

**MedDRA® MSSO International User Group Meeting
San Antonio, TX (USA) – 19 June 2003**

The agenda for the meeting was as follows:

1. Welcome Comments
2. MSSO Overview
3. Regulatory Update
4. Breakout Sessions
 - a. Points to Consider Document
 - b. Standardized MedDRA Queries
 - c. Versioning

I. Welcome Comments, Elizabeth d'Alelio, Manager of MSSO Customer Operations

Hello. My name is Liz d'Alelio and I am with the MSSO, we like to get started right now because we have a number of people that are trying to catch their planes this afternoon. I'd like to go over the agenda, Jim Mundell the director of the MSSO will provide an overview of what's been happening with the MSSO. Andrea Feight will be speaking from the FDA. She'll be doing what's new with the regulatory update, we'll have short networking break. We've changed our format a little; if any of you have to been at any of our User Groups in the past, we have had breakout sessions where we've gone to two different rooms and they have been running at the same time. We have had a number of people approach us wanting to be at both sessions. We'll be in here for the entire time with three mini breakout sessions and the order that they will be presented is; the Points to Consider Document, presented by JoAnn Medbery; SMQs will be presented by Patty Mozzicato; and Versioning presented by Pat Revelle. Without any further delay, let me introduce Jim Mundell, the director of the MSSO.

II. MSSO Overview, Jim Mundell, Director of MSSO

Mr. Jim Mundell presented for the main part of the meeting.

Mr. Mundell gave a brief MedDRA Update and discussed the following issues:

Transparency

MedDRA 6.1 Freeze date 27 June, available Sept 2003

Posting rejected terms

Website Bulletin Board

Subscriber involvement at Blue Ribbon Panel

Stability without Stasis

Blue Ribbon Panel

1st meeting took place 15 may 2003

Plan to do 2 meetings a year

CIOMS/MSSO

Translations

Currently available-French, German, Portuguese to the PT level
English, Japanese, Spanish to the LLT level
Dutch to the LLT Sept 2003

Technical Issues of the MSSO

Web server hack attack, no subscriber information as accessed or
Corrupted.

Merger to Northrop Grumman requires tighter web security
Changing naming conventions, trw.com to ngc.com

User Group format changed

As a result of feedback from Users

Mr. Mundell spoke of talking with the Management board about changes to the contract. In particular to resolve the issue of companies that are very large but have a pharmaceutical unit that is very small. The MSSO is also in the process of doing a pilot with the EMEA. The EMEA has an online system for filings to the EMEA. If you're a small company and can't afford your own E2B process, you can go to the EMEA website and you can type in your filing, MedDRA is embedded in that filing and you can use MedDRA there. The question was what is the licensing agreement and what has been proposed if you do less than 50 ISCRS a year, you can use the EMEA system to do your filings and you can use MedDRA for free.

Mr. Mundell concluded his presentation with the MSSO Contact information and introduced Andrea Feight from the FDA.

III. Regulatory Update, Andrea Feight, FDA

Good afternoon, I am amazed to see how many people stayed so late on a Thursday afternoon after a long week of DIA meeting. My name is Andea Feight, I'm from the FDA and I am going to talk a little about current status of MedDRA at the FDA and then move on to how it fits within the proposed rule. Along the way, I am going to mention a little about E-sub, we are encouraging E-sub and then talk about the opportunities and challenges that I've presented on Monday. Could I get a show of hands of how many people were about to catch the Monday session that I was in, ok about a third of you so I am going to go over those quickly and then perhaps open it up for a few questions.

Just quickly the current status for FDA: we've implemented MedDRA along with the new adverse event reporting system in November 1997 and in that process we did migrate about 1.5 million reports from the old spontaneous reporting system, we certainly didn't want to have two systems on go at once so we did bring old records. In order to do that we performed a one-to-one mapping of the COSTART codes to the MedDRA preferred terms of MedDRA version 1.9. Since then we've entered about 1.5 million reports coded in MedDRA into the database so now we're at about 3 million total. We are entering those using MedDRA

preferred terms. We're receiving both paper and electronic submissions and when we do receive paper we of course code those from the start. The process is data entry, double data entry to catch any mistakes perhaps in the actual transposing from paper to electronic. MedDRA coding is then done followed by quality control of the coding. Thus a lengthy process for reports coming in on paper. For those reports that are submitted electronically, they are not as resource intensive and in fact those that are pre-coded in MedDRA can go right into MedDRA quality control so saving us time and resources. Since we're working with contractors, it's important that we keep our FDA contract level to a minimum otherwise we'd have all kinds of people outside the agency looking at us.

