Farmakovijilans için ICH ve EMEA Gereklilikleri
Güncel Uygulama / Geleceğe Yönelik Eğilimler
ICH & EMEA Requirements for Pharmacovigilance
Current Implementation / Future Trends

Dr. Tomás Moraleda
MedDRA MSSO
ICH EDI Coordination

M1
Medical Terminology

M2 (ESTRI)
- the transport vehicle and format definitions

E2b
Clinical Safety Data Management: Content of Report

Electronic Standards for the Transfer of Regulatory Information

Pharmaceutical Company

Regulatory Authority
“Efficacy topics” (E) on safety

- E2A: Definitions and Standards for Expedited Reporting
- E2B: Data elements for transmission of adverse event reports
- E2B(M): Data elements for transmission of individual case safety reports (ICSR)
- E2C: Periodic Safety Update Reports
- E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited
Multidisciplinary Topics (M)

- M1: Medical Terminology
- M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)
- M3: Timing of Pre-clinical Studies in Relation to Clinical Trials (See Safety Topics)
- M4: The Common Technical Document
E2B(M) – “the grammar”
I2BM2

• Information about the safety report itself
  – A.1 Report identification
  – A.2 Primary source of information
  – A.3.1 Who sends the information
  – A.3.2 Who receives it
I2BM2

• Case information
  – B.1 Patient characteristics
  – B.2 Adverse reaction/event
  – B.3 Investigation test and procedures
  – B.4 Information about drugs (both suspect and concomitant)
  – B.5 Narrative case summary and further information
<table>
<thead>
<tr>
<th>ICH ICSR Section B.1 Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.7.1a.2</td>
</tr>
<tr>
<td>B.1.8f.2</td>
</tr>
<tr>
<td>B.1.9.2.b</td>
</tr>
<tr>
<td>B1.9.4b</td>
</tr>
<tr>
<td>B.1.10.7.1a.2</td>
</tr>
<tr>
<td>B.1.10.8f.2</td>
</tr>
<tr>
<td>B.3.1c</td>
</tr>
</tbody>
</table>
## E2BM & MedDRA

<table>
<thead>
<tr>
<th>ICH ICSR Section B.2 Reaction(s)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B.2.i.1.b</strong></td>
<td><strong>Reaction in MedDRA terminology</strong> (LLT must closely corresponding to the reaction as reported by primary source....)</td>
</tr>
<tr>
<td>B.2.i.2.b</td>
<td>Reaction MedDRA term (Preferred Term)</td>
</tr>
</tbody>
</table>

### ICH ICSR Section B.4 Drug(s) Information

<table>
<thead>
<tr>
<th>B.4.k.11b</th>
<th>Indication for use in the case</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.4.k.17.2b</td>
<td>If yes to item B.4.k.17.1 (did reaction recur on readministration), which reaction(s) recurred?</td>
</tr>
</tbody>
</table>

### ICH ICSR Section B.5 Narrative case summary and further information

| B.5.3b | Sender’s diagnosis/syndrome and/or reclassification of reaction |
Safety Communication Network

Country A
- Patient
- Health Professional
- Medical Association

Investigator
- Marketing Author Holder
- National Authority

Country B
- Product Headquarters

Country C

Country D

WHO, EMEA
Linking 3AEs from the same patient

AE: Adverse Event report (case)
HP: Hospital observing the event
  Report of AE
    ICSR report
FU: Follow up
The implementation of M2 in Europe:

“EudraVigilance”
Member states in the EU
EudraVigilance

• One single electronic reporting point within the European Union
• One standard for all regulators and pharmaceutical industry
  – Receive pharmacovigilance reports in XML format
  – Provide acknowledgment of acceptable file structure
• All reports to be sent by companies are re-routed to all Competent Authorities - All reports from Competent Authorities are channeled to companies
EudraVigilance Objectives

