



# MedDRA<sup>®</sup> and the European Regulatory Environment

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# AGENDA

- Volume 9A
- Guidance on adverse reaction reports arising from Clinical Trials
- Application in EudraCT Database
- **Proposal** for a revision of Summary of Product Characteristics document
- Guideline on Risk Management Systems



# **VOLUME 9A of The Rules Governing Medicinal Products in the European Union**

**Guidelines on Pharmacovigilance for Medicinal  
Products for Human Use**



# Expedited Reporting of ICSR, E2B

- Section B.1 Patient Characteristics
  - Structured information on relevant medical history
  - Relevant past drug history (**indications**)
  - Reported cause(s) of death
  - Autopsy-determined cause(s) of death
  - information concerning the parent
    - Relevant medical history and concurrent conditions of parent
    - Relevant past drug history of parent (**indications**)



# Expedited Reporting of ICSR, E2B

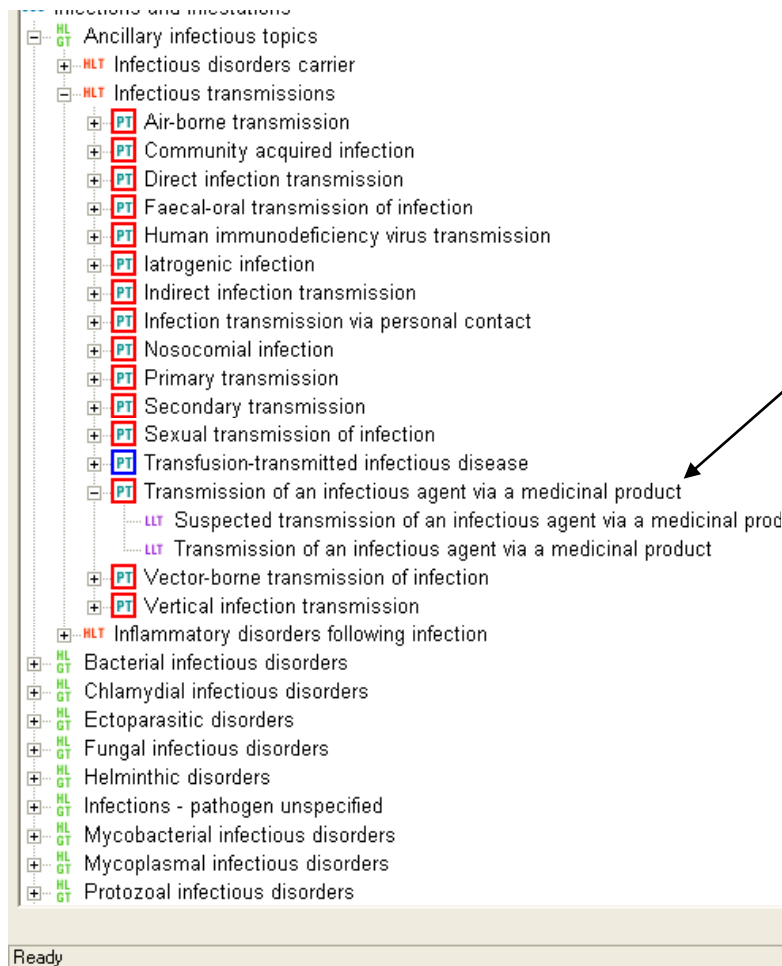
- Section B.2 Reaction(s): Reaction in MedDRA terminology (LLT)
- Section B.3 Results of Tests and Procedures Relevant to the Investigation of the Patient
- Section B.4 Drug(s) Information
  - **Indication** for use in the case
  - did reaction recur on readministration)?
- Section B.5 Narrative case summary and further information:
  - Sender's diagnosis/syndrome and/or reclassification of reaction



# Follow-up information report

- “A change of the status term *due to a version change* of MedDRA can be considered as a non-significant change as long as this change has no impact on the medical content of a case.”
- “A change in the MedDRA coding due to a change in the interpretation of a previously reported adverse reaction may constitute a significant change and therefore should be reported on an expedited basis.”

# Reporting in Special Situations



- The requirement to apply MedDRA coding to the reporting of cases of suspected transmission of an infectious agent.



# Requirements for Periodic Safety Update Reports

- Description of the Adverse Reaction: The reaction terms used in the PSUR should be in accordance with the MedDRA terminology
- PSUR section “Presentation of Individual Case Histories”: Line-Listings should be organised (tabulated) by body system (MedDRA System Organ Classes (SOCs))



# Presentation & Line-Listings

- Retrieval and presentation points to consider release 1.4, based on MedDRA version 10.1
- Overall presentation of safety profiles
  - Overview by primary system organ class
  - Overall presentations of small datasets
  - Focused searches
    - Focused search by secondary SOC assignments
    - Search by Standardised MedDRA Queries (SMQs)
    - Search by ad hoc queries



# SMQs used for signal detection

- “Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases.”
  - PSUR section “Overall Safety Evaluation”
  - Part of the Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action
  - Part II: Guidelines for Competent Authorities and The Agency



# Part II: Guidelines for Competent Authorities and The Agency

- General principles / Signal detection
  - Database functionality should enable users to search and retrieve data to facilitate cumulative data review, signal detection and trend analysis.
- DatRet PTC R1.4 “Organization-Specific Data Characteristics”
  - Limitations/restrictions. For example, one should not assume that secondary PTs will be seen when searching using a specific HLT; this is only the case if the database configuration allows for output by secondary path.



