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Role of signal detection in assessment of benefit risk

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Acknowledgement

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Signal detection in real time

- How signal detection is conducted using MedDRA as the standard coding dictionary
  - From FDA perspective
  - From MHRA perspective
  - From industry perspective

Agenda

- Drug development process ~ overview
- Understanding benefit risk
- Sources of safety information
- Systematic approach to signal detection
- Future challenges
- Conclusions

This presentation will not include a comparison of data mining algorithms

Drug development

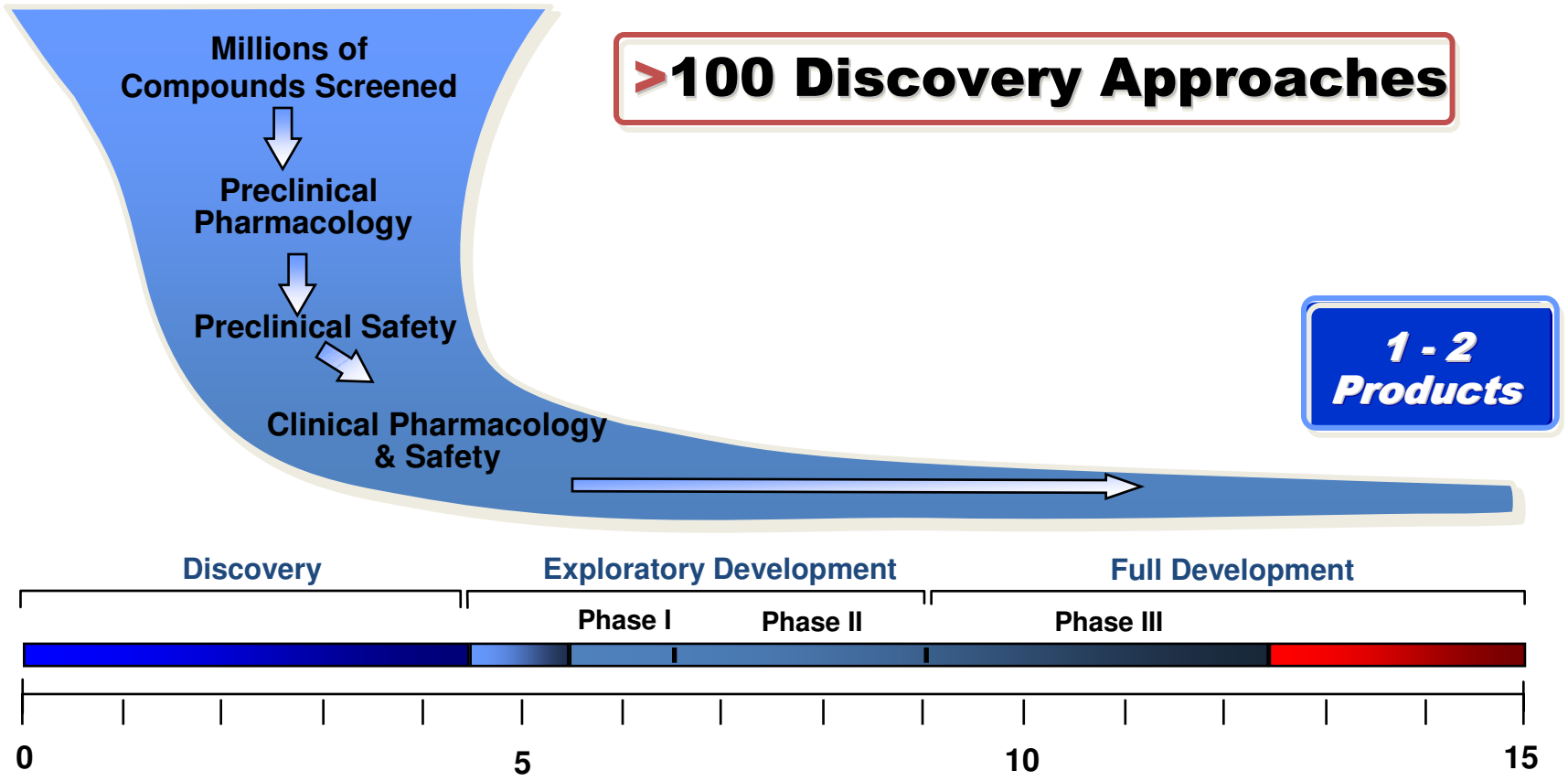
process overview
understanding risk

ALL SUBSTANCES ARE POISONS ...

