

MedDRA™ MSSO International User Group Meeting Chicago, Illinois (USA) - 20 June 2002

The agenda for the meeting was as follows:

1. MSSO Overview
2. Status of Regulatory Implementation
3. Questions and Answers
4. Networking Break
5. Breakout Sessions
 - a. Overcoming MedDRA Implementation Challenges –
 - b. Why Your Data Looks Different –

1. Jim Mundell, MSSO Overview

After reviewing the agenda for the meeting, the MSSO presented general statistics about the MSSO and MedDRA.

The User Group meetings give the MSSO a chance to come to you; we go once to each ICH region, come this November, we'll be in Japan. We encourage and want to get comments, feedback, information either through questions and answers, informal discussions. The breakout sessions are a result of those types of discussions where people have asked for a more involvement in an open discussion, instead of sitting there and listening to information. Times have been expanded of the breakout sessions to give people more of a chance to meet with fellow subscribers. Communication is the primary goal with you as the subscriber. Again emphasizing communication, the website is there for the subscriber. The MSSO is trying to post things that are going on, conferences we are involved with, training activities that are going on, questions about the terminology that have been raised, what we do about a specific issue, etc. and we look for the subscribers to comment back so that would help us with our guidance. In some cases, we really don't get back sufficient number of comments back to take any action and so they get tabled until somebody else raises the case again in the future. In addition the MSSO puts out the newsletter, the Messenger. The MSSO does email messages. If you are not getting email messages from the MSSO about postings on the website or about questions or releases and such, go to the website, there is a place where you can request to be added to the mailing list so that you will be included in our email broadcast messages. On the website, right now we post policies, we have guidelines that go up for comments, we are starting with the 5.0 release to incorporate those guidelines in the Introductory Guide and the Users Manual so that it becomes part of an established reference for people. There are certain ICH documents that we are given to put on the website such as the Points to Consider document, that is not an MSSO generated document but it comes from the ICH Expert Working group, it's also posted on the IFPMA website. .

We want to hear from you so that we can make sure that we have information before a final decision is made. Just because we posted a proposal and it says it's a proposal, does not mean this is what's going to happen. This is how we use the website, we put out information and try to get as many people as we can to make their comments.

We also post on the website the consecutive files, the different files of the changes that are going on in MedDRA (provisional or supplemental files depending on what you are used to referring to them as). Again that is so you know what is going on in the change with the terminology, you can pull those files, they are in ascii format, they are not in pdf format so if you have a batch load program, you can manipulate them and load them into your data set. It also let you see if we have made a change that you religiously disagree with, then let us know. This will gives us another step to make sure we are doing the right things.

The next issue addressed was translation information. We are holding the translations that we have been given. These translations were generated by the different regulatory authorities in the EU and were passed on to us. We have French, German, Spanish and Portuguese. With the exception of the Spanish, they are all only down to the PT level. The Spanish goes to the LLT level. We would like to make those available but we are waiting for the property rights to be signed off on. We have permission distribute Portuguese and Spanish. Next week we will probably make Portuguese and Spanish available. We have sent out emails asking people to verify if they want one of these two languages so we could ship to them on a CD. We were also going to make them available on website, I don't know if any of you remember the flurry of emails maybe a year or so ago about having website issues; but that was the result of a hacker who kept attaching our website and causing trouble so we had to take the website down for a while to add additional security measures. We had another incident recently but it turned out it wasn't a hacker but rather it had to do with Microsoft, it was because of conflicting Microsoft programs on there that was causing the problems. We have that straightened out now so hopefully we can get back to using the website for distribution.

Every now and then we get comment back from our folks who are giving training or going out meeting clients where someone will make a comment that "ah, the MSSO, they never call you back or I call the helpdesk and nobody answers," this concerns me because I am responsible for that, but when I try to follow up on it and if I am lucky enough to find out who said that, when I well "who you were trying to call," there's never any response. I don't know who's being called, how they are calling or if they are even calling the right number. I found out there are 3 helpdesks involved at different times with the MSSO. There's a primary helpdesk, but then there's the AutoCode helpdesk and there's the Biopharm helpdesk, so there's plenty room for confusion. If any of you, or any of your friends or you hear of any of your

friends saying they never return my call, please tell them to send an email to the MSSO or call Liz d'Alelio, there was an email that had been put out about it and it's even in the Messenger newsletter, there's a section about communication, it says if you have problems call Liz d'Alelio, she is the lady who started the meeting; she is in charge of Customer Operations and the helpdesk, it has her phone number and email address. Please call, tell her who they are trying to get in touch with and what phone number or email address being used so we can find out if this is really an issue or is it a confusion caused by misspelled name or wrong number or something like that. That would help me tremendously if you could pass that information along to your friends.

