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FOOD AND DRUG ADMINISTRATION

PUBLIC MEETING

THE FUTURE OF THE INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH)

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C O N T E N T S

P R O C E E D I N G S

MS. LIMOLI: Good afternoon. I welcome you to this public meeting in preparation for the ICH-6 meeting in Osaka. I am Michelle Limoli, FDA's new coordinator for the ICH initiative, and I have just recently, in the last couple of weeks, taken over Janet Showalter's duties in this area and if you can indulge me as I'm getting up to speed on this topic. Janet has left me some very big shoes to fill.

As you know, we are being recorded today by Miller Reporting. So if you have any questions for our experts, please be sure to speak into the microphone. There is one back there or you can certainly come up here if you need to use this one.

I have with me today some esteemed colleagues, experts in the area who are going to help out in this talk and I'm going to rely on them heavily to bring you up to speed on some of the most recent activities in ICH and talk about some new topics.

I also wanted to let you know that we have

gotten a message that sometime between now and Wednesday, there is going to be a building evacuation drill. So it could happen at any time. I'm hoping it won't happen this afternoon, but if we do hear some alarms and we have to evacuate the building, that's just a drill. It's not the real thing.

So without any further ado, I'm going to introduce Justina Molzon, from the Center for Drugs, who is going to give us a brief overview on the ICH process and then talk about the CTD.

MS. MOLZON: Good afternoon, everyone. Originally, Kristel Onki, who assists Michelle in her responsibilities for ICH, was supposed to give a presentation on the overview. So there's actually a set of handouts out there that may be a little more detailed, but I'm hoping to just go through this very quickly, because most people that are at this meeting actually know what ICH is and so we don't need to spend very much time on this.

For the people that just arrived, we'll get you a complete set of handouts.

ICH is a unique approach. It was created in 1990 and so it has been in existence for 13 years. It was an agreement between the European Union, Japan, and the U.S. to harmonize regulatory requirements for drug applications.

This includes pharmaceuticals, which also includes biologics. So these three regions, Europe, Japan, and the U.S., represented 95 percent of global research and development. So that is why those three regions were included in ICH.

ICH was often criticized for being a closed model, so to speak, but the truth is those three regions was where 95 percent of all global R&D took place and since ICH deals with the technical requirements for pharmaceuticals, it was logical that these three regions joined together to create ICH.

So the objectives of ICH are to identify and eliminate duplicate studies to meet different regulatory requirements, and the best example of this is an ICH document called Q-1-A, which is about drug stability studies.

Before ICH harmonized on this guidance, Japan, the U.S., and the European Union had three different sets of requirements, three different temperature and humidity settings. So a drug company, if they wanted to market it in the U.S., EU, and Japan, had to do three different sets of stability studies.

Once the temperature and humidity setting was harmonized, they only had to do one set. So literally we saw buildings that were formerly used for stability studies turned into other things. So a company that had three buildings all of a sudden just needed one.

So this was a substantial change, all based on one small guidance.

So ICH basically wants to make sure there is a more efficient use of resources in terms of clinical trials, pre-clinical studies, and CMC materials. From a public health perspective, and this is what we're interested in as regulators, it would allow for quicker access for patients to safe and effective new medications.

So ICH, I've already mentioned, is an activity between Europe, Japan, and the U.S. It's basically three regions, six parties. A unique part of ICH is that it's a combined effort for regulators and industry associations within that region.

So for Europe, it's the European Union and the European Federation of Pharmaceutical Industries Associations, or EFPIA, Japan Ministry of Health, Labor and Welfare or the Japanese Pharmaceutical Manufacturers Association. In the U.S., it is FDA and PHARMA.

ICH does have several observers to this process that also sit at the steering committee level. It's the World Health Organization, Canada, and EFTA, represented by Switzerland.

ICH works through a series of expert working groups. These expert working groups are the actual entities that harmonize the documents.

So the working groups are divided into four different categories: safety for pre-clinical studies, efficacy for clinical studies, quality for

CMC information, and regulatory communications is the miscellaneous category, and this is where you will find the common technical document, MEDRA, the electronic technical document and other things that don't fit into safety, efficacy, or quality.

These groups work on their documents and then reports to a steering committee, which meets in conjunction with the expert working groups and the steering committee monitors and facilitates the expert working groups, moving them along on their time frames or helping resolve sticky issues.

So it's working groups and a steering committee and that's basically the foundation of ICH.

So in terms of expert working groups, there is an expert working group for each ICH topic. So within that working group, there are representatives from the six parties that I talked about, including observers or additional representatives, such as representatives from the generic industry or over-the-counter industry in the quality area, depending on the topic.

It's the expert working groups' job to develop a consensus document on these technical issues, and this results in ICH guidelines, this alpha-numeric soup, so to speak, for safety, efficacy, quality, and for regulatory communications.

So to date, there's been over 50 harmonized guidelines in these areas. For efficacy, there are 12 topic headings, but 14 guidelines, because some of the documents have sub-headings. Safety, seven topic headings with 14 guidelines. Quality, seven topic headings with 19 guidelines. Then I have already mentioned MEDRA and some of our electronic standards documents and also the common technical document.

ICH has a very delineated process. It's a step-wise process. At step one, the working groups build scientific consensus. At step two, they agree upon a draft text. At step three, this draft text is posted by the regulatory authorities for comment. The comments are then gathered at step five and put into a consensus document.

The comments are incorporated into the consensus document and then at step five, it's implemented by the region.

So in the FDA, to comply with good guidance practice at step three, we post a notice of availability in the Federal Register and then post these documents on our website for comment. The comments are then gathered and our representatives submit them to the ICH process. Then at step five, when we have a final document, there's also a notice of availability and the documents are posted on our web.

We used to publish them in the Federal Register, but that took way too long. So now we just publish a short notice of availability and we post documents that have been reformatted into good guidance practice, which is a very specific template and format, according to our regulations. We post them on our website and that is considered implementation of the ICH guideline.

In an effort to become more transparent, ICH has a series of conferences that alternate

between the ICH regions and these are basically so people that have not been involved in the ICH process have a chance to ask experts of the various working groups specific questions.

So here you have there were conferences one through five have already been conducted. ICH-6 is going to be taking place basically next week in Osaka, and that's the reason that we are having this meeting. We like to meet with people that are involved with these topics, so they have an opportunity to let us know beforehand, before we go into the meetings, topics of concern.

The fifth conference was in San Diego in 2000 and it focused on the common technical document. So that is going to be my next talk.

I did a very brief overview and sort of combined these and tried to make them blend into one another. So now I'm going to provide an update on the common technical document in terms of the status in the U.S. and some statistics that I have pertaining to that.

But does anyone have any questions at this

point about just the overview of ICH?

[No response.]

MS. MOLZON: There is a lot of information. If you do have some basic questions, if you go to ICH.org, that's the site of ICH secretariat and that's where all the documents are posted.

It explains the process in more detail and basically any question you might have would be answered there.

In terms of the CTD, it's a very specific format that relates to just the format for a document that can be submitted to the U.S., European Union, and Japan and, also, Canada and Switzerland. All it does is take those 50 or so guidelines that have already been developed and sort of stacks them in the same order.

It is merely a table of contents. We have not discussed content. The language in the CTD is purely illustrative. We have never totally agreed on the total content of a submission, but we have agreed on specific guidelines that are now stacked

in a very specific order.

So the U.S., in order to help applicants understand how the CTD applied to our submissions, which would be an NDA, a new drug application, or a BLA, a biologics licensing application, we created a document called a general considerations document and we posted this in September of 2001, after the ICH-5, where all of these documents were signed off.

We originally had just a two month time period, but we only got 12 sets of comments and that was before any of the companies had actually experienced putting these documents together.

So I reopened the docket until June 16th of this year. So people that had more experience could make comments, but we haven't received that many more. But the point here is that comments are always welcome.

When you're working on these documents, if you have comments, we would welcome them, because eventually we will incorporate all of these comments and also comments from the steering

committee and expert working groups and meetings such as this into a final draft of this document.

But it's still premature, as I will explain, because we really haven't had that much experience with these documents ourselves.

So the general considerations guidance explains what we expect to be submitted. This is especially important for a description of module one, because that's the module that contains all the administrative information. So it is up to each region to describe module one within their region.

This generally contains administrative prescribing information. The general considerations guidance also gives a physical description of the submission. It talks about CTD requirements, lists some of the obsolete guidances, logistics of submission, and the time frame for submission.

