

**MedDRA® MSSO International User Group Meeting  
Tokyo Japan – 15 November 2002**

(Minutes are taken verbatim from recording; please excuse incomplete, omitted or paraphrased comments, questions or answers contributed by attendees due to poor quality of recording)

The agenda for the meeting was as follows:

1. Welcome Comments
2. MSSO Overview
3. Electrical Submission of ADR Report and Use of MedDRA
4. Networking Break
5. JMO Overview
6. MedDRA/J Update from Industry
7. Question & Answer Session

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

Welcome to the MSSO User Group meeting, my name is Elizabeth d’Alelio. I would like to go over the agenda for today’s meeting. First, I’d like to apologize, there has been a change to the program. You were all given a package that looks like this. In the first page there’s an agenda, well it’s been changed. You should have been given a schedule that looks like this; there has been a schedule change and a speaker change. I’ll go over the agenda very quickly. Our first speaker is Jim Mundell, the director of the MSSO, he will give an overview of the MSSO. Next, we’ll have a speaker from MHLW. He is Mr. Kenichi Tamiya, who will speak about the electronical submission of ADR report and use of MedDRA/J. We’ll then have a tea break followed by an overview of the JMO presented by Mr. Reiji Tezuka; then we’ll have Mr. Yasuo Sakaurai talk about the MedDRA/J update from industry. We will then close out the meeting with the question and answer session. So with no further ado, I’d like to present Mr. Jim Mundell.

**II. MSSO Overview, Jim Mundell, Director of MSSO**

Good afternoon. I like to start by explaining a little bit about who we are. We represent the MSSO, the MedDRA Maintenance Support and Services Organization. It is a contract held by TRW, which is a company in the United State (US) and we hold the contract from the International Federation of Pharmaceutical Manufacturer Association (IFPMA), who is the trustee of MedDRA. Our relationship with the JMO, the Japanese Maintenance Organization for MedDRA is that they have a special sublicense with us for distribution and maintenance of MedDRA in Japanese, which is why I am speaking in English and they will be speaking in Japanese. Here in Japan for companies that are headquartered in Japan, the MSSO, which I represent, takes

care of the overall maintenance support and services for the United States and European Union (EU). The first couple of slides we'll be going through are general statistics to give you an idea of the subscription base of MedDRA at this point in time. This is our fourth I believe annual meeting here in Tokyo for the MedDRA Maintenance Support and Services Organization in conjunction with the JMO for the JMO subscriber base here in Japan. As you can see, actually the largest section of the pie chart is in Japan right now with the other part being then United States and then the European Union. The fourth smaller wedge of this pie is people outside the ICH region. The ICH is the International Conference on Harmonisation and they are founded by the IFPMA and the pharmaceutical regulators in the US, EU and Japan. The 8% of others represents subscription holders outside of those three regions. General types of companies that hold subscription are primarily pharmaceutical, followed then by contract research organizations (CROs), support groups for the pharmaceutical group, biotechnology and academics. The other categories here tend to be non-profit organizations as well as software developers. The final pie chart here is just to show the subscription base; this includes the Japanese as well as the MSSO base. There are several levels of subscriptions possible, with basic subscription being the lowest level available, next is the developer, the others are based on revenue, with Core 0 available for companies with less 1 Million in revenue and Core 5 for companies with revenues greater than 5 Billions a year. Currently, as far as regulatory guidance that are out right now about the use of MedDRA; Japan was the first region to put out guidelines on the use of MedDRA. At the last meeting of our management board, it was indicated that back in May 2002, guidance was put out that come 1 October 2003, MedDRA will be required in electronic filing and you will learn more about that in the afternoon from Mr. Sakurai and Mr. Tamiya.

The EU has several guidelines out right now for the use of MedDRA. They currently require MedDRA for electronic filings of single case reporting, safety reports (ADR) and starting in 2003, they are looking for all historical reports of single case reports going back to 1995. They also have a draft guidance being reviewed for the use of MedDRA in clinical trials. In the US, there still has been no guidance for the use of MedDRA. It is going through the US rule making process. It is about to finish the governmental review and will be released for final public comments in the next few weeks. This is a list of regulators in the various countries that have subscription to MedDRA. As you can see, there are places outside the ICH regions that hold MedDRA. MedDRA, since the beginning of its public distribution in 1999 has been available in both English and Japanese. The Japanese is maintained and distributed by the JMO here in Tokyo and we distribute the English version. We also have available Portuguese and Spanish to preferred term (PT) level. We have French and German to the preferred term level but we have not been given permission to distribute as the French and German governments have not signed over distribution rights to the IFPMA. The Spanish is also done through the lower (LLT) level term but has not been released for distribution yet; it is still completing its final review. Hopefully it

will be released before the next release of MedDRA, which would be March of next year. A Greek translation is also in the work and they expect to complete it in 2003. Translation, besides the translated terminology, includes all the supporting documentation, the "What's New Document", the "Introguide", and other resource materials.

There is another document called the "MedDRA Term Selection Points to Consider" which we have on our website and is on the website of the ICH; this is not our document, we did not create it, the ICH created it. It is meant as a guideline to help with creating MedDRA coding convention and the committee that put it together included representatives from the MSSO, JPMA, and various other EU and US groups. Its current release is 3.0, and it reflects the terminology of MedDRA as of the 5.0 release. MedDRA 6.0, which is the next release of MedDRA is due out in March 2003. All change requests will be accepted through the 20<sup>th</sup> of December 2002. As JMO subscribers, you of course would submit your request to the JMO. If there is any MSSO subscriber here, you would submit yours to the MSSO. This release will also include some complex changes, that is why it's a 6.0 release. Complex changes are any changes to the hierarchy structure of MedDRA; it is not changes to the PT or LLT levels. Other issues that will be addressed in 6.0 include the modified term. That would be any term that uses a modifier, such as aggravated, worsening, exacerbated; these terms could be applied to many different events in MedDRA. This is an issue that the management board and ICH is looking at and until they come up with a resolution, we have been asked to review these three modifiers for their appropriate use at the PT level. The International Federation of Pharmaceutical Manufacturer Association (IFPMA) in response to an EMEA requirement in Europe, is looking at the use of investigation terms in MedDRA, the EMEA guideline requires the use of MedDRA for reporting investigations, laboratory tests in their documentation. They will review and submit to the MSSO additional terms that they feel need to be added to the Investigation System Organ Class (SOC). There is also an ongoing issue between British and American spelling of the LLT level. Up until now, not much was done about correcting this issue because of translation issues. Now that we have gone through the first series of translations, we are proceeding to balance the American and British spellings properly. Stabilization is an issue we have heard about and the MSSO has sent out the recent Newsletter about the item. During the MedDRA 4.0 release, the MSSO was given permission to do a complete review of terminology and to make corrections as needed. Those corrections took a year and a half to implement through release 4.0 through part of 5.1. During which there was a lot of comments about the number of terms being moved, modified, added to MedDRA and concerns that the terminology was growing too quickly and that it needed to slow down. The MSSO was given permission from the Management Board to require additional information as far as the requests of changes to MedDRA. They have to be justified with specific information. However, the response to the stabilization efforts, though positive also cautioned that it shouldn't mean that stabilization stand still and that