I would like to talk about contract changes this year, actually it was last year, but also this year; with the start of 2001 the contract went through a renegotiation which was part of the original contract. It stated that after two years of service because nobody had really done this before and nobody was sure of what the impact was going to be, it was agreed that after 2 years of running the contract, TRW and the IFPMA would sit down and talk about things that worked and things that didn't really work and try to fix them. As a result, it was agreed that the definition of Basic was never provided and as a result we had over 50% of the subscribers buying Basic and that was making it very difficult to try to meet our obligations. So the definition was changed to restrict it to non-profit and governmental groups. In order to meet the needs off those companies that were primarily Systems we added a System Developer license. We also added in 2001 a Core Level 5. This was because nobody anticipated all the mergers that were going to take place. We lost a large percentage of our first year and second year subscriber base because they disappeared; they became one company. So another level was created to try to offset that loss of subscribers. Last year we created a Core level 0, this was again in response to information from meetings like this and email messages and contact with subscribers concerned about revenues and prices and what can be done and what can be affordable. So this was created for companies with revenues less than a million dollars.

As many of you may recall in release 4.0 or setting up for release 4.0, the MSSO was given permission to do a complete quality review of the terminology and we did that, and it took a long time, a lot of effort was put into it, several outside groups were involved with it as well. We began making a lot of changes, now if you look at it, some of the changes even though you were seeing thousands and thousands of changes we're talking about switching primary and secondary, we're talking about correcting spelling issues or moving some terms from one HLT to another HLT, but there were holes filled where terms just didn't exist, you couldn't code to things, we did a lot of that. But it also didn't all make it in, there was so much to do that we couldn't get it all done for the 4.0 release, so those changes rolled on to the 4.1 release and finished up most of it in the 5.0 release that just came out.

There were a few more changes that rolling into the 5.1 release. But those are all the results of this earlier review, and again with that review, we posted everything we were doing on the website and solicited companies to comment on them. Many companies did. Those comments were taken into consideration and implementation, and in some cases were modified based on the comments received from subscribers.

The NOS issue sometimes you will hear it as the NEC/NOS issue, and it's originally was proposed that way, has to do with NOS/NEC for consistency. A lot of the 4.0 changes had to do consistency, how come I got to remember 5 different ways to query the same thing. You know if you had consistent wording I would be able to get better queries with fewer variations in them. What we found was that NOS/NEC were being used inconsistently for the rule that was proposed from the working groups as well as just what levels they were applied to. It was agreed that NEC based on comments back and medical review should be a grouping term above the PT level and that was implemented and that was completed in previous releases. The question that was left over was the NOS and we were preparing to implement the NOS for the 4.1 when we posted the proposition again, when we got a proposition back to delete all NOS. So we posted that and we only got back 6 responses, out of 470 some subscribing companies. that was not an overwhelming response that would give us any kind of confidence that we should do this.

We also got comments saying whatever we did do with NOS would have a tremendous impact on everyone because there are so many of them and that people have coded them and captured them that we would need to announce this at least 6 months prior to implementing for a release so that people have time to make database analysis and application adjustments if necessary. In September the MSSO Management Board will be meeting and one of the agenda topics is what to do with the NOS. One suggestion is do nothing just leave the way it is and let people use it for awhile and see if it causes problems. Another is to make all NOS non-current and demote them LLTs and replace them with non-NOS terms. I don't know if somebody will bring a third option at this point but it will be discussed in September at the Management Board meeting, the results of the discussion will be published on the website as far as we're not going to do anything with this or we are going to do something and this is the plan that we will follow and this is the target release that it will be implemented for.

The same thing is this topic about Neoplasm, when we did our review, as I said we had outside groups involved. The Cancer Institute was involved in providing information about the Neoplasm SOC. After we were completed other people have come back and didn't think there was enough of a review done on that and they wanted to provide additional information. What we have agreed to do is take the additional information that's come in or will be coming in and we will analyze it, we will then share it with the Cancer Institute

for comments and we will then post the information on the website for comments. As far as this is the proposed plan on implementing changes to the Neoplasm SOC. As way of giving you a target date, this would targeted for release for 6.0 or 7.0, depending if it is a complex change or just minor changes, maybe the 6.1 release.

This then ties to the bottom bullet about stabilization of the terminology which is another reason I don't want to make changes and make more changes, without everyone knowing what it is and when it's coming. Before I talk about the stabilization, the modified term one if you are not familiar with it, is there a lot of aggravated terms, worsening terms, I believe this was in your presentation yesterday, the counts of some of these, we had again posted several variations of proposals, don't allow them, get rid of them, if you are not aware of it originally, it says in our contract actually and in the Intro Guide that only medically significant modifiers would be accepted. Unfortunately, that doesn't tell you what it means, what makes it medically significant and what one person thinks is medically significant some body else may disagree completely and say that was silly why did you take that. There has been a debate of what to do with it. Again outside groups were involved, this goes back to the 4.0 release. The EFPIA group in Europe wanted to be part of that discussion, they took it on as topic and discussed, they proposed a White Paper to the Management Board about it, they proposed coming up with a separate list of modifiers, a discrete list of modifiers that you would say since, in theory most of the terms in MedDRA can be modified, multiple times, can it be acute, can it chronic, can it be aggravated, can it be exacerbated, is it worsening, and then you can get into different things, is it a family history, is it recurring, you can just go overboard with it. To put in consistently all the terms you have expanded this what everybody says is already 'too big' terminology of 60 thousand terms to what a million terms. So one of the proposals was to create another way of saying somewhat like CTC codes, here's the base event, as is stage 1, 2, 3, or 4. But to do would require modifying E2B at this point. E2B is scheduled to consider anything. So it's been put on E2B's list of considerations by the Management Board secretary for the IFPMA as a consideration topic if and when they ever do reconvene.

