Questionnaire regarding nomenclatures for concepts related to health technologies

1. Name of the "nomenclature"

MedDRA
The development of a “Medical Dictionary for Regulatory Activities” was approved by the ICH (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Steering Committee in 1997 and the MedDRA terminology launched in 1999.

2. Name and legal status (Inc, Plc, Ltd, …) of the organization that manages the nomenclature system

MedDRA is an ICH product, managed by ICH.

3. The organization that manages the nomenclature

a. Please describe the governance and management of the body responsible for maintaining the nomenclature.

The MedDRA Management Board, appointed by the ICH Steering Committee, has overall responsibility for direction of MedDRA. The Board operates under formally agreed rules on membership and mode of operation. The Board oversees the activities of the MedDRA “Maintenance and Support Services Organization” (MSSO), which serves as the repository, maintainer, developer and distributor of MedDRA.

The Management Board is composed of the six ICH Parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, the Health Canada and the WHO (as Observer).

b. How is broad stakeholder representation ensured?

MedDRA is a terminology whose development is driven by its users who come from over 60 countries worldwide including regulatory authority, industry, academia and health care professionals.

Input can be provided through various mechanisms including the MedDRA Change Request Process and MedDRA User Groups with significant changes or expansion in MedDRA scope requiring review and endorsement by the ICH MedDRA Management Board.
c. **How is broad geographical representation ensured in governing bodies?**

MedDRA being an ICH product, the governing body is composed of the three ICH regions (EU, US and Japan) and Canada. WHO, as an Observer, makes the link with the non-ICH countries.

Since 2010, five Regional Harmonization Initiatives (RHIs) have been invited to provide input to MedDRA Management Board discussions, namely, APEC, ASEAN, GCC, PANDRH and SADC. Regulators from Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore are also invited.

4. **Background to the creation of the nomenclature**

**Please outline the scope of the mandate to engage in classification and naming**

The objective of the ICH MedDRA initiative has been to develop a standardized international medical terminology for regulatory communication in the registration, documentation and safety monitoring of medical products, i.e. for use in both pre- and post-marketing phases of the regulatory process (clinical trials, reports of spontaneous adverse reactions and events, regulatory submissions, and aspects of regulated product information, such as summaries of product information). It is also the objective to support the electronic communication.

This international medical terminology is designed primarily for communication among regulatory authorities and the industries they regulate in the registration, documentation and safety monitoring of medical products.

This initiative was undertaken to address the problems with the use of different terminologies in various regions at different stages in the development and use of products that impaired international communication necessitating conversion of data from one terminology to another, with consequent time delays and inevitable loss or distortion of data.
5. **What is the intended purpose/use of the system?**

MedDRA is a rich and highly specific standardised medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale.

MedDRA is used in the full lifecycle of product development and use. MedDRA is used to codify indications for use in the registration of products for clinical trials. During Phase I-IV clinical trials MedDRA is used for adverse event reporting and also for collecting investigation names & qualitative results, medical history, diseases, diagnoses, signs and symptoms, medical & surgical procedures, and social and family history. MedDRA is used during the post-approval stage by manufacturers to meet regulatory reporting requirements for expedited and periodic safety reporting. More recently, regulatory authorities have started to use MedDRA for direct patient reporting to regulatory authorities.

Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products. MedDRA includes over 425 device specific terms that have been added at the request of users. Many manufacturers are developing combination products that are part device and part drug. The need for the device terms in MedDRA has been growing to match the increasing use of devices and combination products.

6. **Mandatory use of the nomenclature**
   a. **Has any country or organization made it mandatory to use the nomenclature for specific purposes?**

   Regulatory authorities from EU, Japan, US and Canada are requiring the use of MedDRA for safety reporting within the pre- and post-market surveillance environment (SUSARs, ICSRs, PSURs). Other mandatory uses include the use of MedDRA for product labeling (Summary of Product Characteristics) and for reporting infection terms for medical devices with biologic components.

   A growing number of national regulatory authorities are evaluating MedDRA as their medical terminology as they modernize their respective pharmacovigilance infrastructures.
7. Please comprehensively describe the structure of the system. The structure and format of terms, the relations between terms, design principles for creating terms etc. Current IT implementations by the "management organization" and by users are also of interest.