MedDRA freezes, MedDRA needs to evolve as appropriate as long as it is appropriate. Under this type of thing, we have other ongoing initiatives with the stabilization effort is to make clear this transparency of process so the users of MedDRA what we are doing, how we are doing it, what are the requirements and the guidelines we are following; so that they can response and comment with us in a more open manner. As a follow on activity, we're increasing our communications on the MSSO website, with regarding to the posting of the rejection criteria, rejected terms, etc. in addition to creating a more interactive medium for users to get together to learn from one another and possibly adding more User Group meetings in the US and Europe to discuss specific English issues. Bottom line, as far as ongoing activities with the terminology that need to be addressed that have been pointed out in the past are the appearance of NOS at the PT level, where we have almost reached a consensus that it should not be there, we're trying to work out the final step of that so it could be implemented in 6.0, modified terms as mentioned before, and the Special Search Category (SSC) where we are trying to improve them. Also there is the Neoplasm SOC, where there was concern a while ago that there was a third party review of the SOC that would require a major change to the terminology; once that third party review was completed, it turned to be minor changes to PT and LLT levels so they are being implemented as part of 6.0 normal change request process. Final note as this slide is that the E2B, which is the electronic filing format, that committee has be reopened to deal with the harmonization issues; one of the issues that they will be addressing is the modified terms. The SSC, one of the problems is that they were envisioned as to help with data retrieval and querying of specific information. However, feedback from users about the SSC has been about too broad, incomplete, not used, companies build their own query set rather than using the ones provided by the MSSO through MedDRA. Even the CIOMS working group, out of Geneva had two meetings to discuss the SSC and whether CIOMS will become involved in reviewing them and proposing changes to the SSC to make them more useful. The MSSO itself has recognized the lack and deficiencies of the SSC based on our own experience as well as comments we have received the subscriber based and we have come up with what we're calling MedDRA Analytical Groupings as a solution to help improve the SSC data retrieval issue. Special search categories as they exist currently in MedDRA, are used to take medical concepts across systems organ classes that can be grouped for a query. As you saw in the previous slides, these queries tend to be very broad in nature and not necessarily useful when trying to retrieve a specific issue or signal in your safety monitoring. They also link preferred terms and they generally deal with as I said general relevant issues together. They are however maintained by the MSSO so there a benefit there. This is a list of the current special search categories as you can see, anaphylaxis pain, thrombosis; they are rather generalized. MedDRA in that analytical groupings as I said is a concept that we are proposing, we're in the process of the doing some prototyping so that we can make a presentation to the MedDRA management board for permission to continue development and distribution of these MAG's, as we are calling them. They would be used as a way to improve the querying data analysis & retrieval of

MedDRA coded data. They will improve upon the SSC's and again the MSSO will maintain these and keep them updated with each release of MedDRA. I am not going through every piece of this, but this is doing a comparison to the special searches versus the MAG's that we're proposing; generally the MAG's as opposed to the SSCs, we're looking upon as a hierarchy of queries that would be to the statistics and analyzing of MedDRA what the current hierarchy does for coding as far as helping to locate and identify terms to be used. This is a list of MAG's that we are prototyping, the red ones have already been drafted for comment, we have looked at them internally and we're having selected companies take look and make comments on upon what we are proposing to do with them. As you can see they are targeted more to specific issues that you are going to follow or look for as far as pharmacovigilance. This is a rough structure to give you an idea, I'm not go in a lot of details about the MAG's right now but the intention is that you would have a very broad category such as the cardiac as a query group, you could query broadly through the cardiac or you could get something more specific like the arrhythmia; or you can narrow your focus and just query down to the qt prolongation. It is hoped that perhaps we could provide some filters within that to include or exclude investigation terms, operations that type of things. Again, we would maintain the MAG's and distribute them with MedDRA, we would also make them available for change request processing so that subscribers would have input in their modification and maintenance. The benefits again, we are maintaining it so you don't have to, it's to meet future analysis needs and reporting and it is hoped that it would become a common basis of communication in the future. A future activity at the MSSO by contract, we're to address ICD10-CM that's the clinically modified version of ICD10, which is published by United States Center for Disease Control. This has not been published yet, but once it is published we have a year to create some sort of interface to MedDRA. In the past this has been incorporated in MedDRA but that has caused a lot of problems, we'd like to do an external crosswalk or mapping between MedDRA and ICD10-CM. The last slide is really more for the MSSO subscribers, you as JMO subscribers primarily here, so contact and discuss with the JMO, if you have a more MSSO questions, you should funnel them through the JMO. But if there are MSSO subscribers here, you should contact us and the contact information here is for your reference. I would like to thank you very much for your attention.

### **III. Electrical Submission of ADR Report and Use of MedDRA, Kenichi Tamiya,**

My name is Tamiya and I come from the MHLW Safety Division Initially Mr. Takeda was supposed to come and present but because of an urgent business he was able to come. I would like speak on his behalf. Today I would like to talk about the introduction of electric system for adverse event reporting and the use of MedDRA/J. If you look at the examples of the safety issues, within 2002, well in fact the fiscal year has not ended yet, but within this year we have already seen the use of emergency safety information sent out. We have seen very

severe liver disorders, has resulted in acute pulmonary disorder and interstitial pneumonia, acute renal failure. The information doctor's letter has to be disseminated at an early period on after the launch of the new drug. What we can say from these examples is that immediately after marketing, the launch of product, in order to insure appropriate use of pharmaceutical product, it is important that we send a post marketing survey, particularly for diabone. Last year starting from October we had initiated a new program under the name of Post Marketing survey, we see that the sponsor efforts to collect information immediately after marketing has contributed to the fact that we are able to pick up some of the very serious adverse events and we are able to response to such problems very early point on. So you see that the Post Marketing program has become very important and we've seen that the enhancements of the safety program Post Marketing has been one of the important improvements. Here you see the reviews that have taken placed with the amendment of the law. First the establishment of a division devoted to post marketing safety program has now been raised in terms of its level of requirement level to mandatory level. In other words, the manufacturing approval is inclusive of this function. In other words the marketing and the necessary rights can only be given to a company when a division devoted to post marketing safety is implemented and therefore it used to be that this was only a matter of requirement but this now considered a mandatory status. It used be that this was a requirement under GPMC we had to have the allocation of the person responsible for safety management of post marketing has now been become a mandatory issue and requirement so this will be provided as administrable for Health and Welfare. In addition in terms of amendment to the pharmaceutical affairs law, we have seen that we now require companies to make a report on a periodical basis of any infectious diseases particularly for biopharmaceuticals in addition to the conventional report required for adverse events. Furthermore, coming back to the earlier point the new pharmaceutical affairs law requires, stipulates that the companies are obliged to implement safety programs and this line is representing pre and post amendments of pharmaceutical affairs law in terms of relationship between government and the sponsor, and you see that it has now become mandatory that the companies make a very expedient report of the safety related issues. So you see trend in terms of number of reported adverse event, it has been a system for report of adverse event one is a company-initiated report on the basis of pharmaceutical affairs plus one voluntary report to be made by the hospital and pharmaceutical healthcare provider. You see the trend has been increasing quite rapidly in 1995, 14288 cases were reported by companies which has increased to 22451 cases in 2001. The number of cases to be reported by the hospitals has also changed, particularly in July 1997, we have integrated the monitoring system of the past which was picking up on the specified number of healthcare providers is now inclusive of all medical institutions and pharmacies. Therefore doctors, dentists and pharmacists are required to make reports relating to any information relating to safety. This number has increased again from 1859 in 1995 to 5229 in year 2000; the number has declined to some degree in 2001 with 4094 cases, but together with the company reports the annual reports