THE RIGHT DOSE DISTINGUISHES A POISON FROM A REMEDY

Paracelsus *1493 - 1541*

Attrition is high during the R&D Process



High risk process taking 12 - 15 years

Few candidates become medicines

- For every 1,000 drug candidates in pre-clinical (non-human) testing, only about 1 will enter human trials

- For every 100 drug candidates entering human trials
  - 30 will fail during Phase I
  - 37 will fail during Phase II
  - 6 will fail during Phase III
  - 7 will fail during Regulatory Review
  - 20 will achieve approval for marketing

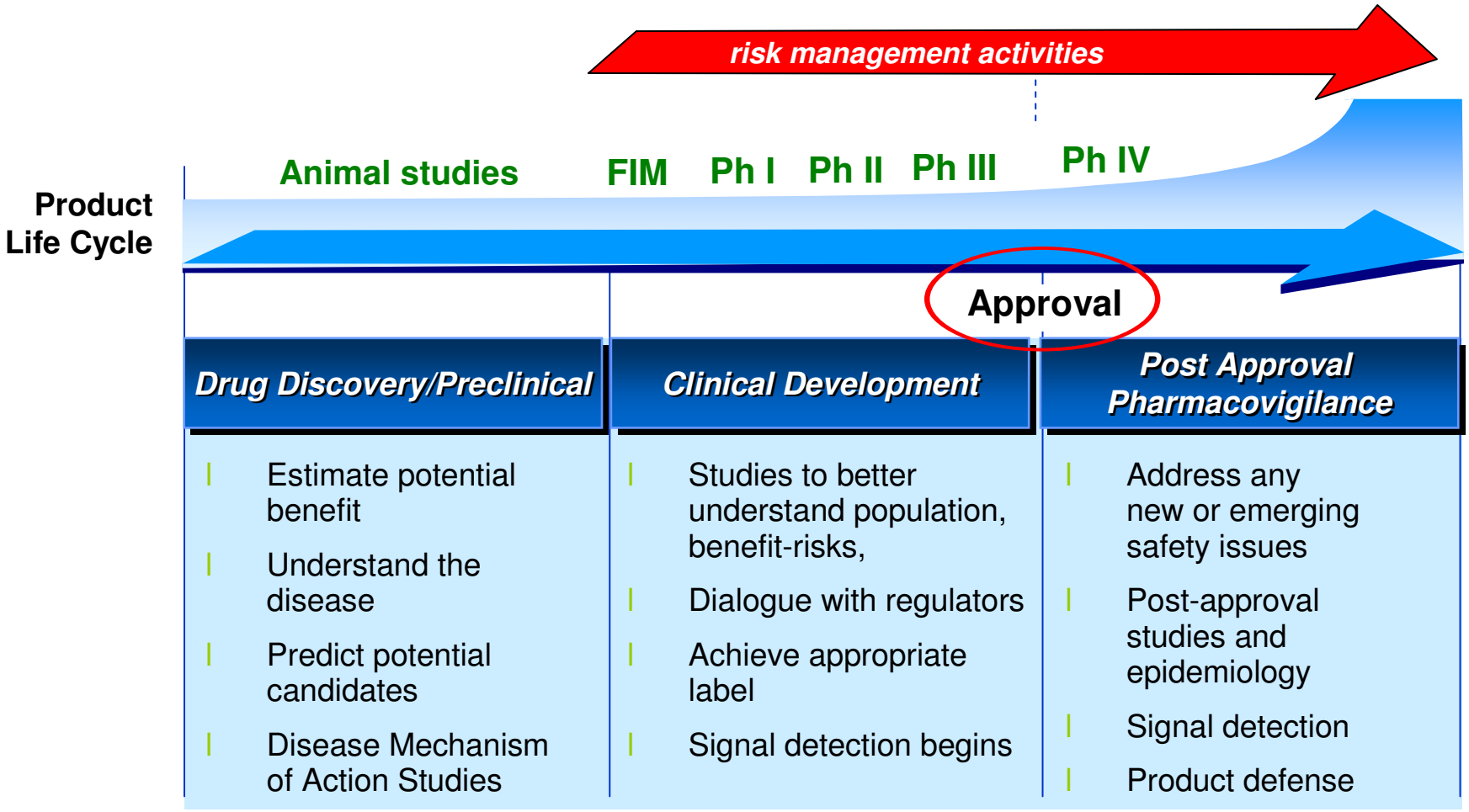
Only 2 in 10,000 will gain approval

Kaitin KI: Worthwhile persistence - the process of drug development. Odyssey. 1995; 1(3)

Identifying safety risks

- Step 1: Collect adverse event data
- Step 2: Organize ADR/AE data
- Step 3: Analyze ADR/AE data
- Step 4: Identify Safety Issues

