Introduction to MedDRA – An ICH Product

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Disclaimer:

- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

Agenda

- **What is MedDRA?**
  - MedDRA – an ICH product
- **Why MedDRA?**
  - An ICH standard
  - A drug safety terminology
  - Features of MedDRA
  - ICH-endorsed guides for users
  - Active maintenance
  - Support for users

MedDRA – An ICH Product

MedDRA

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities

MedDRA Is Developed under the Auspices of I C H

INTERNATIONAL CONFERENCE ON HARMONISATION of Technical Requirements for the Registration of Pharmaceuticals for Human Use

http://www.ich.org

What is ICH?

- **ICH is a unique harmonisation project involving the regulators and research-based industries of US, EU and Japan**
  → started in 1990
  - **WHO, Canada, and EFTA are observers**
- **Well-defined objectives:**
  - **To improve efficiency of new drug development and registration process**
  - **To promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness**
- **Accomplished through the development and implementation of harmonised guidelines and standards**

ICH Accomplishments

- **60+ harmonised guidelines on technical requirements (quality, safety, efficacy)**
- **Electronic standards (ESTRI, E2B)**
- **Common format and electronic specification for marketing applications : CTD and eCTD**
- **MedDRA – ICH's standard for electronic safety data exchange**

→ 2010 marked the 20th Anniversary of ICH

The ICH Members

Europe

EC – European Commission – European Union (EU)

EFPIA - European Federation of Pharmaceutical Industries and Associations

Japan

MHLW - Ministry of Health, Labour and Welfare

JPMA - Japan Pharmaceutical Manufacturers Association

United States

FDA - Food and Drug Administration

PhRMA - Pharmaceutical Research and Manufacturers of America

Observers

WHO – World Health Organization

Health Canada

EFTA – European Free Trade Association

…Expanding beyond ICH regions

Protect Public Health

- **Drug approval – evaluate and decide**
  - Is the drug safe and effective?
  - What should the label contain?
  - Does the method of manufacturing preserve the drug's identity, strength, quality, and purity
- **THE THALIDOMIDE TRAGEDY**
  - An estimated 10,000 human birth deformities
  - Dr. Frances Kelsey, the Medical Officer of the Food and Drug Administration, rejected the drug firm's application to market Kevadon (thalidomide) in the United States

The Need for MedDRA

Before MedDRA:

- Impossible for electronic communication
- Some used WHO-ART, COSTART, ICD-9, ICD-9 CM, HARTS etc
- Some used their own customised versions of these
- Some used their in-house developed dictionary
- Inadequacies of previous terminologies
  - Not enough medical terms - low specificity
  - Not medically valid
  - Poor or no maintenance - addition of terms
  - Poor hierarchies hinder retrieval of grouped data

The Need for MedDRA

- **In both pre- and post-authorization situations, a recognized terminology is an essential requirement**
- **For protection of global public health: need for an international, standardized, multi-lingual, robust, medically validated terminology which facilitates electronic communication.**

→ MedDRA

ICH M1 MedDRA EWG

- ICH “Multidisciplinary” Expert Working Group 1 developed MedDRA
- Made up of drug safety experts from regulatory authorities and industry
- UK's Medicines Control Agency (current MHRA) terminology – MEDDRA – used as the basis
- Capability testing conducted by US FDA and others
- Produced the final product - MedDRA

(Mozzicato, P. “MedDRA – Past and Future” Dec 2006, RAJ Pharma, p797)

