SIGNALING METHODS AND SIGNALING PROGRAM DESIGN

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SIGNALING METHODS/PROGRAM DESIGN

AGENDA

- Reasons for signaling
- Data sources for signaling
- Signal detection
- Signal prioritization
- Signal evaluation
- Signaling program design
REGULATORY REASONS FOR SIGNALING

• References in guidances and consensus conferences
  ▪ ICH E2A (1995) – *implicit requirement*
  ▪ EMEA Conduct Of Pharmacovigilance for Centrally Authorized Products (1997) – *explicit requirement*
  ▪ ICH E2C (1997) – *implicit requirement*
  ▪ EMEA Notice To Marketing Authorization Holders: Pharmacovigilance guidelines (1999) – *implicit requirement*
  ▪ EMEA Position Paper On Compliance With Pharmacovigilance Regulatory Obligations (2001) – *explicit requirement with penalties*
  ▪ CIOMS VI Report (?2004) – Good Safety Practices will be described – *probably an explicit requirement*

• Implies documentation of regulatory responsibility
SIGNALING AND SURVEILLANCE
LEGAL REASONS FOR SIGNALING

• Phen-Fen litigation – aggregate assessments of individual case safety report (ICSR) databases are expected under the law.

• Compliance with ICSR expedited reporting requirements is not a “sufficient” surveillance activity.

• Implies documentation of legal responsibility.
SIGNALING AND SURVEILLANCE
SOCIAL EXPECTATION FOR SIGNALING

Patients

Products/Companies

Prescribers

Signaling provides value to all stakeholders
INTRODUCTION

SIGNALING-RELATED DEFINITIONS

• Adverse Event Signal -- a potential relationship between a product and an AE deserving of further consideration.

• Adverse Event Signaling Method -- any procedure, statistical or non-statistical, by which an AE signal becomes evident.

• AE Signaling Program -- a group of one or more AE signaling methods.
DATA SOURCES FOR SIGNALING SOURCES OF INFORMATION

- **Pre-Clinical & Tox Data**
  - Through the manufacturer
  - Direct to regulatory agencies

- **Literature Cases**
  - Published or unpublished
  - Clinical or epidemiological

- **Spontaneous Reports**
  - Through the manufacturer
  - Direct to regulatory agencies

- **Human Studies**
  - Published or unpublished
  - Clinical or epidemiological

- **Product Class Experience**
DATA SOURCES FOR SIGNALING
INDIVIDUAL CASE SAFETY REPORTS

- Passive Surveillance
  - Spontaneous ICSRs
    - Health care provider (HCP)
    - Non-health care provider (consumer)
  - Literature case reports (ICSRs)

- Active Surveillance
  - Clinical study (serious adverse event [SAE] reports)
  - Other structured environment ICSRs (solicited reporting)
DATA SOURCES FOR SIGNALING
INDIVIDUAL CASE SAFETY REPORTS

Subtypes of ICSRs by reporting environment differ by:

– Reporting rate (active versus passive)
– Pertinence to signaling activities (HCP versus consumer)
– Data completeness (clinical versus spontaneous)
INTRODUCTION
MIXED ICSR DATABASES

• Pan-Agency Databases
  – World Health Organization
  – EudraVigilance (not currently available)

• National Agency Databases
  – Freedom of Information (FDA)
  – LAREB (the Netherlands)
  – Canadian postmarketing database

• Company Databases
  – Multi-product databases
  – Single product databases (PSUR level)
Manufacturer HCP Reporting Rate / 100,000 United States; 1998-2001 Averaged
Consumer Reporting Rate / 100,000
United States; 1998-2001 Averaged

- Age Range
- Reporting Rate

MALES
FEMALES
SORTING

IDENTIFICATION

CASE SERIES FORMATION

CASE SERIES CHARACTERIZATION

SPONTANEOUS SIGNALING ARGUMENT

SPONTANEOUS DATA
<table>
<thead>
<tr>
<th>Functional Step</th>
<th>Qualitative</th>
<th>Quantitative</th>
<th>Inter-Product</th>
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<tbody>
<tr>
<td><strong>Signal Detection Phase:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorting</td>
<td>• Key content</td>
<td>• Subjective</td>
<td>• N/A</td>
</tr>
<tr>
<td></td>
<td>• Subjective</td>
<td>• Cutoff criteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rule-based</td>
<td>• Serial methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bayesian</td>
<td>• Cluster methods</td>
<td>• 2x2 tables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Data mining</td>
</tr>
<tr>
<td><strong>Signal Evaluation Phase:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Case Series Formation</td>
<td>• Subjective</td>
<td>• SRR</td>
<td>• Cohort type</td>
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<tr>
<td></td>
<td>• Rule-based</td>
<td>• Associative case-control</td>
<td>• Case-Control type</td>
</tr>
<tr>
<td></td>
<td>• Bayesian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case Series Characterization</td>
<td>• Descriptive</td>
<td>• Numerator-only</td>
<td>• Comparative</td>
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<tr>
<td></td>
<td></td>
<td>• Comparative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Characterization case-control</td>
<td></td>
</tr>
</tbody>
</table>
The application of signaling methods to a database to find “interesting” product-adverse event relationships.
SIGNAL DETECTION
PROCESS STEPS