amount to 26455 cases so such adverse event reports has been made in a smooth manner and this is a very important information source for companies to initiate a safety program but for the government, for us Health and Welfare Ministry, it is a quite indispensable that we get a hold of such information in order for us to be able to spell out the next round of guidance and policies. As I will discuss further later on there is these programs expected to introduce the electronic system for adverse event reporting and the language to be used to reporting shall use MedDRA/J. At this point I would like to report to you some of the progress we have seen in the recent discussion within ICH, in particular relating to post marketing safety issues. November 2000, ICH 5, the ICH terms of reference was recommended and it was agreed that post marketing safety program was to be included as part of ICH reference. Upon receipt of such development in Tokyo conference in May 2001, it was agreed that PSUR, periodical safety update reports as well as individual single safety reports are to be considered the priority topic to be determined the method for specific post marketing survey and was agreed also that specific discussion to take place in the next round of discussions. It was also agreed that the content of the safety information and the good pharmacovigilance practice was to be taken considered as a very long-term task. In Brussels conference, February 2002, it was that the guideline being produced for the operations of PSUR and the good case management practices. In the London conference in June 2002, in its ad hoc meeting, it was agreed as the first topic v1 PSUR, expert working group was held and within industry guidelines the addendum was to be create and the main gist of the content was upon and within the same conference there was a v2 topic US case management practice, again here the expert working group was held on the concept paper the position in the guideline to produce the necessity the scope of application handling and policy was discussed. As v3, the post marketing pharmacovigilance was the topic within the brainstorming meeting. In the September 2002 meeting in Washington, topic v1 has now reached step 2 and for v2 some comments are still remaining within the EU so we hope it to reach step by the Tokyo conference. As for v3, the concept paper is to produce and this is going to be an official topic the name here is the prospective planning of pharmacovigilance, this has been introduced as the new name, so this has been adopted as the official formal item of discussion. Next, I'd like to talk to you about the safety periodical reports, which is a requirement for drug is subject to re-examination. You see that in November 11, 2002 there was a notification given by the review & safety director. You know that the PSUR has been discussed as a safety program within ICH and we've amended our notification as MHLW. Conventionally we had a system for the reporting of adverse events to be filed on a periodically basis and we did have a format to be used for reporting purposes but we didn't have mention of MedDRA but for the reporting post marketing survey results and for the adverse events infectious disease reporting the type of terms to be used for such shall be changed to MedDRA/J. Also post marketing special surveys and post marketing clinical trials when we look at the type again we have decided to use MedDRA/J. Now this change is going to be effective starting for safety periodical reports after April 2003 but it would be

acceptable after the announcement was made that the periodical reports take the form of the MedDRA/J use and we're trying to promote the use of MedDRA/J by the pharmaceutical companies for the reports to MHLW. Next I'd like to talk about the electronic reports for adverse events report. Within ICH, discussions regarding electronic report of adverse events reports we had discussions within the E2B & M2, E2B being the monitoring item for adverse event case report and M2 dealing with electronic transmission. So up to 1999, there has been an agreement for ICH E2B guideline and ICH M2 concerning transmission specifications. There has been notifications sent out by a division director for the use of MedDRA in November 9, 2000; indeed we have recently sent out in May of this year another notification by the division director promoting the use of MedDRA/J and there has been a revision of A2B guideline. Hopefully beginning in March of 2003, there's going to be new guidelines established and for the use of message specification; there's going to be another notification expected again in March of next year. This year in May, with the announcement from the division notification has been information relation to data items in message specification, in addition to what has been discussed so far, data items, what we call the J item, for use of in particular by reviewers in Japan. We've also seen which of the items necessary for the first report and last of the report of which items in the terminology that has to be incorporated in report in terms of incidents. For use of electronic, we expect it to be in place for use in October 2003 and at this time when electron report to be implemented on large scale, we expect that MedDRA/J be used as the reporting language. Next, I'd like to show you some of the recent developments outside of Japan. As far as I know, within FDA, the actual implementation phase has been reached by these companies that you see here, Bristol-Myers-Squibb, GlaxoSmithkline, Johnson&Johnson, Merck and Roche. As we understand EMEA's implementation will start in January 2003 but we don't know currently where they are in terms of test phase. Looking at these recent developments, the initial movement we have seen within the FDA; the FDA itself has not made any announcement or notification about the actual operation, certainly they have announced or made public the ICH document, but other than that they don't seem to have made any official announcement as to the use of this. Within EMEA, they have emulated the procedure of FDA and they've sent policy paper in January 2002 for the implementation of the electronic report and also a notice for guidance I believe was sent out in March 2002. What we understand is that according to the FDA says is that there are some companies running some tests but when it comes to the actual implementation, meaning complete paperless reporting being possible, among to only five companies; of all reports approximately 20% is now in the form of electronics by those five companies. The companies are now required to submit plans for the introduction; I understand that officials are saying to make sure to know well as to what might be happening. In initial test phase, samples cases are used. In the next test phase, the actual cases will be reported both by paper and electronically as so that the input will be stabilized. This practice will have to continue complete stabilization of system is confirmed. Here you see the situation in Japan for MedDRA use, what is different here as opposed to the rest

of the world is there is a coexistence of reports for MedDRA and J-ART reports. Some times, a company can have both types of reports. Well if you are interested in introducing MedDRA, it would be best that the companies make more greater effort so that the people in charge can be trained to be accustomed to the use of MedDRA, other is a problem of perhaps depending on some of the companies, the adverse events databases are not in compliance with MedDRA as yet. That may be one of the reasons for this complication. In Europe as I said before the introduction of MedDRA is starting next year and therefore if you have a partnership company in Europe, when you exchange information perhaps you may be using paper now but you would have to expect that the overseas cases would most likely be reported in the MedDRA terminology so therefore in preparation for the actual implementation of the electronic reporting particularly prior to the pre-implementation test for July of next year you should make the best efforts so that you'll be best prepared for this test. The situation at FDA is somewhat different from Japan, the primary objective for them is to establish good electronic system to allow electronic reports and MedDRA is only a collateral issue. Out of the five companies currently involved in electronic reporting one or two companies have not yet been MedDRA compliant and therefore non-MedDRA electronic report is still coming in to FDA. The terminology used there is COSTART and when there is a paper-based report written in COSTART then a dedicated staff is translating, doing the coding process so that terminology be put into MedDRA. I don't know how many companies are in compliant with MedDRA at the moment. In Europe as with the EMEA, the use of MedDRA is going to be a requirement starting January 2003. This is my last slide, when you look at the actual use of electronic reporting with MedDRA, this is where we are at the moment in terms of implementation. Up to November 5<sup>th</sup> of this year, there was a large-scale test being performed by many companies. When we had the exploratory meeting, one hundred sixty five companies came to listen to the presentation. Out of that one hundred fifty five participated, out that companies who are members of the JPMA registered seventy-seven. The result of this large-scale test, most specifically, it identified the type of errors that would most likely to happen. Late November there is going to be a JPMA symposium at which time the results would be announced. There is a MHLW research group involved, which is going to make this report. According to this research group, whether this research group will submit early next year a final report to MHLW on its research on the electronic reporting practice in Japan. There is the question of encryption and authorization, the process will only be determined when the vendors responsible for the maintenance & servicing is determined and therefore, only become clear January next year. The MHLW itself is trying to promote the electronic reports and we have drafted an action plan for electronic reporting. We have seen that there are some procedures that will need to become electronic by the end of this fiscal year. For the processes of encryption and authorization we are going to make use of these information as reference. For system development we don't know who the vendor is going to be because we have had the results coming from the research group, because we have an off the shelf E2B M2 compliance software,

it's most likely we'd be able to development a system in time for the implementation test for July 2003. For the exchange of data in the large-scale test, we have exchanged data with email system but we don't know what is going to be the actual process used in the future. One of the problems, is that the manual work is necessary to send out response message but when you have a mail system, there were difficulties with automatic sending of received mail and there was a problem of not being able automatically validate the identification number and so forth, so such issues as identification, authorization and encryption are some of items that will need further study. As I said there is going to be a pre-implementation test in July 2003, methods of receipt and sending will have to be considered and in this test we'd like to do the test in a way that is probably going to be the closest to what's going to happen when there is a full implementation. During this test, there will be modifications to be made to the system so that the database development will be complete. This concludes my remarks thank you very much.