We up versioned to MedDRA 6.0 on May 19, which was quite a feat. From the time the version was released to the time that we up versioned, it took about a little bit over two months and during this up version we went from MedDRA 4.0 to 6, which was done in a step-wise fashion with our AERS contractor. We're now hoping to do the up versioning twice a year and of course this involves expenditure of funds, and sometime things have get put aside for other priorities. But our intent is to up version from now on twice a year. The trend is still upward in the number of reports that we receive. If we get everything implemented in the final SADR rule that is now on the street, we're going to see that skyrocket and so that really why it's really important for us to move from paper base reports to electronic reports because the costs involved in entering a report from paper to the final step of the database entry is very expensive.

This schematic shows when the four companies that we're working with who were currently submitting in MedDRA began submitting electronically and then began submitting electronically with MedDRA coding; four very active companies and we're working with some additional companies who are submitting but not yet in MedDRA. This is analysis done recently as one of the activities of our internal coding group. We looked at a number of reports that were entered into AERS in 2002 and just looked at how many terms were reported per report and so by far, over three quarters less, than five terms are included in the database. In fact 93% of the reports have less than ten terms but we do have the occasional outliers where we get as many as thirty codes that describe the adverse reaction. We've actually looked at some of these reports before and try to determine somehow we could streamline the process but unfortunately have determined that it's not possible and not worth it after our analysis.

I just want to emphasize a few things about electronic submission: First I want to say this is not addressed in the proposed SDAR rule; you might recall that when MedDRA was first mentioned at all by FDA in a publication, it came out in a federal registrar announcement back in November 1998, as an advanced notice of proposed rule making, and in that advanced notice, it was actually an E-sub advanced notice, so it's sometimes confusing to some people. Some may not realize that MedDRA was pulled out of that electronic submission advanced

notice and put into the SDAR rule because it was felt that was the quickest way to get it out into a final rule rather than the E-sub, which is still not published.

In electronic submission we're accommodating through MedDRA 6.0 in addition from this last upgrade of the AERS system, we're now able to accommodate either code or text but more and more we're moving towards the code, whereas before we're asking for text; just as Europe is asking for code. A few words about coding in these electronic submissions, the key point is the narrative is the basis for the coding if we receive reports not coded in MedDRA, but if the company reports with their terms already included then we use the narrative as the basis for quality control of that report.

Here are a few things that various FDA staff are participating in: the Management Board, with my involving for CDER and Ann Gaines for CBER Biologics; in the past we've had Mac Lumpkin on the board, also Peter Honig and Miles Braun. MedDRA Terms Selection Points to Consider, in this working group we have a couple of people involved now, Toni Piazza-Hepp, Ann Gaines, I was a part of this until the last meeting that was held, I've rotated off. We've also had Brad Lisa, from the pre-approval side of the house but when he moved on to counter-terrorism, we've had to fill in that vacancy, so at the next meeting in Brussels, we'll have Jack Calci attending from the office of new drugs, our other person is Steve Kelsey, from the pre-approval side. We also have people participating in the new Standardized MedDRA Queries working group. When the group first formed, Melissa took with her some of the saved searches developed within FDA in-house to be incorporated. We are glad that the MSSO will be maintaining these because that will save us a lot of work. We also have a MedDRA person on E2B implementation working group to modify E2B such that it will accommodate both levels of the terminology for each MedDRA required field; we hope to be successful there but there is some resistance there so if you have any way to influence what's going on in that working group through your channels, I encourage you to do that.

Now on to the SADR, which came out on April 14th, the original comment period was to be July but industry asked for the extension of the comment period that's why it's extended to October 14th. In the proposed rule it does require that the SADR each be coded at the PT level for the ICSRs, this also applies to any SADR associated with a Medication Error. In addition, it does say that the agency intends to grant waivers on MedDRA requirement for small companies and it would be on a case-by-case basis. Along the same line of small companies, the small business analysis was done. As well as the economic impact analysis for the MedDRA implementation was done for the industry and included in the rule, which outlined both the one-time costs associated with it and some of the recurring costs. The proposed rule addresses the potential savings in clinical trial management if MedDRA is used during drug development as well as postmarket safety reporting. As the rule began working its way upward, this was added some time after we had last seen it, the proposed implementation

scheme is that MedDRA requirement to effect 1 year following Federal Register publication date of FINAL rule thereby giving industry a cushion to get MedDRA implemented if they haven't already done so. Often in a proposed rule, FDA invites comment and has to respond to the comment, even from parties not subject to SADR reporting requirements regarding any unintended potential impact. In addition, we also invite comment on potential approaches for facilitating seamless cross-standard communications, such as mapping between alternative terminologies and MedDRA.