The MedDRA structure provides degrees or levels of superordination and subordination. The superordinate term is a broad grouping term applicable to each subordinate descriptor linked to it. Hierarchical levels thus represent vertical links in the terminology.

MedDRA has a five-level structure that provides options for retrieving data by specific or broad groupings, according to the level of specificity required. The Lowest Level Term (LLT) level provides maximum specificity. A Preferred Term (PT) is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. High Level Terms (HLTs) and High Level Group Terms (HLGTs) facilitate data retrieval and presentation by providing clinically relevant grouping of terms. Collectively, the HLT and HLGT levels are sometimes referred to as the “grouping terms” in MedDRA.

The 26 System Organ Classes (SOCs) represent parallel axes that are not mutually exclusive. This characteristic, called “multi-axiality,” allows a term to be represented in more than one SOC and to be grouped by different classifications (e.g., by etiology or manifestation site), allowing retrieval and presentation via different data sets. Grouping terms are pre-defined in the terminology and not selected on an ad hoc basis by data entry staff. Rather, the terminology is structured so that selection of a data entry term leads to automatic assignment of grouping terms higher in the hierarchy. Multi-axial links of terms are pre-assigned, ensuring comprehensive and consistent data retrieval, irrespective of which SOC is selected at data retrieval.

The current version of MedDRA (version 14.0) has over 70,000 terms to support the requirement by industry and regulatory users to supply the appropriate level of granularity while providing features to pool data for statistical analysis and data mining.

MedDRA is maintained by the MSSO using a series of IT tools. The primary tool is a workflow tool that allows direct change request entry by users to the MSSO. These changes are then reviewed by the international medical team within the MSSO and a decision is made for each change request.

MedDRA is distributed in ASCII text format to users to allow for ease of import to the variety of IT tools that use MedDRA (e.g., clinical data management system, safety system, data mining tools).
8. **Are the terms used in the classification system generic i.e. non proprietary?**

   MedDRA is a copyrighted terminology (the relationship between the terms). IFPMA owns the copyrights and trademarks as a trustee of the ICH. The copyright allows ICH to protect the integrity of MedDRA.

9. **Maintenance of the nomenclature system**
   a. **How is the system maintained?**

   The long-term maintenance and updating of the terminology and its evolution in response to medical/scientific advances and changes in the regulatory environment is vital to its success. ICH has contracted a Maintenance and Support Services Organization – MSSO - to maintain, develop and distribute MedDRA. The ICH MedDRA Management Board oversees all financial and technical (maintenance and development) activities of MSSO.

   The MSSO is audited every release by an independent physician to review the medical decisions made and to provide feedback to the MSSO and the MedDRA Management Board. The MedDRA Board also conducts periodic clinical audits to review the MSSO maintenance process, to provide feedback for potential improvement and to provide an independent assessment of the MSSO’s medical process.

   The MSSO maintains an ISO: 9001:2008 Certification for the Quality Management System developed by the MSSO for the maintenance of MedDRA. This involves regular audits by an external ISO auditing organization.

   b. **Please describe the process for creating or modifying terms in the system.**

   MedDRA users submit change requests to the MSSO. Change requests can be requests for new terms or changes to existing terms. Users can enter change requests with a web-based tool or by sending an email with the change. All change requests are acknowledged (i.e., the MSSO has received the request) via email and then reviewed by the MSSO medical staff. The medical staff then provides a final disposition to the user for all change requests. The final disposition is either an acceptance of the change or a rejection of the change with a rationale for the MSSO’s decision. All approved changes are posted weekly on the MSSO website.

   Following the Management Board review and approval, MedDRA is released twice a year (March and September) with all approved changes and updated user documentation.
c. **How is transparency ensured with regard to development and maintenance of the nomenclature?**

To support transparency, the MSSO maintains and distributes user documentation that describes the maintenance process and rules for maintenance. The MSSO provides access to users to view change requests received (both accepted and rejected) with the MSSO rationale for acceptance or rejection. If a user is not in agreement with an MSSO decision, they can re-submit the change request to the MSSO with additional justification.

