

**MedDRA™ MSSO International User Group Meeting
Basil, Switzerland, 5 March 2002**

The agenda for the meeting was as follows:

1. MSSO Overview,
2. MedDRA Implementation
3. Status of Regulatory Implementation
4. Questions and Answers
5. Networking Break
6. Breakout Sessions
 - a. Use of MedDRA in Clinical Trials –
 - b. MedDRA in Pharmacovigilance –

1. Yann Doucot-Hermelin, MSSO Overview

The MedDRA subscriptions broken up by region, shows that Japan leads in subscription rate with 39%, U.S. with 35%, while the E.U lags behind with 19%, and Other, which includes Eastern Europe and many others outside ICH region, with 6%. MedDRA subscriptions by category shows the pharmaceutical industry leads in percentage with 40%, CRO follows close behind with 32%, regulatory agencies and the biotechnology industry, both come in with 10%, and the remaining 8% is comprised of academia, other related industries. MedDRA subscriptions by level shows changes in all levels since the reclassification of subscription levels which became effective the past year. Subscription rate increased for all core levels while the rate of basic subscribers decreased over the past year. Core service 1 increased to 40% from 30, core service 2 to 23%, core service 3 to 4% and core service 4 and 5, both to 5%, while basic decreased from 31% to 13%. The remaining percentage is comprised of regulatory at 9% and developer, a new level of Core service 0 for companies with revenue less than a million and not eligible for Basic. The subscribing regulators by ICH region shows EU leading with 51%, Other, which include Eastern Europe and Asia with 40%, and U.S. and Japan with 6% and 3% respectively.

Many of you are MedDRA MSSO User Group attendees so the objectives of the user group are known to you. Foremost, the user group allows for an opportunity to discuss terminology issues, policies and practices. Identifying issues that are important to our subscribers is another objective. Finally, this forum encourages communication among our subscribers and with the MSSO.

We have a web site, and you can e-mail us from the web site or directly. If you are trying to contact somebody through the MSSO, go through the help desk. The help desk tracks requests and makes sure somebody responds to you. We also send broadcast e-mails. You may request to be added to this

list through our web site. We also have a quarterly newsletter that we put on to the web site as well. The MSSO utilizes the web site to post policies and guidelines, MedDRA/ICH documentations, terminology and data sets, proposed complex changes/conventions and a multitude of other announcements for subscriber access.

As of January 1, 2001, our contract with the IFPMA was modified. When MedDRA started in 1998, a two-year clause was built in to modify the original contract. The specific points that affect subscribing to MedDRA are: basic subscriptions are now restricted to non-profit organizations and governmental groups. A system developer license has been created; like a basic license there is no change request. The core levels have been changed also. Core service 0 is a new addition for subscribers who no longer qualify for the basic subscription. A core service 5 is now available for subscribers with revenues greater than \$5 billions.

For the MedDRA version 6.0 release, several issues will be addressed for SOC review by the MSSO. First, the review of Neoplasm SOC need to be completed. In particular, the linking of the Metastatic terms and Metastases terms need review. The use of NOS will need to be rationalized, current tendency is to demote the PT with NOS at LLT level and to have the same term at the PT level without NOS. Both Swelling and Oedema will need to be reviewed. Finally, the stabilization of the database and reduction of number of internal maintenance changes will be addressed.

- A summary of changes for MedDRA 5.0 are as follows:
 - ?? Changes

○ New terms added	1574
○ Terms removed/merged	460
○ Terms renamed/modified	3596
○ PT/LLT terms promoted	169
○ Primary SOC reassigned	133

 - ?? Percentage of Terms Affected
 - 0.0% of the SOCs
 - 5.75% of the HLGTs
 - 7.25% of the HLTs
 - 11.50% of the PTs
 - 9.12% of the LLTs
 - ?? HLGT Impact
 - 4 HLGTs were added
 - 5 HLGTs were removed/merged
 - 9 HLGTs were modified/renamed
 - ?? HLT Impact
 - 37 HLTs were added
 - 39 HLTs were removed/merged
 - 46 HLTs were modified/renamed

?? PT Impact

- 807 PTs were added
- 416 PTs were removed/merged
- 220 PTs were modified/renamed

?? LLT Impact

- 726 LLTs were added
- 2816 LLTs were renamed/modified
- 169 LLTs were promoted

The future plans of the MSSO include the web distribution of the MedDRA terminology and the translations of MedDRA when available. Supplemental terms, ICD10-CM mapping and coordination with NCI on the common toxicity code (CTC) mapping are some of the issues being worked on. The MSSO has been increasing its activities in the areas of advanced MedDRA training, CRA training, implementation support, data conversion particularly in the USA for the moment, increased tool suite and the development of MedDRA computer based training (CBT). On the regulatory point of view, in Japan, MedDRA is currently accepted. As Europeans, you are aware of the dates in Europe, with electronic ADR by 1 January 2002 and all reporting by 1 January 2003. In the USA, they are still in the rule making process and are assume to be similar to the EU.