MedDRA Governance: ICH MedDRA Management Board

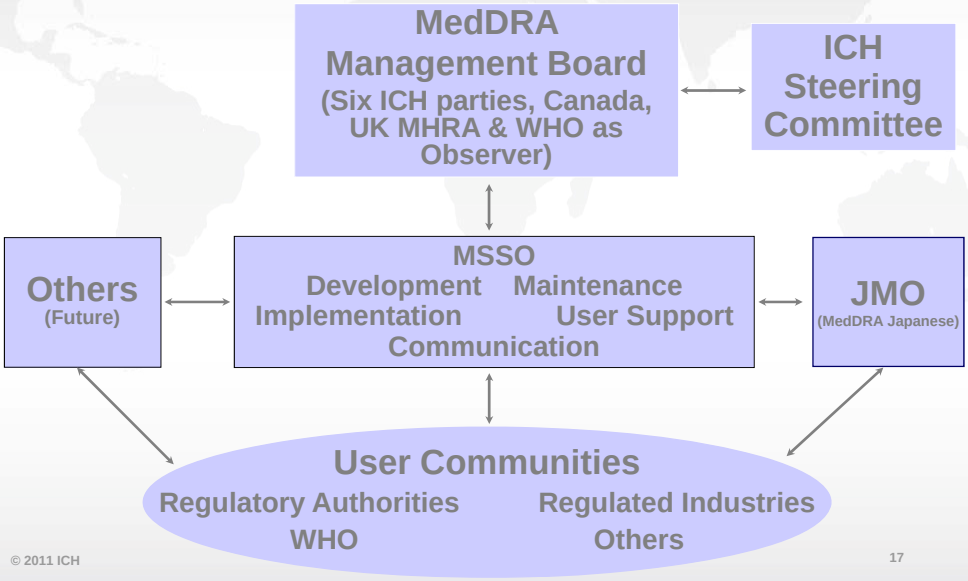
MedDRA Management Board
Purpose & Responsibilities

- **Oversees financial and technical operations of the MSSO**
  - **Examples: Review MSSO costs and fee structure**
- **Ensures the continued development and viability of MedDRA**
- **Ensures that MedDRA is easy to use and accessible to all**
- **Ensures MSSO is meeting the needs of users**

IFPMA
International Federation of Pharmaceutical Manufactures and Associations

- Non-Profit, Non-Governmental Organisation
- Represents national industry associations & R&D companies from developed & developing countries
- Hosts the ICH Secretariat
- Holds ownership of MedDRA, as a trustee of ICH
- Contracts the maintenance organization of MedDRA (MSSO) on behalf of ICH

ICH Management Structure of MedDRA (cont)



MSSO

Maintenance and Support Services Organization

- Contracted by ICH (Nov. 1998 -)
- Activities directed by the MedDRA Management Board
- Maintains/develops & distributes MedDRA (twice a year)
- Support Subscribers with Help Desk support and training
- MSSO activities self-funded through MedDRA subscriptions
  - Free for all Regulators worldwide
  - Free for all Healthcare providers and academics
  - Sliding scale subscription rates for commercial organizations
  - Special licenses to provide access to low revenue users

JMO
Japanese Maintenance Organization

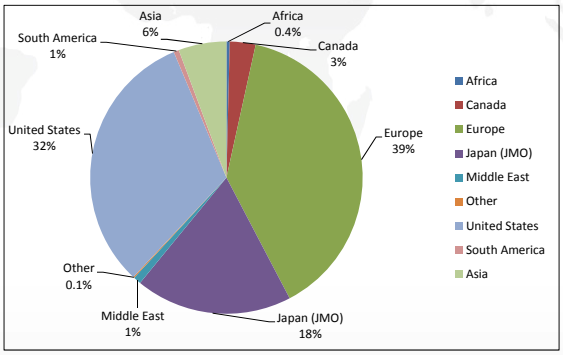
- MedDRA MSSO partner (Nov. 1998 -)
- Operated by Pharmaceutical and Medical Device Regulatory Science Society of Japan
- Maintains & distributes Japanese MedDRA translation (MedDRA/J) to companies headquartered in Japan
  - Works with MSSO to ensure consistency of MedDRA/J with original English version
- Supports MedDRA/J users with Help Desk support and training in Japanese
- Activities self-funded through MedDRA/J subscriptions

Interest from Beyond the ICH Regions

- November 2010 MB special session at Fukuoka included representatives from
  - SFDA (中国)
  - APEC (亚太经济合作组织)
  - ASEAN (东盟)
  - SADC (南部非洲发展共同体)
  - GCC (Gulf Cooperation Countries)
  - KFDA (南韩)
  - HSA (新加坡)
  - Chinese Taipei Department of Health

MedDRA Subscriber Worldwide

2847 organizations as of 31 March 2011



Why MedDRA?

