1 MedDRA as an ICH Product

MedDRA was developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Board, which is composed of the European Union (EU), European Federation of Pharmaceutical Industries and Associations (EFPIA), Ministry of Health, Labour and Welfare (MHLW) of Japan, Japanese Pharmaceutical Manufacturers Association (JPMA), the US Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, the World Health Organization (WHO), and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). See page 10 for a list of the individual Management Board members.

2 MedDRA MSSO Mission

The MedDRA MSSO is tasked with two functions:
- Establish and maintain a mechanism for international support and development of the MedDRA terminology
- Foster the use of MedDRA worldwide through communication, education, and services

The goal of the MSSO is to maintain MedDRA as a stable, consistent terminology to suit the needs of regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing; and for data entry, retrieval, evaluation, and presentation.

3 Highlights for 2012

3.1 Subscription and Subscription Rates

The year 2012 was a year of continued growth and development of MedDRA. MedDRA had 3606 subscribing organizations worldwide by the end of 2012 (3085 in 2011). Of the 3606 worldwide subscribers, 3035 were MSSO subscribers (2546 in 2011) and 571 were JMO subscribers (539 in 2011). The 3035 MSSO subscribers represent a 16.1% growth in subscribers in 2012 over 2011 (12.5% the year before).

Figure 3-1 depicts the distribution of MSSO subscribers by region.
At the end of 2011, the Board approved the 2012 subscription rates (including Chinese translation rates) that were unchanged from the rates in 2010. (see Tables 3-1 and 3-3). MSSO’s subscription rates have either been unchanged or decreased for the past 7 years (since 2006).

The 2012 rates are as follows.

<table>
<thead>
<tr>
<th>Subscription Level</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>$0</td>
</tr>
<tr>
<td>Core 0 (&lt; $1M)</td>
<td>$190</td>
</tr>
<tr>
<td>Core 1 ($1-10M)</td>
<td>$804</td>
</tr>
<tr>
<td>Core 2 ($10-500M)</td>
<td>$5,529</td>
</tr>
<tr>
<td>Core 3 ($500M – 1B)</td>
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</tr>
<tr>
<td>Core 4 ($1B – 5B)</td>
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<tr>
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</tr>
<tr>
<td>Developer</td>
<td>$2,990</td>
</tr>
<tr>
<td>Regulatory Authority</td>
<td>$0</td>
</tr>
</tbody>
</table>

Table 3-1. 2012 Annual Subscription Rates (in US Dollars)
3.2 Major Developments of MedDRA Terminology

In 2012, MedDRA, including its translations and Standardised MedDRA Queries (SMQs), continued to grow and evolve. A summary of major additions and modifications in the 2012 releases of MedDRA are shown in Table 3-2.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Version</th>
<th>Initiator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy exposure terms, complex changes*</td>
<td>15.0</td>
<td>Discussions with ICH Points To Consider Working Group</td>
</tr>
<tr>
<td>Pharmacogenetic terms, complex changes*</td>
<td>15.0</td>
<td>A user proactive Terminology Maintenance initiative, which originated from several MedDRA user-submitted change requests</td>
</tr>
<tr>
<td>Bleeding and hemorrhage terms</td>
<td>15.0</td>
<td>MedDRA user proactivity request.</td>
</tr>
<tr>
<td>Removal of legacy codes</td>
<td>15.0</td>
<td>MedDRA Management Board</td>
</tr>
<tr>
<td>SMQs - one new SMQ added</td>
<td>15.1</td>
<td>CIOMS SMQ Working Group</td>
</tr>
<tr>
<td>Addition of missing American and British spellings counterparts</td>
<td>15.1</td>
<td>MedDRA user proactivity request.</td>
</tr>
</tbody>
</table>

Table 3-2. Highlights in v15.0 and v15.1

* Some of the effort to complete these tasks was performed in 2011 for MedDRA v14.1.

Chinese Translation

Table 3-3 provides the 2012 MedDRA Chinese translation subscription fees; the fees were the same as those for 2011. Users subscribing to the Chinese translation must also have a MSSO subscription.

