

MedDRA and Product Safety Labeling

Industry perspective, practical experience

Dr Ilona Große-Michaelis

Global Medical Development - Medical Coding Standards (MCS)

AGENDA

- **Short information about company**
- **Regulatory and relevant group activities**
- **Company activities, Labeling Guidance for use of MedDRA in the company**
- **Experiences with use of MedDRA for Safety Labeling within company and with Authorities**
- **Challenges**

Berlin



**Ernst Schering (1824 - 1889)
bought a pharmacy in 1851, “Grüne Apotheke”
- Founded “Chemische Fabrik Ernst Schering”
(1864)**

- 1st contraceptive pill in Europe 1961 (Anovlar)
- Headquarters in Berlin, Germany
- > 25.037 employees world wide, net sales (2005): 5.3 billion €
- **Medical Business Areas:**
 - Diagnostic Imaging
 - Gynecology & Andrology
 - Specialized Therapeutics
 - Oncology
- **Top-selling products:**
 - Magnevist
 - Yasmin
 - Betaferon
 - Fludara
- **Use of MedDRA:** for coding since 7/ 2002
for labeling since 5/ 2005

Regulatory and relevant group Activities

- 1) EMEA - Notice to Applicants, Vol 2C, The rules governing medicinal products in the European Union, A Guideline on Summary of Product Characteristics Rev 1, Oct 2005
(Proposal for revision of a Guideline on Summary of Product Characteristics 2005, transmission to CHMP 14 Jan 2005, release for consultation 3 Mar 2005)
 - MedDRA request for EU-label (Chapter “Undesirable effects”)

- 2) MedDRA and Product Labeling: “Best practices” Recommendations, MSSO-DI-8381-1.0.0, 13 January 2005
(position paper open for comments)
Observations at the Blue Ribbon Panel, 16 Mar 2005, Zoetermeer, NL
 - Additional recommendation for MedDRA Labeling Entities (MLE)

Regulatory and relevant group Activities

- 3) FDA – Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (Jan 2006)
 - **No MedDRA request for US-label**

“Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database.”
 - **FDA announcement (Press release, Apr 2006)**

Use of SNOMED in electronic US Structured Product Labeling Initiative to electronically code important terms in patient records, prescription and the Highlights section of US label implementation deadline: ?, > end of Jun 2006

Guidance for use of MedDRA in Safety Labeling

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects” (EMA – Guideline)
 - **(1) In MedDRA terminology (flexible approach, “grouping terms”, Preferred Term (PT))**
 - **(2) Any ADR should be assigned to the most relevant MedDRA System Organ Class (SOC) related to the target organ and the clinical appropriateness**
 - **(3) The internationally agreed order of the MedDRA SOCs should be followed**