ICH Standard Terminology

For better protection of global public health

- **Speaking the same language in product safety**
  - No matter where you are
    - FDA (AERS, VERS, CAERS) – MedDRA
    - Health Canada (Canada Vigilance) – MedDRA
    - EMA (EudraVigilance) – MedDRA
      - EU national regulatory authorities
    - MHLW (MHLW database of pharmaceutical ADR reports) – MedDRA
    - WHO/UMC (Vigibase) – MedDRA
    - Regulated industry

WHO & MedDRA

- **As of March 2008, MedDRA has been implemented in WHO's Global Safety Database (Vigibase)**
  - **WHO National Centres can review data and conduct analyses in both WHO-ART and MedDRA**
    - **Data can be sent/entered in either MedDRA or WHO-ART**
    - **Reports generated in either MedDRA or WHO-ART**
- **With Vigibase containing >6 million ICSRs, it now provides a global repository of MedDRA-coded safety data:**
  - **Substantial tool for pharmacovigilance**
  - **Of significant benefit to global patient safety**

WHO & MedDRA

- **WHO Uppsala Monitoring Centre (UMC) has developed with ICH/MSSO a "bridge" or mapping from WHO-ART to MedDRA:**
  - **Allows conversion of legacy data from WHO-ART to MedDRA**
  - **Maintained current with every version release of WHO-ART and MedDRA**
  - **Does not work in the other direction since MedDRA is more granular than WHO-ART**
- **WHO UMC receives most of ICSRs coded in MedDRA**

ICH Standard Terminology (cont)

- **Speaking the same language in product safety (cont)**
  - Applicable through all phases of development, from clinical trials to the post-marketing period
  - Applicable for a range of medicinal products
    - Drugs
    - Biologics
    - Vaccines
    - Medicine/devices combination products
  - Available in 11 languages
    - Chinese, Czech, Dutch, English, French, German, Hungarian, Italian, Japanese, Portuguese, Spanish

ICH Standard Terminology (cont)

- **Clear and accurate communication of drug safety**
  - Regulator – regulator (drug safety alert)
  - Regulator – industry (regulatory submissions)
  - Industry – industry (collaboration)
- **Eliminate potential mistranslation from one terminology to another**
  - Comparison with other drugs of the same class or therapeutic indication
  - Drug approval by multiple regulatory authorities

ICH Standard Terminology (cont)

- **Work together with other ICH standards for electronic submission:**
  - ICH E2B form: data elements for transmission of ICSR

MedDRA Code

ICH Standard Terminology (cont)

- **Work together with other ICH standards for electronic submission:**
  - ICH Common Technical Document (eCTD): Common format for drug registration
    - M4E Guideline: MedDRA is recommended in adverse event summary tables
    - Mandated in EU and Japan
    - Recommended in US and Canada

MedDRA

A. Module 1 Administrative Information and Prescribing Information Folder

1. *eCTD backbone document information files*
2. *Cover letter (optional)*
3. *Labeling*
4. *Advertisements and promotional material*
5. *Marketing annual reports*
6. *Information amendments*

B. Module 2 Summary Folder
C. Module 3 Quality Folder
D. Module 4 Safety Folder

1. *Study reports*
2. *Literature references*
3. *Datasets*

E. Module 5 Clinical Study Reports Folder

1. *Tabular listing of all clinical studies*
2. *Study reports*
3. *Case report forms*
4. *Datasets*
5. *Periodic safety update reports*
6. *Literature references*

FDA: eCTD Submission Specifications (October 2005)
http://www.fda.gov/RegulatoryInformation/Guidances/ucm126959.htm

A Drug Safety Terminology

- **Developed by a group of international drug safety experts (ICH M1 EWG)**
  - Experts from regulatory authorities
    - Regulatory perspective
  - Experts from pharmaceutical industries
    - Industry perspective
  - Lessons learned from other terminologies
    - Limited scope
    - Limited granularity
    - Lack of analytical capability

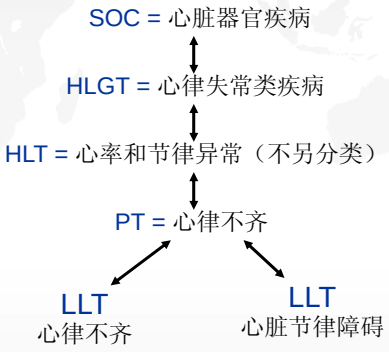
Features of MedDRA

- **Widened scope**
  - Diseases, diagnoses, signs/symptoms, therapeutic indications
  - Investigations, procedures, social/family history
  - Medication errors
  - Product quality issues
  - Device issues
  - Pharmacogenetic/pharmcogenomic terms (new)
- **Increased granularity and specificity**
  - About 70,000 terms

Features of MedDRA (cont)

- **MedDRA analytical features**
  - Five levels of hierarchy

系统器官分类 (SOC) (26)
高位组语 (HLGT) (335)
高位语 (HLT) (1,710)
首选语 (PT) (19,086)
低位语 (LLT) (69,019)