In the mean time, instead of saying we're not going to accept an aggravated term will apply the standard MedDRA rule that if you submit an aggravated term we would consider it if you provided justification for it. And it's not because it's not there, it's not because I need it, it's what means this medically significant to you and then we would consider it, and if the medical doctors. We have a medical doctor in France, Germany, Spain, in fact today the breakout session next door will be Dr. Moraleda Garcia and he is our Spanish doctor, our French Doctor is here for part of the day actually over in that corner, Dr. Doucot-Hermelin, and we also have a medical officer in the United States and in Japan; and it's a combination of these things that

decides whether it gets in, it's not just the MSSO arbitrarily flipping it down the stairs and see if it makes it all the way.

These next slides I am not going to talk about, are here for your reference, it's statistics for the 5.0 release about the percentage of changes and number of changes.

Future plans for the MSSO. Again, as we talked earlier about it; we're starting with the translation distribution on the web. That's just a precursor, of trying to make MedDRA available for distribution on the web. Supplemental terms are available on the web already. ICD-10 and the NCI on CTC mappings, we have an ongoing relationship with NCI, we have a meeting coming up in July to talk about CTC mappings. We've been doing 5.0 mapping of the CTC codes for them already and that's been done. I had a meeting with Ralph Edwards of Uppsala Monitoring Center, several weeks ago to talk about ICD-10 mappings and a collaborative effort in that relationship.

It seems to me for the past few years the focus has been on what is MedDRA, how do I put it in my machine. But where we need to be thinking is how do I get the benefits of MedDRA? That's through data analysis and what structures are best suited for this and there has been a lot of discussion lately, some members of CIOMS have proposed CIOMS involvement in looking at the SSC, the special search category as a method of providing signal detection, we ourselves have been discussion that with people independently. We have talked with World Health about it. There is also in my view, I would like to see that MedDRA is maintained as what MedDRA is but that doesn't prevent somebody like World Health or even you know John's software house to come up with a pharmacovigilance structure that can be related into the existing MedDRA. It won't impact those people that don't care about that because they have the plain MedDRA but you can additional structure in that are specifically geared to an analysis task, be it pharmacovigilance, HIV studies, neoplasm issues for CTC. And it opens a whole range of how do you data mine this without really reengineering the whole terminology. Say there is the base terminology, think of how you engineer the tools that use it and bring out the data. And that's hopefully will come up more next-door in the discussion on data analysis. This is a just general thing that is going on; the regulatory mandates, I think everybody knows Japan is accepting them. The last time I heard they said at least 30% of their reports are in MedDRA. I got not an official estimate that they thought it was now closer to 45% maybe even 50%. Sabine will be talking about the EU. The US if you saw the email that went out, the rule has been signed off by DHHS and has gone back to the OMB and now is in the 90 day cycle so we will what happens from there. Status of translations, just that we have the translations, we only have permission to distribute Spanish and Portuguese. The Spanish because with all of the LLTs, it's taking a while to try to review it

for consistency but the EMEA says that they would approve distributing down to the PT level which means LLTs will be in English at this point, just to get the translation for people to start looking at them and evaluating them. Other ones are in the works and being considered. Our next User Group meeting will be held in Tokyo as I said in November.

2. Sabine Brosch, Status of Regulatory Implementation

Good afternoon, I would like to summarize a little bit the activities with regards to MedDRA from the EU perspective and I would like to thank the MedDRA MSSO for giving me the possibility to summarize the activities here today. I would also like to encourage you if you have particular questions that you would like to have them addressed then please ask them and I hope we can discuss them very openly. I have participated the first time at the MedDRA User Group in Basel back in March this year. For me this was a very important and a very useful meeting because we had after my presentation a lot of feedback and a lot of input, especially from the colleagues from pharmaceutical industry and I think that is very important for the regulators to have your feedback in order to learn what we need to consider and what needs to be taken into account in the regulatory process so that we are all happy and familiar with what we are doing. So in my presentation today what I would like to give you very briefly an overview of the use of MedDRA in the pharmacovigilance post authorization activities, the timeframe the team has pointed out already, the mandatory use and the format that we are anticipating in Europe and also a short description of our database management system and how we are going to MedDRA in it.