<table>
<thead>
<tr>
<th>Subscription Level</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>$50</td>
</tr>
<tr>
<td>Core 0 (&lt; $1M)</td>
<td>$50</td>
</tr>
<tr>
<td>Core 1 ($1-10M)</td>
<td>$50</td>
</tr>
<tr>
<td>Core 2 ($10-500M)</td>
<td>$150</td>
</tr>
<tr>
<td>Core 3 ($500M – 1B)</td>
<td>$300</td>
</tr>
<tr>
<td>Core 4 ($1B – 5B)</td>
<td>$600</td>
</tr>
<tr>
<td>Core 5 (&gt; $5B)</td>
<td>$850</td>
</tr>
<tr>
<td>Developer</td>
<td>$450</td>
</tr>
<tr>
<td>Regulatory Authority</td>
<td>$0</td>
</tr>
</tbody>
</table>

Table 3-3. 2012 Chinese Translation Subscription Fee (in US Dollars)

**SMQs**
The total number of production Level 1 SMQ topics is 87 as of MedDRA Version 15.1.

New SMQ *Generalised convulsive seizures following immunisation* was added in MedDRA v15.1.

**Pharmacogenetic Terms**
In MedDRA v14.1 (2011), the MSSO added to MedDRA an initial group of pharmacogenetic and pharmacogenomic concepts of relevance to MedDRA users. This was a proactive MSSO initiative, which originated from several MedDRA user submitted change requests. The criteria used to add new terms focused on those genetic concepts and factors that have a potential impact on drug therapy.

In MedDRA v15.0, changes to pharmacogenetic and pharmacogenomic concepts were made at the High Level Term (HLT) level to complete this initiative.

**Pregnancy Exposure Terms**
In MedDRA v14.1 (2011) new sets of pregnancy exposure terms (Lowest Level Terms [LLTs] and Preferred Terms [PTs]) were added and existing terms reorganized to make them more self explanatory and easier to use for pharmacovigilance purposes. These changes were based upon suggestions from and discussions with the ICH Points To Consider Working Group.

In MedDRA v15.0, changes to pregnancy exposure terms concepts were made at the HLT level. The MSSO plans on additional complex changes to this area of MedDRA in 2013.

**Removal of legacy codes**
The initial release of MedDRA (v2.1) in March 1999 included numeric or symbol codes from earlier terminologies used in the biopharmaceutical realm. The codes were links from other terminologies to similar or identical terms in MedDRA and included codes from COSTART, WHO-ART, ICD-9, ICD-9-CM, HARTS, and J-ART. The ICH M1 Expert Working Group – who created the original version of MedDRA – included these codes with the text of the terms with the intent that the codes could be useful in the transition to MedDRA by early adopters. Since most organizations have long since migrated to MedDRA, and since the codes have not been maintained or updated since the original release of MedDRA, the MSSO has removed them from the MedDRA files.

**Proactive Maintenance**

Beginning in 2011 and with the approval of the Board, the MSSO took a more proactive approach to MedDRA maintenance. Proactive maintenance means the MSSO may make corrections or improvements to MedDRA that it identifies without receiving specific change requests from users. MedDRA users may also request more general changes to MedDRA – perhaps correcting a series of outdated terms or addressing an area of inconsistency – outside the change request submission process.

Two proactivity proposals, that originated from MedDRA users, were implemented in 2012:

- Addition of missing “bleeding” LLTs under existing “haemorrhage” PTs to improve MedDRA for coding and consistency

- Addition of missing American or British spelling counterparts to existing MedDRA terms to improve MedDRA for coding and consistency. The terms added addressed the submitter’s specific concerns. The MSSO began a comprehensive review for missing American or British spelling counterparts and expects to add more terms in 2013

**3.3 Significant MSSO Activities**

**MVAT**

The MSSO deployed the MedDRA Version Analysis Tool (MVAT) in the first quarter of 2012.

MVAT provides a series of static reports similar to the existing MedDRA Version Report spreadsheet produced for each release. The principal difference between MVAT and the version report is that users are able to choose to view differences
between any two versions of MedDRA while the Version Report spreadsheet only displays differences from the immediately prior version.

MVAT also provides an interactive function allowing users to identify MedDRA changes that impact their own coded data based on a list of MedDRA LLTs or PTs input by the user.

The results of both the static and interactive outputs can be exported to a spreadsheet for use in the subscriber’s own systems.