#### **IV. JMO Overview, Reiji Tezuka**

Thank you very much I would like to speak about the JMO overview for the past 20-year period. First of all, the subscriptions and the breakdown of the subscriptions. Overall there are 278 companies, or 278 subscribers. And here is a break down. Let me show you that in a graphical manner. The 66% is represented by the pharmaceutical companies, and in this order, the regulatory authorities, 60% MAJLW, and if you prefectural authorities are also members as the subscribers and the CROs the KIKO are also subscribers of MedDRA/J. If you look at the CRO down at the bottom, CRO represents 4% of the total and the hospitals have been using MedDRA/J and they are 60% of the total. Educational institutions like Universities, some universities have been using MedDRA/J, 4% of the total. And non-profit organizations like the JAPIC and IMIC have been the subscribers, 3% of the total and others represent 11% of the total. For example, translation agencies, and they have been using MedDRA/J. And overall 278 subscribers have been using MedDRA/J. Change Requests; one of the characteristics of MedDRA/J has been to work on the change requests and we add or modify the terms based on the change requests from the subscribers. Here is the trend of the change request numbers: the number is declining based on this graph but the 2002 figures include the ones up until October 31<sup>st</sup> so this is not an annual number. I believe we are going to have more by the end of this year; and the subscribers contributed change requests and they cannot carry them over to the next fiscal year so towards the end of the fiscal year, say the end of March, they submitted lots of change requests, and because of that, certain companies may submit 30 change requests towards that timing and these numbers all go into these numbers. And once MedDRA becomes more stable, the numbers should be also stabilized. So far, the change requests numbers have been shifting like this. And the JMO and MedDRA/J questions have been worked on through help desk. And through help desk the questions about

MedDRA/J have been answered. Conventionally we only have the telephone based help desk but beginning of this year we have been receiving e-mail questions. In a given year, there has been about 100 questions, and although I have not brought the specifics, the specific breakdown of the questions, the specifics of MedDRA for example, specific terms have been inquired, some of the questions, give specific terms and the question is whether it is appropriate to use the MedDRA term for such a term. So the questions have been more and more specific these years. And here again, the 2002 figures include the ones submitted up until October 31<sup>st</sup>. So the numbers should be bigger as of the end of this year. When the version 2.1 was made available back in March of '99, that was one of the 1<sup>st</sup> and originally on a quarterly basis the new versions released and at the time of the availability of the new version we provided materials providing information about the revisions. One is the introductory guide, that is the Japanese translation version of the introductory guide and every time we had a new version, we provided "What's New", we pointed to the specific changes in the newly revised versions and third of all we also have offering the revised Japanese translation file. That is basically the information as to the revision of the Japanese language file, its also in the CD-ROM and its also offered on the website. So conventionally we offered these materials and formerly we did not offer explanatory meetings at the time of the revision but just last month we started out explanatory meeting, we provided materials but we also wanted to have a gathering, explanatory meeting, we thought it might be better to have a face to face explanatory meeting. So we provided the version of explanatory meeting in Tokyo and Osaka, and a meeting was attended by so many subscribers, total 163 subscribers were represented and 355 participants came to the meeting and this is the total number for both Tokyo and Osaka so the meeting was attended by so many and we explained the specifics about the revision and as we had so many participants we keenly felt the need for the explanatory session to coincide with the revision. And here is the breakdown at the explanatory meeting participants: we had subscribers most of them pharmaceutical companies and we also had other participants. Here is the response to the questionnaire: the great majority of participants said the participation was very beneficial, when it comes to the pharmaceutical company reps, 88% said that the attendance to the meeting was very beneficial and the non-pharmaceutical company people said it was beneficial, 73% of them said it was beneficial and 27% of them said the meeting was very beneficial. And small number said that the attendance was not beneficial, 2% but based on this we felt that the JMO should hold an explanatory meeting at the time of future revisions. At the time of the meeting, we experienced that we didn't expect. It's about one of the materials we had been providing conventionally, the introductory guide/"What's new" and revised Japanese translation file. Because we've been providing them for such a long time we expected everybody to read them thoroughly and we expected everybody to be familiar with the substance of these reference materials but we discovered surprising as we conducted the questionnaire about the use of the situation. Introductory guide survey: the Japanese version is read often 55%, English version often read 1%, 5% said

they read English as well as Japanese versions a lot, 24% said they don't read either version a lot, 15% said they had never seen that, so there are not a few people not familiar with the Introductory Guide at all. And here is the result about "What's New": 5% of the responses said they read both versions a lot (English and Japanese), and 40% of the respondents said that they read the Japanese version a lot, 34% of the people said that they don't read either version a lot, 22% said that they have never seen that. So more than 50% of the respondents said that they are not familiar with the substance of "What's New". On the left hand side is the respondents with pharmaceutical companies and on the right are the respondents with non-pharmaceutical companies. And here are the results of the Japanese translation file. As translation has to be made, there are lots of challenges between Japanese and English languages and there is so much impact of MedDRA to the translation. Here again almost 46% of respondents said they have either not read it a lot or have never seen it. It's the response rate for the pharmaceutical companies. The MedDRA users may have been reading it a lot but overall people are not so familiar with the substance of the Japanese translation file. And this finding surprised us. I truly wish this kind of reference material should be utilized to their benefit and we certainly have to learn a lesson from this finding. We really hope to devise a method to ensure that people use such reference materials and going back to the introductory guide, and "What's New", we notice that the Japanese version is read by so many people, and we have been offering a Japanese version of the Introductory Guide and "What's New" and based on the finding of the questionnaire we reconfirmed the importance of the Japanese version offering of these materials. As I mentioned we conducted explanatory meetings and besides that JMO had been conducting some training sessions such as the introductory course and basic course. We have conducted these two different kinds of sessions and when it comes to the introductory course we originally planned to have two sessions in each of the Tokyo and Osaka and there were so many applications to participate in the introductory sessions, we simply found that two sessions each would not suffice. We planned to have one session in Tokyo and one in Osaka. The July 9<sup>th</sup> session was participated by 134 people, the July 11<sup>th</sup> the Osaka was participated by 85 people, and July 23<sup>rd</sup> we had 74 participants, greater number than we expected. Well actually the numbers I just mentioned are not stated in the materials you have. I apologize. We had the basic session one in Tokyo one in Osaka and the one in Tokyo was participated by 77 people and the one in Osaka was participated by 47 people and the questions that were asked during the session and the responses to the questionnaire distributed at the session provided us with lots of insight as to the future maintenance of MedDRA/J. We had lots of inputs so based on this such we hope to provide introductory and basic training sessions we have to continue the initiative. And other than that, there are many people who request how to use MedDRA for coding, the coding course including practical exercise is what many people would like us to provide as training sessions. Later we will show you our plan for next year. Next year the coding training course will be provided, that is what we are expecting to do so at present we are now making preparations for that. Version 5.1 is the current