And then another important topic, which has raised a lot of questions, is the use of MedDRA in SPCs. You know that we have agreed the implementation timeframe in the European community for MedDRA and it has been discussed and agreed in the pharmaceutical committee. The committee is a very important forum, which is managed by the European Commission, and all the member state authorities are also represented there. And in September 2000, they have agreed on the timeframes, indicating that Single Case Reports received electronically should be coded in MedDRA as of January 2002 and then all Adverse Drug Reaction reporting should take place using MedDRA as of January 2003. With regards to the mandatory use of MedDRA in pharmacovigilance, we have now release a note for guidance; it is technical a note for guidance for the electronic transmission of individual case safety reports, it has been adopted in March in our telematic implementation group, the EUDRA Vigilance Telematic Implementation Group and this guidance document is now available at the EMEA website and it summarizes the use of MedDRA for electronic data transmission in the area of pharmacovigilance and post authorization activities and you will find there the specifications that for Individual Case Safety Reports, MedDRA Lowest

Level Terms should be used in the EU either as text at the moment or as code and you know that the ICH, E2BM and working groups have recommended that as of January 2003 only codes should be used for Adverse Drug Reaction reporting in all regions. So that is not something that we have as a particular requirement from the European Union but that was a recommendation from the ICH, E2B and working groups.

I have tried to summarize for you here very briefly to give an overview on all the data elements in the ICSR where we will require the use of MedDRA. Also in the new notes for guidance that we have published you will have a clear description also with the data elements based on the E2B requirements. So we ask the use of MedDRA on the Lowest Level Term for structured information relevant to the medical history, for past the drug history indication, then if there was a cause of death, we would also like to have that coded in MedDRA, autopsy-determined cause(s) of death, also here MedDRA should be used the relevant medical history of the parents, for instance if you have a parent child report, and the same applies to the indication of the parent child report. The main section of course is the use of MedDRA for the description of the reactions and also in section of the drug information we ask the use of MedDRA for indications or for reactions that may have recurred. Finally, in the case for the narrative section, we have the sender's reclassification of reaction, where we also recommend the use of MedDRA; as well also for the testing investigations that have been performed with the patient. For the tests, let me explain to you if you go to the relevant section in ICH E2BM, with regards to the tests and procedures, you will find there is a field, which says structured information on the tests. And we would like to have the tests there coded in MedDRA but you will have a field in this section which allows you to provide in free text format a full description of the test or investigations that has been performed on the patient. For the Periodic Safety Update Reports, at the moment we have not yet define any data format for electronic transmission of periodic safety update reports. But from the pharmacovigilance working party there is the recommendation that when you prepare periodic safety update reports the summary tabulations should be prepared using MedDRA preferred terms. With regards to our pharmacovigilance system which we have established at the European community level, the EUDRA vigilance system, we have currently implemented MedDRA version 5.0 and what we are doing when we receive an individual case safety report electronically, our system checks automatically for first of all for the version of MedDRA that has been used, and you know that in DTT version 2.1 you have the possibility to indicate the MedDRA version that you have used for the coding. So when you look in our guidance documents we have recommended for the regular transmission for the individual case safety reports always the latest version of MedDRA should be used. This will be automatically checked by our system so the version that is indicated but also the terminology so if the MedDRA LLTs are really LLTs or something else. In the DDT 2.1 you have also the possibility to indicate the

preferred terms and also to explain a little bit to you we have in our guidance document, we specified that only the LLT term should be provided. We had several questions from pharmaceutical companies with regard to this requirement. We do not reject reports if you put both the PT and the LLT levels so it's not a problem for us but we do a consistency check as well. We have seen in several reports that for instance the PTs and the LLTs that have been provided to some times not match. So it is important, this has been identified during the testing if you specify both levels than you should also make sure they correlate to each other. Another important aspect in our pharmacovigilance system is the browsing and coding tool. Also, I think that has pointed out by Jim, it is a very important aspect to have data analysis tools available. I think it is a big advantage of MedDRA to have the possibility later on to have a validated approach for data analysis. Here we would also like to work together closely with the MedDRA MSSO but also we would like to have some feedback from you on the experience from a scientific point of view with regard to the use of MedDRA and signal detection and data analysis. There is at a moment a discussion going at the European community level regard to the version control of the semi-annual releases of MedDRA. This is quite a complex issue. We have looked at the proposal on the guidance document from the MedDRA MSSO regarding the version control and you know that there was a recommendation to implement a new MedDRA version within 60 days. So I think that this is a very good proposal but the issue that we are facing now; here we had a lot of discussion with pharmaceutical companies during our joint pilot and implementation activities, what is the exact date, so from which date on can we use a new MedDRA version. I think here, we need to discuss very carefully also with the regulators in the community and we have to have all some feedback from the companies who are using MedDRA for a long term. How long does it take to implement a new MedDRA version and how can we make sure that there are no problems? Then we have to make sure that when we have an exact date, that this date is followed by all regulators in the community and you know where at the moment 18 plus the EMEA so 19 regulators who have to follow the approach and the exact same date so when you submit reports with the new MedDRA version it can be accepted all over the European Union. Then we are looking at the possibility to support 2 MedDRA versions during a certain period of time so for those companies for instance who need a longer time period to implement the new MedDRA version so that we support 2 MedDRA versions for a particular period of time. We have foreseen the 60 days, but I have some feedback that perhaps it may be necessary to extend this time period but I think this will need some more practical experience and then we can see how we can find the best and pragmatic approach. Then of course we would like to whatever the time period finally would be, if we look at the moment at the 2 months, we only support the latest MedDRA version. I had several questions received on that as well. So our intention is for the expedited safety reports we will only support the latest MedDRA version after this transitional period of time. But as I said, we are working now in our

