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P R O C E E D I N G S

DR. LIMOLI: Good afternoon. I'm sorry for the delay. Welcome to our public meeting on the ICH process as we prepare for our meetings in Virginia June 7 through 10.

I'm Michelle Limoli, the FDA ICH coordinator, and I just want to remind you that we are having a meeting transcribed. Sharon Shapiro is here. And we ask that if you have any questions or comments for our speakers, would you please speak into the microphone? We have one set up here in the audience, so you'll have to get out of your chair and come to the microphone so that Sharon can hear you.

Our agenda, we have agenda and handouts in the back, and we are pretty flexible today with the exception of one presentation, which is by Tim Mahoney at 2:10. Tim is between meetings today, so he's going to have to leave us I believe at 2:40. So we're going to try and adjust our schedule when Tim comes in today.

We're going to start off with Justina

Molzon from the Center for Drugs, and Justina is going to give us a quick overview of the ICH process and then talk about the eCTD. Thanks, Justina.

DR. MOLZON: Good afternoon, everyone. I actually have some of the same slides that Christelle had in her overview, so I can cover the same points, and we'll just get started.

Basically, ICH is a unique approach. It was created in 1990. It's an agreement between the European Union, Japan, and the U.S. to work on harmonization of regulatory requirements for submission of new molecular entities to the various regulatory authorities. And at that time, in 1990, those three regions--European Union, Japan, and the U.S.--represented 95 percent of global research and development, and that's why those three regions were selected.

The objectives of ICH are to identify and eliminate the need to duplicate studies to meet different regulatory requirements, and the best example here is Q1A, the stability ICH guideline.

And at one point, there were three different temperatures and three different humidity settings for companies to do their stability settings on. So there was one temperature, one humidity setting for Japan, one for Europe, and one for the U.S. A company literally had to do three sets of different stability studies, and you could picture three different buildings, one for each. After harmonization on one temperature setting and one humidity, they could eliminate two of those buildings, so this really helped industry in cutting down on some of the duplication needed for submission to the various regulatory authorities.

So this leads to a more efficient use of resources in terms of human for clinical trials, animal preclinical studies, and the material for CMC issues, and helps make a more efficient R&D process.

From a public health perspective, this means quicker access for patients to safe and effective new medications.

This is just a picture of the three

regions, six parties. Each regulatory authority is associated with its trade association. So for the European Union it's FPR, for FDA it's PhRMA, for the Ministry of Health, Labor, and Welfare it's JPMA. And these are the six parties that make up ICH. I would also like to indicate that there are observers from WHO, Canada, and EFTA also at the table.

The way ICH works is there are a series of Expert Working Groups that are described by the category of their topic, so there are Safety, Efficacy, Quality, and Regulatory Communications Working Groups. These working groups work on their topic and then report to a Steering Committee made up of the six parties and observers that monitor and facilitate the Expert Working Groups' activities.

So there's an Expert Working Group for each ICH topic. There's a topic leader, one from each of the ICH parties, and the whole point of this group is to develop consensus on technical issues, and this results in ICH guidelines that are

described as Safety--S, E, Q, or M. This leads to some confusion if you're not familiar with the nomenclature.

To date, there's been over 50 harmonized guidelines. Some of the efficacy topics include the recent E14, which is QT prolongation; 11 was pediatric topics; E9 is statistics; E5, ethnic factors; safety, we're working on a topic right now that will be linked with E14, QT prolongation. So we're looking at QT prolongation preclinical studies.

Quality, there's been seven topic headings with 19 guidelines. They're split out with many of the topics also having guidelines on biological-type products.

The medical dictionary MedDRA you'll hear about later this afternoon.

Electronic standards, ESTR I is the Electronic Standards for Transmission of Regulatory Information. We have done a lot of work to be able to communicate with our fellow regulators. The eCTD, the electronic Common Technical Document, is

an offshoot of this work. And the culmination of all of these guidelines is actually the Common Technical Document, where if you picture these 50 harmonized guidelines being building blocks, the Common Technical Document merely puts those building blocks in the same order so that a company can just put together an application in one format and then submit it to the Europe, Japan, and the U.S. CTD is merely a formatted table of contents, taking advantage of the fact that we harmonize over 50 different topics.

This is a picture of the ICH five-step process. The first step, Step 1 in pink here, is to build scientific consensus, and then you sign off on an agreed-upon text after you've had a comment period. Step 3, the regulatory authorities start working with the documents and incorporate those comments, and then, finally, it's adopted as a harmonized guidance at Step 4, and at Step 5 it's implemented into the region. So the governments of Europe, Japan, U.S., Canada, and Switzerland implement it into their process. And for the U.S.

this follows good guidance practice. So our good guidance practice, which is now a regulation, is in step with the ICH five-step harmonization process.

Part of ICH's efforts to be transparent is to put on large conferences every two or three years so that people not involved in the ICH conference can come and meet with the ICH experts that have worked on the various documents and, you know, interact with them and ask questions.

We recently had one in Osaka last November, ICH 6, but the conference I want to focus on is the fifth conference in San Diego, which focused on the CTD.

This is a picture of all of the people that worked on the creation of the Common Technical Document. This is a picture of the Steering Committee and then all the Expert Working Groups for the quality, efficacy, and safety groups. And these were the people that actually worked very, very hard right before ICH 5 to get these documents finished so that they could be burned onto CDs and distributed to the participants at the ICH 5

meeting in San Diego at the end of the year 2000.

So it's because of all this flurry of activity that the ICH CTD documents weren't exactly perfect when they were issued because the groups had little time to interact with one another in terms of the style, the formatting, the numbering, et cetera.

So as I've already said, these groups worked in isolation. After ICH 5, we realized that the documents had to be edited for consistency, and the FDA volunteered to do this so that there would be consistent numbering systems, style, and format between the safety, efficacy, and quality aspects of the Common Technical Document.

Once all of the regulators started preparing their documents for publication, we realized that some areas needed clarification and that the CTDs should be as clear as possible. So we devoted much effort to do away with ambiguities and inconsistencies. This, of course, is a continuous process. This is why the ICH Q&A process was developed, to help people that had

questions that might be ambiguous or needed clarification, to submit questions to the ICH process so we could respond to these issues.

So the CTD has evolved and I would say improved over time. This is the very simple triangle. This was the concept at the very beginning. But when we started talking to different groups at DIA raps and other outreach meetings, things that we thought were obvious weren't. So we had to change the format a little bit to include numbers to indicate the order that we wanted these documents submitted in.

We had intended a layering effect where you'd have overall summaries and overviews above more detailed information. Some people were presenting it in a silo fashion, so all of the same information was grouped. So we had to clarify how we actually wanted this information to be presented.

In terms of FDA's Guidance, we created a General Considerations Guidance back in 2001 on how to submit marketing applications according to the

ICH/CTD format. We had a lengthy--it took a while for us to actually get the documents into a form that we could post them. Then we had a comment period, and we recently reopened this docket last year so that people that were then working with these CTD formatted documents could once again submit comments. And I always like to point out that comments are always welcome. If your company is starting to work with these documents and you would like to point out something else that still needs clarification, the docket still remains open.