- Intra-Product Signal Detection
  - Data Source
  - Potential Signal List
  - Signal Detection Output Report
  - Signal Evaluation Requests
  - Case Series
  - Surveillance Documents

- Inter-Product Signal Detection
  - Data Source
  - Inter-Product Signal Detection Methods
    - 2x2 methods
    - Bayesian data mining
  - Prioritization Algorithm
  - Signal Evaluation Methods

Intra-Product Signal Detection Methods
- Sorting
- Imputation
- Serial
- Others

Request For Query System
**SIGNAL DETECTION FEATURES**

- Automated or semi-automated
- Hypothesis generating
- Based on AE reports (electronic database abstraction of a source document)
- A form of database screening that is subject to sensitivity/specificity calculations
- Two kinds of methods used in tandem – increases efficiency
Signal detection can use information technology to efficiently locate potential adverse event issues.
Signal detection can result in an unacceptable false positive rate (i.e., low positive predictive values).
SIGNAL DETECTION

SIGNAL DETECTION METHODS

• Sorting methods
  – Qualitative (E2B data fields)
  – Quantitative (counts, proportions)

• Identification methods
  – Intra-product (traditional signaling)
  – Inter-product (non-traditional signaling)
SIGNAL DETECTION
SORTING METHODS

• Intra-Product Qualitative
  – Demographic
  – Fatal, serious
  – Designated medical events
  – Reports that meet quality criteria
  – Lot number

• Intra-Product Quantitative
  – Cut-off number or proportion
Intra-Product Qualitative
  – Imputation (causality assessment) procedures
  – Causal test criteria

Intra-Product Quantitative
  – Serial identification methods (time clustering)
  – Geographical cluster identification methods

Inter-Product Quantitative
  – 2x2 table methods
  – Bayesian data mining
IS INTER-PRODUCT SIGNAL DETECTION SUFFICIENT?

NO, BECAUSE:

• Can’t locate some kinds of safety problems (e.g., lot number)
• Long time lag versus intra-product methods
• Legal and regulatory responsibilities
• Basis for regulatory documentation (e.g., PSURs)

CONCLUSION:

• Intra-product methods applied to *publicly available* databases are adjunctive to, but do not replace, company product signaling
CAN INTER-PRODUCT SIGNALING METHODS BE USED ON COMPANY DATABASES?

FOR MID-SIZED AND SMALL COMPANIES – NO:
- Insufficient numbers of comparison products
- Adverse event reporting per product may be insufficient

FOR LARGE COMPANIES – MAYBE – BUT:
- Bayesian data mining and 2x2 tables assume a “large” number of products and a “large” number of AEs/product

CONCLUSION:
- Intra-product methods applied to company databases are adjunctive to, but do not replace, company product signaling
SIGNALING PROCESS

POTENTIAL SIGNAL LISTS

• Includes all potential signals generated by all signal detection methods

• Usually far exceeds the capacity to perform signal evaluations

• ISSUE: How are potential signal lists reduced to a workable size?
SIGNAL
PRIORITIZATION
The use of impact-oriented criteria to prioritize which signal detection output is sufficiently important to merit evaluative scrutiny.
GENERAL SCHEME FOR SIGNALING
PROCESS STEPS

Intra-Product Signal Detection Data Source

Inter-Product Signal Detection Data Source

Potential Signal List

Signal Detection Output Report

Signal Evaluation Requests

Case Series

Surveillance Documents

Intra-Product Signal Detection Methods
- Sorting
- Imputation
- Serial
- Others

Inter-Product Signal Detection Methods
- 2 X 2 methods
- Bayesian data mining

Prioritization Algorithm

Request For Query System

Signal Evaluation Methods
SIGNALING PROCESS
PRIORITIZATION ALGORITHMS

• Weighting factors
  • Strength of association
    – Numerical values for particular methods
    – Numbers of methods indicating signal
  • Seriousness
    – Report serious percentage
    – Report fatal percentage
  • Absence of biases
    – AE not logically related to indication
• Labeling status
  – Unlabeled

• Desirable features
  • Full automation
  • Documentation of results
• Provides signal detection program results
• Provides rationale and documentation for methods
• Provides rationale and documentation for prioritization algorithm
SIGNAL
EVALUATION
The application of signaling methods to a case series derived from an ICSR database in order to summarize causal evidence.
GENERAL SCHEME FOR SIGNALING