• Provide a complete and high quality pharmacovigilance **data set** for all medicinal products authorised in the Community independent of the authorisation status

• Support the establishment of **benefit-risk profiles** of medicinal products or classes of products and the targeted surveillance and continual assessment through the life cycle of the product(s)

• Provide sophisticated data analysis tools to support **signal detection** and evaluation
EudraVigilance Objectives

• Integrate drug utilisation data and extend the use to non-expedited reports
• Provide alerting mechanisms to rapidly notify about potential safety issues
• Support efficient communication of safety issues to healthcare professionals and the general public
• Technical support, implementation and maintenance of all EudraVigilance related aspects
The EudraVigilance System

- EurdaVigilance Gateway with restricted accessibility of data via the Internet.
- EudraVigilance Database Management System (DBMS) with query features, with access to...
- Standard Terminology:
  - MedDRA
  - EudraVigilance Medicinal Product Dictionary
  - Other ICH relevant standard terminology
- Reporting tools for SMEs
- **electronic safety reporting**
  - interoperability

**Drug Information System**
- Product dictionary
- Medical dictionary
- PharV System

**application-services**
- Data Access
- Transforms
- Presentation

**icsr web-service profile**
- Messaging
- Security
- Description
- Discovery
- Semantics
  (Web-Service Interoperability Framework)

**application-services**
- Data Access
- Transforms
- Presentation

**Message processor**
- Message Sender

**message layer**

**transport layer**
- Message Receiver/Intermediate

---

Copyright © 2002 Esteban Gonzalez Juarrons
The expressed views engage only the author and in no case can they be understood as an official position of any organization
EudraVigilance Gateway

• Secure Messaging
  - (provides private, authentication, integrity and non-repudiation of all transactions)

• Transmission Process
  - Data Encrypted
  - Messages Routed
  - Transactions Acknowledged
  - Exceptions and Errors Logged
  - Alerts Triggered
EudraVigilance DBMS

• Two main components:
  – Reporting DB: Designed to automate the message processing, validation, classification and storage to the greatest possible extent
  – Analytical DB: Supporting signal detection and evaluation providing query and analytical functions.
EudraVigilance DBMS

- All incoming adverse reaction reports are automatically classified through an algorithm as:
  - **Case report** (the report with the latest information used for signal detection and analysis)
  - **Replaced report** (Case reports replaced by follow up reports)
  - **Duplicated report** (Identical Case reports)
  - **Error report** (did no comply with business rules, after DTD validation)
What is XML?

- XML is the Extensible Markup Language. It is designed to improve the functionality of the Web by providing more flexible and adaptable information identification.
  - It is called extensible because it is not a fixed format like HTML (a single, predefined markup language). Instead, XML is actually a `metalanguage' — a language for describing other languages—which lets you design your own customized markup languages for limitless different types of documents.
What is XML?

<ANA106>
  <Screening visit>
    <Inclusion criteria>
      <Inc1>YES</Inc1>
      <Inc2>YES</Inc2>
      <Inc3>YES</Inc3>
      <Inc4>YES</Inc4>
    </Inclusion criteria>
    <Exclusion criteria>
      <Excl1>NO</Excl1>
      <Excl2>NO</Excl2>
      <Excl3>NO</Excl3>
      <Excl4>NO</Excl4>
    </Exclusion criteria>
  </Screening visit>

  <Visit1>
    <Demographic/Investigator>
      <Sex>Male</Sex>
      <DoB>07/26/1966</DoB>
      <Smoke>YES</Smoke>
      <InvNo>128</InvNo>
    </Demographic/Investigator>
  </Visit1>

  <Visit2>
    ............ (more pages)
  </Visit1>

  <Visit3>
    ............ (more blocks)
  </Visit1>
What is XML?