The General Considerations Document basically describes how to organize NDAs, ANDAs, and BLAs based on the ICH Guidelines on CTD. And at the end of the document, in Appendix B, it actually lists the location of regulatory requirements for these submissions.

The General Considerations Guidance explains what we expect to be submitted. It describes Module 1 in terms of its administrative and prescribing information. It gives a physical description of the CTD submission. It talks about

requirements, some of the obsolete guidances, the logistics of submitting these documents on paper, and then the time frames are included.

We also posted the actual CTD documents back in 2001. We kept these in the review discipline so that people could print them out easier instead of incorporating them in one great big document. And we also split off the safety appendices because there were a large number of tables, and we posted those documents in Word so companies could populate the tables without have to re-create them.

This is just to give you an idea of some of the submissions that have been submitted to CDER. This just indicates--and Farid Benhammou, who's been an immense help in doing the statistics for a lot of these documents, will be going into this later. But this just gives you an idea that most of the review divisions within the ODEs have had experience with these products, and we've also had nine ANDAs submitted to the Office of Generic Drugs. So this just gives you an overview of the

divisions that have had submissions.

So, to date, we've had 93 submissions in CTD format to 17 different review divisions, and this includes all six ODEs, Office of Drug Evaluation I through VI, and the Office of Generic Drugs. Some of these in the beginning were hybrids. They were safety or quality modules or new formulations, new dosage forms, new salt, also new indications. And we're just now starting to get complete CTDs for new molecular entities.

CBER has had four prior approval supplements for four recombinant products. These were all on paper. They were not electronic Common Technical Documents.

Now, what I tried to do here is just give you an indication of what a typical NDA review team is, and here I've tried to show that we've marched through the different types of CTD submissions. More people have been exposed to the various documents.

The very first document we received in CTD format was actually a pharm tox hybrid. That meant

that just the pharm tox section of the document was submitted in CTD format. Then we started to get quality hybrids where the quality sections, the CMC sections of this document would be submitted in CTD format; then new formulations; then new indications; then new combination products; and then, finally, new molecular entities. So as the submissions became more complicated, more and more people became exposed to CTD. So it's only through exposure to these new documents will our staff have a better understanding of the intent of this process.

The good news is we've had no refuse-to-files. Some of these weren't perfect submissions, but they could be reviewed. We've been flexible during the voluntary submission phase, and these were for documents before July 1, 2003. To date, we've had submissions from 59 different companies. This includes large "PHRMA" companies and midsize companies, small companies, and even the World Health Organization has submitted a document in CTD format.

This is just a summary of the NDAs CDER has received, at 93. CBER had four BLAs, and so the total is 97, which, you know, I'm looking forward to breaking 100. I remember when we used to have like 9, 12, so to me this is pretty exciting.

Something that is misunderstood is the language that we've used to describe our intent for submission to CTDs. The CTD is mandatory in Europe and Japan, but in the U.S. it's highly recommended. This is because we, as I mentioned, follow good guidance practice, and this is the strongest language we were allowed to use because ICH guidances are not mandatory in general. So good guidance practices require that the CTD not be mandatory, but this is not an indication of our lack of commitment. It's just our peculiar regulatory structure. And so highly recommended to me is like a very, very strong indication that we expect the applications to be submitted in this format. And the presubmission meetings indicate that most companies are following this

recommendation.

I've been invited to over 30 presubmission meetings. I help the review divisions that have not had experience with CTD to walk them through the structure of the document. I'm also available to sponsors if they have questions. I'm sort of turning that responsibility over to our Office of Information Management because now they have people in place in each of the ODEs to help with these issues. And we're trying to collect areas of concern and issues still requiring clarification.

Tim Mahoney--I saw him here. Where did he go? He will be talking about the eCTD, and last August, there were some new documents issued on the eCTD. And these are very helpful because they actually give you the cumulative table of contents for a complete paper CTD. We have not finalized the Draft General Considerations Document because we figured we've evolved past that, so we're focusing more on the eCTD and using some of the documents that are being created for the eCTD to explain in more detail this structure of also the

paper CTD process. So I've provided you the website for the most recent version of these documents.

So this is actually what was posted and has recently been updated in March of 2004. There's the Module 1 Specification. We've had many changes in submissions, including risk management plans, pediatric information, since the original CTD was established. It gives you the specifications for Modules 2 through 5, and more information on table of contents heading and hierarchy, and Tim can explain study tagging files.

If you have questions, we want to make sure that you all get the same answer to similar questions, so we've created specific mailboxes for the CTD and e-sub, as I've indicated here.

So, in terms of next steps, we're going to continue meeting with project managers for feedback on CTD submissions. The project managers are the ones that organize the review of the documents. We're increasing our interactions with the Office of Generics staff because they're starting to get

ANDAs in CTD format. And increased submissions will help determine effects on the review process, and as I've already said, presubmission meetings indicate more CTDs are on the way. What we're doing is just-in-time reviewer training. We don't want to have massive training programs until people have actually worked with these documents and have an understanding of what they are. So we have just-in-time training by our Office of Information Management. Someone will sit and meet with the person. Or we have something called over-the-shoulder training where someone will actually sit with a person and go over on their own computer, you know, exactly how these things are put together. And we're looking forward to receiving submissions so both industry and regulators can experience the CTD format.

Now I'm going to turn this over to Farid, and he's going to walk us through some of the most recent statistics on CTD submissions.

MR. BENHAMMOU: Good afternoon, everyone.

As Justina has just said, I've been

helping her with her presentations and with tracking the CTDs within the agency. And I'm going to provide a short overview of the CTD experience to date that she already talked about a little bit, and I will follow with an overview of the complete CTD NMEs among NME submissions.

This is here a picture of our experience with the CTD submissions, and this represents approximately the structure of CDER, and you can see that for the different offices, ODE I, the Office of Drug Evaluation I, we got 21 submissions; ODE II, 14; ODE III, 10; ODE IV, 14 CTDs; and ODE V, 13 CTDs. And you must remember that most of the therapeutic proteins already transferred to CDER are the ones which are in the CTD format. That's why ODE VI, recently created, has this important number of CTDs submitted.

Here we can go into details through the different divisions. For the Office of Drug Evaluation I, the Neuropharm Division, we got seven Common Technical Document submissions; for Oncology, 10; Cardio-Renal, 4. And I'm not going

to go through all of them, but just notice that for the OTC Division and the medical imaging or Radiopharm Division, we didn't receive any.

Here this is the CDER CTD submissions by month. This is just giving you an idea of the rate the applications are coming in. At the beginning we had voluntary phased submission, so that's why we didn't have a lot of CTDs submitted. And at this time companies could submit an hybrid. Instead of submitting a complete new drug application in the CTD format, they could just submit the quality section in the CTD format and the other sections in the old format.

You need to remember that we're really committed to this process, and even if our guidance says that this is only strongly recommended--and Justina explained that very well--I think that companies understood that. And you can see in this graph that just a couple were submitted in 2001 and 2002. But the number really increased after it became highly recommended in July 2003. Then CTDs were submitted in September, and July and August we

received six.