A pharmaceutical company perspective…



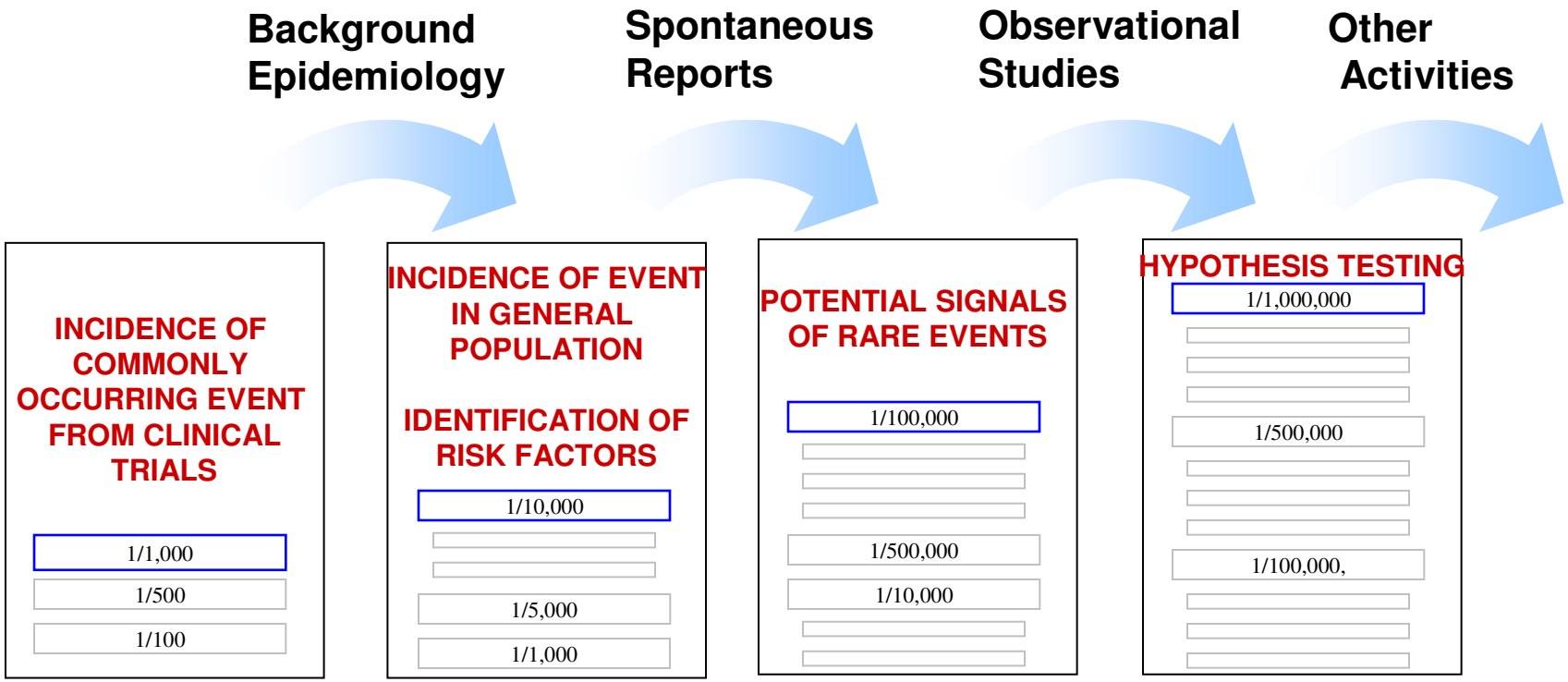
Role of drug safety in the product development cycle

Pre- and post-approval safety monitoring

- Pre-approval focus is on characterizing the safety profile of the drug in relevant patient population
- Assessment of benefit risk to support appropriate labeling

- Post-approval, the emphasis shifts to monitoring safety to minimize risk and maximize benefit to all patients using the drug