**MedDRA Desktop Browser Upgrade**

The MSSO deployed an updated version of the MedDRA Desktop Browser (MDB) in July 2012. In general this release improved the support for MedDRA translations. The upgrade, beta version 3.1, has the following new features:

- A network-based installation option which allows IT departments to centrally install the MDB without having to install the program on every computer
- A new synonym pair for haemorrhage/hemorrhage and bleeding for English MedDRA
- Synonym lists for each supported language
- An option to set the dual panel display to view two languages of the same MedDRA version as a default when starting the MDB
- Ability to ignore diacritical marks when performing searches in non-English languages
- A history file for each language
- Several bug fixes.

**MSSO MedDRA Training**

During 2012, the MSSO provided free MedDRA training to 1,419 people. Of this number, 595 attendees were from regulatory authorities representing the following countries: Canada, China, Denmark, France, Germany, Hungary, Turkey, and the United States.

The 1,419 trainees include attendance at 6 free subscriber webinars which were well received by MedDRA users. The MSSO plans to continue to provide webinars in 2013 on a variety of topics including Introduction to MedDRA,

In 2012 the What's New webinar was added to the list of free webinars to subscribers. Free training videos were expanded to include topics of MedDRA fundamentals, such as “MedDRA Structure and Scope”. The videocast is available in five languages (English, Chinese, French, German, and Spanish). More topics will be available in 2013.

The MSSO made training course materials available for download on the web site for user's convenience.

**MedDRA in China**

The MSSO continues to provide user group and training services in China. In May, the MSSO conducted a two-day face-to-face free training and a User Group meeting in Beijing. The training consisted of “Coding with MedDRA” for Day 1 and “MedDRA Safety Data Analysis and SMQs” for Day 2. There were about 60 attendees each day. The User Group meeting topics included an update from the MSSO and Traditional Chinese Medicine and MedDRA.

In October, the MSSO participated in ICH MedDRA and e-submission training in Beijing. Speakers from the ICH delegation, China’s State Food and Drug Administration (SFDA), and Johnson & Johnson presented and discussed with the audience about MedDRA, E2B, eCTD, and Identification of Medicinal Products (IDMP; ICH M5) topics. The training was attended by 102 attendees from SFDA, provincial FDAs, and industry.

**ICD-10-CM Mapping to MedDRA**

The MSSO continues investigating the business case for, and feasibility of, an ICD-10 mapping to MedDRA. Together with the ICH Secretariat, the MSSO met with a representative in the Classifications, Terminologies and Standards Department of the Health and Statistics and Informatics Group in WHO to discuss the potential of a mapping between ICD-10 and MedDRA.

In October, the MSSO completed the initial draft of an ICD-10 to MedDRA mapping. This mapping is performed at the 3rd digit level of ICD-10 and equates to approximately 2000 ICD-10 terms. This mapping will be reviewed in 2013 by stakeholders and WHO for accuracy and utility.

**SNOMED to MedDRA Mapping**

Early in 2012, the MSSO met with the UK’s MHRA to discuss their need for a SNOMED-CT to MedDRA mapping. MHRA needs to automate the conversion of EHR data (with adverse events coded in SNOMED-CT) to MedDRA. The pilot is intended to identify high frequency adverse event terms and use them as a basis
for the mapping. An expert from the UK National Health Service had been identified to provide the SNOMED-CT expertise.

The MSSO assisted MHRA by working to find the appropriate tool to create the mapping. When use of a tool developed by a US government institute did not prove feasible, a different tool (Snapper) was identified. Snapper is made available through the Commonwealth Scientific and Industrial Research Organisation (CSIRO) of Australia. In discussions with CSIRO and MHRA, the tool looks very useful to produce what is needed.

As of early 2013, MHRA and CSIRO are finalizing an agreement to use Snapper for the SNOMED-CT to MedDRA mapping. MSSO will provide clinical and MedDRA knowledge to review the results of the mapping produced by Snapper.

**MSSO ISO Certification**
In August 2012, the MSSO passed an independent re-certification audit for compliance with the ISO 9001:2008 standard for Quality Management Systems. The certification (also known as registration) period is from September 2012 to October 2015. The MSSO will have annual surveillance audits in August of the interim years to ensure continuing compliance with the standard. The ISO certification reinforces to MedDRA users, through an independent third-party, that the MSSO operates an effective quality management system that delivers a quality product.