There is usually an increase of the submissions at the end of the year, and apparently at the beginning of 2004, it's not really too bad. So it means that clearly the companies are moving towards this new format and adopting the Common Technical Document.

Here this is a nice chart comparing 2001 with 2002 and 2003 and 2004, and it shows clearly where everything started. You can't really miss it. It was in 2003 when the CTD became highly recommended and we received 52 submissions at that time.

I wanted to add something else. I think that you can see that for 2004, we have already received 21 submissions, and if you compare that to 2002, we can, I think, easily double the number of submissions we received in 2003.

Now I will just give you an overview of the new molecular entities, and usually companies kept asking us how many--do you know how many new molecular entities have been submitted in the

Common Technical Document format? And I tried to bring an answer to this question, but because we don't have a lot of data about that, I will just show you a trend.

You can see that the different offices have received new molecular entities in this new format, from I through VI, and here you can see the different divisions in the text. And so the NMEs are represented by a dot. Let's just look at the Office of Drug Evaluation I. For the Neuropharm Division, we received one new molecular entity in the Common Technical Document format. And one of the most dynamic fields, Oncology, we received seven new molecular entities among the ten CTDs received by this division. And for ODE VI, we received three new molecular entities.

So here is the number of the new molecular entities in the CTD format for each month, and for July, we received one new molecular entity, but it wasn't in a CTD format. August, you can see that we received one, and it was in the CTD format. September, 2 among the three were CTDs. October,

one only was a CTD. And December, one among eight.

And I told you that there is usually this increase of submissions at the end of the year. That's why there is this big difference between the number of NMEs and the number of NME CTDs. So I guess that companies were not really ready to submit new molecular entities in the CTD format. But I'm really convinced that at the end of 2004, the difference will be very small, and most of the NMEs will be in the CTD format.

Now for 2004, in January, we received two NMEs, and those two were in the Common Technical Document format. And so for sure, at the end of the year at least half of the NMEs will be in the Common Technical Document format.

Here this is just a graph showing what I was talking about. So for January, you can see that the two were in the CTD format.

I think this is my last slide. This is a cumulative view of the CTD submissions, and presubmission meetings are really indicating that more CTDs are on the way, and Justina said that

before. After July 2003, the number of CTDs increased really quickly. In July, we reached 37 CTD submissions, and after less than just one year, there is this big jump until 93 submissions in the Common Technical Document format.

So I will just leave you with this nice picture of the Common Technical Document, and I want to thank you all. And if you have any questions--or we are going to the next speaker?

DR. LIMOLI: Are there any questions?

[No response.]

DR. LIMOLI: Thanks, Farid.

MR. BENHAMMOU: Thank you.

DR. LIMOLI: We'll now hear from Tim Mahoney about the eCTD, and I just wanted to remind you that Tim has to leave at 2:30. So if you have questions for Tim, you might want to ask them during the presentation, if that's okay, Tim?

MR. MAHONEY: I'm sorry?

DR. LIMOLI: If they ask you questions during your talk?

MR. MAHONEY: Sure, absolutely.

Good afternoon. I'm actually speaking across the hall at 2:35, so I'll make it quick. My name is Tim Mahoney. I work in the Center for Drugs in the Office of Information Technology. I'm the Director of the Division of Application Development and Services. We basically develop any CDER or jointly with CDER and CBER applications and maintain them in operations and maintenance.

I'm also the rapporteur for the M2 Expert Working Group and the ICH eCTD Implementation Working Group. It's the same working group, but depending on the topic, we take on a different role. The M2 Expert Working Group administers standards related to technology. The eCTD Implementation Working Group works on implementing the eCTD. So we split our meeting up depending on the agenda.

What I'd like to talk about are the agreements and the information that was published at our last meeting in November as well as the agenda for the upcoming ICH meeting in June in a few weeks, as well as where you can find all this

information. One thing about the eCTD is there's lots of information.

For those of you not familiar with the eCTD, it's no more than the electronic transmission format of the Common Technical Document from industry to regulator. So any CTDs that come in electronically would come in the electronic Common Technical Document format. The hierarchy, the headings mimic those from the CTD, and we're not a content group. We get everything related to content from our CTD Implementation Groups.

The eCTD has been final since September of 2002, and that means in ICH it's reached Step 4 for Step 5 implementation in the regions.

What we found, though, during that time is that we needed to manage and control the eCTD specification, because no matter how much testing we did, there were still going to need to be modifications that we couldn't really see until we implemented the specification.

Based on that, we have a pretty good process to manage the changes, and pretty much

anyone in the world can submit questions or submit a change request.

We had enough of them at the last meeting, 19 in total, minor change requests that we needed to publish a new version of the eCTD specification. So in November, we recommended that 3.2 be released with generally fixes and some clarification on language. So really minor changes.

What you'll find in the spec is in very beginning it lists the change request numbers that were implemented. So, in a sense, you could then refer to our change control document as a version description document to see what's really changed. But if you had been implementing the eCTD, it didn't really affect you.

We also worked last meeting at the long-term requirements, the business requirements for study file management. This goes into a long history--well, my entire history with ICH since about September 2002. When the eCTD specification went final to Step 4, the FDA in implementation found that there was lack of granularity,

identified granularity for clinical and nonclinical study reports. And from the meetings follow that, we've been presenting that issue to our partners in ICH and reached agreement last summer to move to something called the study tagging file, which the JPMA developed the technology for, but the FDA has pretty much alone been implementing. And we received harmonization for that within ICH.

The issue was it was developed sort of off the cuff. It didn't go through the ICH step process, but it was preventing the FDA from implementing the eCTD. So we called ourselves on the point: You know, does the FDA wait for a long-term solution or a solution? Or do we implement something and also work on the long-term solution?

So what we agreed to do was implement in the FDA the study tagging file, but also re-evaluate the business requirements needed for study file management, as we're calling it, and look at a solution through a step-wise process. So at the last meeting, we baselined at least the

requirements for study file management.

This is a follow-up to the last public meeting, but we mentioned that in November we'd be talking about a PDF broken link issue. And it's an issue that is not yet defined. So we deferred that issue, if you've been following that along.

Usually, we're going to be publishing a new Q&A document after every meeting. We generally have gotten questions or at least change requests for every meeting, so from the eCTD IWG you can expect an updated questions and answers document generally after every meeting.

So for this meeting--excuse me. It's still going on. I'm sorry. For the last meeting, again, the dual role that we serve. The M2 Expert Working Group needs to look at the recommendations, and we did look at two of them related to media type, CDs and floppy disks, as well as recommended a new media type for DVD ROMs.

To finalize that, we'd also like to publish them in a user-friendly format in one notebook scenario. So in between the last meeting

and this meeting, we've been consolidating all of our recommendations that relate to security, the ESTRI gateway, as well as media types and that sort of thing, and combine them in one place to be published on the ICH web. Right now the FDA hosts them, which is not really the proper place for them. So at the end of the June meeting, we expect to have all those updated recommendations published on the ICH web where they belong.