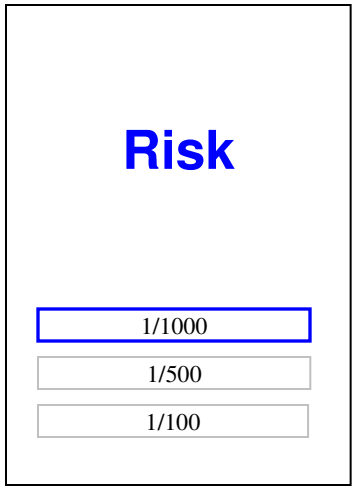
Our evolving understanding of risk

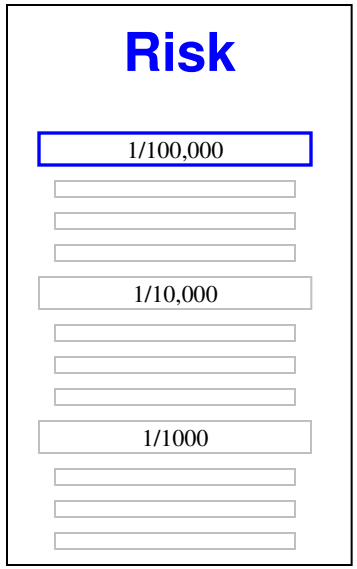


Post-approval experience allows for identification of smaller risks

Expectation of our understanding of risk

Public expectation of risk knowledge at approval is greater than reality





Pre-approval
(10,000 Patients)

REALITY

PUBLIC EXPECTATION

Post-approval
(1 Million Patients)

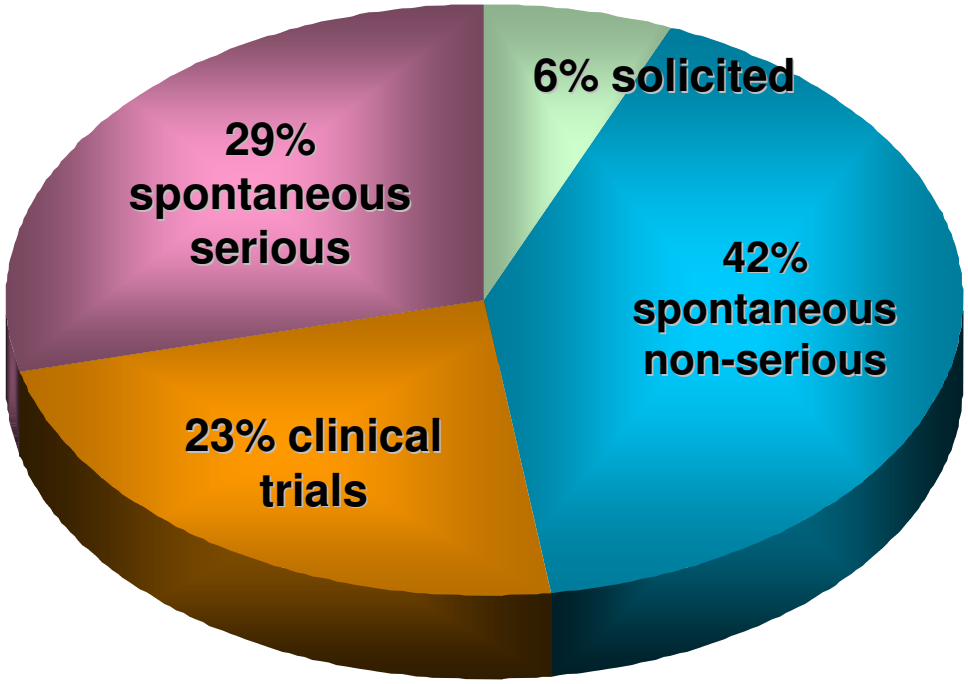
Data quality can significantly affect the validity of the signal detection process

sources of safety reports

Types of adverse event reports

Clinical Trials	Product can be investigational or marketed, reports received from HCP; well documented, ability to obtain appropriate follow-up information, relatively low volume
Spontaneous Reports	Unsolicited reports received on marketed product, HCP, patient, registry, HA, literature; initial information may be minimal, appropriate follow-up may not be possible with less available information, very high volume
Solicited Reports	Company initiated contact, organized data collection, similar to 'spontaneous' in information quality (examples, patient support or disease management programs)

Sources of adverse event reports



Typical annual pharma data

Role of signal detection in a systematic approach to understanding risk

Ensuring consistency of risk management activities

- Risk management committee with responsibility for the regular review of safety data is needed
- Representation should include safety, regulatory, legal, clinical, medical; others *ad hoc*
- Each drug needs a formal safety review plan/risk management plan
- Committee needs the ability to escalate issues to senior leadership for rapid resolution
- Processes must be documented, with decisions appropriately recorded

Defining a 'Signal'

- The term safety signal is commonly used but misleading
- One proposed* alternative is the term 'signal of suspected causality'
  - 'Information suggesting a new potentially causal relationship between a drug and a related event which requires investigation and, if warranted, remedial action'

*See Hauben & Aronson; Drug Safety 2009, 32 (2) 99-110 for further discussion

Detecting signals

- The signal detection process can be:
  - Based on the evaluation of a individual case safety report (ICSR) or a similar case series

  or

  - An analysis of cumulative data using either simple frequency calculations or more complex statistical algorithms that address confounding factors