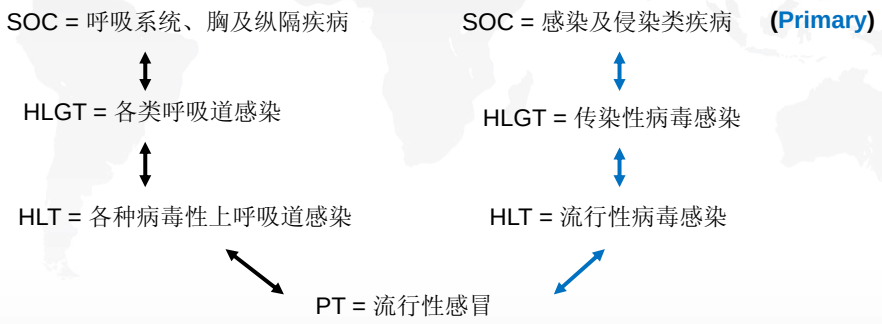
Features of MedDRA (cont)

- 26 System Organ Classes

- 血液及淋巴系统疾病
- 心脏器官疾病
- 各种先天性家族性遗传性疾病
- 耳及迷路类疾病
- 内分泌系统疾病
- 眼器官疾病
- 胃肠系统疾病
- 全身性疾病及给药部位各种反应
- 肝胆系统疾病
- 免疫系统疾病
- 感染及侵染类疾病
- 各类损伤、中毒及手术并发症
- 各类检查
- 代谢及营养类疾病
- 各种肌肉骨骼及结缔组织疾病
- 良性、恶性及性质不明的肿瘤（包括囊状和息肉状）
- 各类神经系统疾病
- 妊娠期、产褥期及围产期状况
- 精神病类
- 肾脏及泌尿系统疾病
- 生殖系统及乳腺疾病
- 呼吸系统、胸及纵隔疾病
- 皮肤及皮下组织类疾病
- 社会环境
- 各种手术及医疗操作
- 血管与淋巴管类疾病

Features of MedDRA (cont)

- Multi-axiality and primary SOC



Features of MedDRA (cont)

- **Standardised MedDRA Queries (SMQs) (标准 MedDRA 分析查询)**
  - Groupings of terms from one or more MedDRA System Organ Classes (SOCs) related to defined medical condition or area of interest
  - Included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to medical condition or area of interest
  - Intended to aid in case identification and signal detection

An SMQ Example

Lactic acidosis (SMQ) 乳酸中毒 (SMQ)

Definition
Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Peripheral arterial vasodilatation and central vasoconstriction can be present. Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may occur. Characterized by an increase in plasma L-lactate. Acidosis is seldom significant unless blood lactate exceeds 5 mmol/l. Clinical presentation in type B lactic acidosis: Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain. Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness

Source
1. Braunwald E, Fauci A, Kasper D. Harrison's Principles of Internal Medicine. 15th Edition, 2001 pp 285-9
2. Weatherall D, Ledingham J and Warrell D. Oxford Textbood of Medicine. Third edition, 1996; volume 2 pp 1541-44

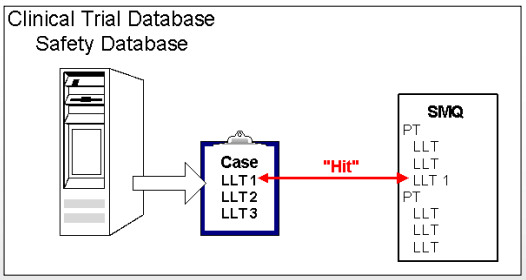
Note
Testing in two regulatory databases confirmed that the term list is adequate; in one regulatory database, the term "acidosis" identified cases, but this may be a phenomenon of the database characteristics (coding of verbatims to terms of an older terminology or other coding conventions).