version and at that time not only the new terms but the terms we choose to be in MedDRA/J the Japanese translations had some inconsistency. This is a problem specific to Japan. That is for the same terms the depending the use example are sometimes mixed together so when we issue the next version we did improvement for that and as for the 5.1 the Japanese translation file in that document. The consistent usage of Japanese terms was included as part of the guidance and at the time after 5.1 released we received various comments from subscribers and recently the MedDRA/J has been utilized as part of the systems in various companies these days. We had given the Japanese translation to them and some companies were some what confused by receiving just sudden information about the change of the Japanese translation so in the future when we make changes in order to make the Japanese translation consistent for example then our policy would be to make a draft translation of the form and then show it to subscribers on the website for comments from subscribers so in the future we will clearly state to the subscribers as to when the draft change will be shown through the website for comments and to be finalized. Another point also specific to Japan for when the term in English may be the same or similarly used for several number of Japanese terms but currently the MedDRA system is one English term to one Japanese term and there are cases where one Japanese term applied to several English terms then the plug is used. But in the case where one English term has several Japanese terms, then according to the current system only one of the Japanese terms can be taken up in MedDRA so considering this issue one possibility will be that there may be a Japanese alone sub-file prepared, so that several Japanese terms could be useable for one single English term. This issue has been address for a long time by us but currently we are on the final stage of discussion for this. But when the draft idea comes up then prior to the official use of that, we will publish it to the subscribers for their comments and then after inviting comments and review, then it will be finalized. It will still take time until we can actually do that and once we come up with a draft and it made open to subscribers and after receiving comments we will have to finalize based on those comments it will take time therefore its to early for us to say that we can make it applicable to 6.1 version for example but currently we are preceding with the preparations so that we will be able to apply it system to correct the situation shortly. And as I said earlier we have so far provided explanatory meetings and training courses and we will continue these efforts and the outline of our activities taken in the year 2000 have been explain to you through my presentation. With this I conclude my presentation. Thank you very much.

## **VI. MedDRA/J Update from Industry Mr. Sakari**

Thank you very much for your kind introduction. My name is Sakari. I'd like to talk to you about the latest situation with the introduction of MedDRA/J from an industry perspective. A lot of what I prepared has already been covered by Mr. Mundell of the MSSO, Mr. Tamiya of the MHLW and Mr. Tezuka of the JMO. I may be overlapping but maybe we are looking at the same picture from a

different angle and different perspective. So I'd like to present my case. Now ICH recent agreement about the use of MedDRA July 1997 in 1999 the measure was commercially made available with the establishment of the MSSO but then it has been around for some time but the actual use has started quite recently or it is still evident and there has been some questions about the use of MedDRA, its an international standard tool that is now established but that doesn't mean that there is a standardization of information per say so the question is how can we go about the use of this standard? One is relating to the standardization relating to data input system, this is really on the basis of the points to consider document the coding guideline is already available and that is the main standard and the question is then how are we going to use that data? No matter how uses the MedDRA has a different profile and there may be some different ways of using it and currently as Mr. Mundell mentioned there is the SSC in MedDRA, this is the function that is already made available and we need to have an enhanced version of this and there is also the question of maintenance. As was mentioned by the MSSO representative there has been some discussion currently ongoing for improvement of maintenance, and the other point cited by Mr. Tamiya, there have been some very important impacts in the area of E2BN2 and this is for the intro of MedDRA for regulatory reporting system. So this going to have a very big impact on the use of MedDRA so these are some of the aspects I would like to cover in my presentation this afternoon. What you see at the bottom, ICH conference, these are the conferences held, JPMA has had this special sub-committee working on terminology and they are regulatory affairs authorities I have contacted. These are the sources of my information. As you see I have mentioned the mere creation of terminology or dictionary is not sufficient and it is important to be able to use the terminologies and so there is with in the maintenance board conference, working groups have been established within the efforts of ICH so middle terms like " was document to be created in these efforts. Several meetings have already taken place February 2000 release 1.1, 1.0 was published. Well in fact this is where the conference was held to produce the document, the actual release came a little later and then you had the November 2000 conference where release 2.0 was produced and then April this year release 3.0 was produced. As Jim mentioned, this is the current version and in fact September of this year quite recent, 3.0 is compliant with MedDRA 5.0 and in November conference we produced release 3.1, which is compliant with MedDRA 5.1. And so currently we are finalizing the English terms as well as the Japanese terminology or translations and should be available to you soon. So what have we done with release 3.1? There have been some comments given by the users and on the basis of that we have made amendments. MedDRA 5.1 was used as a basis for further maintenance. In addition to that we introduced 3.0 we've seen the adverse events, medical, and social history were the targets but here we are looking at E2B and with the introduction of that system for the regulatory authorities so we decided to add a guideline concerning the recent use and investigations data. Currently this is in the process of production the English version is about to be established and when the Japanese translation is ready we will be able to give you the full picture very soon. "Points to Consider" is the

document that is established on the ICH level. I am also sitting on the special committee at the JPMA and what we are doing at the JPMA special committee is to use or produce a document that gives additional explanation in order to use Japanese version. We are trying to look at the English version and we are looking at some of the specific issues relating to the Japanese terminology and if you can, get the approval or acceptance by the ministry of health, labor and welfare then we'd like to produce this as a green book by JPMA. So additional explanation has to be there to explain specific issues relating to Japanese terminology and this is going to be positioned as the coding guide for the use of the Japanese version of MedDRA. The current schedule calls for the completion of this document by the end of this fiscal year or May 2003. By then we should have the JPMA green book. So on the basis of these efforts there are some other efforts on the practice on the part of the pharmaceutical industries, individual companies what do we need to do? "Points to Consider" 3.1, you might have seen the English version and when you discuss the points to consider document, there are some regional profiles or company based characteristics, something that is historically inherited, you might have specific rules, specific back drop that maybe different from company to company and in fact with in the points to consider document, for one event it could be A, B, or C so you have an option, a multiple option to choose from. The most desirable is that there is a single rule for the use of MedDRA, so no matter where you are, Japan, US, or whether you work for company A, B, or C, it has to be the same rule but the backdrop is different, the database is different, so considering that, it definitely need an option based on this, the condition of the different companies has to be presented. For instance, safety database, the coding for the safety and clinical trial. The coding in these two databases may be different b/c the objects of each are different, so there has to be an individual conditions prevailing in individual companies and therefore there has to be some good balance taken in terms of establishing a good coding group between the pharmaceutical companies and the question is which end of the options do you want to choose? Shown in "Points to Consider." You have to have very specific rules as well as additional rules to be established based on the structure of the objectives of the databases of the pharmaceutical companies and that has to be also developed. When you consider these points, as is described within the PTC document you should avoid trying to formulate your own solution. Otherwise if you don't see any good terminology with in the glossary you don't want to add any unique terminology that is specific to you company but rather change process, the formal procedure has to be undertaken. I think that is the most appropriate way to go about this. So in terms of rules as well, if possible, if at all possible, you should go through the JPMA or Users Group. You should at least make a submission of your proposals to one of these stakeholders so that this is shared amongst all and also a training of the users is definitely a must. The next point again concerns input of version control. The maintenance board conference of the ICH had been discussing this for a very long time now. Currently Mrs. O. has a prepared document. If this is approved by the management board, then this is going to be published as a recommendation of the MSSO soon. There are 3 possibilities;