So, for June, we'll be continued the long-term study file management, hopefully to the point where we reach a Step 2 document, which is then something that you can see and comment on. And we actually welcome and need your comments, particularly those who have experience in implementing the eCTD.

That's going to take up most of our meeting time, trying to finalize this Step 2 document, which is then ready for testing. So, in addition to the document, we'll also need to identify a test bed of scenarios where each of the regions can go back and test our recommended Step 2

document.

The comments we're looking for, particularly from the general public, are: Do you see any issues with that? Have you done your own testing? What are your feelings on that approach? And we actually welcome and need that information once that document's published and it's able to receive comments.

Again, that's most of our meeting, we're going to be working on and looking at the deficiencies in the study tagging file. If you represent a solution provider or an industry submitting to the FDA and you've submitted via the study tagging file, and if you're not technical, you don't really need to know what the study tagging file is in terms of technology.

But if you are and you're working on those solutions, that's a consideration we're also keeping in mind. Does it make sense to switch from that interim solution? And how long is interim?

Again, we're going to move our recommendations from the FDA Web to the ICH Web, or

at least propose it, hoping the Steering Committee approves on that.

We have some minor corrections to a common view style sheet of the eCTD. A style sheet is very much like a Web page, for those of you not familiar with the term, where two people, regardless of their software infrastructure and the tools they use, can take a common view of an electronic Common Technical Document; as well as every meeting we'll be processing any change requests or questions that we receive. But the majority of the meeting will be on the long-term study file management.

There's lots of information up here. What I tried to avoid in my presentation was re-posting information that's actually published in a format that makes a little bit more sense. So from the ICH Web, you go to the Common Technical Document section, and I think we've got the biggest one in there under electronic. And there you'll find the ICH specifications as well as a detailed description of our change control process, the eCTD

style sheet, change requests t we've reviewed, and we either approve or we reject them as out of scope. We defer them to be answered in Q&A or we defer for testing or to a lack of time.

So if you have a question, a good place to start is has anyone asked this already and see what the status is up on that change request document, and all that information you'll find on the ICH website.

Now, the FDA also has some regional guidance and specifications that we've tried to assemble in a logical order for those of you thinking about submitting electronic Common Technical Documents to the agency. And that first website under FDA eCTD lists those logical steps. First is read all of this information that exists in both ICH and the FDA. And we provide a copy of the software that we use to process and view eCTDs. This is a copy of the software. This is not a software installation. So you would need your technical folks to take a look at it and see if it's even possible for you to install.

We provide a sample view of how the FDA reviewers will do and actually will view eCTD submissions, as well as many specifications geared towards the regulatory, scientific, or IT professional.

And, as usual, at least from the CDER perspective--we meet weekly with our CBER colleagues on this--you can send an e-mail in if you have a question. We're actually implementing eCTD as a dialogue since it's new for industry, it's new for the FDA. And it's worked out quite well.

That's my presentation at this time, and I already see a question. So what questions do you have/

DR. LIMOLI: Please identify yourself.

MR. PALMER: Donald Palmer with Octagon Research Solutions. I'm just wondering, a number of the other specifications of eCTD are like C-disk and a couple of other things related to HL7. I'm just wondering, do you have any comment about how the standards related to HL7 and standards with ICH

for eCTD are going to operate together or not?

MR. MAHONEY: The question relates around--the eCTD is a transmission mechanism that transmits electronic Common Technical Document information. You're looking at that--and I think Justina had it once as lobster strings, and the eCTD holds that content. The HL7, particularly the SPL, the labeling issues, are that content. You know, so you could have PDF files in there for narratives. It really depends.

We haven't implemented that yet, so I would be wary to provide insights until it's defined. But basically the eCTD is just--it provides the hierarchy for where that information will sit, and that information could come in multiple file formats. So that's something that we have to look at as we implement each standard. So when the FDA implements something like SPL--structured product labeling, excuse me for the acronym. Labeling is a component of a CTD and an eCTD, so how does that interchange? But it would be when we implement those file formats.

That's an excellent question. It's the same question I had, by the way, as an IT person. How do you want us to implement this? And we figured that out through a project where we defined the requirements, defined the technical architecture that that has to exist in, and then either procure or customize or develop the solution.

So that was pretty much a non-answer answer, but basically we don't know yet.

Any other questions?

[No response.]

MR. MAHONEY: Well, if you think of one, I'll be across the hall in D and E, so you can just come over.

Thank you. Have a good day.

DR. LIMOLI: And now we're going to have a presentation on other regional perspectives from Christelle Anquez. Christelle has been with our office over the past four years working on the ICH process, and this will be her last meeting representing FDA, and we're dearly going to miss

her because she's been a great asset to us. She's going to be leaving at the end of June.

So, Christelle, are you ready?

MS. ANQUEZ: Good afternoon, ladies and gentlemen. I will begin by presenting you the implementation status of the CTD in the other ICH regions: the EU, Japan, and Canada.

After the sign-off at Step 4 in November 2000, each regulator published the M4 guidelines. Since the CTD format was introducing a big change, a two-year transitional period from July 2001 to July 2003 was deemed necessary. During these two years, the sponsors could use either the old format or the new CTD format. At the end of this period, the CTD became mandatory in Japan and the EU, and highly recommended in Canada. I'll present the transitional phase and then the current phase.

Europe, Japan, and Canada published the CTD guidelines and also published guidance for industry. The EU revised the Volume 2B of the Notice of Applicant in July of 2001 to introduce the CTD format. Japan published in June 2001 an

Organization of Application Dossier appended to new pharmaceuticals applications for approval. And Canada released its Preparation of Drug Submissions in CTD format in September 2001.

Once the CTD guidelines and recommendations were published to assist the sponsors in using the new format, industry was encouraged to do so. Sponsors were given some flexibility and were allowed to mix formats between the old and the new format, provided that the format used within a module or part would be the same.

During these two years, communication was essential to provide additional guidance, tools, and also receive feedback which would help the regulators to highlight what needed some more guidelines, more explanation, clarification.

EU, Japan, and Health Canada organized respectively internal meetings, external workshop responses for submission meetings, also in some cases internal evaluation forms for reviews or external surveys. Regional questions and answers

based on regional experiences were also posted on each website, and ICH Q&As were also provided to help sponsors.

So how many submissions were received during this transitional phase? In the EU under the centralized procedure, 25 submissions total were received: 6 concerned Part A products, which is biotech products; 19 for B products, the chemicals and all others.

In Japan, 16 submissions were received: 5 for biologics and biotech products; 11 for chemical drugs, of which 5 were new chemical entities, 5 already approved drugs, and 1 combination.

Sixty submissions were received by Health Canada, of which 50 chemicals and 10 biologics and radiopharmaceuticals.

July 2003 marked the end of the transitional phase. In the EU, the Annex 1 to Directive 2001/83/EC, which is now Directive 2003/63/EC, was revised to reflect the CTD format. By introducing the CTD into the directive, the EU made its use mandatory. As a quick reminder,

guidance, whether in Europe, Japan, Canada, here a guidance. In the EU, regulation directives and decisions are binding.

