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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Statistical signal in Practice: Industry Perspective

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Disclaimer

The views expressed in this talk are those of the author.

They do not necessarily represent those of Novartis.

Bayer HealthCare

Signal Detection Concept

Basic Principle:

- The module runs for any active Bayer drug including drugs in development.
- Each unlisted event in the database for each drug is analyzed (no limitation of time frame!).
- The analysis is done on the MedDRA PT and the HLT level.
- The analysis runs in five steps (see next slides).

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Signal Detection Concept

Step 2: Define the score system

- Cases are weighted by creating a score that reflects:
  - case quality (according to Ralph Edwards*)
  - seriousness
  - causality
  - diagnosis assured
- Each case contributes to the signal score as the score is always > 0.

*Edwards R, Lindquist M, Wiholm BE. Quality criteria for early signals of possible adverse drug reactions. Lancet 1990; 336:156-8

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Signal Detection Concept

Step 3: Calculate the summary score per event

- For a given **event** (MedDRA PT) all sub-scores of the four parameters are multiplied to get a score per case.
- The scores of all cases with the same event are summarized to calculate the summary score.
- A single case can have a maximum score of 216 for a certain event if it is well documented, serious, with a positive rechallenge and an assured diagnosis.

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Signal Detection Concept

Step 4: Display the summary score per PT and HLT

- Summary scores are calculated per PT and HLT. The summary score for the HLT is calculated by summarizing all PT scores of those PTs which belong to a HLT (primary path).
- This grouping allows to find signals that are "smeared" across several terms (by coding etc).
- For each drug the scores of PT and HLT are listed for those HLTs with a summary score larger or equal to 216. This limit was chosen as it represents one case with a maximum score (well documented, serious, positive rechallenge, diagnosis assured).

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Signal Detection Table

MEDDRA HLT, MEDDRA PT	N	SUMMARY SIGNAL SCORE	LABELING DATE
ACCELERATED AND MALIGNANT HYPERTENSION	6	344.25	
HYPERTENSIVE CRISIS	6	344.25	
ASTHENIC CONDITIONS	23	269.25	
ASTHENIA	15	69.75	29OCT1998(GDS)
FATIGUE	5	48.75	29OCT1998(GDS)
MALAISE	3	150.75	29OCT1998(GDS)
BODY TEMPERATURE PERCEPTION	32	572.25	
FEELING COLD	5	156.75	
RIGORS	27	415.50	

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Signal Detection Concept

Step 5: Evaluate the potential signal

(Drug Safety Manager)

- Not all potential signals are real signals!
- For each potential signal the Drug Safety Manager will evaluate the data and generate a statement, that is signed by him/her and the Head of GDS.

Signal Detection Process at Novartis

The signal detection process at Novartis Pharmaceuticals relies on traditional methods supplemented by data-mining techniques using comparisons of relative reporting frequencies in spontaneous reports from all sources, including reports from the literature.

The traditional methods

Medical safety experts review

- single cases during case processing
- listings of cases
- the medical and scientific literature
- clinical study reports of Novartis-sponsored studies
- and all safety requests by health authorities.

Data Mining Tool

- From 2004 until December 2008, SMTs used a fully validated homemade data-mining tool using the proportional reporting ratio as a detection algorithm. Hits above the thresholds (PRR $\geq$ 2, n > 5, and P < .05 (χ2).
- 2009 Empirica Signal System was introduced and became central to the signal detection process in the postmarketing setting.

Data Mining Tool Configuration

In 2009 Empirica uses two algorithms for routine analyses: empirical Bayes Multi-item Gamma Poisson Shrinker and logistic regression.

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ORIGINAL REPORT

Are all quantitative postmarketing signal detection methods equal? Performance characteristics of logistic regression and Multi-item Gamma Poisson Shrinker

Conny Berlin*, Carles Blanch, David J. Lewis, Dionigi D. Maladorno, Christiane Michel, Michael Petrin, Severine Sarp and Philippe Close

Novartis Pharma AG, Basel, Switzerland

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Data Mining Tool Configuration

Table 4. PPV, specificity, and sensitivity for signal detection performed on new drugs with "leading" terms and narrow MedDRA queries

	Threshold	LR05	LR0005	EB05
PPV	1.8	75.00	85.19	88.00
	1.9	76.32	85.19	88.00
	2.0	77.14	88.46	86.96
	2.1	78.13	88.46	86.96
	2.2	82.76	88.46	86.96
Specificity	1.8	93.71	97.48	98.11
	1.9	94.34	97.48	98.11
	2.0	94.97	98.11	98.11
	2.1	95.60	98.11	98.11
	2.2	96.86	98.11	98.11
Sensitivity	1.8	40.00	30.67	29.33
	1.9	38.67	30.67	29.33
	2.0	36.00	30.67	26.67
	2.1	33.33	30.67	26.67
	2.2	32.00	30.67	26.67

Table 6. Differences of performance measurements between LR0005 and EB05 (%)

Group	PPV (LR0005–EB05)	Specificity (LR0005–EB05)	Sensitivity (LR0005–EB05)
New drugs			
Leading terms, narrow search	1.51	0.00	4.00
Leading terms, broad search	−0.43	−0.63	2.67
All terms, narrow search	−0.53	0.00	−1.33
All terms, broad search	−0.97	−0.63	1.33
Established drugs			
Leading terms, narrow search	−0.63	−1.57	6.90
Leading terms, broad search	−2.34	−4.71	7.59
All terms, narrow search	−3.57	−2.75	6.90
All terms, broad search	0.03	−3.92	9.66

Final configuration

In addition to the empirical Bayes geometric mean (EB05 > 2 and n > 3),

three other quantitative methods were configured:

Table 1. Three methods in the Empirica signal system supplementing the empirical Bayes geometric mean.

Hit Type: Method	Signal Criteria and Threshold
DME: Count	The Empirica algorithm generates a hit when it detects 1 or more unlisted DMEs[13] in the review period.
Increased frequency: RP	The Empirica algorithm identifies DECs with >2× increase in RP over the prior cumulative period in the last 2 consecutive years or with >5× increase in RP compared to the prior cumulative.
Increased severity: Proportion	The Empirica algorithm identifies (1) a serious DEC when its proportion of serious cases in the annual period increases by at least 50% compared to the proportion in the cumulative total of all prior review periods, with a minimum of at least 3 additional serious cases in the current review period and (2) DECs with an increase of at least 50% in the proportion of fatal (case-level) cases for a product to all serious cases (event-level seriousness). The comparison is the current period against the cumulative total of all prior periods, with a minimum of least 3 additional fatal cases in the current period.

DEC, drug event combination; DME, designated medical event; RP, reporting proportion.

Re-evaluation of hits

For all 3 methods, Empirica automatically suppresses the generation

- of a hit when a given designated medical event is already listed or
- has been marked previously with a "stop monitoring" comment by the medical reviewer.

All comments and decisions about the disposition of a hit in Empirica are recorded in the Empirica audit trail.

References

Berlin C, Kraemer HP. Bayer's approach to Signal Detection. IIR Conference – Signal Detection practices within your Pharmacovigilance plan. 2004 Jun 28, London, UK.

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