We also posted in October of 2001 our implementable versions of all of these CTD documents themselves and we kept these in review

and the review discipline format for ease of printing and navigating.

People were used to seeing these documents in terms of safety, efficacy and quality. So that's the way we kept them. We also tried to be helpful by splitting off the safety appendices, because they were so large. These are a large number of tables, and we posted these documents in Word so that companies could populate the tables with data without having to re-create the tables themselves.

So this is a picture of our experience with CTD submissions to date. This represents the structure in Center for Drug Evaluations and Research, our Office of Drug Evaluations, one through five, with our consolidation of some of the offices from CBER into CDER.

There will be an office of drug evaluation six, but that org chart has not been posted yet. So we haven't been tracking things according to that new model.

So this just shows you the distribution

between all of the different modes. So if you're a company and you're working on a specific type of product, you can look at this chart and realize which division you might be submitting to and it would be helpful for you to know whether that division has experience or not.

The asterisks represent the number of new molecular entities that have been submitted in CTD format. So that would also be helpful if you're putting together a complete document to one of these divisions. You would have a level of comfort knowing that that division has experience.

This is just a pie chart showing you that there's really sort of an equal distribution between the five divisions, I mean, five offices. And here is just a graph that explains how these applications have been coming into the Center for Drugs.

Once again, this is another graphic display. You have these in your handouts. They just sort of trickle in, but, generally, before the end of the year, there is a little increase in the

numbers submitted.

So to date, CDER has had 47 submissions in CTD format to 14 different review divisions, all five offices, ODES-1 through 5 have experience with these documents.

At the beginning, we received hybrids that were either the safety module or the quality module. So companies could have experience with these documents.

For the same reason, companies early on submitted applications for new dosage forms, new indications, but now we're starting to get complete CTDs for NMEs.

To try and give you an idea of our experience with these documents, I have listed a typical new drug application review team, consisting of a project manager, a medical officer, a chemist, a statistician, a pharmacologist, a pharmacokineticist, a clinical microbiologist, and a microbiologist.

I have sort of listed different types of submissions in a CTD format. At first, I called

this slide CTD experience by discipline, but I don't know if I could actually say what these people have right now is experience, but basically exposure to these documents, because some of them are still in the queue. They're not completely reviewed.

So people are now starting to be exposed to these documents.

So if you look at, say, a pharm-tox hybrid, where just the toxicology section came in in CTD format, the only people that would be exposed to that document within the review division were the project manager, who would then turn it over to the pharmacologist for review.

In terms of a quality hybrid, the project manager would then turn it over to the chemist and perhaps the microbiologist to look at sterility information.

In terms of a new dosage form, once again, the project manager, a chemist, a pharmacokineticist would look at this information to check out bio availability, and, also, a

microbiologist could be involved.

Then in terms of a new indication, the medical officer would get involved, because they would have to look at these safety and efficacy data. A statistician could be involved because clinical trials were involved.

A kineticist, again, for the indication and perhaps a clinical microbiologist, if it was for an anti-infective or some other type of indication requiring a clinical microbiologist to attest to the efficacy of that product.

A new combination. You get more people involved and it is only when a new molecular entity is submitted does the entire review team become involved in this review.

So this is just to give you an idea of how we have a tiered approach to experience or exposure to these documents.

Now, the good news about CTDs that have been submitted to CDER. So there have been no refuse to file letters. These weren't all perfect submissions, but they could be reviewed. We have

been flexible during the voluntary submission phase, which was through July of 2003.

We have had submissions from 34 different companies and these include large pharma companies, mid-sized companies, small companies, and even the World Health Organization has submitted an application in CTD format.

Here I have listed some of the sponsors that have submitted CTDs. This isn't a complete list, because I could not show you the smaller pharmaceutical firms, because they didn't have a very large number of applications and I would be revealing confidential information by listing them on this list.

But this is a fairly large number of people that have started to work with these documents and submit them to us.

Now, CBER has also received some CTD submissions for BLAs. There has been one full CTD based BLA. This was on paper, completely on paper. But they have also had three electronic submissions that if they were printed out, they would have been

full CTD based BLA.

CBER has also received numerous submissions partially in CTD format. So that's the hybrids I was talking about.

So CBER has also had some experience, and Bob Yetter could answer specific questions, or Joan Blair, but we are just now starting to track some of this information and because of the consolidation of CDER/CBER, ODE-6 will now be part of our tracking system.

So the therapeutic products that have come over from CBER will be included in information that I receive when a CTD is submitted.

Now, there is some confusion about language that the FDA has related to CTD. We see that CTDs, as of July 1, 2003, are highly recommended by the FDA.

This is in contrast to the European Union and Japan, where they are mandatory. They became mandatory on July 1, but highly recommended for the FDA. Now, this is not an indication of our lack of commitment, but is because of our good guidance

practices, regulations.

ICH documents have always been considered guidance by FDA and never mandatory. So we can't say that these are required. We can't say that documents are required to be submitted in CTD format because of good guidance practices, but we are very committed to this process. We've put a lot of energy into it and we want to see this format used, but we just can't say that it's required.

That is probably the most confusing part of this whole process. And pre-submission meetings indicate that companies are actually following this recommendation, because we are getting an increased number of meetings, pre-submission meetings related to the CTD format.

I have been invited to 29 pre-submission meetings. This is an indication that there are more documents coming in in CTD format. Companies are planning to use these. We sit down and talk with them about the CTD to see if there are any questions.

So those of us that are involved in ICH and the CTD process are available for consultation to the review division and also the sponsors.

We are also trying to collect areas of concern and issues requiring clarification in the CTD process, because as more and more people start looking at these documents, there might be some issues that weren't quite clear when we issued these documents.

Now, the FDA has also issued a guidance for industry. It was issued at the end of August this year and it is called providing regulatory submissions in electronic format-human pharmaceutical product applications and related submissions.

These documents relate to the CTD. So make sure you have the most recent version by referring to the web that I have listed in this slide.

And part of this guidance, there are several for the exact stand alone documents. So this guidance has a stand alone document that

addresses the FDA comprehensive ECTD table of contents heading and hierarchy.

So this is a complete listing from top to bottom of all the headings for the CTD. It specifically lists what should be contained in FDA's Module 1, and I talked about how we have a general considerations document out.

This FDA Module 1 specification is much more up-to-date, because many things have changed since we issued that general considerations document. We are now dealing with risk management plans and some other areas that are to be included in Module 1. So you should look at this specification to see what is listed.

It also provides the specifications, the ECTD specifications for Modules 2 to 5, and has a document that address study tagging file specifications.

So these are documents that Tim Mahoney will be talking about after me, but this is all part of the ECTD. But if you look at these documents, it actually gives you helpful

information for even assembling a paper CTD.

We have also developed an ECT viewer and you can get a demonstration of what this ECTD viewer system does by clicking on a demonstration link. This just helps companies understand what our reviewers see when you submit the information into us in an ECTD format.

So some companies are concerned about we put so much time and effort into formatting our information to send in to you, what do you actually see now that we're using an electronic means for submission.

We are trying to triage all of the questions that are related to the CTD and E-submission process through two specific websites, ctd@cder.fda.gov and esub@cder.fda.gov.

The same person actually answers both of these mailboxes, but that person also checks with various people as to a consensus response before we send it out.

But this is also very helpful to us to figure out what other problems are still out there.

If people aren't understanding something, maybe we can do a little better job at explaining it.

So in terms of next steps, we're going to continue to meet with project managers for feedback on CTD submissions. I periodically meet with some of the super project managers and project managers just to see how CTDs are going in their various divisions.

Increased submissions, as I mentioned at the beginning, will help determine the effects on the review process to see if this really makes a difference.

It wasn't really intended to make a difference, but it will lead to more consistent documents coming into the FDA. So we would be interested to see what that actually means in terms of review time, et cetera.

Pre-submission meetings indicate that more CTDs are on the way. Because it is difficult to provide training to people in the abstract, we provide just-in-time training. The documents come in. People can ask for assistance and we have

staff from our Office of Information Management that actually meet with the reviewers and explain the documents. I meet with project managers and go over the CTD process, so they have a better understanding.

So as documents come in, we talk to the people as it relates to the specific submission that they have received.

We are looking forward to receiving submissions, so both industry and regulators can experience the CTD format. As a company gets more involved in the CTD, I think they will find that it's a very helpful change to the submission process and we are also looking forward to receiving consistently documented applications that will help with our process and the templates we have developed for reviews.