The CTD format became mandatory in the centralized procedure as of July 2003. November 2003 for the mutual recognition procedure, which means the national member states, and also some more flexibility was given in certain cases. In some cases, the transitional phase was extended to May 2005.

The CTD was mandatory in Japan as of July of 2003 and highly recommended in Canada.

What's the scope of the CTD? In the EU, it covers all product type. Recently, further clarification was provided for variation and renewal submissions in the form of questions and answers which are posted on the EU website, and I give you the website if you want to go look.

In Japan, CTD covers new chemical entities, new biologics, new indications, new dosage forms?dose, new route of administration. It's to be noted that generics and OTC are not

covered.

In Canada, for Health Canada, the intent is to apply the CTD format to all application types, including OTC drugs. Format of clinical trial applications have been recently adapted to be consistent with the CTD.

How many CTD submissions have been received to date? In the EU, as of May 2004, 51 new submissions have been received, of which 15 line extensions, 648 variations of Type I, and 584 variations of Type II.

In Japan, as of March of this year, 52 submissions total, 23 NMEs, two new combination, five new routes, 19 new indication, three new dose.

And in Canada, as of April of this year, 233 submissions: 43 new drug submissions, 77 supplemental new drug submissions, 104 abbreviated new drug submissions, and 9 supplemental abbreviated new drug submissions.

So if we compare those numbers to the ones in the previous slide, the number of submissions received during the transitional phase, if you

recall, it was 25 for the EU, 16 for Japan, and 60 for Health Canada. We can see that there was a sharp increase due to the fact that the CTD became mandatory or highly recommended. The transitional phase was thus critical to get everybody on board and ready to use the CTD format.

So at the conclusion, I just would like to highlight that in the three regions mentioned, the CTD works well, a positive experience. The transitional phase was critical to get ready. The harmonized time frame within ICH contributed to the success of the CTD implementation. Last year, we'd like to note and acknowledge the full participation of Health Canada since the beginning despite its observer status. It did a great job.

In my last slide, I provide you some websites where you can find the guidance documents I mentioned.

Thank you.

DR. MOLZON: Whoever has the sign-in sheet, could we make sure that it's circulating? Because some new people have come in. Does anyone

have the sign-in sheet? Do we need to start a new one? No answers?

PARTICIPANT: Yes, it's right here.

DR. MOLZON: Okay.

DR. LIMOLI: Now we're going to hear from Dr. Bob Yetter, who's from our Center for Biologics, on ongoing and new topics.

x DR. YETTER: Good afternoon. Contrary to what you might have thought up until now, not everything at the ICH has been the CTD. There are a number of topics that are going on that are available for harmonization. Some of them, particular ones of interest, are S7B and E14, which deal with nonclinical and clinical aspects of QT prolongation; quality systems, pharmaceutical development, risk management; the Gene Therapy Discussion Group; bio-comparability, which is Q5E. And we'll take these in turns.

S7B and E14. S7B deals with the safety pharmacology studies for assessing the potential for delayed ventricular repolarization, that is, prolongation of the QT interval, by human

pharmaceuticals. E14 deals with clinical evaluation of QT and QTc interval prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs.

This is sort of a unique pairing. S7B started and then E14 was paired with it after a need was identified to qualify the nonclinical assessment of QT risk with the clinical assessment. S7B had been released in February of 2002 as a Step 2 document. The Steering Committee agreed in July of 2003 that the two topics should progress in tandem with joint consultation between the two Expert Working Groups. E14, because it was starting, shall we say, from behind, was done by a streamlined process agreed to by the Steering Committee. The starting point, rather than the usual ICH concept paper, was a Health Canada draft document. A public meeting was held to get broad input on the issues. Considerable progress has been made on these two issues, including interactions between the two Expert Working Groups.

E14 has the potential to reach Step 2 in

Washington in June. If that, in fact, occurs, it will be necessary to re-release S7B as a Step 2 guidance so that it is in combination with E14 and the two proceed together.

Quality systems: Pharmaceutical development and risk management have been something that have been of interest to the FDA for a while. The agency is undertaking or has undertaken current good manufacturing practices for the 21st century. One of the goals of that initiative was to explore relevant scientific aspects of the initiative in the ICH as possible topics.

To facilitate that, we held a two-day workshop in Brussels last July. One of the outcomes was a vision statement: "A harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science." There were also five proposals brought up to the ICH Steering Committee; three of these were selected as having the potential as ICH topics. Those were pharmaceutical development, risk management, and

quality systems scoping.

Pharmaceutical Development became Q8. It is essentially intended to describe the suggested contents for the P2 pharmaceutical section of a regulatory submission under the Common Technical Document format. And it is intended to include risk and quality by design. The concept paper was endorsed October of last year. There was an interim meeting this March in conjunction with Q9, and considerable progress was made on this topic. We expect that more progress will be made during the Washington meetings with a targeted sign-off as a Step 2 document in November of this year.

Risk management became Q9. It is intended to provide a definition of principles on how regulators and industry integrate risk management into decisions on quality. The concept paper was again endorsed last November. The interim meeting in March 2004 was not held in conjunction with Q9. It was held in conjunction with Q8, but what the heck.

Again, progress was made on this topic

along with Q8, achieved considerable agreement on outlines and key definitions, and, again, as with Q8, we expect progress to be made in Washington that will allow us to proceed to a targeted Step 2 sign-off in November.

The quality scoping document was a little different. An industry team was charged with addressing perceived differences in regional approaches to this. The industry presented the document, and we decided that it was worth pursuing. However, the regulators indicated that we would have to defer further work on this because of resource limitations. We simply could not support pursuit of all three quality system topics at once. The proposal was presented by the industry, and resource constraints are still present. We will revisit this in November.

The Gene Therapy Discussion Group is also an unusual situation. It does not follow the typical ICH pattern. The ICH explored the pursuit of gene therapy or specific associated issues as candidate topics for several years. However, most

harmonization topics have the advantage of a considerable body of experience and science to support the harmonization effort. That's not the case with gene therapy. The experience and science in this field is not yet mature enough to support the type of technical harmonization that is the hallmark of ICH. However, we did identify a need for gathering and sharing information and data on the state of the art of gene therapy. Such things as dose definitions and standardization, virus shedding and its importance and effects, and the potential for germ line integration were all topics that were thought to be important and where information needed to be shared. To that effect, on September 9th there was the first Scientific Workshop on gene therapy supported by ICH.

A proposal was put forward for a public workshop to be held in the U.S. late this summer. The suggested topic was replication competent oncolytic viruses. It turns out that that was felt to be premature for the other regions. They would not be ready to hold this. And so the time frame

is possibly going to be the spring of 2005, and at the upcoming meeting, we'll be discussing the topic and the logistics of the meeting.

Another issue that is ongoing in the ICH are data elements and standards for drug dictionaries. This was a proposal originally raised by the World Health Organization prior to the Brussels meeting last July. Discussions were held by an informal group to further assess specific requirements in ICH regions, the benefits and objectives of a harmonized dictionary, and to evaluate the work that would be required to develop such a dictionary. Also, it was to consider the needs for maintenance and concomitant costs of developing and maintaining such a dictionary.