one currently prepared this recommendation for single case reporting. When do you change the version, at which timing? The second point concerns the question of clinical trials. Which version would you want to use in the process of clinical trials? There has been some multiple options that have been proposed so the best suited for the pharmaceutical companies should be opted. Semi-annual version control is being provided for the single case reporting. The third point is with the change requests, if supplemental terms suggested, the question is how are you going to use additional terms? So these are some of the recommendations that are currently in the process of production and this is going to be produced as a recommendation by the MSSO very soon. If there are additional guidance given by any other countries or regions then that will have to be taken into consideration. The recommendation its self would only point to multiple options so each organization, companies would have to produce its own SOPs for in terms of version control. Before moving on to the question of output, you see that a lot of people are complaining about the difficult to use aspect of MedDRA; different from all the conventional scientific glossaries, in fact multiple glossaries or terminologies. When you discuss these issues, you have to come back to the original starting point of MedDRA. Why was it established to begin with? MedDRA itself in fact was established as a medical terminology for the sake of pharmaceutical regulation and also as an international standard within the framework of ICH, the US, Japan, and Europe to put together should have a common standard. So this is not necessarily a scientific glossary to begin with. You know, ICD or any international classifications there may be some excessive fragmentation and introductory guide of MedDRA says that within MedDRA the level required for the sake of regulatory purposes. If differences of the left and the right organs do not make any difference in terms of regulation, you don't want to differentiate the two. So this is not strictly speaking, a scientific terminology. And the other point that has often been pointed out is that the MedDRA currently as it stands has too many words and for the sake of input into the database, of course you can ensure high accuracy b/c you can get a very good linkage with the existing database but because there are too many words being used, for instance, for safety signals, detection for instance, there is a dilution of information and many people are concerned about this issue. This is not only pointed out in Japan but also in Europe and US as well. This related to the question of how could we identify a good search tool? More accurate information wants to be fed and more accurate signal detection must be assured and for this purpose, an output tool is definitely insufficient. As Jim from the MSSO mentioned there is the question of stability of MedDRA. I think what he meant to say is that good stability is being obtained actual users still complain of the lack of stability and the maintenance efforts must be continued. I may be repeating myself, but well standardization of input, taking the Points to Consider as a standing point, there are additional efforts being required and like wise the efforts for standardization of output and retrieval or search is definitely necessary again. Kindly several parties are discussing issues of search and output tool, improvement shall I say or perhaps the development of a new tool. As you are aware, the current MedDRA has the SSC and special search category. This is

the amalgamation of PT and the maintenance board has discussed the possibility of improving this and the other is the HLT, HLG T level which is a multi axial structure that can be used for searches and this is what is currently provided by MedDRA itself. As opposed to that as Jim himself mentioned, again the SSC the objective is quite obscure. It tries to cover too wide of scope. That's the criticism that has been voiced so far and so currently there this an effort of a MAG group, a MedDRA and a group starting to look at other possibilities but the MSSO, this is only internal to the MSSO. They are trying to find better ways of going about this issue and the other is a CIOMS group, has proposed a very similar point, race being a question and then they have a started the efforts of a SSQ, standard search query, and what's going to happen to these new efforts, we don't know but this is where they stand currently. First as Jim has already discussed, I may just be repeating, it's good to come back to important issues. The current SSC is an amalgamation of PTs but within the hierarchy, HLT, HLG T, and others can perhaps being put together and the issue constitute the MedDRA group, the objective which is to, well not necessarily to create a scientific search tool but a tool that would enable a search for pharmaceutical safety issues. I think similar point to mention, with a greater number of issues, prolongation, Robdimalitus, some of the most current issues of safety should be used. MSSO shall provide maintenance inclusive of the feedback from the users so that what is currently planned. Then you have the concept of SSQ, standard search quarry, by CIOMS working group. We really have met twice and CIOMS, as you are aware, is CIOMS 1, CIOMS 5, in addition to the adverse events definition is. The definition of adverse events itself, is recently published as a part of such an on going effort, for instance with the use of MedDRA, if you see FDA is trying to search they do this, if MCA wants to do a search they do that, if they are trying to do the same thing then what if the efforts entail different contents then that could have a problem. So standardization of the search tool is definitely a must. And on the basis of that concept the administration companies of the US, Europe, and WHO have participated in this practice. And if the search methodologies are different, from one organization to the other, the content certainly will be different so what ever can be standardized should be standardized for this purpose. The currently provided SSCs are not sufficient. As Jim said this is incomplete, and certainly this is what I mean. Now a preliminary meeting was held in May and actual discussion was started in September this year. I have looked at what they have sited so far, the ultimate deliverables may be different may be different but the basic concept, pretty much the same as MSSO MAG. I haven't asked any examples here but what is considered important is the links to the definition of adverse events as stipulated by CIOMS before hand but it seems like their concept is pretty much the same. The question is whether we need two of these initiatives or two of these tools? Well at least US, Europe, they feel this is an immanent issue and much labor is put into this effort. Now on the standard search query, there is a very strong participation of administration and that could probably considered an advantage. This is to just give you an example, currently SSC (Special Subject Category) for instance you have anaphylaxes. What this is again the current SSC is an

amalgamation of PT and so any of the PTs associated on one way or the other, to anaphylaxes linked together, 28 PTs in fact linked for instance some of the events or episodes that are expected as a result of anaphylaxes is also included with in this group. So if you use an SSC you must be able to see that anaphylaxes or anaphylactiod reaction may have developed but you don't know exactly whether that was anaphylaxes per say. On the right hand side, you see the current of examination by SSQ if you are looking up anaphylaxes, with in the HLT, you use anaphylactic reaction and what is linked to this is just these three PTs, anaphylaxes, anaphylactic reaction, anaphylactiod reaction so with a Special Search Category, for the MedDRA group, standard search query. What are they trying to accomplish with their respective objectives may become clear if you look at these examples. So with a number of regulatory authorities giving off approvals, such a common tool could be a very important tool. Next I would like to talk about the currently ongoing maintenance practice. As again, Jim mention some MSSO is trying to improve transparency of the maintenance information to be disclosed with in the discussion that is currently ongoing. The handling of modifier terms is part of the discussion and the out of that some of that may be included as a part of MedDRA 6.0 and for words with NOS the handling has been discussed and some degrees of agreement have already been reach but in the Management Board Meeting in September out of the 6 sponsors of ICH, I see only one has taken this as pending, we don't know whether we can make it to 6.0. Basically PT will not use NOS words, other than the 5 sponsors agree to it but EU has with held their position as yet. So we don't know whether this will become coming time for 6.0. As Jim mention again, well this has really nothing to do with us yet because we are speaking Japanese, but MedDRA has English and American spelling or words and the question of handling these English and American words will in fact MCA was the initial body to start this effort, so English spelling tends to prevail. The rule if you are trying to establish consistency you might encounter some difficulty. Again on top of HLTs, some changes have been proposed for MedDRA 6.0. Agreement has already been reached. Next as Mr. Tezuka mentioned there have been some issues about the Japanese language maintenance. As Mr. Tezuka mentioned at the time of 5.1 the Japanese language consistency has been addressed and there may be future challenges and regarding this point I really welcome your input. There have been also some translation issues. And these issues will be resolved, with a tighter coordination between the JMO and the users and another thing Mr. Tezuka mentioned, when translated more than one Japanese terms may end up with one English term and the current system cannot handle that so Japanese synonym as a file may have to be managed. Maybe that will be used for further maintenance. I believe this is a future challenge and E2BMT implementation shall be looked at in conjunction with code mobility and certain other situations and these will also be covered with MedDRA and then the question is can we cover everything with MedDRA? Is it sufficient really? M1 Group in ICH identified this issue early on and currently at JBMA we have been using the Emedes, a disease name code 28,000 or 29,000 codes are included and this code have been used and there is an improved version or a standardized version