This is just an indication of the steep increase in the number of applications we have received.

I think that is my last slide. I want to thank you all and if you have any questions, I can

take them now. I know that Tim has a presentation after me. So you could wait till after his presentation on the ECTD or you can ask me now.

No questions?

[No response.]

MS. MOLZON: Thank you.

MR. MAHONEY: Welcome to Miami, Florida. That's what it feels like out here. Running over here, it's unusual. But anyway, I would like to thank Justina for pushing all the questions till after my presentation, as well. That was very sly of her.

My name is Tim Mahoney. I work in the Office of Information Technology in the Center for Drugs. I am the rapatore for the ECTD/IWG, which is also the M2 expert working group. So we handle a specific topic with the ECTD, as well as electronic submissions topics, media types, recommendations like that.

Justina gave you a really good overview of the ECTD and where it is, and my presentation is focused on, okay, what is happening right now, what

just happened at the last meeting and what are we going to be talking about at the end of this week, as well as the FDA status, where do we sit in terms of the ability to accept and review ECTDs.

We spent a lot of time in the February meeting going over a process for administering and maintaining the ECTD so that things could flow. There was a place where people can send in information or request more information and we could respond.

So that prior to every meeting, we knew what we were going to be doing, and that process is well underway.

In the July meeting, we posted a good amount of information up on the ICH web that talked about this process, that tells external folks, okay, how do they administer this ECTD specification. One of them is a study tagging file.

Now, when we went to step four, which then is implementation, the FDA had an issue with the level of granularity for study file management for

clinical and non-clinical study reports.

It was keeping us from going to step five. Our partners in the United States, particularly, JPMA, helped us write an interim solution until we could start a step process to look at, okay, study file management, maybe what the FDA needs is a little different than what your needs and what Japan needs, but we need to take a little more time to look at that.

So in the meantime, there is an interim solution for our study file management. It is posted up on the ICH web.

It's a little different as it has not gone through a step-wise process, but it went through our change control process in the ECTD. The style sheet is a technical file that if you want a common view to look at an ECTD, a style sheet is provided.

A question that comes into the ECTD could actually be a change request and say why did you do it this way or why is 50 megabytes the only size limit for files, and when we discussed them in our process, we find out that, hey, we may need to

change something as implementation goes on.

So we have a tracking table that tracks incoming questions and change requests and gives the outcome. We have approved several.

At the last meeting, we processed about 40 of them in a day and a half. So our process works. Anyone can send in a change request or a question and there is a form. The reason there is a form is we need information.

We're only in these rooms for a short period of time, together for a short period of time. So if someone is sending in a request, fills out the form, it will help us process that request more quickly.

And there is a document out there that explains how--you know, our ground rules for ECTD change control. So since that time, actually, the 28th, I believe we released the draft guidance for ECTDs, and posted on the website where it says steps to submitting an ECTD. The website is listed again here.

The very detailed specifications that

Justina mentioned earlier, an example of the ECTD viewer system is up there. Now, we are committed in both ICH and through our PADUFA-3 goals to make that publicly available and as soon as we work out a couple of glitches, we will. So the public download is ready, we're just still testing it.

But our hope is that when the clock starts for an ECTD submission, there won't be any technical issues getting in the way.

So these steps are how to actually test that the companies are creating the XML and it's very technical, or it's not that technical, and that their submission would work when they are actually ready to submit an ECTD.

So we have received several samples for testing. We are receiving more, communicating, and we have received actually one ECTD. We had training on Friday for the reviewers and they are using the EVS right now.

For the next meeting, our big topics are our change requests, media types. Particularly, Japan had questions about the recommendations we

made. A very technical issue, which is Leaf ID. We approved a change request on how files are referenced in the ECTD at the last meeting, but the question came up is this how things should be done right now.

The FDA thinks yes, because it's a much more eloquent approach. Other regions want to just make sure we're all on the same page, because if we deviate, and we see some of this in the E2B for a case safety report, if we deviate and we are not doing the same things in each region, then it sort of defeats the purpose.

You know, why even spend the time? It's a long trip to Osaka and if we're not going to harmonize, then it's really not worth our time.

So bringing things to the change control process keeps that harmonization going. So the FDA wants to make sure that we are all on the same page.

Another big one is the file size recommendations, 50 megabytes, where the FDA is not an issue. Our partners are also going to report

back on if we can increase that. That will reduce the amount of time to create an electronic submission.

There is a major flaw with the ECTD. It uses two types of technology for linking. One of them is the XML, which provides the backbone, the referencing. The other you may be more familiar with. Our hyperlinks, go to this file and this folder.

The two aren't compatible. So we have had small subgroups since the last meeting documenting the issue, looking at any known solutions right now that exist, and we will have a further discussion on what is the long-term solution, can we still maintain those two types of technologies or is the burden too great; do we have to look at a different file type for documents, per se.

Long term study file management. The study tagging file was an interim solution. The FDA has consulted with companies. Whoever wants to talk about study file management, but we also need a more eloquent solution in ICH.

Our goal is to have a step one document, which is just a general agreement on what the issue is and we are not scientific in the group, we are more technical, but is this the issue, could this proposed solution meet that need, and that wouldn't be distributed externally until it was step two, ready to be tested.

At the last meeting, we agreed and proposed to the steering committee that by the end of 2005, we fix the kinks that are in the ECTD specification. We have to let it run for a little while before we do that, but it would be a good idea, by 2005, particularly in the areas of life cycle management.

What does new, what does append, what does replace really mean, as well as the dozens of change requests that we've already approved. We need to integrate them into a new specification.

The ECTD website contains lots of information. The FDA site, the ICH site, we've got a huge--we're the biggest table on there probably with the amount of documents we post.

The reference we have up here is the ECTD web site and there's lots to read. Again, the e-mail, the central point, esub@cder.fda.gov, if we have one central point to receive questions, it makes it easier to have an FDA consensus answer.

So what questions can I answer for you today?

QUESTION FROM THE AUDIENCE: If you go back to your slide topics from the November ICH meeting, you have long term study file management and when you talked about that, you said that that's currently--I guess that's a step one document and you mentioned that that wouldn't be released or available until it reached step two.

So this is a question for you, but maybe for the entire group, because it relates to other documents that just haven't graduate to the step two status.

From the early days, when I was working on ICH, we had a legal opinion about the releasability of those step one documents and because the industry sits at the ICH table and is actively

working on the step one documents, that means that they have already been shared.

So when you look at that in the context of the FOI regulations, because you have already shared it, I mean, technically, what we found is that any version of any step one document really is releasable.

MR. MAHONEY: Fantastic. For technology, the more the information gets out, the more people have a chance to comment on it, the better we are.

QUESTION FROM THE AUDIENCE: And it's great that that was the legal opinion that was rendered. However, the practice is that it's not currently being abided by. So I'm just wondering how we can fix that.

MR. MAHONEY: I can answer ECTD related questions. See, the people leave the FDA and the first public meeting they get to. If someone wants to copy it, we're allowed to release it, by all means. I will send a copy if someone wants a step one document.

The study of tagging file, as well as the

previous interim proposal that was up there, is pretty much the gist of it. So if I can't answer for all of ICH in terms of availability of step one documents, Bob can.

MR. YETTER: FOI.

MR. MAHONEY: FOI. So send an FOI request.

MR. YETTER: Make a request for freedom of information.

MR. MAHONEY: I don't work in FOI. So please don't send it to me. Send it to FOI.

QUESTION FROM THE AUDIENCE: And how long will it take to get it back?

QUESTION FROM THE AUDIENCE: Two years.

QUESTION FROM THE AUDIENCE: For something in the public domain, that doesn't really seem right somehow.

MS. MOLZON: But remembering those discussions, there was the point made that these step one documents move so quickly, we did not want people acting on something that had not been sent. So while step one is releasable, when people start

acting on that document before it even gets to step two, they have to be aware that that is not a final document and things could change.

QUESTION FROM THE AUDIENCE: That's why we had draft and even a disclaimer page, so that people would understand what the status of that document was. In effect, that model still exists.

I think it would be a good idea to--of course, that makes absolute sense that you want people to appreciate what they have, but one of the problems that I think you're encountering as a regulatory agency, when you've got some companies that are actually sitting at the table and are part and parcel on the document, at times, there is some favoritism going on by virtue of the people that are sitting at the table.

So when counsel looked at this prior, they thought that that really wasn't a very good way of doing business and that is why the message that had always been put out there was that every version of every draft is, in fact, releasable.