- electronic safety reporting
  - icsr

- structure and fields
“EudraVigilance”

SMEs
(small & medium co.s)
EudraVigilance for SMEs

• Secure communication over the Internet by using a “web trader” that allows:
  – Online function to create fully E2BM and M2 compliant safety acknowledgement messages.
  – Access to all relevant standard terminologies (last version of MedDRA, EudraVigilance Product Dictionary and others) with query functions
  – Query function with restricted access to the ICSRs submitted by a pharmaceutical company
  – Input on co. medicinal products
EudraVigilance for SMEs

• Administrative requirements:
  – Registration process with the EMEA for each pharmaceutical company through the responsible person for pharmacovigilance
  – European MAH must be situated in the EEA or a Candidate Country
  – If annual revenue < 500,000 $ per year, MedDRA EudraVigilance subscription is 1,000 $.
  • If besides less than 100 ICSRs per year, license is free.
“EudraVigilance”
Some hints on current implementation
Current implementation status

- First phase of the implementation is focusing on expedited reports

<table>
<thead>
<tr>
<th></th>
<th>EU REPORTS</th>
<th>NON-EU REPORTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally authorised</td>
<td>22.000</td>
<td>35.000</td>
</tr>
<tr>
<td>Mutually recognised &amp; nationally auth</td>
<td>87.000</td>
<td>180.000</td>
</tr>
</tbody>
</table>
## Current implementation status

<table>
<thead>
<tr>
<th>Company</th>
<th>EU-Reports</th>
<th>Non-EU Reports</th>
<th>Percentage Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>8,954</td>
<td>3,926</td>
<td>4%</td>
</tr>
<tr>
<td>Eisai LTD.</td>
<td>320</td>
<td>600</td>
<td>0.28%</td>
</tr>
<tr>
<td>Gilead</td>
<td>200</td>
<td>300</td>
<td>0.15%</td>
</tr>
<tr>
<td>Lundbeck</td>
<td>521</td>
<td>454</td>
<td>0.3%</td>
</tr>
<tr>
<td>MSD</td>
<td>2,500</td>
<td>6,000</td>
<td>2.6%</td>
</tr>
<tr>
<td>Novartis</td>
<td>10,000</td>
<td>6,000</td>
<td>4.9%</td>
</tr>
<tr>
<td>Roche</td>
<td>3,000</td>
<td>9,000</td>
<td>3.7%</td>
</tr>
<tr>
<td>Wyeth</td>
<td>3,789</td>
<td>3,456</td>
<td>2.2%</td>
</tr>
<tr>
<td>Schering Ploough</td>
<td>4,100</td>
<td>16,100</td>
<td>6.2%</td>
</tr>
</tbody>
</table>
## Current implementation status

<table>
<thead>
<tr>
<th>Competent Authority</th>
<th>EU-Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish Medicines Agency</td>
<td>900</td>
</tr>
<tr>
<td>INFARMED</td>
<td>1,263</td>
</tr>
<tr>
<td>Norwegian Medicines Agency</td>
<td>1,300</td>
</tr>
</tbody>
</table>
Current implementation status

• 66 pharmaceutical companies have currently interest to use the web reporting tool as part of EurdraVigilance version 6.0 and plan to contribute with 5,779 EU reports and 69,024 non EU reports

• 48 pharmaceutical companies and 8 Competent Authorities are in the testing phase with the EMEA
Contacting MSSO
MSSO Contacts

• Mail
  MSSO
  VAR1/8A/MSSO
  12011 Sunset Hills Road
  Reston, VA 20190-3285
  USA

• Telephone
  – 703.345.7799
  – 877.258.8280 (AT&T toll free)
MSSO Contacts (cont.)

• To Subscribe
  – Send e-mail to subscribe@trw.com
  – Call 703.345.7765
  – Fax 703.345.7755

• Web Page
  – www.meddramsso.com

• Products and Services
  – 703.345.7799
How to get in contact with me ...

- Tomás Moraleda
- Spanish International Medical Officer
- Telephone: +34 91 518 70 13
- Email: tmoraled@teleline.es