telematics implementation group together with the regulators in the community on a common and harmonized policy to implement at the European community level. The next important point that we need to consider is the acceptance of supplementary terms. At the moment most of the regulators in the community are not very much in favor of supporting supplementary terms in addition to the semi-annual releases. We would also like to look into that issue a little bit closer. I think the reluctance of supporting supplementary terms is a little fear from a technical point of view and a data management point of view. Also here I also think we need to gain a little more experience and see how it could be implemented on a day to day basis. Once we are confident with it we can perhaps also agree on the use of supplementary terms later on. Let me now come to another aspect and that is the use of MedDRA in the summary of product characteristics. I have a reminder that from the Basil User Group meeting, about the requirement as to have be defined in the guideline on the summary of product characteristics, which is part of the notice to applicants. In this guideline it is indicated in section 4.8 the undesirable effects, should be reflected to for us the adverse reactions according a standard system organ class hierarchy and there it was indicated to use MedDRA and the MedDRA SOC list should be used in the internationally agreed order. In the guideline it is indicated that the adverse reaction description should be based on the most suitable representation between the MedDRA terminology, usually that will be the PT level. But it is also indicated that there may be instances where the use of the LLT terms or exceptionally other group terms such as the HLT may be appropriate. So when I present this guideline of summary product characteristics, people became quite concerned as to what they need to do with the existing SPC or what they need to do when submitting a new application. I brought this concern back to the EMEA. At the moment there is a working group at the level of the EU regulators, which is working on the revision of the SPC guideline in the framework of the notice to the applicant activities. We have indicated it is important to have an agreement on the timeframe for the update of the SPC in accordance with the SPC guideline; that means when should MedDRA be implemented for section 4.8. I think that is a very important issue and we are looking into that at the moment so we can give appropriate guidance to the pharmaceutical companies. Then it is also important, or it has been raised several times that legacy terminology may have different primary system organ class for a particular event and that may imply that for instance the position of the adverse reaction will change with the first update of MedDRA. Then we have the discussion of the placement of reactions that appear in several system organ classes and here we have to follow the internationally agreed order. Companies have pointed out to us there should be some kind of flexibility for instance for the most clinically important adverse reactions should appear on the top of the top and if you follow the international order that may perhaps not be the case any more. There was also a point that has been raised regarding management of descriptive terms outside the maintenance scope of MedDRA for instance acute, chronic,

persistent and recurrent. So there was also the topic raised there should be a kind of maintenance tool to control these descriptive terms. Another important issue for us in the European community is of course the management of the SPC translations where no official MedDRA translation is yet available. And I think for us, the translations of MedDRA in the community language is very important activity as it is maintained by the MedDRA MSSO and it is not only an aspect for the adverse drug reaction reporting but as you can see will be a major support in the future for us when we have to perform translations of the SPC and I think this is also a major consideration, a major point for pharmaceutical companies, that if they have a standard translation of MedDRA available the translation of the SPC in the different community languages will be much easier to maintain in the future. So there were a lot of points and issues that I tried to summarize in the few slides. I would really like to encourage you if you have any questions please put them forward then we can discuss them very openly. Also from our side, I think we often don't know your concerns so it's important that we learn your experience as well. Do you want to do the questions now?

3. Question and Answer

Q. Fred Schneiweiss, Alcon Labs

Dr. Brosch I need some clarifications on a couple of points in your presentation which was very good by the way concerning using the latest version for reporting the safety report within the community. Did you say if we do not submit using the latest version your quality assurance system will return the report to us or how will that work if we are not up to date?

A. Sabine Brosch, EMEA

If we would follow exactly, restrictly the rules that we have intended normally your report would be rejected so in the acknowledgment you would get the feedback that you are not using the latest MedDRA version and that you would need to resubmit the report with the latest version. If I just may explain also, I had a discussion with a colleague here just prior to the presentation and she asked me we are using at the moment MedDRA version 4.0 in our company so what happens if we submit now the MedDRA version 4.0? So here perhaps my colleagues from the MedDRA MSSO will correct me if I say something wrong. In principle that should not affect the validation of the system, because normally a MedDRA term from 4.0 should also be included for instance now in 5.0, the only issue is that now we may face is that it may have become a non-current term. So at the moment we are not that strict that we check to see if the term is current or non-current term but that is something that we may perhaps consider for the future but I think for us at the beginning we need to have some flexibility for the companies to get this thing moving and then see at the later stage in time perhaps to restrict our rules.

Q. Fred Schneiweiss, Alcon Labs

And one further question, clarification on the SPC issue, are you going to be requiring recoding of all prior SPCs or just new products that are approved?