But from the agency's perspective, when I

was working on ICH, we did want people to understand exactly what those draft documents meant.

So there was a disclaimer page that went on it to take care of the problem that you're talking about, Justina.

MS. MOLZON: Industry gets the documents from other industry and we have had very few requests for these documents.

QUESTION FROM THE AUDIENCE: But the reality is that if industry can do that, but if you have a consumer organization, for example, that wanted the document, you could be telling them to go through FOI, and, again, I mean, it's not really a very level playing field.

The earlier opinion was that every version of every draft would be available. It just seems that that is a much better way to operate.

MR. MAHONEY: I can't speak for PHARMA, but PHARMA is also another player at the table and has access to the step one documents. So if you are a member of that association, you could also

ask your PHARMA representatives for ECTD.

QUESTION FROM THE AUDIENCE: We can't post a step one document.

MR. MAHONEY: For ECTD, which is the topic right now, I'm sort of limited by the policies for ICH and FDA.

MR. YETTER: Since this has come up, what we will do is we will go back to counsel and discuss appropriate approaches to this and see what we can do and what appears to be the most reasonable approach to the transparency in the situation.

It's not that we are trying to keep secrets here, but, frankly, as has been pointed out, anybody who takes action on a step one document is really stepping off into the deep water, because step one documents can go through many iterations.

The step one document that is eventually--that eventually becomes a step two document may well resemble the first step one document not in the least. So there are concerns and even though

we put disclaimers on them, we want to be sure that people are not misled, that they don't take inappropriate actions based on something that is still in, shall we say, early gestational phases.

QUESTION FROM THE AUDIENCE: And I understand that, Bob, and that may well be true and, again, I think that there does have to be some caution put there. The thing that you also want is for people to be able to comment and comment wisely when it gets to step two.

So you do want people to have an opportunity to sort of see what the rationale and the thinking is as it progresses, so that they can make well educated moments when you get to that point.

When you get to step two, you're talking about something that's out there for about 45 days and if you have not been part of the process, you've got a huge educational situation that you've got to deal with, as well.

So there are countervailing courses there.

QUESTION FROM THE AUDIENCE: Janet's

comment came up in the context of a step one document for the long term study file management. In that regard, the study tagging file seems to be a source of some confusion multiple interpretation as it relates especially to non-clinical study reports, especially the linkage conceptually with the study tagging file to the E3 document, which was initially developed as a format for a control clinical study, and wasn't structured for a non-clinical study, per se.

There aren't enough similarities, presumably, that it gave reason for those who don't necessarily tag any file to extrapolate the clinical study report to non-clinical.

What is going to be the FDA's position regarding a study tagging file and its relationship to non-clinical studies at the steering committee and at ICH-6?

MR. MAHONEY: Some of those points were addressed when the state tagging file--weren't addressed, but were heard when the state tagging file was first posted on the FDA's website.

Actually, your points are why this needs to go through the stepwise process. The study tagging file was sort of everyone at the ICH table, at least for the N2 group, wanted the ECT to go to implementation.

We had a need and there were two paths we could have taken, a stepwise process and then the FDA would have been ready, or something that would work, but not be fully developed.

So the study tagging file works, but you are exactly right. It is not fully developed and we need to develop it.

So until we bring those positions to the table next week, I don't know if the FDA has a position on the long term solution. The study tagging file, I do know we need to tweak some of the language in that specification to make it more clear.

QUESTION FROM THE AUDIENCE: And at present, for at least documents that pertain to a clinical study or non-clinical study in the ECTD format, whether there is a Leaf designated in the

study tagging file or the ECTD guidance saying you could use a study tagging file approach here.

Right now, that includes both non-clinical and clinical studies and at present, if pilots come in and ECTDs are brought forward with that approach, is that the approach that is being officially advocated?

MR. MAHONEY: Yes. The communication in the testing is it's more from not technical, but especially when it comes to the study tagging file, and those of you not familiar with the study tagging file, it leaves a lot open.

There is a lot of interpretation and there's a lot of different and that is one of the reasons why I believe the JPMA presented it, because, as I said, this approach could be used if we have other stopgaps that we need.

But we need to define it better on this side, remove some of that ambiguity, and we have learned some from these testing samples. Really, the hard part about this was we were reviewing software to review an ECTD while we were building

the ECTD. So when you're doing software design, you want to do a lot of tests, but you didn't have anything to test.

The standard wasn't even out yet. So there are two parts. For the interim solution, until we have a step for a document for study file management, we do need to clarify some of the issues with the study tagging file, from the FDA's perspective.

We're the only ones using it right now. I hope that was an answer, a good answer.

MR. ROSS: Hello. My name is David Ross. I work at AstraZeneca. I'm here with my colleague, Carol Stinson Fisher, and we have been both in the ECTD steering group at AstraZeneca for some time now and we have submitted several CTDs.

We are very excited to be here today to give you some input regarding our questions with ECTD and some issues that we have encountered as part of our steering group.

AstraZeneca fully supports the ICH efforts for globalized ECTD as the standard delivery

mechanism and we support the following principles, each of which relates to meeting the CTD original objectives via the ECTD delivery mechanism.

Now, at AstraZeneca, it's a global company. So we have sites in Sweden, United States, England, and many marketing companies, and we all share a common document, so we share common systems, common approval process, everywhere from authoring through to life cycle management, through to submissions.

So the principles that we are going to talk about all relate to the harmonization that was spoken about earlier and essentially it is what we are striving for.

So the first thing is that ECTD must be accessible to and harmonized in all ICH regions and must not present technical burden to any ICH region. So any authority that cannot accept a technical solution we have to consider, because, again, we are addressing everybody.

The ECTD must be consistent with and facilitate the CTD review and it must not lead or

drive towards any negative change in review process, including longer review times in any ICH region, which means late delivery of our drugs.

The ECTD should not increase the regulatory burden of filing post-approval changes, for example, SNDAs and should increase the ease with which documentation can be filed.

So, again, we are grateful for this opportunity to present some potential barriers to global harmonization and some potential recommendations that we as a company have come up with.

The first one Tim mentioned, the obsolete hyperlinks. So presently hyperlinking will not function properly between separate, but related ECTD submissions. For example, if a source document--we're considering the ECTD obviously as a continuum of submissions.

So if a source document in one submission points to hyperlinks to a target document in another submission and then upon re-submission, the target document changes, either it gets replaced or

it gets deleted, then your source document is now pointing to obsolete hyperlinks.

So, Tim, I think that is what you meant by your example. So we understand that a long term solution, as you are proposing, must release sponsors from the work of redoing hyperlinks and clearly define a hyperlinking strategy for ECTD dossiers, and that is great. We understand you're working on that.

But in the interim, in the short term, what we are asking for is that the ICH specifications should make provision for a type of a document or a document type whose content does not change with incremental ECTD submissions, but whose hyperlinks may be updated to reflect changes to target documents.

So, for example, it would indicate this document hasn't changed, it is still the same, it is still approved, but the hyperlinks have been changed to the target document in order to facilitate review not only for the agency, the authority, but also for the sponsor, because within

AstraZeneca, we want the hyperlinks to point to the right document for review purposes.

So we'll save the questions till the end, if that's okay, and we'll go on.

The next barrier, potential barrier is that we are recommending a harmonized position on re-submission of non-ECTD information within the ECTD. So here we are referring to documents like legacy documents or documents from previous submissions that, again, would help the sponsor internally in their review process for an ECTD dossier, as well as potentially help the agency, the authority.

So what we are asking is the sponsor should not be required to resubmit data that was previously submitted in non-ECTD format, which we understand is that the FDA is recommending. But we're saying that if the sponsor wishes to resubmit the information in ECTD format, that there should be some kind of provision made or some kind of rules made for this kind of data in the ECTD, with the understanding that no requirement for this--

that there should be no requirement that this data be re-reviewed.

So we would have the data, it would be seen in some kind of a document type, some kind of meta data would be associated with it, but with the understanding that we don't need to re-review it. It's there for simplifying the review of the dossier.

Next is past experience with electronic submissions has not eliminated requests for paper copies, whether regulatory authority desk copies or U.S. field copies from health authorities, including the FDA. What we need is guidance to describe procedures that sponsors should follow for regulatory authority requests for paper copies of ECTD content.

Again, we are dealing with a lot of other regions here, regional authorities who do not have the resources to print and don't have the capabilities to produce paper.