Narrow Terms
Blood lactic acid increased
Hyperlactacidaemia
Lactic acidosis

Broad Terms
Acid base balance abnormal
Acidosis
Anion gap abnormal
Anion gap increased
Blood bicarbonate abnormal
Blood bicarbonate decreased
Blood gases abnormal
Blood lactic acid abnormal
Blood pH abnormal
Blood pH decreased
Coma acidotic
Kussmaul respiration
Metabolic acidosis
PCO2 abnormal
PCO2 decreased
Urine lactic acid increased

Features of MedDRA (cont)

- Sample SMQ topics
  - Agranulocytosis
  - Anaphylactic reaction
  - Cerebrovascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Ischaemic heart disease
  - Lack of efficacy/effect
  - Peripheral neuropathy
  - Pregnancy and neonatal topics
  - Pseudomembranous colitis
  - Rhabdomyolysis/myopathy
  - Severe cutaneous adverse reactions
  - Systemic lupus erythematosus
- SMQs – case identification



Features of MedDRA (cont)

- **Available in Chinese**
  - MedDRA Chinese translation – since 2009
    - Linked to English MedDRA via MedDRA code
  - Originally translated by Pfizer (辉瑞)
    - In MedDRA v7.1
    - Transferred to ICH
  - Updated by the MSSO
    - From v7.1 to v12.1
    - Translated SMQs, MedDRA documents, such as
      - MedDRA Introductory Guide, SMQ Introductory Guide

Features of MedDRA (cont)

- **Available in Chinese (cont)**
  - Translation validation
    - MedDRA term translation rules
    - Translation correctness of terms and documents
      - Selected terms and documents
      - Eight subscribing companies participated
        - Volunteer physicians - native Chinese from local Chinese branch offices
        - MedDRA users
        - Based on medical specialty

ICH-Endorsed Guides for Users

- **Developed by an ICH Expert Working Group**
- **Current versions available on MedDRA MSSO Web site (http://www.meddramsso.com/subscriber_library_ptc.asp)**

  Or the ICH Web site: http://www.ich.org/products/meddra/meddraptc.html
- **Promote the standard use of MedDRA: two Points to Consider (PTC) documents**
  - PTC: MedDRA Term Selection
  - PTC: MedDRA Data Retrieval and Presentation

Active Maintenance

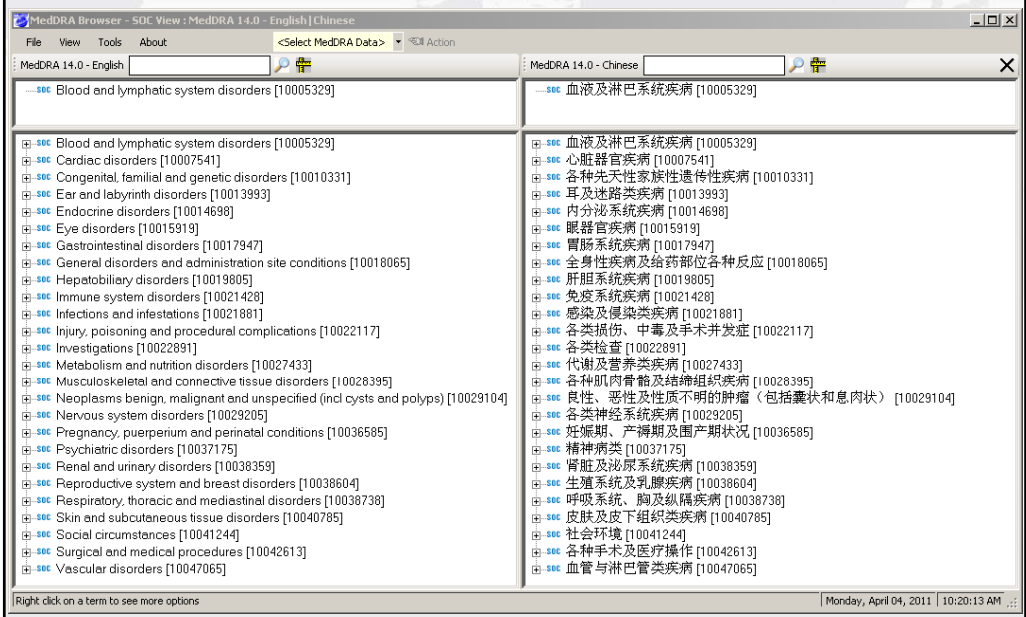
- **MedDRA is actively maintained – user responsive**
  - Need a new term in MedDRA?
  - Need to modify the links in MedDRA?
  - MSSO change request process
  - MedDRA Expert Panel
- **Bi-annual release**
  - March 1
  - September 1