A. Sabine Brosch, EMEA

Now that is a very good question and that is what we are currently looking into the issue because this may be a huge exercise. We will have a look into that; I cannot give you a definite answer. It may be perhaps if you do a variation that in the frame of the variation you may need to recode section 4.8 to the MedDRA terminology but that is something we are currently discussing and I have no answer for you at the moment.

Q. Helena Haapaniemi, Orion Corporation

One question to Sabine Brosch, you mentioned the day before yesterday that EMEA is just now working on the guideline for the clinical part and you are just concentrating on the post marketing and I would just like to ask if you could possibly give any tentative date or month or something when that guideline would be available since in my situation, I am suppose to start to plan in my company, planning what we do for the clinical studies and projects, within one month I have to start the work so what should I do?

A. Sabine Brosch, EMEA

Now I think that this is a very validate point. I am not directly involved in the working group. There is a working group established at the level of the European Commission together with the member states and there are also representatives there from the EMEA. As far as I remember, I think they are meeting either today, I think they are meeting tomorrow in Brussels to finalize this guidance document and to have it in a stage ready for consultation. So the guidance document should be available very soon for consultation. But I know that means when you look the directive the timeframe for implementation for us is also very close so it's 2004 and I think there will be a lot of activities going on the clinical trials perspective as well. From the EMEA perspective, perhaps to explain a little bit we had a lot of discussions about what we are going to do if we should set up a separate database for clinical trials or if we have one and we came now to the conclusion that we will within EUDRA vigilance cover both the adverse drug reaction reports and from post- and pre-authorization but there will be a separate system in the community which will focus on the tracking of clinical trials that are going to be performed in the community.

Q. Matt Kuntz, Eli Lilly

I guess this mostly going to be a comment with a little question added at the end but from industry perspective, I am speaking purely from my own company. We are a global company but we use English as our corporate language and my question is these translation, these new translation versions of MedDRA seem to require a lot of effort, and you made a comment that you

would like the MSSO to take on the support and maintenance of the translations eventually, which in my mind would increase operating costs and probably those costs would pass on to the paying subscribing community. And my question is when will we draw the line in the sand and say we can not continue to create these new translation versions of MedDRA and would ask either of you to comment on that.

A. Jim Mundell, MSSO

The MSSO is by contract required to maintain any translation version that is given to us by the EMEA. We have budgeted to do certain maintenance activities. Your question is an open one for us also with EMEA, if EU keeps expanding what is the expectation because this provision was created when there was a specific group of what 15 states that we were talking about; and not all of them had said they were really interested in creating a translation. That's an issue Sabine's group is not really involved with that area, it's Julia Dune, that used to be Emer Cooke but that has been transitioned over and in fact I have a phone conference that I am setting up for either Monday or Tuesday of this coming week to discuss that. But the other thing that I think and you could correct me if I am wrong Sabine, but Sabine is referring to is and one of my reasons for this phone conference as well is I think if the MSSO were given, if we were to re look at how the translations are being pulled together right now it's a very long protracted process because it's coming through the regulatory states through different ways. In France, the French are here and if I say it wrong I am sorry; but I am trying to remember what I had heard because we were not directly involved but rather it was Emer Cook and Julia Dune. That France took it and divided it as they see among a lot of the industry to help to defer the cost of doing it. But it then takes time to coordinate that effort, pull it together and then you have the consistency questions, which are the same consistency issues we have had in MedDRA, we have still a lot of them, but early because you had so many expert working groups that all did their piece, that didn't necessarily talk to the other expert working group about how they were doing it so you had duplications of terms even though they were lexical variants and things. So you really have multiple MedDRA codes for the same concept. But that was the way it was defined and that's made a terrible problem in translation because they are being told you have to have unique translation. But how do you define the British and the English spelling? They are different MedDRA codes by definitions they are different terms. They are the same term, the same concept, we have duplicate terms in MedDRA, we just have different codes for them. So there is a certain coming to the table for a lot of people to recognize what this issue is but there is also the fact that right because the regulators are doing it, it's not their primary job and some are contracting it out while some aren't, that's being done at different rate, different speed with different quality. We would like to get a little bit more involved in trying to even that out, get it consistent and do it in a more timely manner and get it

done quicker. That's part of my conversation that I am planning to have with Julia Dune next week. Would you want to add to that?

A. Sabine Brosch, EMEA

We haven't told the 11 official communities to have community languages at the moment. I don't know how translations are taking place right now. We have just three, French, Spanish and Portuguese, which are quite advanced. We have the Dutch and Belgian, which are going, as well as the Greek. No body has ever looked at Italy for instance; we have no Italian translation at the moment. It's only now that a lot of other members realize that perhaps there is a need for translation and I think it's a very tough process. As Jim has pointed out, the European Commission is coordinating the project for the translations and they have also tried to support the initial translations as performed by some of the member states and as I said now several member states have raised the issue that they want to start the translation. I think the main issue will be once we have the translations is to really maintain them and to translate all the new terms, and this is certainly not an easy task. Also from the EMEA's perspective we have to support all the community languages so we have also from a technical point of view look at the possibility how we can implement all the MedDRA versions, all the languages parallel so that we can support all the languages on community level as well. I think that there was also a nice presentation on Monday about the issues and colloquial use of the different terms and perhaps even to do analysis later on outcome of the evaluation, the scientific evaluation based on different languages that have been used. But I think that will a long time for us.