So we're projecting, again, even for the U.S., we are projecting, based on past experience,

what happens if we need paper. So we need some kind of guidance here.

The next barrier is electronic signatures. The generation of electronic signatures in the U.S. appears to be incompatible with the practices of other regions and for global organizations, this creates a barrier for submissions to ICH regional authorities for shared documentation and it creates compliance issues for the sponsor.

So in the absence of electronic signature technology for all the other regions or for other regions that just don't have the infrastructure or the capability to accept these electronic signatures, what can be done to harmonize that and can we have work-arounds, for example, to electronic signature technology, like adherence to SOPs per Part 11, compliant to Part 11, et cetera.

So we really need guidance here and help with this, because, again, there are many regions who don't have technology that will be compatible with electronic signature technology.

The next barrier is what we're saying here

is a clear harmonized policy on ICH specifications, everything from granularity through to the reuse of documents and, also, the meta data between ICH regions is required to facilitate regulatory reviews amongst the authorities and to decrease the document preparation burden on the sponsors.

So there should be no regional variation from the CTD standard, as ECTD is the delivery mechanism and is not a dossier.

Tim, I know your slide had that point there. So we are--specifically, things like Leaf IDs that might be incompatible with other regions or Japan coming up with rules that would make it technically not feasible, a solution technically not feasible with all the other regions.

So we are looking for harmonization as much as possible, since, again, it defeats the whole purpose to have exceptions, as you said.

So in summary, then, these are some of the issues that we're asking that they be resolved by ICH. The first one is proper functioning of hyperlinks between separate, but related ECTD

submissions, came up with one recommendation, which is a different document type that would indicate that the document hasn't changed, the contents have not changed, but that the hyperlinks now point to another target, because the target has changed.

We are looking for provision for non-ECTD information within the ECTD for prior legacy documents or prior submissions that were not submitted in ECTD format, and that would be for ease of review for both the sponsor and the authority.

We are looking for guidance for procedures requiring paper copies of ECTD content, with the understanding that paper is inevitable, especially for the smaller regions, regional authorities that are still our customers.

We are looking for provision by all agencies for regions unable to accept electronic signatures. So in case the region does not have an electronic signature technology, we need to have a work-around for electronic signatures. This is very real for us, because whatever technology we

have must be global and must be harmonized process-wise.

Finally, the harmonization of ICH specifications for reuse of documents between ICH regions. So what we're asking for is that the meta data requirements and the granularity requirements for all the authorities be consistent with ICH and, again, if they are not, it defeats the purpose of harmonization, which was the whole purpose of this.

So in conclusion, the ECTD provides sponsors with global standards for harmonization of processes and submission life cycle information. We have been using submission life cycle information in our systems for six years now and we are very excited about ECTD, because it fits very well within what we already have in terms of life cycle information, but we really would like to have the barriers to global harmonization, including those due to regional deviations from ICH be removed as much as possible and have efforts to remove those.

Again, my name is David Ross. I am the

global publishing and templates manager at AstraZeneca. My colleague who is with me today is Carol Stinson Fisher. She is the associate director of CMC, and we both sit on the ECTD steering group. This is our contact information if you need to contact us about anything.

Are there any questions?

MS. MOLZON: I have a question about your point about electronic signatures. That is considered administrative information and is part of Module 1. Module 1 is not part of the common technical document, so it is not harmonized throughout the regions.

So I'm not sure I understand the point you're trying to make. Do you want to eliminate electronic signatures or you want everybody to have them? But, as I said, it is part of Module 1, so not--that information is not meant to be harmonized.

MR. ROSS: So an example would be a document in Module 1 for the U.S. might be used in Module 1 for other regions. But if, for example--

what's an example, Carol? A report or something that fits in Module 1 that might be used.

MS. STINSON-FISHER: Labeling.

MS. MOLZON: Labeling would be different throughout the regions. It's not meant to be harmonized.

MR. ROSS: But there are documents that might be reused in other regions or might be required in other regions and that's the problem.

If we have electronic signature technology even within Module 1 for those documents, it would impose that the same technology be used for other documents. Do you see what I mean?

MS. MOLZON: I would say it wouldn't impose, because Module 1 is not harmonized.

MR. ROSS: But the technology is global. So if we build an electronic signature technology for Module 1 documents for the U.S., then that technology for us will be used for other regions and is not accepted in the other regions.

MS. STINSON-FISHER: We don't want to redo it.

MS. MOLZON: I know you don't want to redo it, but just as other things in Module 1 for labeling, you will have to redo it. So if other countries aren't accepting electronic signatures, you would still have to provide it to us even though other countries don't, and if there was an issue where other countries are requiring a different type of electronic signature, I don't think it's the case, that might be something to consider, but I don't think that's the case at this point.

QUESTION FROM THE AUDIENCE: By way of example, if you put an electronic signature on a study report in Module 5.

MR. ROSS: We don't have electronic signatures at this stage. We have SOPs detailing where the electronic signatures are. So we have a signed copy in our records.

QUESTION FROM THE AUDIENCE: So to Justina's question, is there anything in Modules 2 through 5 that you have electronic signatures on that require electronic signatures that are in

Modules 2 through 5 that would be relevant to your concern?

MR. ROSS: I think the whole thing is we are kind of driven by if we have an electronic signature technology or solution for certain documents, then that solution should be used for everything else, for other documents, as well. It is very hard to separate the U.S. from the other regions in terms of those documents.

So if we could have a statement saying you are covered by SOPs, for example, or we are willing to look at your Part 11 adherence and see if that complies with electronic signatures, then that would benefit us, rather than building a solution only for U.S. documents.

Again, our systems infrastructure is global. Everything is based on global working. So for us to have a U.S. only electronic signature solution for only U.S. documents, it is difficult for us. It puts a burden on us.

MR. MAHONEY: I agree a 100 percent with everything in your presentation, yet I have nothing

to bring to ICH, because they all agree, as well.

If you can document for us specific examples of where granularity is different, specific examples of where implementing an electronic signature here would cause a problem here, it would make understanding the problem a little easier, because I didn't see anything in your presentation that we weren't trying to do, the points that you stressed.

MR. ROSS: And when we talk about electronic signatures, we're assuming that your requirement is a 100 percent electronic, that you don't mean paper archival copies of the signatures.

MR. MAHONEY: That's the plan, yes.

MR. ROSS: That's the plan. Okay. So all it is, again, is an imposition on us that we would have a solution for the U.S. only that would be different from the other regions.

MR. MAHONEY: Particularly electronic signatures, we have talked about this in the N2 group and we came at an impasse, because it went beyond the scope of even ICH, because it gets into

a legal question.

We decided to sort of table the conversation for our step five specifications to say, okay, is there an electronic signature, more specifically, a digital signature solution that is acceptable in all three regions, and that was the path we were taking.

But it just seemed for our group almost beyond the scope, particularly since the documents --you wouldn't submit a 356-H form to the NEMA. But the technology, though, and some good points are made that it could cause a burden to have to implement multiple electronic signature solutions, but then there is an assumption because there is no solution yet.

QUESTION FROM THE AUDIENCE: It may really be beyond the scope of the ECTD to get into that N2 responsibility in terms of figuring out what you would sanction, as you are saying, as an acceptable solution. That may be where it really resides in ICH.

MR. ROSS: This does help a lot.

MR. MAHONEY: And Dr. Yetter and I have been in meetings, internal meetings talking about that very topic on electronic signatures, making sure that the approach is reasonable and harmonized, because you could start incurring costs on that and it would prohibit people from implementing electronic submissions.

MR. ROSS: I think that's the point is that our technology then would be only for the U.S. We're sharing documents. So upon approval, you would have an electronic signature, but only for certain documents, not others.

The others would go through the SOP process. So it's just adding a burden of technology, where we are trying to harmonize as much as possible within our structure or organization to avoid point solutions.

QUESTION FROM THE AUDIENCE: But it does fall within the traditional responsibilities of the N2 working group to look at that sort of thing and to figure out what is the best method that would be out there or which methods would be acceptable.

I think that is what you are really asking for.

MR. MAHONEY: One more question and maybe a comment. If you had specific issues and you could grab a copy of that form from the ICH web, if you could get them to me before the end of the day tomorrow, I can bring them to the meeting.

MR. ROSS: Specific issues of signatures?

MR. MAHONEY: And specific examples with ECTD, particularly you mentioned areas of granularity and things like that.

MR. ROSS: Okay. We'll get you some.

MR. MAHONEY: Great.