The proposal was to develop a guideline defining data elements and standards for ICH drug dictionaries, which is somewhat different than developing a global drug dictionary itself. This was endorsed by the Steering Committee last November.

In Washington, there was some progress

accomplished via teleconferences on a regular basis. Some procedural problems were clarified. We expect further progress to be achieved in Washington, D.C. Part of this is to ensure consistency with HL7, which is of increasing importance to us in the United States and also now in the European Union.

Another topic is Q5E, bio-comparability. The scope of this document is to assess comparability of biotech and biological products before and after changes at any step in the manufacturing process, and to assist in the design and conduct of studies to collect data to establish comparability of pre- and post-change products. This is to confirm that a manufacturing change does not have an adverse impact on the safety and efficacy of the product.

The Step 2 document in November of 2003 was published in the U.S. as a Draft Guidance on March the 30th. The comment period ends the day after tomorrow. If you have comments, your time is running short.

The first meeting of quality experts. It was determined--I should say as an aside, part of the considerations associated with this was it was determined that at certain points it would be necessary to ask for clinical or preclinical studies to confirm the lack of an impact. Consequently the first meeting of the quality experts with nonclinical and clinical experts to comment on the section that refers to nonclinical and clinical studies will be taking place at this upcoming ICH meeting in Washington. The intent is still to reach sign-off of a Step 4 document in November of this year. We do not believe that there will be any impediment to achieving that.

Now, I didn't go into any of the many topics that are in maintenance mode. We have a large number of them. As we develop a guidance document or an ICH document, it is necessary to look at maintenance because as science and technology moves on, it may be necessary to go back and re-evaluate harmonization of that area. Consequently, we have a number of topics in

maintenance. The number of active Expert Working Groups is considerably smaller than it has been in the early years of ICH.

That's all the slides that I have.

Justina, did you want to hold questions to the end or deal with them now?

DR. MOLZON: If people have a burning question now, they can ask it.

DR. YETTER: Burning questions?

DR. MOLZON: I think it's better to do it during the presentation.

DR. YETTER: I'm not going to disappear like Tim. I'll stay. So if you think of something in a couple minutes, I'll still be around. Thank you.

DR. LIMOLI: Does anyone have the sign-in sheet? It seems to have disappeared again. Someone's got it? Okay. If you haven't signed in, please do so. There's a sheet and we'd like to get some contact information on you.

Now we'd like to introduce Dr. Andrea Feight, who is going to talk to us about MedDRA.

DR. FEIGHT: Good afternoon. My name is Andrea Feight, and I'm going to present to you some FDA perspectives on MedDRA, basically provide an update, and then directly following my presentation, Dr. Marvin Meinders, from the MedDRA maintenance organization, will be able to provide a perspective from the maintenance organization's point of view, so much broader than mine.

What I'm going to share with you today is just a very brief history of the implementation of MedDRA at the FDA within AERS, a little bit of information about what we've done with upversioning, provide you a status of electronic submissions, and then address briefly MedDRA as a reporting requirement in the proposed rule, and then I'm going to also briefly touch on the July 1st agreement between HHS and CAP on SNOMED, and then I'll allow for some questions.

Okay. Back in November of 1997--so it's been, what are we coming up on, seven years now--we began using MedDRA in AERS, and rather than maintain two separate reporting systems, the old

spontaneous reporting system and the new AERS, we migrated the records from the old database into the new database. There were about 1.5 million records at the time of that migration.

In order to do that, we had to utilize a mapping between the COSTART terminology that was used in SRS and the MedDRA terminology that we designed AERS around. And we did that between COSTART and Version 1.9 of MedDRA, which was actually a pre-released version.

But since November of 1997, we've added an additional 1.5 million records into AERS, so I think that's just sort of testimony as to the increase in reporting to the FDA over the years. We went from 1969 to 1997 with about 1.5 million records, and it's taken only six-plus years to get another 1.5 million. And we are currently using the MedDRA preferred terms as the coding level.

Upversioning history, it took us a long time to get from our original version of MedDRA into the next version, which was actually Version 4.0. And we did that in December of 2001. And

then we took another big leap from 4.0 to 6.0 in May of 2003.

Since then, we've been able to implement each of the upgrades. The reason we weren't able to do it previous to that was just competing resources. It was either update things with the AERS database, make improvements there that were really needed, or update MedDRA. And at the time the choice was made to make improvements to the database. But we do fully intend to keep up with the twice yearly MedDRA releases now.

A big, big concern with the agency, of course, is reducing the amount of paper, reducing the amount of double work. At least that's how we see it in that manufacturers all have databases. If they submit to us in paper form, then we just have to re-enter that information into our database, code it, et cetera. And so there's a lot of--there has been over the years a lot of wasted effort. And so we initiated an electronic reporting mechanism back in August of 2000, and we've really been putting a lot of emphasis on

getting as many reports in electronically as possible.

Right now we have seven U.S. companies that are submitting, and I'll go over those in a minute. And, to date, we've received over 75,000 case reports electronically, which is really great. Of course, we'd like to have more, but we're very happy with that. And many of those 75,000 reports are actually already coded in MedDRA when they come in through the electronic mechanism.

Processing electronic submissions is, of course, much less costly than processing paper, and this is one of the driving forces.

Currently, we're accepting electronic submissions that are coded in MedDRA using either the MedDRA text string or the MedDRA numeric code. At this time Europe is requiring the numeric code alone, so that is mainly what we're getting in just because companies want to reduce duplicate efforts. Originally, we were only able to accept text string, so now we accept duality.

For the paper reports that we receive,

we're using the narrative as the basis of coding. Now, for electronic submissions, we are looking at the terms that are submitted and in many cases just accepting those, and they go right into the database. When the report gets to the step of quality control, then it is the narrative that is used as the basis for the quality checking.

When the MedDRA versions are not the same--and, of course, this used to be more of an issue before we were upgrading more routinely--we would have to recode if the versions were discrepant and there was a term that came in that we didn't yet have in our database. Also, if the coding quality is not considered acceptable by our standards, then the report will get recoded.

Now, we announced recently to the electronic submissions group, the e-Prompt Group that is a joint effort between FDA and PhRMA, an evaluation plan. And so all of the folks who are participants to that e-Prompt Group were able to see this plan in great detail. This plan for evaluating reports as they come in for adequacy of

coding was developed by the AERS Coding Working Group, and with oversight from our super office, which is the Office of Pharmacoepidemiology and Statistical Science.

We consulted with the Office of Biostatistics in order to develop a valid statistical sampling plan, and we now have the same contractor that is performing our MedDRA coding and data entry, performing the evaluations of these reports, the quality control step, under the existing coding contract.

And what we see as the largest problem in reports as they come in is if a medical concept is missed entirely. For example, the narrative will describe something, but there will not be a code in the coding field for what is being described in the narrative.

Another major error is what we refer to as "soft coding," simply because we haven't really been able to find a better term for that, which is the case where the company reports an event but they don't report it using the severity or the

specificity that's reflected in the narrative. For example, pancreatitis may get reported rather than acute pancreatitis or some other version where there are terms in MedDRA that would better describe that condition.