I am going to run through the challenges that are ongoing since I have already gone through them the other day. Maintaining internal coding SOPs; when we first started using MedDRA, we didn't have any guidance or any lessons learned from anybody else to go on so we developed internal coding principals, which then had been shared with the MedDRA Points to Consider working group, we're now using the results of the working group to revise our internal principals. Just to point out, when FDA are asked where people should go for guidance, we point them to the ICH document Points to Consider. The FDA expectation on company coding is another challenge; we do perform quality control on coded reports received. Earlier this year, we looked at the reports from the four companies that are submitting, to determine what the criteria are for determining what is acceptable and what are not, such as missing medical concepts in the processing of coding or using a term that is not as specific as available in MedDRA. How to code indications for product use and how to retrieve those is another challenge; we are coding them when we receive them from manufacturers and feel that this is one of the more challenging areas in coding. Training our reviewers, particularly OND reviewers, is an ongoing challenge.

Another issue is the use in clinical trial AE reporting. Two issues that impact each other are the up versioning process of each MedDRA release and its impact on data mining. Managing change requests, both the process and the content is an issue. The LLT versus PT term as the level of coding and transmission is an issue, if we had to do it over again; I believe we would have chosen the LLT as the level of data entry in transmission. Again, the E2BM specification is a challenge because of the ability to alter the specifications. Medication Errors classification is an ongoing issue for us; we have a proposal to be presenting to the MedDRA management board to consider for inclusion of these medication errors terms in the MedDRA terminology to help distinguish MedDRA as a regulatory reporting terminology and help set it aside from some of the other ones available out there.

As with these challenges, these are some of the opportunities. As it has pointed out several times cost savings from e-sub and pre-coded is definitely an opportunity. The proposed SADR rule is another one now that it is finally out on the street. The MedDRA Term Selection: Points to Consider document as a definite opportunity because we feel that it is going to help industry submit to us in a way that is more consistent which will help us retrieve our reports in a more

uniformed fashion. Again, the CIOMS working group for the Standardized MedDRA Queries is an opportunity. The E2BM Implementation working group, we're hoping they will provide guidance to the user community and resolve the LLT/PT duality needed in all fields specifying MedDRA. If you haven't seen the proposed SADR report, visit these websites:

<http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf> for rule itself and <http://www.fda.gov/oc/initiatives/barcode-sadr> for the fact sheet and Qs & As.

The main portion of the meeting was concluded with a reminder that the presentations would be posted on the web for download. A networking break for 20 minutes was taken as preparations for the breakout sessions were conducted.

IV. Points to Consider, Joann Medbery, RN Training, Implementation Specialist

There is a still lot of confusion about the Points to Consider document regarding what it is and why we need to read it. What it is an ICH endorsed document? It was built as a companion document to MedDRA because what you get as a MedDRA subscriber is 12 ASCII files and an Intro Guide which doesn't tell you how to use MedDRA nor how to do coding. This document is designed to be updated as MedDRA changes; we're hoping to reach a point where it gets updated once a year but until then it's a working document because it changes as each version of MedDRA is released. This is why the document was not taken through the ICH step process, thus never formally an ICH document but rather ICH endorsed document.

The document is maintained by the working group, which is endorsed by the ICH steering committee. The working group is made up of representatives from both the regulatory community and those they regulate, thereby the group is very diverse. The group tries to address both pre-marketing and post-marketing data in the document. The objectives of the document are such: promoting consistent term selection, consistency in term selection which will promote medical accuracy when using MedDRA, to share data worldwide, to facilitate a common understanding of data shared across and/or between academic, commercial and regulatory entities, to provide term selection advice where it is needed either for a business purpose or regulatory requirement in general but not intending to communicate specific regulatory requirement. The document does not state what "shall" be done but rather provides various options to choose from.

The scope of the document currently addresses term selection for ADR/AEs, Medical history, social history, indications, Investigations or the testing system organ class. In some cases we can provide a blanket guidance to cover all these different types of data collections. In other cases, they are a little different so we need to provide some different guidance. We hope the document provides a framework to foster consistent use of MedDRA for data input and retrieval, with the end result allowing for medically meaningful review and analysis of clinical

data. The working group recognizes that this document is not able to address every possible situation; that medical judgment has to play a part in this as well as common sense.