Reviewing the data from ICSRs

- First level of 'signal detection' takes place during medical review by a company physician
- Conclusions that can be drawn from individual case safety reports are often limited
- Single ICSR may not be considered a signal in of itself but constitute an 'early warning'
- Quality and completeness of the data plays a role in interpretation
- Should not be disregarded if not initially medically confirmed (confirmation should be sought)

Challenges of cumulative data review

- What is the base-line data against which frequencies will be measured?
- In house data only or supplemented by external databases?
- Effects of data quality on signal detection
- Effect of under/over reporting of adverse events
- Which detection method will be used
- How frequently should analyses be performed
- How will potential signals be investigated

Systematic review of cumulative data

- One time sweep of all products
- Periodic review of all products for:
  - 'Increased frequency' analysis and newly reported events with 'signal of disproportionate reporting'
  - Re-review of 'designated medical events' by interval
  - Re-review of 'targeted medical events' by interval
- Periodic review for 'increased severity' of specific adverse events

Frequency of cumulative data reviews

Level 1

New products (>2 years since IBD*), products with newly approved indications, formulations, patient populations, or products with evolving safety profiles

Level 2

Young products (2 -5 years since IBD*), products with safety profiles that are stabilizing or that are being monitored for potential safety concerns

Level 3

Mature products (<5 years since IBD*), with established safety profiles for which there may be ongoing or potential safety-related concerns

Level 4

Old products (<15 years since IBD*), with well-established safety profiles and no ongoing safety concerns

*International Birth Date

What is data mining

- Use of statistical analyses that can quantify the frequency of specific drug-event pairs to identify disproportionately high rates of occurrence, which even if rare, represent potential signals
- Followed by prioritization and follow-up of potential signals using predetermined criteria such as:
  - Seriousness of the risk (outcome)
  - Frequency of occurrence
  - Preventability
  - Nature of the disease
  - Treatment benefits
  - Availability of alternative treatments

Ad hoc data mining

- Some of the reasons for using *ad hoc* data mining would be:
  - Further investigation of a potential signal
  - Preparation of PSURs or addendum
  - Response to Health Authority PSUR assessment
  - At the time of product renewals
  - Response to Health Authority inquiries
  - In response to inspections requests
  - In response to published articles
- Generally uses MedDRA PT or SMQ

Databases readily available for data mining

- Company internal database (MedDRA)
  - Prospective pharmacovigilance & *ad hoc* data mining
- FDA AERS (MedDRA)
  - *ad hoc* data mining
- FDA VAERS (MedDRA)
  - *ad hoc* data mining
- WHO Vigibase (MedDRA)
  - *ad hoc* data mining

Event term coding

- Consistent event term coding is an essential component of effective signal detection
- MedDRA coding guidelines* foster consistency
- The broad acceptance of MedDRA as a coding dictionary facilitates searches across databases
- Searches can be performed at different event term levels
  - Preferred terms used for the initial data sweep
  - Higher level terms or SMQ used to further investigate potential signals

*MedDRA Term Selection - Points to consider
ICH 3.14 April 1, 2010

Examples of potential signals warranting further evaluation

- Occurrence of a new unlabeled SAE
- Unexpected changes in severity of a labeled event
- Occurrence of an SAE normally considered rare in the target population
- New drug interaction (with another drug, food, other)
- Identification of novel at-risk population
- Increased misuse or abuse of drugs

Some responses to potential signals

- Internal review using documented procedures
- ICSR targeted follow-up questionnaire
- Instigate a literature review
- Notification of Health Authority
- Convene ‘expert panel’
- Amend protocol design
- Update labeling, communicate changes
- Initiate follow-up studies (e.g. epidemiology)

Challenges for the future

- Earlier detection of potential safety issues during the development process
- Analysis of ever increasing quantities of data effectively
- How to get more complete data for ICSRs
- Develop better multivariate methods of detection
- How to evaluate potential signals more quickly
- Risk factor analysis and personalized medicine adds further opportunities
- How can we best apply signal detection to emerging issues (like counterfeit drugs)
- Better utilization of electronic medical records

Conclusions

- Benefit risk evolves throughout the life-cycle of a drug
- Data quality, especially consistent coding of event terms, is a key component of effective signal detection
- Signal detection is an ongoing process where no single method will meet all needs
- All potential signals need to be systematically investigated appropriately addressed
- Pharma companies cannot effectively monitor the safety of their products without the cooperation of Health Authorities, healthcare professionals and patients

Thank you for listening…