The MedDRA is currently available in English and Japanese since the beginning. Two or three years ago the EU has provided grant to respective countries to translate the terminology to French at the PT level, German at the PT level, Portuguese at the PT level and Spanish at the LLT level; all of which is to be delivered in March/April timeframe. LLTs will be delivered when ready of course, probably by the version 6.0 release. The Greek translation has been completed to the PT level. The Dutch translation is underdevelopment while both the Danish and Italian are still in the planning stage.

Our next user group is in Chicago, Illinois, USA, in conjunction with the 38th Annual DIA Meeting:

20 June 2002
Chicago, Illinois (USA)
Visit the MSSO web site for details
www.meddramsso.com

I would like to thank you; I hope that I was understandable.

Question & Answer Session

Q. When is MedDRA version 5.0 to be shipped out to subscribers?

A. MedDRA 5.0 has been shipped out on 1 March 2002 by UPS Grounds Services for continental US and Canada and Federal Express International Priority Services for all other destinations.

- Q. Has the problem with WHO regarding the integration of ICD-10 been resolved?
- A. It is the MSSO intention to work with WHO to fulfill the contractual requirement of integrating ICD-10-CM into MedDRA.
- Q. Has any dates been set by regulators on submitting PSUR or new submissions in MedDRA?
- A. Based on the agreement on mandatory dates at the 50th Pharmaceutical Committee meeting in September 2000, Single Case Reports received electronically by January 2002 and all adverse drug reaction reporting by January 2003.
- Q. What efforts are the MSSO making to get the buy in from regulators who currently are not subscribers of MedDRA, for example, South Africa and Australia, since there will be regulatory impact if submissions are done in MedDRA?
- A. The MSSO has not made a conscious effort to get to the individual regulators as pointed out. Thus far, regulators have contacted MSSO on their own for subscriptions.
- Q. How subscriptions have been sold thus far?
- A. To date 430 organizations have subscription to MedDRA from the MSSO. Another 250 organizations, which are based in Japan, have subscription through the Japanese Maintenance Organization.

2. Sabine Brosch, EMEA

In summary is an overview of the use of MedDRA in pharmacovigilance and post authorization activities with a summary on the timeframes, the mandatory use & the format for MedDRA in pharmacovigilance. The implementation timeframe that has been agreed upon by the regulators at the 50th Pharmaceutical Committee meeting in September 2000 is such that single case reports received electronically should use MedDRA by January 2002 and that MedDRA should be use for all adverse drug reaction reporting by January 2003. For mandatory use of MedDRA in pharmacovigilance in Individual Case Safety Reports (ICSRs), the agreement had been made for use based on lowest level terms in either text (i.e. English term) or code according to the regional preferences until January 2003, when codes only will be used in all regions. Regulators have approved new adoption note for guidance, which summarizes all data elements for which the use of MedDRA LLTs is required, either as English terms or codes, for electronic data submission. This note for guidance has been adopted Friday, 1 March 2002, during the EudraVigilance Telemedex Implementation Group Meeting and the guidelines should be polished very soon.

The following is a brief summarization of ICH/ICSR Sections B.1, B.2, B.4 and B.5 Characteristics:

- ~~✍~~ Require MedDRA LLT for structured information on the relevant medical history, the relevant past drug history indication, the reported cause(s) of death, the autopsy determined cause(s) of death, the relevant medical history and concurrent conditions of the parents, the relevant past drug history of parents indications, and test procedures & test results that are relevant to investigation of the patient.
- ~~✍~~ Require use of MedDRA for description of reaction term, which is the most commonly used at the moment
- ~~✍~~ Require use of MedDRA for drug information related to indication for use in the case and which reaction did reoccur.
- ~~✍~~ Require use of MedDRA for sender's diagnosis/syndrome and/or reclassification or reaction in the narrative case summary and further information section.

In addition, be advise of the requirement for use of MedDRA in Periodic Safety Update Reports (PSURs), where MedDRA preferred terms should be used in line listings and/or in summary tabulations. Referring to the compliance paper recently published on EMEA website, the non-use of a standard terminology such as MedDRA may be interpreted as noncompliance issue by the regulators.

A brief overview of the EudraVigilance database management system is as follows. As the European pharmacovigilance system, it has been in production since 5 December 2001. The system has MedDRA 4.1 fully integrated and will implement MedDRA 5.0 upon receipt of the terminology by EMEA. For future reports received electronically, strict quality control will be performed on all incoming data based on MedDRA LLTs and MedDRA version that is indicated in the ICSR. System browsing and coding tools have also been integrated; as well as data analysis tools, which are based on the complete MedDRA hierarchy, which is important for the responsibility from the EMEA & EU regulators point of view for signal detection and signal evaluation.