A. Jim Mundell, MSSO

As an aside point is that we always talk about the English translation, the French translation, the Spanish; but in reality we are talking about country translations. France's translation is not necessarily what Belgium wants. Spanish's translation is not necessarily what Mexico wants, let alone pieces within Spain. This is something that really, it's the EU, and these are their translations. Even within there, there is a question of how far will the German translation go to satisfy the Germanic speaking countries. The German translation when you see it is in modern German, there is a state mandate in 5 years to have government documents using modern German so there is no umlaut, the supporting documentation has it but dictionary itself will not have accents in it. Whereas there are accent marks within the Spanish and Portuguese and French. But the Portuguese will not necessarily take care of Brazil and so there will be other issues. So right now the focus is only on the EU.

Q. I just have a comment as opposed to a question for Dr. Brosch and that is I understand the necessity from the regulatory perspective on trying to getting

everyone standardized on using the same MedDRA when they are submitting reports as should you are strongly considering the MSSO guideline of 60 days, from my personal basis I would hope that you would extend that to at least 90 days.

A. Sabine Brosch, EMEA

We can discuss and consider this. We will try to see what we can do.

A. Jim Mundell, MSSO

If I can give you just another update of issues with the Management Board; we have been talking with the Management Board for I don't know how long about version control and we have put out papers about single case, multiple case version controls, we have tried different variations of them, options 1,2,3,4,5,6 types of things. At this point they are also debating the same question about this rollover, there are general concepts that everybody that sits at the table say that makes sense, we need to come up with a solution there or an issue there or an idea there. But at this point no body is ready to say this is where you know FDA stands on this, this where EMEA, this where or you know, even the industrial people, you know Pfizer is not going to tell Merck what to do. But they can agree in principle that this makes sense and so what they have encouraged is that these guidelines that we put just be put out as MSSO guidelines and suggestions that over time will become the basis for creating real guidelines but for now it is an open debate.

Q. To some extent the MedDRA terminology and coding issues can be considered a subset if you will of the broader area of health informatics. I was curious whether if there was any coordination of the efforts underway here with those on the technical committee on health informatics and the various country-based activities related to them?

A. Sabine Brosch, EMEA

At the moment I have to say we are working more at the European level and no we have no contacts or considerations thus far.

A. Jim Mundell, MSSO

As far as I alluded to my meeting with World Health, we are having ongoing discussions about collaborative efforts for data analysis on a global scale and that's as close as anything right now outside of a box, as far as trying to come up with an effort that goes outside to bring in other perspectives in to it.

Q. Because I'd hate to see totally different systems of coding and terminology from two very major activities that haven't worked together but we can talk about that use of contact later if you don't them. A simpler question is I was curious about your NCI contact regarding the oncology issues and if I could get that from you later if you have those names.

A. Sabine Brosch, EMEA

From the WHO perspective we have contact with the WHO and we are looking at the different aspects of what the WHO is doing and what the EMEA is doing and also from a senior management level and from the European Commission level, which are of course to coordinate these activities. As you know that we have now started with our system and we will see over the next year how it is going, how is our data quality and then to see how we can compare with the other activities.

A. Jim Mundell, MSSO

Also I refer to the Management Board for those of you don't know what makes up our Management Board, we have representatives from the FDA, EMEA for the EU, and the Ministry of Health and Welfare & Labor in Japan, we also have the JPMA, EFPIA and Pharma, which are industrial agencies representatives, all under the auspice of the IFPMA, which is the International Federation of Federations of Federations of Pharmaceuticals and we have observers, specific members from the Medical Control Agency in the UK; but then we also have observers from World Health Geneva and observers from Health Canada.

Q. Jean Morrone, Pfizer

I have a question about the "What's New Document" and we have found this to be very helpful. We had a few questions about the social circumstances section and I know this probably came up before, but the explanations didn't really make sense to us as far as distinguishing between addict and addiction at the system organ class level. We're going to have a lot of difficulty training people and so we have put together a list of terms like this like paralyze, paralysis that sort of thing, we wonder if you would consider making these terms multi axial perhaps secondarily to social circumstance and primarily to the organ class affected?

A. Jim Mundell, MSSO

Again, I say submit everything, any idea, it's better to get an idea and then look at it and say this is a terrible idea and send it back to you than not getting it at all because you don't think we'd consider it. There is inherit understanding from the working group about how these things are supposed to be, the splitting of hair and definition that people look at and say, you know if I am on the front line, I am not going to understand the difference between an addict and addiction, an abuser and abused and all these types of nuances that seem to be in these, especially the social circumstances soc, there are things in there that are meant to define people and characteristics as apposed to disabilities and disorders and things like that; because of it, it makes it a very fine hair and you will find that when your people do their coding or not coding but reporting, they will just by habit use these terms interchangeably and that's understandable. How do we deal with it within the terminology? It's been an ongoing debate now for four years and we have

tried different cuts at it, trying to improve it to make clearer that we're talking about a person as opposed to a condition. But we are also stuck with a certain inherent words from COSTART and WHO-ART that can be used both ways. But if you have ideas please send forward and we can consider them. I don't know if we'll ever get a good clean solution to that one, it's been around for a while. And our own trainers have the same issue, you can talk to Joann about that.