In the process of doing this quality control, individual companies that are submitting to FDA into the AERS database electronically are then downsampled. So they go from having 100 percent of their reports quality control checked to--in increments of 10. We now have a couple of companies that are down to 30 percent. And, of course, this helps us maximize our resources and get through the reports more efficiently.

So these are the seven companies that are submitting. We just recently had Amgen begin submitting to us, and they are using MedDRA. So we're very happy to have these seven companies, and we certainly welcome more.

Now I'm going to just briefly address the proposed rule that was published over a year ago, and the comment period for the rule closed on

October 14th. Those comments, of course, are public, and so they're available for review through the docket, and the number is indicated here.

In the proposed rule, the MedDRA requirement specifies that each suspected adverse drug reaction would be coded at the preferred term level for individual case safety reports. There are a number of other things. I'm just going to add a parenthetical to this first point, which is that we are looking in ICH 2BM now at designating the LLT level as the level of exchange. That's what's being required in Europe. That is certainly what we would have implemented had we known at the time the implications of coding at the preferred term level, particularly with respect to version control. It's much easier to control versions if you're coding at the lowest level term. Unfortunately, the decision to code at the PT level was made many, many years ago and was sort of hard-wired into the database. So as we bring AERS into the next decade, we're looking at making that change.

Then in the proposed rule, of course, medication errors are addressed for the first time, and so medication error terms would be selected and coded by submitting companies. That's how we envision that in the proposed rule. There is an intent to grant waivers for the MedDRA requirement on a case-by-case basis for small companies.

Now, of course, a number of comments were received. In fact, there were 109 unique comments received about the proposed rule, and many of these individual comments addressed the MedDRA requirement. We're still in the process of reviewing those comments, and, of course, those need to be considered as we prepare the final rule.

There's been a lot of talk about the SNOMED terminology since the July 1st signing of an agreement between Health and Human Services and the organization that owns SNOMED, the College of American Pathologists.

HHS sees this initiative as important so that a standard electronic medical record can be developed so that the health care community will be

recording information in a standard format. And I think that this became highlighted following the 9/11 events when the VA and DOD and many other parts of the health care organization were unable to communicate using the same type of language. And I think probably events in the Gulf War have only made that a little bit more dramatic.

So there is this HHS initiative, and within the FDA we formed a SNOMED Evaluation Working Group to begin looking at this terminology and try to understand what it is.

Unfortunately, we haven't gotten very far with it, mainly because we haven't had good access to the terminology. But I did learn last week that SNOMED has just now become available, and we've been waiting for this and watching for it through the National Library of Medicine's medical thesaurus, the UMLS. And I think I put a contact in my next slide--no, I didn't. I didn't put a link. But, in any case, you can find that quite easily on the Web if you're interested in looking at that.

The agreement allows any U.S. user to utilize the SNOMED terminology through the NLM's site. So we are hoping to learn more about it. Frankly, it's a very huge terminology, and right now I think it's very difficult to envision that this is something we would be using for adverse event reporting.

However, the department at that level, they are moving very fast forward, and Consolidated Health Informatics, or CHI, has just adopted SNOMED for five of its areas: the laboratory result contents, non-lab interventions and procedures, anatomy, diagnosis and the problem list, as well as nursing.

In order to sort of represent the FDA perspectives, I guess you would say, and the regulated industry's perspectives, HL7 created a Regulated Clinical Research Information Management Technical Committee, the RCRIM. We have representation to that, as do many of the--as does PhRMA, I guess through individual companies. And so they are carefully watching what's going on with

standards in general and also with SNOMED. So beginning May 6th, as I say, SNOMED CT is now available.

Has anybody tried to download it? I'm very curious. Or looked at it? Okay.

All right. That's all I have. I guess I could take questions now, and then we could move on to the next speaker.

Okay. With no questions, then let me introduce Dr. Marvin Meinders from the MedDRA maintenance and support services organization. I'm very glad he's here to provide an MSSO perspective. Thanks.

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DR. MEINDERS: Thank you. It's certainly a pleasure for me to be here this afternoon and be able to talk to you at least about my favorite subject of life, at least one that consumes most of my time per day. What I'd like to do today is just give you a little bit of an overview about the organization that I'm from, about MedDRA, and then also from there I want to sort of just paint you a picture a little bit of what's been going on with

MedDRA, at least how I see it. I work as the terminology maintenance manager at the MSSO, as I have probably a little bit different view of what's going on than what you all do who are users.

How many of you all actually used MedDRA, code data with MedDRA or analyze data? So about two or three, okay.

And then from there, I'll give you just a little peek about what's coming up on the horizon, and then I guess I have another mission here today, too, which I didn't realize until after I got here today. I noticed that I was the last person on the agenda, so I have learned from years of being around that one of the most important things is that I'm the only thing that stands between you and that doorway out there at the end of the meeting. So I've learned that that's probably one of the more important things. So I will expedite this, but hopefully also pass you the information that you would need or like.

MedDRA is an acronym. It stands for Medical Dictionary for Regulatory Activities, and

as has been said today, it has had a life starting in about 1994 and has really been in production use through subscription since March '99. So we've had about five years of maintaining it and working with it and stuff.

But the objectives of MedDRA is to have an international multi-lingual terminology, and also the main thing is to standardize the communications between the regulators and the pharmaceutical companies and also among countries, too, as well. MedDRA was intended for throughout the life cycle, from clinical trials until post-marketing.

I won't go into a lot of detail here. The main thing I wanted to get across here is that MedDRA has--the first release was in 1999 with Version 2.1, the first official release. Anyway, so we've been maintaining this for five years. The key there is that, as I say, we have been maintaining it, but what drives us is different things within the organization. Subscribers put in change requests. Somewhat it's a living database, and it grows and develops as you want it to, to

serve your needs, not by something that we sitting in the back room are thinking about.

I'm from the MedDRA MSSO, and that's an acronym also. I'm full of acronyms today, but that stands for maintenance and support services organization, and our goal is to basically help nurture the terminology, grow it so it will be a useful product for you, number one; and number two is help foster its use worldwide, the people using it, and giving them support in order to make it a useful tool for them, too, as well.

The purpose of this slide here is just to show you that there is not just a few of us in the back room someplace throwing darts and developing the terminology. We are guided from all angles, basically, from on high, from us, from the management board, the ICH, and then from the users also who are putting in change requests. Now the users have two ways of doing it: either directly to us or going around and going over our head, so to speak, and coming in from the top, too, as well.

Now, just to paint a little picture of

what's been going on, at least how I would see the terminology, basically I would call it a maturing terminology. You can see from here, although we started with Version 2.1, probably 4.0 was where the major changes took place, where we looked and did a complete review. And you can see from that time over the last three years that the number of change requests that we have processed are going down. But also the main thing is that the subscriber requests are going down, too, as well. 4.0 was almost 2,000, and now the last couple releases, it is averaging around 1,000 requests for them. This is over a six-month period, normally.