the Japanese standard disease code is been well recommended but these are the Japanese names of the diseases most commonly used by Japanese doctors. Well it will be very nice if we can use them as they are in conjunction with MedDRA but actually some of these terms cannot be readily translated into English so if we try to use them in conjunction with MedDRA there should be pretty much difficulty so unless we have a clear policy, perhaps we should cover this situation with a word-for-word, change request on an individual cases. So this is again one of the challenges the Japanese side has to address. Next, it slightly overlaps with Mr. Tamiya's presentation but it will be to administration regulation will have a pretty big impact on the introduction of MedDRA to corporations. The administrative regulation introduction has been discussed in three regions while they differ in the introduction stage. MedDRA use has been mandated in Europe and Japan in conjunction with the administrative regulation. There have been some piloted tested in July 1999 as to the joint pilot plan and the policy paper has been released just this year and the EMEA it elucidated policy and a revised version went into the Notes for Guidance and it came out in March this year. They made specific recommendations as to what kind of data should be used for what and based on the policy paper discriptions we understand that the EMEA has been leading the international in Europe but they have an idea to prepare a network encompassing the EMEA, the member states and the corporations so that they can exchange information. They have to use E2B. EMEA has been pretty much advanced in the preparation and some of the member states are pretty much advanced in preparation. Some others haven't done a lot so the member states differ from member state to member state. E2BM maintenance and the MedDRA use has been define as certain items and there is one query to find an item. Well the LLT level code usage has been mandated but there is an exception. The PD, IDR items for which PT have been defined at the next maintenance, Europe will present these requests to MedDRA LLT in conjunction with the B31C. That's the lab test items. Mr. Tamiya said that European roll out should begin in January of 2003 but so far none of them have rolled out. It has been a request, just a request that you begin by end of January 2003 and there have also been requested to electronically submit the historical data 1995 through today. And a central approval and country approval and mutual recognition have been used. These different approval systems have been used but also poses a challenge and the member state situation, it differs so based on all these situations, the implementation and the future of the MedDRA situation in Europe will be different but overall some of them, some companies, may start using it by the end of January 2003. So there have been some pilot initiatives. And this is the American situation. There have been a lot in terms of the concept back in November 1997, Airista database rolled out. Back then, ICH guidelines were discussed and a MedDRA was covered it and it has been used as so. First of all FDA's database started operating, and then a public hearing about electronic submission and then pilot tested began too. And FDA acceptance at perforation was completed in Nov. 1999 and after that electronic submission has been rolled out. The memorandum, the first of the memorandum was issued in May 2001 stating that now companies can

electronically submit and after that some companies have been doing the electronic submission. And a vast notice a proposal on making electronic reporting came out in Nov 1998, its been more than 4 year so if our was issued back in 1998, electronic reporting was going to be mandated and MedDRA use was going to be mandated and that was what they wanted to achieve in 1998 and after that the EMPRIM in 1998, there had been discussions about no specific regulation proposals have been out since that so I'm not quite sure if the mandating will really take effect. But sitting aside, in terms of the reality the electronic reporting has been used replacing a paper in part. As some companies have already begun electronic submissions about 20% of the submissions have been made in an electronic matter at FDA. Besides the expert reports, periodical reports, the single case reporting have also been covered but at this time the MedDRA use has not been made a mandatory and Mr. Tamiya spoke a lot about the Japanese situation and the characteristics, there has been no ICH guideline notification per say but regarding the IND study the ADR reporting the use of the MedDRA may be handled in a pretty similar manner to the overall MedDRA use. Japan and the western societies have been different as to MedDRA use but there has been a lot done in this general direction. This is the last part of my presentation. MedDRA/J use for the purpose of the standardization among pharmaceutical companies based on the original schedule, it will be introduced in Japan next year and ADR MedDRA based reporting will come into reality so MedDRA will come to a major milestone and so that is also the case for the E2BN2. And preparing us all for that milestone, we would have to train people to take charge of MedDRA inside a company. Medical knowledge as well as MedDRA knowledge will be necessary for the MedDRA managers so to speak in a company. We also have to properly train the coding personnel and evaluation personnel about MedDRA. MedDRA is a global standardization tool and there fore the use of MedDRA global standpoint will be necessary and therefore the unique proprietary solutions in just one company will be inappropriate. JMO and external institutional seminars have been available when it comes to the training and education of MedDRA users. I think we have to cover these items for example the MedDRA and the JR relationship and the linkage I think it is currently necessary and may be unnecessary in the future though and a MedDRA structure and MedDRA mechanism, and MedDRA objective, and substance, the content, will also have to be educated and a MedDRA concept included in it or excluded in MedDRA will also have to be educated. And because we are talking to Japanese users, we have to educate MedDRA users as to the particular characteristics of the Japanese version of MedDRA. English language is the dominant language in MedDRA. It started out of coarse in English language so it always plays in the word or English language and we have been using it based on the translated manner. There has been some restraint if you have one word one disease, one term and some of the Japanese disease name will be translated into a single English term and we will also have to prepare the records we have to insure there is a rule established and operated in a proper manner at the time of the audit we would need the record. PDC document will be the basic and once the

green book of JPMA is prepared it should provide us with the basic guidance and we also need the awareness that you value MedDRA as the international standard. So we will also have to know the latest contents of MedDRA revisions have to be learned. A PDC document and peripheral information has to be acquired. And a standardization of the search tools will be necessary and we have to pay attention to the trend. The unexpected AE decision and new AE signal dictions may have to be standardized. But once we try to use the standardized detections we may be diluting the very specific information. We may loose specificity. It's a challenge so we will have to consider all these issues. So I have already spoken about the challenges I have been aware of in conjunction with the MedDRA use from the standpoint of a pharmaceutical company. Thank you very much for your attention.

## **VII. Question and Answer**

Q: My question is, the MAG, that is the MAG grouping, around when to be established and classification for MAG will be announced in advanced?

A: The MedDRA analysis groupings, as I was showing that we worked up a few prototypes, this is in preparation for the February meeting actually here in Tokyo with the management board, the MedDRA MSSO management board, to get permission from the to proceed with the implementation of that grouping so that's the 1<sup>st</sup> step. We are doing work to prepare for that presentation. If, and I think we will probably get permission to precede with that, we will post all of that on our websites and will be sharing that with the JMO as well because we want to make sure what we are developing is a useful product. As far as plans, we were also, if it approved, even considering putting a pilot piece of information on our 6.0 release and that's something else that is to be discussed at the management board meeting in February. As far as a long-term timeline, we don't have that yet. As far as when it will be done, I don't think it will ever be done, because it will be an evolving piece that we will be able to release in sections to try to improve. One of the things we are doing now is that the special search categories that exist, we are reviewing them to see if they are really useful, if there are terms missing, if there are new special search categories would be better if we maybe broke a few up into smaller groups. And we have posted several things on our websites for comments from our subscribers asking them for their ideas as to how we can improve our special search categories.

