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

- **Millions of Compounds Screened**
- **Preclinical Pharmacology**
- **Preclinical Safety**
- **Clinical Pharmacology & Safety**

>**100 Discovery Approaches**

- **1 - 2 Products**

**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...
### Risk Management Activities

#### Drug Discovery/Preclinical
- Estimate potential benefit
- Understand the disease
- Predict potential candidates
- Disease Mechanism of Action Studies

#### Clinical Development
- Studies to better understand population, benefit-risks,
- Dialogue with regulators
- Achieve appropriate label
- Signal detection begins

#### Post Approval Pharmacovigilance
- Address any new or emerging safety issues
- Post-approval studies and epidemiology
- Signal detection
- Product defense

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**Product Life Cycle**

- Animal studies
- FIM
- Ph I
- Ph II
- Ph III
- Ph IV

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**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

<table>
<thead>
<tr>
<th>Risk</th>
<th>Pre-approval (10,000 Patients)</th>
<th>REALITY</th>
<th>PUBLIC EXPECTATION</th>
<th>Post-approval (1 Million Patients)</th>
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<tbody>
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REALITY
Data quality can significantly affect the validity of the signal detection process sources of safety reports
## Types of adverse event reports

<table>
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<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Clinical Trials</strong></td>
<td>Product can be investigational or marketed, reports received from HCP; well documented, ability to obtain appropriate follow-up information, relatively low volume</td>
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<tr>
<td><strong>Spontaneous Reports</strong></td>
<td>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</td>
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<tr>
<td><strong>Solicited Reports</strong></td>
<td>Company initiated contact, organized data collection, similar to ‘spontaneous’ in information quality (examples, patient support or disease management programs)</td>
</tr>
</tbody>
</table>
Sources of adverse event reports

- 29% spontaneous serious
- 23% clinical trials
- 42% spontaneous non-serious
- 6% solicited

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 an individual case safety report (ICSR) or a similar case series
  - 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...