What tells you a little bit more about it than number of change requests is what are we really adding to the terminology. The PT, what I would call it, is the preferred term. That's really where your medical information is that helps you describe the adverse event that you're trying to report, that you're trying to communicate. How is that growing or shrinking? You can see that there, again, that has been decreasing quite a bit.

As a matter of fact, even Version 6.1, we had a negative growth of 48. So it even contracted down there.

It looks like things are getting smaller. People are starting to get--this is really sort of what we want now in this terminology.

Now, the other area, the LLT, that's something you've sort of got to analyze that, and it's growing quite a bit. But now what's going on there? That is really where your maintenance terms go. I'll give you an example. I think in 5.1, we were required to have an American English and a British spelled term. If it was spelled different in the other language, we had to have both of them there. So a lot of those changes right there were additional, but it didn't change the medical concept, the PT level. But what it did, it gave more selections for people to code with that they could find their term better. So I would really call that LLT level somewhat of a maintenance level where those things would show up.

Another example is in 6.1, there was a

large number of changes there, too, as well. That right there was the NOS issue, which is not otherwise specified. The management board wanted us to have just a general generic term at the PT level and demote those. So there, again, we didn't add additional concepts. It was the same concept. But we just used that maintenance change, so the NOS term was demoted. But the real key to how the terminology is maturing can be seen at the preferred term level, the PT level.

Now, to give you just a little bit more insight, things are maturing, but what is really going on with this? And so I looked at the number of change requests. How are these differing? Is it the same way or is it different? And you can sort of look at this--you have to use your imagination a little bit, and because everything is reducing, I had to do this, normalize this by putting this into percentages. And you can sort of imagine a little bit there that the number of adding new terms are going down as a total percent of our number of requests. So there, again,

they're saying--the subscriber is telling us, you know, we're seeing the complete set of terms, the concepts that we're needing. I say "complete," but you're getting close to it.

Then, on the other hand, what's going on is that we're having percentage-wise an increase in the requests to move terms, link terms. We have the term there. Now, it's not in the place that I need in order to analyze my data, in order to find it back, or what have you there. I need you to manipulate this and make a better alignment there so it better describes what we need.

I guess the way you can summarize this is that originally people were trying to code their data, get their information into the terminology. Now they're trying to analyze it. Is it in the right place so I can analyze it? So I think that is what's going on here with this.

Another interesting thing--I guess I'm full of figures here, and it's too late in the day for a lot of figures. Anyway, what's going on here is that initially at first we were having a few

companies that were submitting a lot of requests. Now as time goes on, you can see we're having more companies, 15, 24, up to 38, 39 companies that are submitting every six months requests. But the number of requests that each one is submitting are fewer. So there, again, I think what we're seeing, we're seeing more users, and there, again, people are saying, well, we're getting close to what we sort of need in order to be a good terminology for our use.

The other thing about the maturing is that initially we had it just in English, and then there was a Japanese translation, and now we have a total of--it's in seven different languages now. So it's French, German, Dutch, Portuguese, Spanish. And not only do we have it available, but we have people using most of those, too, as well. The Japanese, I really don't have figures on that per se because that's really handled through the JMO, and there's about 345 subscribers there, so it's somewhere that, plus, because some companies have that, too, who have primarily English. And

Spanish, 47; German, 82; French, 60 subscribers to it. So other people--so different languages are being utilized, too, as well.

So what's on the horizon? A couple things that sort of might be of interest, these are things that are fairly close on hand, is the SMQs. This is a cooperative effort between the MSSO and CIOMS, and the SMQ stands for standardized MedDRA queries. As we've gone along now, we are able to code the data pretty well, but now what companies need or people need is to be able to analyze their data, have some things that help them extract the data, and that's really what this is for. It's grouping. The way MedDRA is organized, the basic structure, is through columns, and you roll your data up. Well, the SMQs give you the ability to go laterally, link different things together that are not related otherwise. An example, diabetes mellitus, you would see this in the metabolism and endocrine hierarchy. But if you want to link it with other things that would be a laboratory, which would be in another part of the terminology, like

increased blood glucose, you can link these through an SMQ, through a standardized MedDRA query. So that's the purpose for that. It helps you define certain medical conditions the group picks out. These are the important types of signs, symptoms, or laboratory tests that you would see for this type of syndrome, and they link them together in a predetermined query so that regulators can use it, companies can use it. And so when you establish your results, you'll each know what the person is talking about.

Basically it's intended to aid in case identification. You're looking for that low-level case that you're trying to find, and that will help you to highlight it.

We have two SMQs that are now available that are in a testing phase: rhabdomyolysis and also QT prolongation. There's a total of about 75 that are sort of being talked about now, being planned to be released over time. And like I say, these are available now on our website.

The other thing that's on the horizon is

the modifiers. This is something that has been talked about for the last couple years. It sounds like a very good idea, particularly if you're talking about coding your data. If you have a term like Andrea was saying, pancreatitis, but you want to add the word "acute" to it, well, you can have the modifier "acute," so you can go ahead and mix and mingle these types of terms and get really a very good fit.

That sounds good, very good on the coding side. But then when it comes time to analyze it, there's a lot of problems, like a lot of things that when you starting looking into in-depth, it's not quite as simple as it looks. I'll give you an example: osteoporosis. If you add a modifier, "prophylaxis," now instead of being a disease, now you've got a treatment. So the same thing you could do to something like with chest pain. You could add the word--anytime you add "traumatic," now it becomes an injury as opposed to potentially a cardiac issue.

The problem with those terms is that

they're cyber terms. Those concepts do not exist in the terminology today until you put those two terms together. And so the part of analyzing it and extracting it says, What does this term mean? Now you've fallen within a new structure that has to be worked and developed.

There's a lot of risk/benefit to the user community in analyzing with modifiers that needs to be reviewed and investigated and have a full understanding before we would embark upon that and any type of system changes that would be required of that.

Also, there will be other impacts, too, like how does this impact E2B, when you can start mixing and mingling terms together to make a new concept that is not already there.

But, anyway, these are some of the things that will be discussed. In the blue ribbon panel that will be discussing this, this will be the main topic, and that will be on the 18th of June, and it will be in our office in Reston.

But, anyway, those are the topics. That's

the short of it. And if there are any questions, I'll certainly be glad to discuss those with you, now or later or what have you. Thank you very much.

DR. LIMOLI: Do we have any other questions before you are dismissed for the day? No questions.

I do want to introduce one other person. We have Mike Garvin here from PhRMA because we do have a lot of industry reps in the room today. Just so that you know, he's our new ICH coordinator for PhRMA, and his assistant, Julie Peng, is here also. They would be your contacts if you needed any more information, and we'll be glad to help you out with anything that we can.

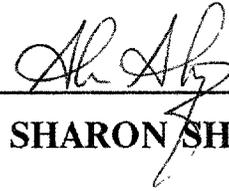
If there are no more questions, we're adjourned for today. Thanks very much.

[Whereupon, at 3:19 p.m., the meeting was adjourned.]

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C E R T I F I C A T E

I, **SHARON SHAPIRO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



SHARON SHAPIRO