Q. Jean Morrone, Pfizer

And my second question has to do with the change request process and the suspended terms. We are really clear on what that actually means, because we have put some terms through the process and gotten the suspension notifications back and later on they are added to the terminology. So it is a consideration process?

A. Jim Mundell, MSSO

You should get, or at least I have asked them to do it recently because there has been this question too so I am not sure of your time frame versus the time frame I am dealing with. But they should try to provide you in the suspension notice a timeframe as to what will happen, what it usually come from is falls into two categories, one you have asked for something that really to implement it, it requires a complex change and we can't do the complex change until we do the X.0 release and we're in a X.1 release so it has to be put off until the X.1 is done and they can deal with it in the X.0 release. Or it's that there is a conflict in the medical group that is reviewing it and that there is no clear decision that can be made because it's such, the term I always use is pseudo aneurysm, that was suspended for how many times and for how long because every time a new person voice an opinion on it, it escalated in to a very large argument about it between the medics and things. Those types of things happen, the people looking at it, it's something that may be very strong opinions and those opinions are opposite or different in some way that it's decided that more has to be done. They need more time to research it so that when a suspension notice would go out. The new suspension notices should and if they don't let me know because I have asked to have a projected timeline, like it's being suspended, you should hear within four weeks, two weeks, you know, whatever. So you should be getting that, if not let me know.

Q.

Again I have another comment that I'd like to make and it's really in regard to the practical use of supplemental terms because our company has decided not to use the supplemental terms because we feel every time we decide to add a new term to our mix that creates a new dictionary version. From the practical ramifications of the dictionary management component to that are tremendous and as we're looking into going to the E2B world next January, the MedDRA version field only accommodate 2 characters and so I don't

know if you have any comments on how if a company were to decide to use the supplemental terms, how they would actually capture the official dictionary version number that they are submitting?

A. Sabine Brosch, EMEA

I think that

Q.

Could you please define supplemental terms?

A. Jim Mundell, MSSO

A supplemental term is a PR approach to provisional terms. And the whole reason for the public relation on it is that when provisional terms were discussed earlier, it was said they were provisional because just because they are in there doesn't mean they are going to be in the release. If you are doing a release and this term comes in, we accept it but as time goes on during the release cycle, something else comes up that we decide we should have never accepted that term and it gets dropped out, and so you are taking a risk using it because it may not be in the actual release. In reality, over four years that has never happened; any thing that we do accept has always been in there and if there was a worse case, it would be some body looks at it and says make it non-current, but it's still in there. None of those that we have added and made non-current in the same release either. So to let people know because they have always heard this about provisional we began calling them supplemental, we were building a supplement for the new release and so we're saying once you get your notice that it has been accepted, you can count that it will be in the release that is coming up. It's the same idea, it's the terms that we accept on a regular basis prior to the actual release. There are companies; especially people involved in clinical trials have said you know it's a big concern for them because if they are doing a clinical trial, they are down to the end, they are trying to close the trial and lock it down, and they find something that they need a term for, so they submit and they are given the term and say it's approved but if it's not in the release, they have to wait for the release; and so it holds up locking down the trial. They want to use that supplemental term and lock down that trial and get on with life. What that has done, we went from you know doing quarterly releases, which people said was too much to now if people all agreed that supplementals are the way to go, you have to update, especially the regulators everyday, that they are going to be receiving terms that aren't in the database. And this is an open debate, the management board having the same debate back and forth, those that are pro and those that are against it. Where they are trying to decide should we allow it or not allow it. We have also posted it because it's part of the review process, do you like it. We said do we take away the ability to download these terms and they said no leave it there because they don't know which way to go with it. So you can download it and load it into your database. I know that Roche takes every provisional

term that's posted or supplemental term and creates a shadow dictionary, at it's the way they used to do it before they got rid of the California group, so while they are using 5.0, they'd know what's going to be in 5.1 because it's going on in the background, so when 5.1 comes out they are already ready and can go live the next day as opposed to taking the new version and verifying and validating it and checking all this and that, they check it everyday and make sure it's working. Every company is doing it differently, everybody has their own opinion, everybody has their own drivers; there are some companies like yours that says there is no way we're going to deal with it. While other companies saying if we don't have it then it's a big business decision.

A. Sabine Brosch, EMEA

I think the point you have made with version control is very important point and that we need to have look as well. But as Jim pointed out the main issue is the reports from clinical trial where they need to have more terminology than what is currently available in the official release. I think for the post marketing activities we can management I think with out the supplemental terms. But it is definitely an issue we have to look at and it was also said that there are really companies who use supplemental terms and then there may perhaps be the issue that we don't accept the terms because they are not in the regular release so that needs to be resolved.