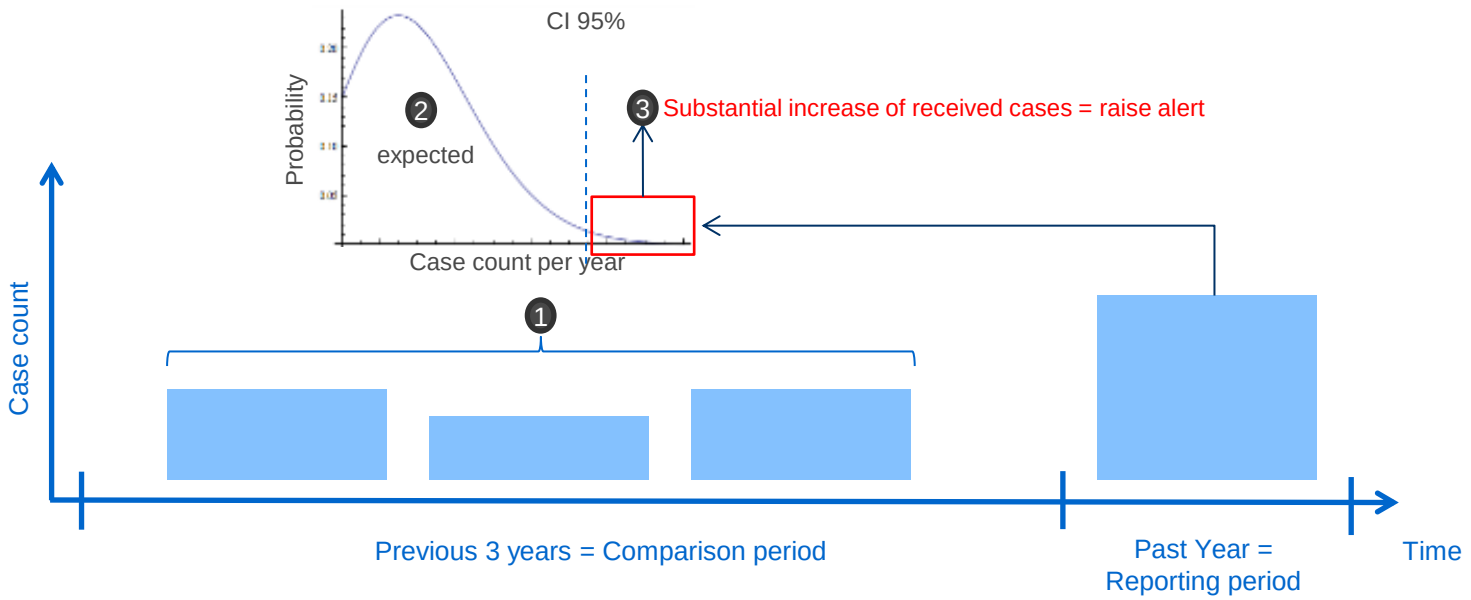


Visualizations and Interactivity

- E.g. sector maps
  - Interactive visualizations representation of signaling values per MedDRA System Organ Class (SOC) and Preferred Term (PT)
  - Each SOC is represented by a large rectangular area of the map
  - Smaller tiles represent PTs
  - PT tiles are colored by values of a signal statistic. The default is EBGM
  - The top-10 event terms by signal statistic are listed below the graph
- **Visualizations are much more helpful for safety physicians to conduct their medical review in signal detection**
- **Interactive data analysis is the future**



Computation of Increased Frequency Alerts



1) Case counts in comparison period are used as reference.
2) Poisson distribution is used to calculate how many reports can be expected in 1 year.
3) Alert is raised when the increase is higher than 95% CI.

Limitations of Quantitative Analysis

- Drug-drug interactions
- Sub-population based analyses
- Designated medical events
- Confounding indications
- Poly-pharmacology
- Dose dependency

- Underreporting of spontaneous cases
- Overreporting due to media or era
- Misspellings
- Prescribing bias

Disproportionality cannot rule out safety issues

Doing now what patients need next

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Literature

- Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA‘s Spontaneous Reports Database, Ana Szarfman et al. (FDA, Drug Safety 2002)
- Practical Aspects of Signal Detection in Pharmacovigilance, CIOMS Working Group VIII Report, Geneva 2010
- Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA 2005
- Guideline on the use of Statistical Signal Detection Methods in the Eudravigilance Data Analysis System, EMA 2008
- Guideline on Good Pharmacovigilance Practices, Module IX – Signal Management, EMA 2012