Guidance for use of MedDRA in Safety Labeling

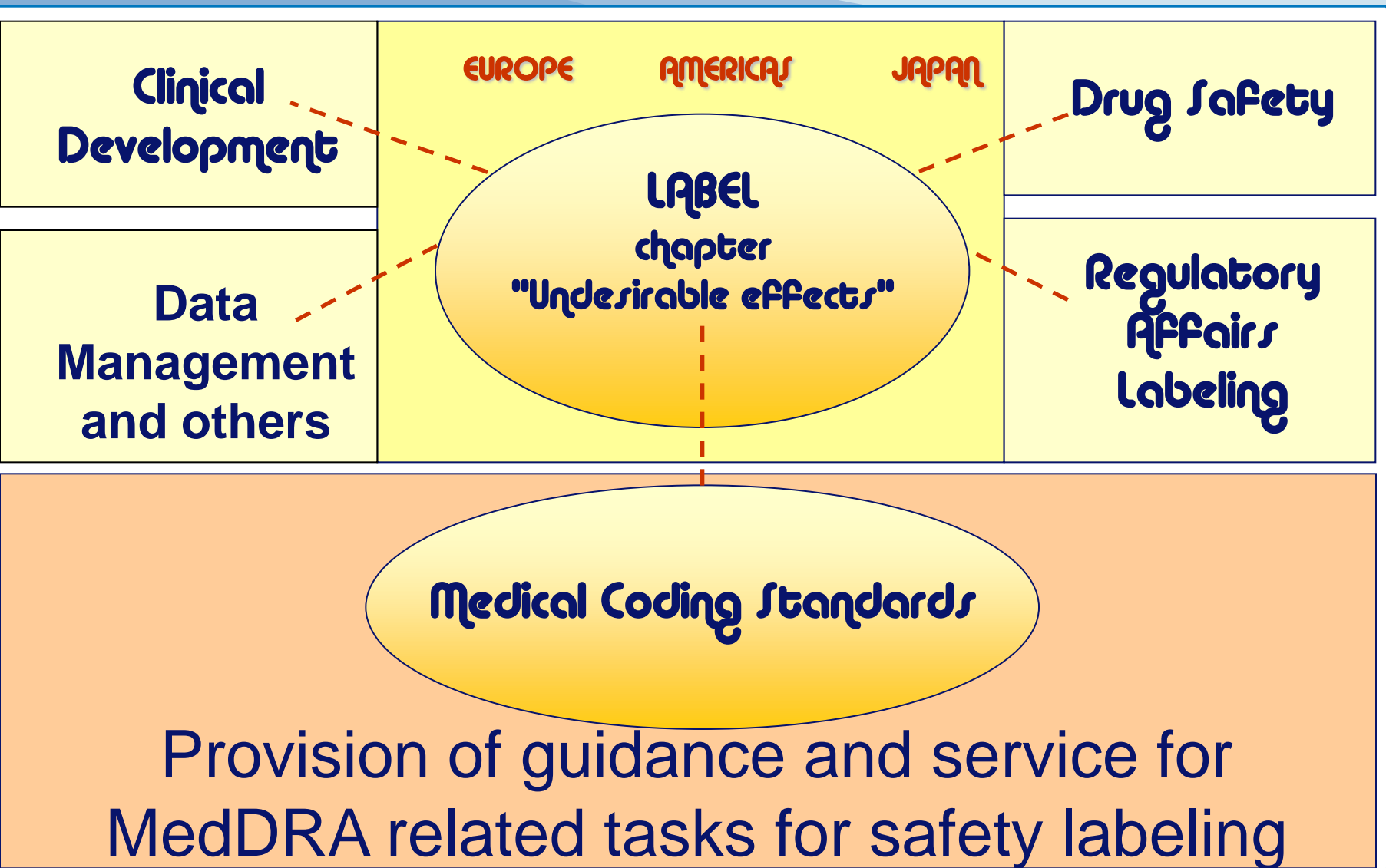
- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects” (EMA – Guideline)
 - (4) Within each SOC, ADRs should be ranked under headings of frequencies, most frequent reactions first
 - (5) Within each frequency grouping, ADRs should be presented in the order of decreasing seriousness
 - (6) Used MedDRA version should be indicated
 - (7) ADRs in legacy terminologies should be mapped to MedDRA

Activities

- Pragmatically decision (March 2005):
in the course of an update of labeling standards, ADRs must be provided in MedDRA terminology/ System Organ Classes
- MCS accompanies and supports the process in close cooperation with all relevant functions (started March/ April 2005)

Goals

- ⇒ **To assure compliance with regulatory requirements for labeling according to MedDRA (content and format)**
- ⇒ **To achieve consistent and standardized usage of MedDRA for labeling purposes**



MCS - Operational MedDRA support for Safety Labeling

Stepwise procedure

- Step 0: Request to MCS for MedDRA representation
- Step 1: Draft proposal for discussion of all involved functions
- **Step 2: Decision by all involved partners**
- Step 3: Provision of final draft by MCS
- Step 4: Document submission for internal approval/
Final decision
- Step 5: Mapping document, expert statement by MCS

**Achieve consistency
over time and across products**

MCS - Guidance for use of MedDRA in Safety Labeling



**1. Guidance for use of MedDRA in Safety Labeling (Adverse Events/ Undesirable Effects)
Conventions for mapping of legacy terminology to MedDRA (1st version in April 2005)**

**2. Expert Statement
for Company Core Data Sheet, section 10
(Undesirable effects):
Conversion/ mapping of legacy terminology to
MedDRA**

Experiences in use of MedDRA in Safety Labeling status

- Experience with 41 products from different therapeutic areas
- Experience with labels at different status (mapped, MedDRA coded/ recoded, updated/ versioned)
- Experience with used MedDRA versions 8.0, 8.1, 9.0

BASIS:

- Therapeutic business area **DIAGNOSTIC IMAGING**
5/1 products - Final/ updates: **5 products**
ONGOING: **1 product**
- Therapeutic business area **GYNECOLOGY & ANDROLOGY**
18/6 products - Final/ updates: **18 products**
ONGOING: **6 products**
- Therapeutic business area **ONCOLOGY**
3 products - Final/ updates: **4 products**
- Therapeutic business area **SPECIALIZED THERAPEUTICS / Dermatology**
7 products - Final/ updates: **7 products**