MR. ROSS: Anything else? Any other questions?

QUESTION FROM THE AUDIENCE: Could you submit whatever you give to the agency to the docket so that we have an opportunity to look at it?

MR. ROSS: Sure. I'm not sure how the forms work, but I'm sure it's in the change control system.

QUESTION FROM THE AUDIENCE: It should go to this docket, shouldn't it?

QUESTION FROM THE AUDIENCE: Would the public have access to the comments that Astra makes?

MR. MAHONEY: You could put a disclaimer there. We do say that these are posted in the tracking table, but you could put a message there saying to please don't disclose the company information and just post the question, if you want, or you can say please don't even post the question and then we would reword it and maybe send the FDA off of it. But it's up to you, however you prefer.

MR. YETTER: The question will be there, because that goes in the tracking table and that is publicly available. Whether it is attributable to AstraZeneca is up to AstraZeneca.

MR. MAHONEY: Or it may be up to the ECTD group. Particularly your digital signature question would be a duplicate and it is one that is already addressed and something that we're looking

at.

So you may want to look at that table first and see. We may have already started talking about some of these.

MR. ROSS: The granularity was with reference to the ECTD and the ECTD specs. The clinical sections differ or we thought they differed slightly from the CTD clinical section. So we were just wondering is there a reason why they're different, why the TOC that was given in the guidance is different from the ICH.

That was the specific point about granularity. Again, the deviations that we talked about here in this slide, the regional requirements, was specifically for items that you mentioned in your slide, like the Leaf IDs that are causing some concern. So anything that would differ from ICH, although it's easier for you, it makes more sense, it would impose a burden on common technology, again.

QUESTION FROM THE AUDIENCE: I'll give you an example, Tim. I was at a meeting, a CTD/ECTD

last week, where discussion was made of the file naming conventions for the ECTD and for whatever reason, I guess the ICH had guidance on ECTD to permit underscore or hyphens, and the FDA guidance does in naming a file.

People were flustered by that, claiming that FDA's guidance allows or permits something that is prohibited under ICH for the file name. That may be something I'm guessing that David is anticipating, but that's a specific example that came up in a meeting last week.

MR. MAHONEY: Maybe I'm missing the point, but don't put the underscore.

QUESTION FROM THE AUDIENCE: But the FDA guidance said you could is what people were saying and the ICH guidance says no. There's a difference. So people were flustered about that. I'm not flustered personally. I'm just trying to give you an example.

MR. MAHONEY: Actually, one of the reasons why we have that form is because, I mean, we're going to miss things and if it is a concern, we

want to hear it, because from our perspective, maybe we need to write that down then and harmonize, so that will save the time that we've been talking about it.

So that's why we have that form up on the ICH web, that anyone can raise an issue, particularly from watching our colleagues in the post-marketing submission groups. We want to make sure we have a method to capture anyone's concerns.

MR. ROSS: Thank you again for this opportunity.

MS. LIMOLI: Now we will have Bob Yetter from the Center for Biologics.

MR. YETTER: Thank you. It is a pleasure to be here this afternoon.

I am going to talk about the non-CTD topic highlights. CTD is over now. You can beat up on Tim later.

Non-CTD topic highlights that are going to be on the agenda in Osaka. These include S7B and E14 that have to do with QT prolongation, pharmacovigilance topics, E2D and E2E, quality

systems initiatives in terms of pharmaceutical development, and risk management, a gene therapy discussion group that will be going on, initiative on drug coding dictionary, and Q5E, that is, bio comparability.

To start with, S7B and E14 deal with non-clinical and clinical evaluation of QT prolongation. It is unique that these two have been paired and primarily they were paired after the need was identified to see how they interplayed to make a proper guidance available.

That is, the non-clinical assessment of QT risk and clinical assessment of QT risk turned out to be not clearly separable issues. So although S7B had been released in February of 2002 as a step two document, the steering committee agreed in July of this year that the two topics would proceed in tandem with joint comment from the public.

Consequently, E14, the clinical part, was dealt with by a streamlined process that was accepted by the steering committee.

Health Canada drafted a document in lieu

of the standard ICH concept paper, the step one document that had been mentioned earlier.

A public meeting was held to get broad input and it was determined that we would proceed with those together.

So in Osaka, it is possible, in fact, I think it is expected that E14 will reach step two. If, in fact, E14 does reach step two, we will re-issue S7B as a step two document, so that the two documents can be commented on in coordination, because these two documents do have such a close interplay, one with the other.

In pharmacovigilance, we have E2D, which is post-approval safety data management. This is primarily a definitional document. It contains definitions and standards for expedited reporting for post-market activities.

It is very similar to E2A, which was the pre-market document. It includes all the relevant concepts from the CIOMS-V pragmatic approaches document and is consistent with our current thinking as laid out in the suspected adverse drug

reaction proposed rule.

E2E has to do with pharmacovigilance planning, specifically pharmacovigilance specifications for the post-approval phase.

Originally, this was a concept from MHLW in Japan dealing with early post-marketing phase vigilance. That is, a sort of increased vigilance in the early, the first stages of release of a product.

Subsequently, with the PDUFA-III legislation in the United States, which mandates risk management components, we revised this somewhat and are proceeding with this pharmacovigilance planning topic.

In Osaka, we will be considering comments received from the ICH step two draft issuance and there is the potential that we might reach step four on the E2D document. That would be a final guidance document.

E2E may well reach step two in Osaka. That would then be put out for comment.

Quality systems is also under discussion,

both in terms of pharmaceutical development and risk management. The FDA, as you are probably aware, is undertaking an initiative on CGMPs for the 21st Century. One of the goals is to explore relevant scientific pieces in ICH as possible topics, and that would include pharmaceutical development and risk management.

We had a two day workshop in Brussels in July, with a number of outcomes. One is 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.

That is what a quality system for a drug is all about.

This resulted in five proposals to the ICH steering committee. Three of them were selected as having the potential for an ICH topic.

The ones that will be explored are pharmaceutical development. There was a previous concept paper which will be revised to incorporate elements of risk and quality by design.

A concept paper will be drafted on risk management. A definition of principles on how regulators and industry integrate risk management into decisions on quality. The third would be quality systems scoping document that will be developed by industry to address perceived differences in the ICH regions.

In Osaka, the P2 concept paper, which was endorsed by the steering committee in a steering committee telecon in October, established an expert working group. The first meeting will occur in Osaka to work on a draft document.

The discussion group will work on finalizing a concept paper on risk management for presentation to the steering committee and the industry document on quality scoping will be presented. We will probably have to defer further steps on that due to resource limitations, but we will be hearing the industry's presentation.

There will be a gene therapy discussion group in Osaka. We have explored the pursuit of gene therapy or some aspects thereof as candidate

topics for several years. One of the problems inherent in this is that the science is not as far advanced as we are usually dealing with in topics that we take to ICH to reach harmonization.

It just isn't quite mature enough yet. But we did identify a need for gathering and sharing information and data on the state of the art in gene therapy, things such as dose definitions, virus shedding studies, germ line integration and other issues that are common to gene therapy.

In fact, we had our first scientific workshop on gene therapy in the ICH context in September of last year.

In Osaka, the discussion group will address the mission and goals of the group and areas of scientific interests to be pursued. Also, as part of the larger ICH-6 conference, there will be a one day satellite session on gene therapy that will include regional updates, outcome of the current discussions, and specific technical topics for discussion.

The World Health Organization, prior to our meeting in Brussels in July of this year, proposed a drug coding dictionary. In July, we had some initial informal discussions of the usefulness or approach to drug coding discussion.

In Osaka, we will continue to discuss this in an informal group. What we are particularly interested in is specific requirements in ICH regions for a drug coding dictionary, the benefit and objectives of a harmonized dictionary.

We will need to evaluate the work that will be required to develop a harmonized dictionary and consider the need for maintenance once one is developed and the costs associated with this effort.

A concept paper is expected to be drafted and that would include a business plan for this effort.

We are also going to be handling bio comparability, Q5E. This is to assess comparability of biotech and biological products before and after changes in a manufacturing process

to assist in design and conduct of studies, to collect the data, to establish comparability of pre and post-change products, to enable a company to confirm that a particular manufacturing change doesn't impact the safety and advocacy of a product.

As you are probably aware, this is far more of a concern with a biotech or biological product than it would be with your typical small molecule pharmaceutical drug.

An interim meeting was held in September of this year in advance to a draft document. We expect the expert working group to continue working on the draft document in Osaka, and there is the potential to reach step two on this topic at that time.