10. **Different language versions of the nomenclature**
   a. **How is the translation of terms and definitions managed?**

If translation activities are undertaken by the MSSO upon request of the ICH MedDRA Management Board, it will liaise with regulatory authorities and the pharmaceutical industry in the region concerned to ensure that the translations developed are clinically validated. A document on “Points to Consider for Developing a Translation of MedDRA” is used as a set of rules to develop a new translation.

All new language translations must be clinically validated by the regulator of the translation prior to being provided to ICH and then to the MSSO for ongoing maintenance.

If the MSSO receives a MedDRA translation from a source other than a regulatory authority, the MSSO coordinates with the appropriate regulatory authority and knowledgeable MedDRA industry users to validate the translation.

In a nutshell, as a general principle, the regulatory authority should be responsible for the initial translation and its clinical validity. During the change request process and update to a new version, the MSSO should raise any significant issues with the regulatory authority.

b. **What language versions exist as of February 2011?**

MedDRA is available today in a number of translations of the original English version – Chinese, Czech, Dutch, French, German, Italian, Japanese, Portuguese and Spanish.

Other translations will be considered, should interest be expressed to the ICH MedDRA Management Board.
c. **What language versions are under translation as of February 2011?**

| Hungarian translation is currently being developed for release on mid-March 2011. |

11. **Endorsement of the nomenclature system**

a. **Has the system been endorsed by stakeholders (healthcare professionals, Ministries of Health, industry, regulatory bodies etc.)?**

- [ ] Yes
- [ ] No

*Please indicate the names of the entities which have endorsed the system.*

| MedDRA is mandatory for use in the EU (EMA and EU member states) and Japan (MHLW). MedDRA has also been implemented in the US (FDA CBER/CDER) and Canada (Health Canada). |
| MedDRA is used by over 2,800 subscribing organizations around the world in over 60 countries. |
| MedDRA users include the biopharmaceutical industry and regulatory authorities, device manufacturers, healthcare professionals, academic institutions, hospitals, and service support organizations. |

12. **Implementation in IT systems, interoperability and intellectual property**

a. **Please outline the intellectual property state of the nomenclature system. Please include reference to the ownership of the terms used.**

| The IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) was established as the Trustee for the ICH Steering Committee to hold the ownership of the MedDRA terminology, including translations, and to award the MSSO an exclusive license to the terminology as part of a renewable contract for maintenance, distribution and updating of the master copy of the terminology on behalf of the Steering Committee. |
b. **Is the system available as a package for integration into user IT systems (maintenance management, adverse event reporting, procurement….)?** ☑ Yes

☐ No

c. **Please specify the conditions of agreements for use in user IT systems.**

<table>
<thead>
<tr>
<th>MedDRA is distributed in ASCII text format to users to allow for ease of import to the variety of IT tools that use MedDRA (e.g., clinical data management system, safety system, data mining tools). As long as the organization maintains a valid MedDRA subscription, MedDRA can continue to be used by the organization.</th>
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13. **Interoperability**

Please specify compatibilities ensured and mappings to other nomenclatures maintained.

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<th>MedDRA is fully implemented in the WHO global safety database allowing entry and retrieval of information in either MedDRA or WHO-ART. A mapping bridge is kept updated by WHO UMC and ICH/MSSO to allow conversion of WHO-ART coded data into MedDRA, allowing users to readily convert their data and use MedDRA.</th>
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14. **Model for sustainable financing**

a. **How is the system financed?** I.e. user fees, member fees, subscriptions, one off payments, open source?

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<th>It is financed by yearly subscriptions on a sliding scale for companies.</th>
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b. **What is the cost of the nomenclature to specific users (governments, industry, health care providers)?**

The MedDRA terminology is free for all regulators worldwide as well as for academics and health care providers while paid subscriptions are on a sliding scale linked to annual turnover of companies.

Every year, the ICH MedDRA Management Board reviews/approves the MSSO budget for development & maintenance of MedDRA and then determines the annual costs for access to the terminology. Since 2005, the Board has either reduced or maintained the fee structure. The Board approach has been to apply larger reductions for the small and medium-sized companies so a larger financial burden is put on the larger commercial organizations.

Recognizing that some companies may only have a few case reports a year, the Board has established a special license agreement to make MedDRA freely available to small/micro sized companies within the EMEA’s EudraVigilance system (EVWEB). A similar approach is being undertaken with USA. Additional agreement will be considered by the ICH Management Board, upon request.