Support for Users

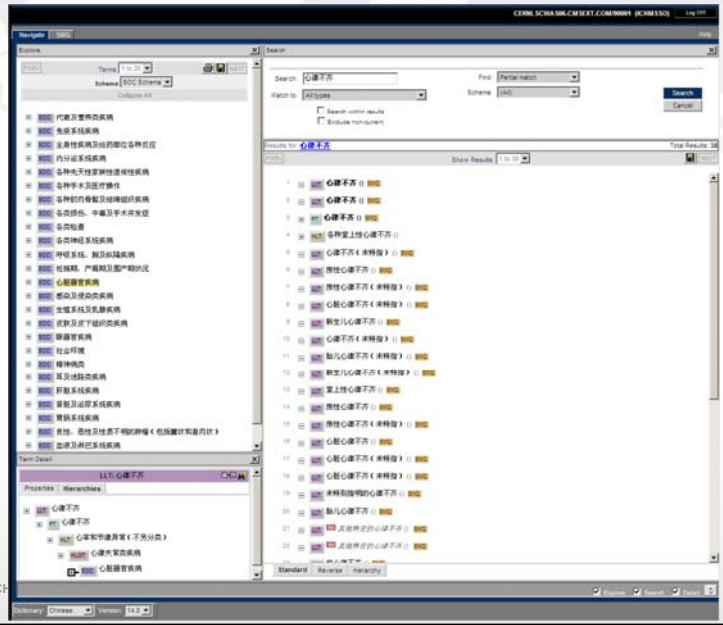
Available with MSSO subscription:

- **Free MedDRA Browsers**
  - MedDRA Desktop Browser (MDB)
  - MedDRA Web-Based Browser (WBB)
- **Free MedDRA Version Analysis tool**
  - To help users assess the impact of a new version on their data
    - Changes identified between any two MedDRA versions
    - Users to decide whether to re-code based on information provided
  - To be available in late 2011

MedDRA Desktop Browser



MedDRA Web-Based Browser



Support for Users (cont)

- **Free training sessions by the MSSO**
  - 2010 Beijing free training
    - 20th and 21st May 2010
    - Day one (Coding With MedDRA) - 64
    - Day two (Safety Data Analysis and SMQs) – 62
  - 2011 Shanghai free training
    - 10th and 11th May 2011
    - Day one (Coding With MedDRA)
    - Day two (Safety Data Analysis and SMQs)
- **Timely MSSO Help Desk service**
  - Available by email and phone
  - English and Chinese
  - mssohelp@ngc.com

Support for Users (cont)

- **Chinese MedDRA User Group (CMUG)**
  - Volunteer group
  - 50 members (22 organizations)
  - Help to organize free training
  - User feedback
  - CMUG web page
  - Continue CMUG activities in 2011 and beyond
- **MSSO User Group Meetings**
  - 20th May 2010 – in Beijing
    - The Use of MedDRA in Clinical Trial Data Management and EDC (Electronic Data Capture)
    - Practical experience in MedDRA coding and analysis
    - The challenges of using MedDRA in clinical practice
  - 10th May 2011 – in Shanghai

CMUG page

中华MedDRA用户小组成员区

Chinese MedDRA Group Member Area

Logout

中华MedDRA用户小组成员表

小组秘书: Dr. Catherine Xie

成员若有问题, 请与秘书直接联系: 电子信箱 (Jun.Xie@pfizer.com) 或者网上提问 or anna.zhao-wong@ngc.com or mssohelp@ngc.com

您的电子信箱: *

问题: *

Submit Clear

此网页记载所有小组讨论课题, 会议记录, 等等, 供成员参考.

中华MedDRA用户小组2011年3月3日电话会议记录

2011年1月9日:
问题 (from a member):
1. Radiofrequency ablation(LLT): The current translation is 软脚成形术. But I think it should be 射频消融. Because its PT is High frequency ablation(高频消融) and the other two LLTs under this PT are High frequency ablation(高频消融) and High frequency hyperthermia(高频热疗).
2. Fatigue extreme: The current translation is 四肢疲累. But I think it should be 极度疲劳。
回答 (from Anna):
I agree with your suggestions. Those are indeed translation errors. We will get them corrected.

2011年1月6日:
问题 (from a member):
I have a question about the CN Translation of "Rheumatoid" in MedDRA. "Arthritis rheumatoid" is translated as LLT "风湿性关节炎", "Rheumatoid arthritis" is translated as LLT "类风湿性关节炎".
回答 (from Anna):
You are right that translation of "rheumatoid" in MedDRA should be consistent. I will run some queries to make sure that they are all translated as "类风湿性".

Acknowledgement

- **SFDA – workshop logistics**
- **ICH Secretariat – program assistance**
- **MedDRA Management Board – program support**

ICH
harmonisation for better health

Thank You!