**MedDRA and ICH Branding Initiatives**
The MSSO worked with the ICH Secretariat to strengthen the link between ICH and MedDRA in user documentation and the MSSO Web site. The user documentation was modified to include the ICH logo, new copyright and trademark statements, and modifications to some of the introductory paragraphs in the documents to better describe the role of ICH and the ICH MedDRA Management Board. This revision was completed with the release of MedDRA v15.1.

The ICH Secretariat and the MSSO worked together to create new content, or revising existing content, for the new MedDRA.org web site that is currently under development. The goal is to launch the new site in the first half of 2013.

**3.4 Outlook and Goals for 2013**
There are several development efforts planned for 2013 that are intended to continue and enhance the MSSO’s support for MedDRA users. The following is a list of the planned development efforts:
• Add more SMQs into production and support their implementation by MedDRA users
• Implement MedDRA Management Board approved recommendations from the BRP meeting on proposed revisions to the Neoplasm SOC
• Coordinate MedDRA development activities with the MedDRA Expert Panel
• Continue a more “proactive” approach to MedDRA maintenance. Gather input for broad changes from users, and, where practical, implement these proposals per existing MedDRA rules and conventions
• Enhance the MedDRA Desktop Browser
• Continue implementing a broader and more comprehensive free MedDRA training program for regulators and subscribers, and respond to requests for training from ICH Global Cooperation Group members beyond the ICH regions
• Expand MedDRA e-training on online training videos
• Continue the feasibility study of ICD-10 and MedDRA mapping
• Continue to provide input to MHRA on a mapping between SNOMED-CT and MedDRA
• Engage expert users in discussing the potential to expand product quality terms in MedDRA
• Continue to promote the use of MedDRA worldwide

**MedDRA Management Board and the Senior Members of the MSSO**
The individual members of the MedDRA Management Board are listed with their organizational affiliation.

Dr. Sébastien Goux - European Commission  
Dr. Sabine Brosch - European Commission (Alternate)  
Mrs. Hilary Vass – EFPIA  
Mrs. Claudia Lehmann – EFPIA  
Dr. Christina Winter – EFPIA (Alternate)  
Dr. Omar De Mol – EFPIA (Alternate)  
Mr. Mick Foy – MHRA - UK  
Dr. Shinichi Watanabe – MHLW  
Ms. Makiko Isozaki - MHLW (Alternate)  
Mr. Daisuke Sato - MHLW (Alternate)  
Mr. Hideyuki Kondo - MHLW (Alternate)  
Mr. Yo Tanaka – JPMA  
Dr. John (Jake) Kelsey - FDA  
Dr. Daniela Vanco - FDA (Alternate)  
Dr. Paul Lagarenne – PhRMA
Ms. JoAnn Medbery – PhRMA (Alternate)
Ms. Heather Sutcliffe – Health Canada
Dr. Christopher Turner – Health Canada (Alternate)
Mr. Osamu Handa – JMO
Mr. Reiji Tezuka - JMO (Alternate)
Dr. Odette Morin – IFPMA
Dr. Lembit Rägo – WHO Observer
Mr. Patrick W. Revelle – MedDRA MSSO
Dr. Patricia Mozzicato – MedDRA MSSO (Alternate)
Dr. Anna C. Zhao-Wong – MedDRA MSSO (Alternate)

The MedDRA MSSO is international in nature with team members who were educated in Canada, Germany, Spain, China, India, UK, and the United States. In addition to the MSSO Medical Team, the MSSO has an ongoing partnership in Japan with the MedDRA Japanese Maintenance Organization (JMO).

The following is a list of the senior staff members and their role in the MSSO.

Patrick Revelle, Director
Anna Zhao-Wong, M.D., Ph.D., Deputy Director and Manager of MedDRA Terminology Development and Services
Patricia Mozzicato, M.D., Chief Medical Officer
Brian O’Hare, Manager of Terminology Maintenance
Eva Beate-Rump, M.D., Medical Officer Germany
Tomás Moraleda Garcia, M.D., Medical Officer Spain
Savian Nicholas, M.D., Medical Officer USA
Nandini Mehrotra, M.D., Medical Analyst
Judy Harrison, M.D., Senior Medical Officer

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