Data quality is an important issue in the document. Good MedDRA term selection is best accomplished with good, clear initial data. It is necessary to obtain clarification of data that are ambiguous, confusion or unintelligible, therefore, the quality of the information originally reported directly impacts the quality of data output. The proper term selection allows for systematic and consistent recording, interpretation and comparison of data. The key is quality of the information originally reported which directly impacts the quality of the data output. Some of the things covered in the document, again what it is striving for is consistency, are provisional diagnoses, how to manage/handle death, conflicting/ambiguous/vague information, combination terms, body site versus event specificity, location versus infectious agent, pre-existing medical conditions and congenital terms, medical/surgical procedures and investigations or the testing of system organ class. In addition to the coverage of these items medication/administration errors and incidental exposures, overdose/toxicity/poisonings (a hot topic for recent revision due partly to MedDRA changes and to achieve consistency from among the colleagues), drug interactions as well as no adverse effect present, unexpected therapeutic effect, modification of effect of the drug and the social circumstances, medical and/or social history data fields and finally, indication for product use.

Data quality is a key bullet to the document, so anybody using MedDRA need to really set up their internal process to have careful design of data collection forms; provide training to all individuals involved in the data collection and follow-up processes to ensure the quality of data, to be more precise, concise medical information for better data output.

Quality assurance is another key bullet, where tools such as auto-encoders may be helpful but there must be human intervention; to promote consistent term selection, organizations are encouraged to document their selection strategies, methods and quality assurance procedures in coding guidelines and these should be consistent with the points to consider document itself; ensure term selection should be reviewed by qualified individual who has medical history and/or training and should understand MedDRA and its use. What's new for the document, the working group will be meeting in July to update the document to reflect MedDRA 6.0. We will be soliciting feedback from you on the current document very shortly, comments will be accepted until 10 July 2003. The document is available at these websites:

<http://www.ich.org/pdf/ICH/MedDRA%20Points%20to%20Consider%203.pdf>

or

http://www.meddransso.com/newwebaug2001/meddransso/whatsnew/pdfFiles/ptc_3.1_final.pdf.

V. Standardized MedDRA Queries, Dr. Patricia Mozzicato, MSSO US Medical Officer

I am kind of the fish who swims up stream sometimes in the MSSO so I am going to break a little bit with the format up to now. I am going to give you a very brief presentation, mainly because Jim has already mentioned most of the points I was going to talk about in his opening remarks. I'll expand upon a few of them. Also I am going to leave questions towards the end and there'll be questions and the questions will be directed at you since I am more interested in hearing you talk to each other. My presentation is on the standardized MedDRA queries (SMQs), hopefully you will not leave here more confused but part of the thing we have to get passed first is the names, acronyms and initials so forth. Those of you who have in your hands the latest MedDRA Messenger, you see an article that I wrote there on MAGs, well SMQs have evolved from MAGs, which were the MedDRA Analytical Groupings which were introduced for the time last year at another User Group meeting. However, they have also evolved from the Standardized Search Queries (SSQs) which were created by a CIOMS working group. We realized part way through the process that the CIOMS SSQs and the MAGs initiatives we're really trying to come to the same thing so it made no sense to do these in separate groupings. Now we are part of the CIOMS working group developing the SMQs, which stands for the Standardized MedDRA Queries. The SMQ is defined as grouping of terms from one or more MedDRA System Organ Class (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification. The terms included may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to the medical condition or area of interest. The terms can be at any level of the terminology, the only exclusion are the lowest level terms (LLTs) that are not subordinated to an included preferred term (PT). Again to remind you how these things came about, they are now being developed by a CIOMS working group, which as Jim mentioned has MSSO representation. The ownership of the SMQs is the same as the terminology itself, which is the IFPMA. The SMQs will be maintained and distributed by the MSSO once the CIOMS working group has developed them. The file format has been developed and I am going to excuse myself from any technical questions regarding the file format and refer those to my colleague Mr. Pat Revelle who can probably answer those questions for you.