I didn't address a number of topics and there are a lot of topics that are currently in maintenance. That is, we have achieved harmonization and now we have to maintain harmonization.

As has been pointed out, if you don't keep

up with them, things start to diverge.

You may have noticed that the current number of active expert working groups is smaller than it was in the early years of the ICH. What I think this balance between new topics and maintenance reflects is the maturity of the ICH process.

We have come a long way from the early days. We have achieved an incredible amount of harmonization. Those things are in maintenance so that we can maintain, we can stay harmonized.

Why have all of that effort if we don't intend to keep up with it? Also, one of the things that will be going on in Osaka, as I mentioned here and in other places, will be discussions that reflect the scoping of potential future work for the ICH, both new topics and topics to move into maintenance.

So if there are any questions about that, I would be happy to try and answer them or and them off to somebody who can do a better job than I can.

MS. STINSON-FISHER: The pharmaceutical

development concept paper, the goal there would be to try to get the three regions to agree on the types of print systems and risk, elements of risk and quality that's been built in by design and how they are put into the P2 module.

MR. YETTER: That is the general approach. Yes.

MS. STINSON-FISHER: The quality systems scoping document, are you talking about PHARMA and the other partners in the ICH process or how would that be done?

MR. YETTER: As I recall, PHARMA took the lead, but it was going to be all of the partners. Is that correct, Justina?

MS. MOLZON: The scoping document, I think the lead on that is Joyce Graham from EFPIA. In terms of the pharmaceutical development topic, I think the point there is the risk management group is going to talk about the basic definitions and then the pharmaceutical development group will talk about the types of information that should be provided in order to make the risk management

decision.

So it's the underlying information that would help go into that thought process as opposed to the written analysis itself, I would think. But these are just going to start discussion.

MR. YETTER: That's where we think they are now. Where they end up, we'll see where the discussions go.

QUESTION FROM THE AUDIENCE: What is going to be in that scoping document, what is the expectation that that document will --

MS. MOLZON: That document will only be presented, not discussed.

QUESTION FROM THE AUDIENCE: I know, but what will the elements of the document be? What do you expect?

MR. YETTER: Until we see it, we won't know. It was presented or spoken of as sort of a big picture item and, as such, until I actually see the document, I don't really know what they are planning on putting in there.

I haven't seen any preliminaries. I

haven't --

QUESTION FROM THE AUDIENCE: I'm actually trying to get at what is the big picture going to be. I mean, it's a big picture of what?

MR. MAHONEY: It talks about the differences between the three regions. I think the substance of the document is something that may be discussed, but basically there is no agreement on it.

QUESTION FROM THE AUDIENCE: And the document is going to be presented for the first time in Osaka, as I understood it. There is not going to be any sharing prior to Osaka. Then it will be distributed at the meeting in Osaka.

MR. YETTER: We haven't seen it so far and I doubt that we are going to see it before Friday when we're all on our way.

QUESTION FROM THE AUDIENCE: I've got another question for you, Bob, also, on the S7B document. You said if the E14 reaches step two, then there will need to be a revised step two issuance I guess of E14. I'm sorry. Of S7B.

I didn't realize that S7B had been released as a step two, but it has been.

MR. YETTER: Yes. Sure.

QUESTION FROM THE AUDIENCE: A while ago and was sort of put on hold.

MR. YETTER: Yes. It was last year.

QUESTION FROM THE AUDIENCE: So then it's going to be looked at again as --

MR. YETTER: Essentially, it would be re-released, I guess, is as good a term as any, for comment, so that it is available for comment at the same time that concomitant document is available.

QUESTION FROM THE AUDIENCE: But even if it doesn't change, you will release it at the same time so they can be looked at together, even if it is identical.

MR. YETTER: That is my understanding of how we decided to proceed with that. Yes.

QUESTION FROM THE AUDIENCE: The drug coding dictionary. What is the FDA's view on how it would like to see that approached? How, if at all, do you see the business plan evolving as it

relates to the--are they talked about with the same view or are they different approaches? What is the FDA's view?

MR. YETTER: Let's see. We have a presentation on MedDRA.

QUESTION FROM THE AUDIENCE: There is a presentation on MedDRA, but when it comes to the drug coding dictionary, which you alluded to as part of your presentation, what is FDA's position going into that meeting in Osaka going to be?

MR. YETTER: I'm certainly not the person to speak to that, since I'm far from being any kind of an expert on drug coding dictionaries and, unfortunately, the only person who comes close to that who is here would be Tim in terms of understanding the technical aspects of it.

On the other side of that, we're certainly open to suggestion. I mean, we have a proposed rule out, actually, the comment period is closed now, that deals with the very fact of multiple languages for reporting adverse events.

Would a single drug coding dictionary be

useful? Perhaps. Is it actually feasible? That's not clear. Would it be supportable? That is also not clear. Who could create it? It would require something like the ICH to create a harmonized drug coding dictionary across multiple areas.

But the issue is--I mean, the charge has been like the ICH is a closed shop. We're trying to work on that through the global cooperation group.

MS. MOLZON: To help Bob out a little bit, this is still a fact-finding. I don't believe we have a position yet, because the group is tasked to do some feasibility work. They were asked to look at the different requirements in the three regions and benefits and objectives of the three regions in harmonizing a dictionary, how much work would be needed to establish such a dictionary, the maintenance costs.

So they sent a questionnaire out to the specific regions to gather this information. So they're still in the information gathering point. So I don't believe we have a position at this

point, until we see what the results of that information gathering is. Then we will see what is being proposed. So nothing has been --

MR. MAHONEY: So we're a long way from even step one on that.

MR. YETTER: We're definitely at step one on that. I'm sorry. I didn't realize that was the nature of the question. This hasn't been accepted as an ICH topic yet. This is exploratory. We'll see where it goes.

QUESTION FROM THE AUDIENCE: I have sort of a related question. Well, not related in the sense--with respect to gene therapy, is the expectation from the agency that there might be concept papers that will be requested?

Will there be concept papers that might be requested as a result of whatever discussions occur on gene therapy? Do you see that going forward as a potential ICH topic at a meeting next year?

MR. YETTER: I think we are still a little early for that. I mean, we're still collecting data. Again, where harmonization works is where

you have a reasonably mature technology, where you have a fairly broad base of understanding, and where you can bring people together to discuss that.

I'm just not convinced that gene therapy is quite there yet. We'll see where we get to, but I don't believe that we are really expecting concept papers to come out of this discussion. I think it is too early for that.

QUESTION FROM THE AUDIENCE: Not even an assignment for a concept paper perhaps presented at the meeting in 2004. You don't even see it getting that far?

MR. YETTER: I don't know. We'll have a better handle on it after this meeting as to whether that is a reasonable expectation or not.

If I had to make the decision right now, I would say, no, I don't expect that. Maybe that would change after this meeting. We'll have to see how that goes.

Part and parcel of this is the exchange of scientific information to allow you to determine

whether harmonization is really possible, whether it's feasible. So far, the basis for any of these is a solid body of scientific and technologic information and so far we are still trying to build that solid body in gene therapy.

Now, every time we have one of these meetings, every time we get together and exchange information, we are that much farther along towards building that solid base, that foundation for building harmonization.

But as of July, we weren't there.

QUESTION FROM THE AUDIENCE: With regard to E14 and S7B, in Osaka, will there be a working group or a general conference --

MR. YETTER: That's going to be dealt with in the expert working group. The steering committee has already agreed on a process to move forward. I mean, the steering committee agreed to the accelerated, if you will, process for E14 and the idea that we already agreed that these would go out together.

So, no, that is not a question of process

for the steering committee. This is going to be worked out in the expert working group and if they can reach a harmonized document, then it will proceed to step two for both documents.

QUESTION FROM THE AUDIENCE: With respect to the comment period on E2D, do you want to just tell us a little bit about how that went? The comment period closed on E2D, correct?

MR. YETTER: Right.

QUESTION FROM THE AUDIENCE: Do you want to just give us a little two cents worth of the comments that were received? Were there any comments received? What were the comments like, in general?

MR. YETTER: We received a fair number of comments. We extended the comment period. I don't believe we got that many more comments after extending the comment period.

MS. MOLZON: Again, it's talking about the document itself and I don't think there were that many comments.

MR. YETTER: The document itself, no. I

don't believe we saw that many comments at all. We received--well, the SADR received a lot of comments, but the E2D, relatively few, a couple or three.