A brief overview on the guideline on Summary of Product Characteristics with respect to use of MedDRA as found in the Notice to Applicants is as follows. At the moment, the use of MedDRA in SPC is foreseen in section 4.8 for Undesirable Effects, where a table of adverse reactions according to a standard system organ class (SOC) such as in MedDRA , should be presented. The order in such table of adverse reaction needs to follow the MedDRA SOC list in the internationally agreed order. According to the guideline, adverse reaction descriptions should be based on the most suitable representation within MedDRA, usually at the PT level, although there may be instances where the use of the LLT term or exceptionally group terms such as HLT term may be appropriate. It is also an important factor to consider when

submitting an evaluation or new an application to present section 4.8 based on the MedDRA terminology.

The following are highlights of activities the EMEA are currently focusing on. An agreement on MedDRA terminology version control for semi-annual release is being worked on. Currently under consideration is the proposal from the MSSO, proposing that all parties should implement new releases of the terminology within a period of 60 days from release date. In addition, the implementation and management of the MedDRA Supplementary Terms during the semi-annual releases by all the regulators, is being closely looked at. In terms of MedDRA multi-lingual use, which is of great relevant to the European regulators and community, the EMEA is awaiting the availability of the French and German translations with English LLTs around the week of 11 March 2002, the Portuguese, also with English LLTs by the end of March, and Spanish, with translated LLTs in early April. The issues of providing support for the multi-lingual use of MedDRA are being closely looked at by the EMEA. EMEA is in the process of launching a EudraVigilance Drug Dictionary initiative, which is looking to in the possibility of coding medicine & products of information in the standardized way. In which extend the use of MedDRA in other SPC sections as an absolute requirement for improved future signal detection and generation tools.

In a brief view, the policy paper that had been adopted by heads of agencies at the EMEA back in November 2001, that has been sent out to marketing authorization holders for centrally authorized medicinal products. It should be release on the website very soon. A major aspect addressed in the policy paper is the recoding of legacy data retrospectively to January 1995, which is the official date of the establishment of the EMEA based on the council regulation 230993. This requires retrospective data submissions of all expedited safety reports that have been received by previous regulator parties since 1995 to EMEA and use a standard terminology, such as MedDRA. This will harmonize the approach in the coding of different terminologies in which MedDRA applies so that a harmonized comparison of data is possible.

Questions & Answers

Q. Is there any guidance for ways to carry out simple searches for answers to issues being looked at?

A. A subgroup of pharmacovigilance party working to define pre-defined query so that different users of eudravigilance systems can use these standard queries. In addition, there is possibility to perform your own group queries. Depending on the issues, you can use the predefined queries or define your own queries.

Q. When do you think this will happen?

A. The EMEA expects feedback on the policy from industry, agreement on the policy must be reached, and implementation the various aspects defined

previously in the presentation must be done so we are looking at a timeframe of 31 January 2003.

Q. Can you elaborate on what EMEA will do with the multi-lingual?

A. We would prefer the use of codes as soon as possible but at the moment, our system supports both codes and English terms. For the opening of the eudravigilance system, we will be looking at the aspect of multi-lingual use of MedDRA within the system and its support on the community level.

Q. Is there any prevalence view among regulators about the location of preferred terms within primary or secondary system organ class locations for PSURs or any other tabular data?

A. Unfortunately, at this time there has been no discussions to such detail level by the pharmacovigilance working party and there is no communication of that requirement in any official document. The issue will need to be brought up with the pharmacovigilance working party for clarification.

Q. Regarding the resubmission of all expedited reports, does this apply to all marketed products or is it limited to centrally approved products?

A. It refers to all medicinal products authorized in the community.

Q. When will papers on the legacy data conversions be available?

A. EMEA is currently preparing press release and publishing within the frame of the press release is a whole range of documentations and communications. Looking to publish the information on the website within a few weeks.

Q. Is there any clear regulation as to when E2B has to be implemented?

A. 31 January 2003 is the suggested date as recommended by the joint pilot as available in the policy papers. This date is for both E2B format and electronically to be met by both community and regulators.

Q. In regards to the recoding should it be done on the PT or LLT level?

A. Everything that refers to Individual Case Safety Report should be carried out the LLT level.

Q. Would it better to use an original version of MedDRA or the translated version when submitting?

A. The advantage of transmitting a code is that the regulatory authority can choose which MedDRA version to use, in many cases, when submitting a code, the code will appear to the authority system in its national language.

Q. Is there an initiative to educate physicians and pharmacists if the SPC is to look different due to increased use of MedDRA?

A. There is still the need for more intensive look into the use of MedDRA in the SPC. So far only in section 4.8 does it specify the use of MedDRA.

Regarding to the Drug Dictionary Initiative, we are looking further into from a coding perspective on the use of MedDRA in the different sections of the SPC.

The meeting broke into two breakout sessions: Use of MedDRA in Clinical Trials and MedDRA in Pharmacovigilance. The Meeting was adjourned after the breakout sessions.