Along with first SMQs that we expect to release with MedDRA 6.1, besides kind of testing them if you will, field-testing them by using them, we also need to get your comments and feedback on the file format to see if we can improve those at all. There is a whole issue of versioning of SMQs. SMQs are created at a certain static point in time, the first ones will be created and released for MedDRA 6.1. They obviously have versioning, maintaining and upkeep issues themselves just as the terminology does so those strategies are under development, and Pat Revelle will talk a little more about that versioning of SMQs when he talks about versioning in general. Just to let you know what SMQs are currently under

development, the CIOMS working group started out with a list of about 95 potential SMQ topics (SSQs at that time), the MSSO had about 85 potential MAGs, almost the same number. So the SMQs are being prioritized as they come out, trying to hit the hot button safety issues first. These are the ones currently considered and developed under the working group, those four with the asterisk, are being targeted for version MedDRA 6.1 release: Anaphylactic reaction, Acute renal failure, Rhabdomyolysis/myopathy and Torsades/QT prolongation. Part of the format of the SMQ will be the definition as well as a source of that definition.

Now SMQs probably remind you a little bit of some other structure related to MedDRA, which are SSCs. In cases where you want a sensitive tool pick up cases where it really isn't relevant but you want make sure you don't miss any so that will be the concept of a broad SMQ. There'll be times when you're not interested in the cases that may fall off the edges, you really want thing fairly targeted to that something area of interest, that would be an SMQ narrow search. Here is an example of a SMQ under development, Acute Renal Failure, where you can see the different results for the Narrow terms and the Broad terms for the two types of searches. Along with the SMQs coming out, methodology papers are also being developed by the CIOMS working group that we hope to have in the completed form at the time of the release of the SMQs.

VI. Versioning, Patrick Revelle, Deputy Director of MSSO

Versioning is an issue that I think because it has multiple levels, has been a continuing question, as you can see it in the other discussions that we're having. Obviously back by popular demand, every time we have a User Group, people say could you please speak about versioning because I think people are coming to this not only from the post-marketing side, which I think we've gotten some data points now, which I'll talk about in a little bit. But now it's starting to hit the clinical trial side so maybe the answer isn't completely the same for both. Now with the introduction with the SMQs, there is the question of versioning with those as well. To some extent it prolongs the versioning discussion.

This gives a little bit of the background with what we've done in the past, these documents are still available on the website for you to look at. We've developed a series of best practice papers that address versioning for clinical trials, post-market versioning. The idea was similar to the Points to Consider document, which was to harmonize the use/versioning of MedDRA; the MSSO Management Board has endorsed the papers and regulators are starting to reference them in their guidance. The following MSSO recommendations have been accepted: Regarding post-market/safety reporting, reporting is done with the latest version of MedDRA, when new version is released, the data do not need to be re-coded with the understanding of the impacts the new version may have on the data, and 2 months from release date for the mandatory use of new releases. Regarding clinical trials a paper was developed that had 6 different options of freezing

versions of MedDRA for a trial or set of trials. The MSSO recommends two of the most effective options, which are freezing the version at the beginning of each trial and optionally re-coding at the conclusion of the trial based on study criteria (option 5) or recoding all trial data with each version as each version is released (option 6). Most companies have found that implementing option 6 based on the feedback to the MSSO from a survey we conducted is viable. These points you would consider at a minimum regarding the impacts of new versions of MedDRA; at the coding levels of MedDRA, the LLT and PT terms are never deleted but they can change in subsequent releases. This should be considered like currency changes, moved in hierarchy structure, gain/lose a multi-axial link, change primary SOC or new terms added. Another Best Practice is the review of the Supplemental terms. These terms have been approved for inclusion in the next release and are available on the MSSO core web page, they should be reviewed periodically. It is easier to review a small number of changes at a time rather than at the release when you're dealing with tens of thousand of terms.

In regards to versioning and SMQs, which will be provided with each release of MedDRA we hope to begin with MedDRA 6.1, new versions of SMQs will reference the terms of MedDRA that is specific to that release. This will take advantage of new terms and will stay synchronized with hierarchy changes for that version and we recommend to use SMQs on data that has been coded with the same version of MedDRA.

An article, "MedDRA Implementation: An Informal Industry Poll" authored by Marlo Ross, published in SCDM Newsletter Data Basic, volume 9, Number 1, Spring 2003, is fairly useful for its purposes, though some of the information may be dated, it provides actual subscriber experience based on a poll conducted within the Informal US MedDRA User Group. Sixty-four respondents from 29 biopharmaceutical companies responded to the 30 questions posed regarding MedDRA implementation status and approaches used. The few questions and responses presented here have specific implications to versioning, which affects both the clinical side and the post-market side at the same time (see slides 12-14). At this point I think I need to cut it off because we are into overtime, but I very much appreciate your participation and look forward to seeing you at our next meeting, thank you.