Q: I'd like to ask a question of protocol use. When we ask the investigators or CROs to putting the adverse events to the case report using MedDRA, what is necessary?

A: Let me respond in Japanese. Well there have been questions raised by Japanese users. The question is whether you should ask the investigators, the doctors to use MedDRA. The idea is good of coarse. The M1 of ICH or the current MedDRA concept does not include such a concept. MedDRA is for the

sake of regulation of pharmaceutical products and therefore as we said in my presentation, if a doctor wants to classify adverse events in a scientific manner, is MedDRA appropriate? That is something you have to question and so I don't know whether doctors are willing to use that. Now in reality for instance we wanted to use this and include in clinical trials, case report form is to rate them by the investigators, that's the rule, and of course that's not a scientific judgment but rather an adverse event reporting so it is for the purpose of regulatory objectives. In such uses perhaps it should be promoted. I mean the use has to be promoted there. Well JART has been used in the past and I don't think the position of MedDRa should be interfering with the use of JART.

Q: What about copyright contract? That is my concern.

A: There is a question right now in Europe with the EMEA. The EMEA is coming on line next year with a web-based reporting system and in Europe; individual doctors are required to file to the government their adverse events. They do not file to the pharmaceutical company. I'm not sure in Japan what the guideline is. There is a question of how do they afford a MedDRA subscription? Do they get a MedDRA subscription? We are in discussion with them b/c any decision is not our decision. We can make proposals, we can come work out an idea but it has to go back to the MedDRA MSSO management board for discussion and the IFPMA, the trustee, approval of whatever solution comes up. It is an issue, it is being discussed, there is no solution right now. As far as do you give every doctor in the world a MedDRA subscription? I don't think people want to do that, people don't even want to have social security numbers so I don't have an answer for you. The EMEA is expecting people to use MedDRA for their clinical trials as well as their safety reports and pharmacovigilance reports. But the question comes when you become a small individual reporter, what are you supposed to do and how do you do it legally without violating licensing and subscription rights. Does that answer your question?

R: Yes. Thank you.

Q: This topic was not including today but the September version MUST that is the updating tool, that is being prepared I read, let us know about that.

A: Yes. It is a tool that has been proposed. We are in the position right now of finding some people to partner with in the pharmaceutical industry to help us develop the tool. I have no other information about it right now. We don't have a prototype. We have been in discussion with at least 3 different mid size to large pharmaceutical companies that have expressed and interest in helping to develop it but so far nothing has happened to actually start the work.

Q: Now TRW has an Autocode system I believe, are they any different from the MUST?

A: Yes. The MUST that is being proposed is a specific tool for version analysis so when a version is released, a new version of MedDRA, it would hopefully allow the company who is using this tool to find out how it affects their coded data. As far as are there now exact matches in MedDRA that did not exist before? Have primary SOCs been reassigned to SOCs that are important to the specific company? And it gets into several layers of possibility on how the development goes, the type of information to help companies deal with versioning issues. There are a lot of different factors about version control besides just when you go live with the next version of MedDRA? How does it affect your legacy data? Do you recode your data? How do you analyze the impact of data that is potentially may need to be reviewed for recoding? These types of things so that is what the MUST tool is trying to address some of those issues as far as its intention. The Autocode tool that TRW has is a tool for actually coding data. It has a built-in smart knowledge base system that learns from its historical coding as far as how companies want to code certain events. It also has the syntactical manipulation of the terminology. Again, just as Mr. Sakaria said, Auto code is based on an English-based system at this time and doesn't deal with any European or Asian languages. The Autocode however, that TRW has, has been taken off the market because we are in discussions with another company of potentially buying the product from us and they would take over the continued maintenance and development of the product in the future. So right now, we are no longer selling Autocode but that's the difference between the two products. Ok?

R: Ok.

Q: A fairly simple question I think. How did you decide on new terms to be included in the MedDRA dictionary sort of what areas do they come from?

A: Primarily from the user group, from the subscribers. We have in the past when we were doing the 4.0 review that I spoke of earlier, we came up with holes in MedDRA where you had some of the infection terms but not others, that type of thing. But that primarily even came from feedback from training classes, through conferences from again subscribers that said "I'm trying to use MedDRA, I can't code this set of issues because you only do A and B but I have to deal with X, Y, and Z. Diabetes mellitus was the only diabetes in MedDRA for a long time and there were other examples where you would deal with a certain type of condition but ignore a lot of other conditions that were in the same area. So in the 4.0 based on that type of guidance that we got we added terms ourselves that we thought were important. But primarily most of the direction we got from the subscriber base submitting change requests to us, which is part of their subscription benefits. JMO subscribers have the same right only they submit the requests to the JMO for review, which in turn pass them on to us and we go through the process. The term that comes in is reviewed by the MSSO medical staff which is made up onsite of 3 doctors and 2 registered nurses, and then goes to international review which again includes JMO and their medical

expertise plus a doctor in France, German and Spain, which are part the MSSO supporting Europe. There has to be a total consensus that this is a recognized term internationally, what that definition is and that it should go in MedDRA, that there is not already a condition that exist so that there is no “why can you use these other terms?” because this is just a synonym of an existing event. Now that said, there are a lot terms in there that are synonyms and that come from the fact that when it was created a lot of terms were put in to help with coding as was mentioned earlier by Mr. Sakurai and they also came from other legacy terminologies that were part of the original development, like WHO-ART, COSTART, ICD-9, so that’s where they come from, primarily it’s all from the users, that’s why the slide says if you want to help, if you want to know what’s going on, participate, send in change requests, check the website, we post most of our major questions/issues about development on the website for comments, contact the helpdesk at the MSSO or the JMO.

Q. I have a question about the SSCs. New concept is being debated/discussed with the CIOMS, MAGs, for MedDRA the results of the two groups will be put together to create one single new concept, is that how it’s going to work?

A. I don’t know, we don’t know because totally different groups discussing ways of using MedDRA but from the prospective of the users, we are saying that there should one way of going about it. But they are totally separated and doing different work.

Q. The MedDRA version control is my question. The other day using MedDRA, we are to make safety updates starting in April of next year, but the special investigation reports or the safety reports concerning the MedDRA version control in relevance to the re-examination, I would like to hear.

A. Sorry, Mr. Tamiya has returned to his office. But as of today I have not heard of anything being discussed now regarding that point. Currently the MSSO recommendation is the one, which is issued. The Clinical Safety Report supports the recommendation from the MSSO. Six options have been recommended so among those six options for example at the time of clinical study which version of version control, as for the PMS, such version control is to be done so that you should decide by yourselves. But as to whether the MHLW will issue some instructions over-riding that I am not sure.

A. Basically no of the regulators have address guidelines on version control. The MSSO has provided some papers in response to these same questions as far as discussions we have had with different groups in terms of how they deal with version control. We have posted them as sort of best practices being done in industry right now to help companies who don’t know how they want to approach it and they can look at these papers for ideas but no regulator has yet put out a real guideline as to what they expect. The closest I have heard is to

say if you as a company set up a practice or policy that is documented and you follow it then they will, if they audit you, they will audit that you were following your own practices that are good clinical practices or whatever practices appropriate. But that is all that is there right now.