**Detailed guidance on the  
collection, verification and  
presentation of adverse reaction  
reports arising from clinical  
trials on medicinal products for  
human use**

**April 2006**



# Format of the SUSARs reports

- The current version of MedDRA or the previous one to it should be used for the coding of adverse reactions terms. Lower level terms should be used.



# Clinical trial Annual Safety Report

- Part 2: Line-listings and Annex 4
- A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial, including also serious adverse reactions from third countries
- Cases should be tabulated by body system (standard organ system classification scheme).
- Where medically appropriate, signs and symptoms can be lumped into diagnoses



# **Application for the request for authorisation of a clinical trial in EudraCT database**



# Trial general information

MedDRA Browser - SOC View : MedDRA Version 15feb08

File View Tools Help

- SOC Infections and infestations
  - Virals infectious disorders
    - Hepatitis viral infections
      - Hepatitis B
        - HBV coinfection

Expanded view of Hepatitis B terms:

- Asymptomatic viral hepatitis
- Congenital hepatitis B infection
- Gianotti-Crosti syndrome
- Hepatitis A
- Hepatitis B
  - Acute hepatitis B
  - Chronic hepatitis B
  - Chronic hepatitis B atypical
  - Fulminant hepatitis B
  - HBV coinfection ←
  - Hep B
  - Hepatitis B
  - Hepatitis B aggravated
  - Hepatitis B reactivation
  - Hepatitis homologous serum-like
  - Jaundice homologous serum-like
  - Serum hepatitis
  - Viral hepatitis B
  - Viral hepatitis B with hepatic coma
  - Viral hepatitis B with hepatic coma, with hepatitis delta
  - Viral hepatitis B with hepatic coma, without mention of hepatitis delta
  - Viral hepatitis B without mention of hepatic coma
  - Viral hepatitis B without mention of hepatic coma, with hepatitis delta
  - Viral hepatitis B without mention of hepatic coma, without mention of hepatitis delta
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Hepatitis F
- Hepatitis G
- Hepatitis H

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- Applicants are encouraged to provide the MedDRA lower level term if applicable and classification code.



# TS\_PTC & Indication for product use

- Term Selection: Points to Consider
  - Release 3.9, Based on MedDRA Version 10.1, 12 September 2007
  - Medical Conditions:
    - Where the indication is a medical condition, a term that expresses the medical condition should be selected.
  - Prevention and Prophylaxis
  - Diagnostic Testing
  - Procedures
  - Supplementation and Replacement Therapies



# **Proposal for a revision of the European Commission guideline on Summary Of Product Characteristics**



# General aspects of the document

- Consistent medical terminology should be used throughout the SmPC. The use of MedDRA, at the “Preferred Term” level, is therefore recommended.
  - Exceptionally HLTs and LLTs could also be used as codes



## May be in contradiction? ...

- When a Preferred Term is assigned to a preferred System Organ Class, the MedDRA hierarchy should be followed.
- The table should be presented according to the MedDRA, but for a pragmatic approach, it may be helpful on some occasions not to follow MedDRA architecture
  - solely in the context of the SmPC



# ADR descriptions and tabulation

- Use secondary links for some PTs
- Represent Investigation terms under the manifestation site SOC
  - "Liver function test abnormal", "Hepatitis" and "Hepatic encephalopathy" all under the "Hepato-biliary SOC"
- It may also be appropriate to use *ad hoc* groupings of terms
  - PT "Diarrhoea", "Diarrhoea aggravated", "Loose stools", "Stools watery", and "Intestinal hypermotility" are present in MedDRA under separate HLT and might all reasonably be represented as the single term "Diarrhoea"
- **Remember: deadline for consultation on proposed changes  
28 march 2008**



# Guideline on Risk Management Systems



## Template for “EU-RMP”

- In the Interface between European Risk Management Plan (EU-RMP) and EudraVigilance, MedDRA codes used for
  - **Indications**
  - Identified risks
  - Potential risks
  - Identified **Interactions**
  - Potential Interactions
- both MedDRA version and term level to be indicated in each case



# Regulations & MedDRA “headlines”

	Data aggregation	SMQs	Up version	MedDRA in indications	MedDRA rules	Mention to PTC documents
Volume 9A	PSURs	PSURs	ICSR follow up	E2B		Electronic reporting guidelines, E2B
		Overall PhV Evaluation				
		Guidelines C.A.				
AE reports in CLTs	Annual Safety Report					
EUDRACT application				√		
SmPC	Data aggregation (against rules)			√	Coding to HLTs, use of 2ry link	2005 document, not in new draft
EU-RMP		Identified and potential risks and interactions		√	SOC, HLT, HLT and PT. SMQ Broad and narrow searches	



**QUESTIONS ?**