PROCESS STEPS

Intra-Product Signal Detection Data Source

Inter-Product Signal Detection Data Source

Potential Signal List

Signal Detection Output Report

Signal Evaluation Requests

Case Series

Surveillance Documents

Intra-Product Signal Detection Methods
- Sorting
- Imputation
- Serial
- Others

Inter-Product Signal Detection Methods
- 2 X 2 methods
- Bayesian data mining

Prioritization Algorithm

Request For Query System

Signal Evaluation Methods
SIGNAL EVALUATION

FEATURES

- Human resource intensive (non-automated)
- Usually hypothesis strengthening
- Based on a product-AE case series (report output + source documents that meet a case definition)
- It is a form of evidentiary assessment, not screening
- Comprised of descriptive statistics with comparison to an expected model
• Postmarketing AE signal evaluations always refer to a case series, even if non-contributory
• May incorporate other relevant data sources (e.g., toxicology studies, clinical studies)
• Links signal detection to surveillance documents
• ISSUE: What database should the case series be constructed from?
SIGNAL DETECTION

INTER-PRODUCT SIGNAL DETECTION

IS INTER-PRODUCT SIGNAL DETECTION SUFFICIENT?

NO, BECAUSE:

• Can’t locate some kinds of safety problems (e.g., lot number)
• Long time lag versus intra-product methods
• Legal and regulatory responsibilities
• Basis for regulatory documentation (e.g., PSURs)

CONCLUSION:

Intra-product methods applied to publicly available databases are adjunctive to, but do not replace, company product signaling
PSUR-ELIGIBLE CASES (MOST PRODUCTS)

WHICH IMPLIES:

- Company database
- Date specific data extract
- Cases meet PSUR criteria
DESIGN OF SIGNALING PROGRAMS
SIGNAL DETECTION
TIME TO DETECTED SIGNALS

- **Real Time**
  - “Time Of Occurrence” Signaling
  - Hypothetical Ideal
  
- **15 Days**
  - Expedited Signal Detection
  
- **1-3 Months**
  - Monitoring Signal Detection
  
- **6 Months**
  - Periodic Signal Detection
  
- **6-9 Months**
  - Inter-Product Signal Detection
  
**TIME LAG TO SIGNALING**

**Company Product Databases**

**Prioritization Algorithm**

**Signal Evaluation**

**FDA FOI Database**

**WHO Database**

**Large Company Databases**
<table>
<thead>
<tr>
<th>*<em>Software Product</em></th>
<th><strong>Pre-Designed Hosted Service</strong></th>
<th><strong>Product-Specific Hosted Service</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Client-directed</td>
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<tr>
<td>Client Direction</td>
<td>YES</td>
<td>NO</td>
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<tr>
<td>Data management control</td>
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<td>NO</td>
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<tr>
<td>In-House Resource Needs:</td>
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<tr>
<td>Technical</td>
<td>HIGH</td>
<td>LOW</td>
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<tr>
<td>Process</td>
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<td>Usable With:</td>
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<tr>
<td>Company database</td>
<td>CP, SP, DVS</td>
<td>NO</td>
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<tr>
<td>Multi-product database</td>
<td>CP, SP</td>
<td>YES</td>
</tr>
<tr>
<td>Prioritization algorithm</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Documentation:</td>
<td></td>
<td></td>
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<tr>
<td>Output Reports</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Data Extract</td>
<td>CP, DVS</td>
<td>NO</td>
</tr>
</tbody>
</table>

*Software product includes custom programming (CP), software products (SP), and database vendor software (DVS)
SIGNAL PRIORTIZATION
PRIORITIZATION ALGORITHM

- Impact variables
- Relative weighting for each impact variable
- How to automate the prioritization procedure
- How to document the prioritization procedure
SIGNALING PROGRAM

DESIRABLE ATTRIBUTES

• Pertinent and comprehensive
  – Product-specific
  – Intra-product and inter-product strategies
• Reproducible, validated, surveillance oriented
  – Company product database extracts (PSUR)
  – Multi-product database extracts available
  – Software validation
  – Signal evaluation requests for queries
**SIGNALING PROGRAM**

**DESIGN FEATURES**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client-directed, product-specific</td>
<td></td>
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<tr>
<td>In-house human resource needs</td>
<td>Technical, Workflow and process design</td>
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<tr>
<td>Usable with:</td>
<td>Company database, Multi-product database</td>
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<tr>
<td>Prioritization algorithm</td>
<td></td>
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<tr>
<td>Case series query system</td>
<td></td>
</tr>
<tr>
<td>Documentation</td>
<td>Procedural, Output reports, Data extract or equivalent, Software validation</td>
</tr>
</tbody>
</table>

*Customized programming (CP), AE database vendor add-on (AE), software product (SP)*
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