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - (1) In MedDRA terminology (flexible approach, “grouping terms”, Preferred Term (PT))

Experiences:

- Flexibility highly appreciated vs. difficulty to reach consistency
- Mainly Lowest Level Terms (LLT) and PTs preferred, “grouping terms” not much liked
- Flexibility for the label vs. recommendation for clinical data representation (LLT vs. PT)
- For all products only 60 - 90 MedDRA terms used

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - (2) **Any ADR should be assigned to the most relevant MedDRA System Organ Class (SOC) related to the target organ and the clinical appropriateness**

Experiences:

- Chosen primary or secondary SOC depends on the product class (mainly one preferred SOC per each term)
- Different product groups evaluate SOC differently
- Linkage of terms from SOC Investigations often controversial discussed

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - **(3) The internationally agreed order of the MedDRA SOCs should be followed**

Experiences:

- **This order is not very much liked, but finally accepted**

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - (4) **Within each SOC, ADRs should be ranked under headings of frequencies, most frequent reactions first**

Experiences:

- **No problem (due to history), no real MedDRA issue**

Experience in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - **(5) Within each frequency grouping, ADRs should be presented in the order of decreasing seriousness**

Experiences:

- Often debates about definition of seriousness
(seriousness: death, life-threatening, involved hospitalization, prolonged hospitalization, involved persistent disability, congenital anomaly, important medical event e.g. seizures, blood dyscrasias;
non-serious: does not meet above criteria)

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR)
in chapter “Undesirable effects”
 - **(6) Used MedDRA version should be indicated**

Experiences:

- Non-MedDRA users do not understand the MedDRA versioning and the necessary update
- Version number always indicated

Experiences in use of MedDRA in Safety Labeling with EMEA Guidance

- Provision of Adverse Drug Reactions (ADR) in chapter “Undesirable effects”
 - (7) **ADRs with legacy terminology should be mapped to MedDRA**
 - Experiences:
 - Mapping to MedDRA with the help of a central function is no problem
 - Mapping ends very often on the LLT- or PT-level
 - Mapped data and recoded data are slightly different (needs explanation and help)
 - Source of data is always indicated

Experiences in use of MedDRA in Safety Labeling with Authorities

Caution: currently limited experience due to pending reply of Authorities

- **No approval for Medicinal Products (MP) without MedDRA representation, rejection of submissions (NL, DK, D)**
 - **Approval for most MPs with MedDRA representation without comments**
 - **Approval for one MP (Diagnostic Imaging) with comments (2 Authorities)**
 - Proposal of a not existing MedDRA-term, of a mixture of PTs
 - An existing LLT was characterised as not existing
- ⇒ **Clear request for ADR representation of MP in MedDRA terminology, wide range of MedDRA expertise in Authorities**

Experiences in use of MedDRA in Safety Labeling Summary

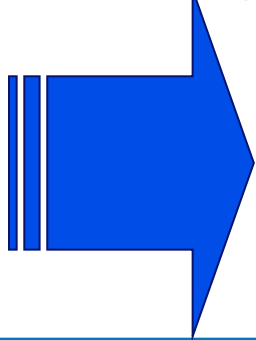
- **No problems for MedDRA representation/ mapping until now**
- **Critical attitude regarding MedDRA mapping of legacy safety (labeling) information reduced**
- **Understanding of MedDRA terminology/ linkage to System Organ Classes increasing**
- **Assessed/ appreciated as helpful for internal standardization of labeling text**
- **Evaluated as compliant with Guidelines**
- **Customer survey (end of last year): excellent, fast, unbureaucratic service (often on very short notice), satisfying due to single contact person**

MCS - Operational MedDRA support (future requirements - outlook)

Strategic importance - basis for risk-benefit evaluation

**Consistency and comparability of products,
compliance with class labeling required by
Authorities**

**Consistency and comparability of safety information
between the Investigators Brochure (Clinical), the
Data Sheets (Drug Safety), the Label (Regulatory
Affairs)**



challenges: e.g.

**operative support for MedDRA term translation,
compilation of MLEs**

Requirements for Safety Labeling Challenges

- **EU requirement for MedDRA representation vs. US requirement for SNOMED representation (mapping perceived as urgent, maintenance)**
- **EU-label:**
 - Only chapter “Undesirable Effects” in MedDRA required, other chapters not, inconsistencies (e.g. Special warnings and special precaution for use)
 - Aggregation of grouping terms, MLE-like concept would be helpful for consistency
 - MedDRA translations important for local labeling and patient information

Berlin



End of presentation

THANK YOU