Other questions? No. Good.

MS. LIMOLI: We now have a presentation by Patrick Revelle on MedDRA.

MR. REVELLE: Thank you for inviting me to the meeting. We appreciate the opportunity to do a little bit of an update. What I will try to do is provide some basic information about MedDRA, in case this is a brand new idea to anybody in the audience. Then I will go through a sample of the issues that we will be talking about with our management board that we will be meeting with. I'll give a little bit more detail about that.

So you will see these items as I bring them up in each section. First, just if nothing else, we'll get the acronym out of this talk. It's the Medical Dictionary for Regulatory Activities.

The scope is to provide a multilingual terminology for a standardized communication,

obviously, at least between regulators and industry, if not between industry and themselves, to include clinical trials, as well as post-marketing.

A little bit about the time line. This has been what I would consider one of the success stories of ICH. It has been going for a long time. It started back in 1994. The first release of MedDRA came out in 1999 Version 2.1. We are up right now to MedDRA 6.1, which comes out twice a year at this point.

I work for the maintenance and support services organization. It is the organization tasked with the maintenance of the terminology. So we receive change requests from subscribers. We maintain it. We distribute it and we are essentially a single point that people can come to for questions or issues about the terminology.

We have a mechanism for international support and development. In other words, we have physicians around the world that receive change requests from subscribers, review the change

requests and decide about what sort of changes will be made in each version of MedDRA.

We also have an arm of our organization that is really there, and it's part of what I am doing here today, is to support, foster the use of MedDRA through communication, education, and services that we provide, whether things like training or data conversion services, as well.

I will just give you a sense of the various organizations that we report to. We have a meeting scheduled for Friday and Saturday of this week with our management board, which is made up of the typical ICH members, each of the three regions, plus the industry leads from those three regions.

They, in turn, report to an theory committee. We have a sister organization we call the JMO, the Japanese maintenance organization that handles the change requests in Japanese for us.

Obviously, we report or receive input from user communities or other user groups that we have that are associated with MedDRA.

So there's a lot of different

communication between these various groups. Let me go into some of the topics that we will be talking about with our management board in Osaka.

First, the current release of MedDRA is MedDRA 6.1. I won't bore you with all the details, other than we're still doing a fair number of change requests associated with each release. We're looking for that number to go down.

I would expect you'll see some numbers here about the next version that we are already starting to see numbers go down fairly dramatically.

One of the things that's really been driving it is that we have been kind of given guidance by the management board to implement a series of consistency sorts of issues, where some people would look at one part of the terminology and say you're doing this, but you're not consistent with this other side.

So we launched on a series of those and one of which I am describing here is this NOS or not otherwise specified consistency check that

drove a large number of those changes.

So not all of these changes are actually coming from subscribers. A lot of these changes are really coming from management board direction to implement consistency issues.

I won't go through the rest of the detail there, other than to give you that level.

MedDRA 7.0 is our next release, which will come out in March of 2004. The freeze date, in other words, the last date that you can submit a change request to have it be considered for that release is the 19th of December of this year.

That release of MedDRA, each major release, the ones with a zero on the end, are what we consider the complex changes. In other words, we can change not only the lower levels of the terminology, but portions used for coding, but we can change the higher levels, the HLT, HLGT. Some more structural sorts of changes we only do once a year. So that's what is called a complex change.

We had proposed 17 complex changes via our website. We are only going to be implementing 14

of those based on comments we have received from subscribers.

As I mentioned before, we are seeing a number of change requests go down. We've got about 1,200 change requests as of the end of October. So if you compare that number to the previous numbers that you saw, it is a much more palatable number, I think, as far as the number of changes.

We are still doing some of the consistency things, but at least a number of terms being affected by consistency is much farther down.

Standardized metric queries. That's what the acronym SMQ stands for. It is a significant, I would say, change not in the basics of MedDRA, but in a new component of MedDRA that will essentially be what I would call a stored query. So it will be looking at significant safety issues to be looked at in both post-marketing data and clinical data.

Originally, we had looked to release the first SMQs with MedDRA 6.1. There was some concern raised by our management board about the level of testing and the methodology that was done to

develop to this point in time. So they asked that they would be delayed so it gives them more time to take a look at the documentation.

We expect to do that during this management board. They have seen the documentation to review. We don't have a specific release date today, although we would expect that if things go well in Osaka, that they would be released in conjunction with MedDRA 7.0, which would put it in March of 2004.

The SMQs are being developed with the CIOMS group, which was actually an interesting point, that they had started to develop something very similar. We had developed something very similar, as well, but decided to pool our efforts. We met with them last month to focus on the first three SMQs that we looked to release and develop and make sure the appropriate documentation was available for not only the management board, but for subscribers, as well.

So the first three SMQs I have listed there for you. We looked to--the contents are

essentially set right now. We need to get just the approval from the board and then go through the process of making them available.

We would likely make them available as downloads from our website as opposed to putting them on the CD-ROM, just because it's a little bit easier, I think, for people to get them versus sending a single CD-ROM to a company and then try to find a person in the company that has that CD-ROM is somewhat difficult.

Besides the first three SMQs, there are roughly 90 that are being considered or under development at this point. So there's a fair number of different topics being considered.

We also look to get approval from the management board to post the SMQs on our website to get a sense of what will be coming and potentially even a schedule associated with those developments.

We do have a draft SMQ file structure available on the MSSO website. The point of that really is that once we deliver the SMQs, you need to be able to bring that into either your own

commercial systems or your own homegrown systems to really be able to use them.

So we're trying to make sure people are available to see the formats we plan on.

MedDRA, a very common question that we got at the MSSO, it really became a much bigger issue as a result of the Brussels meeting, the ICH Brussels meeting in July. A lot of concerns were raised by the FDA's plans regarding SNOMED and MedDRA. I think it has become somewhat more clarified, although my next slide will hopefully help with that a little bit.

If you are unfamiliar with SNOMED, it is a product of the College of American Pathologists. It's a very large terminology. The original intent I think of the terminology really was for electronic patient records.

The concern that was raised I think initially in Brussels was maybe this should take the place of MedDRA and then people were very concerned about the amount of effort already put into the implementation of MedDRA, so why would you

want to replace it at this point.

That same point is actually made and is true for the FDA, as well. A lot of effort has been put into it, not just human effort, but other effort as well.

This is a posting from the FDA website that came after the July ICH meeting. Essentially, someone said what are the plans based on SNOMED and what is FDA going to do with it. Essentially, the key part of this statement, I think, for me, is that the FDA has proposed to require that reports from industry be coded in the ICH international drug regulatory terminology, MedDRA.

This remains the agency's proposal. It doesn't mean they won't consider it in the future. It doesn't mean they won't consider something different for clinical reporting, but at a minimum, what the scope of the proposed rule was really for post-marketing reporting and MedDRA still is their recommendation to use for that.

It doesn't mean they won't consider other things, but at least it is clearly stated there.

So our proposal really to the management board is we essentially gather a group of kind of interested parties, and that would be the College of American Pathologists, obviously, the MSSO, the FDA, potentially others, to really look at a potential mapping and don't just start the mapping, look at the requirements that would really be necessary, because I think it is important to understand what are the scenarios that the mapping would really be used.

So you develop the mapping appropriately. You've got two terminologies that are relatively large. They are changing on a fairly frequent basis. So identifying the development and maintenance requirements I think are really important just before you launch on it.

You could waste a lot of money and time if you don't think those sort of things through.

So we are hoping that the management board will be agreeable to that. The MSSO's intent is to be involved really just in the planning phases and just making sure, quite honestly, that MedDRA is

properly supported and that that mapping is something of value to MedDRA subscribers in the end.

MedDRA translation issues. If you are familiar with MedDRA, it is available in a number of different languages. We are encountering some issues right now regarding the translations.

If you are familiar with MedDRA, and, as I said, there is a theme with the British way of spelling it, as well as the American way of spelling it, which causes problems when you do translations.

Obviously, it's exactly the same meaning, just spelled two different ways. Right now, there is a divergence in the solution that has been implemented for the European translations of MedDRA versus the Japanese translations.

We do have a potential solution for that, but that is hopefully one of the conclusions we will come to in Osaka, as well.

The last thing I want to talk about, an opportunity for anyone who is interested to just

kind of get a sense of issues related to MedDRA, is we have started a forum page off of our website that allows anybody that's really interested to take a look at what are discussion issues, what are people's particular opinions to raise an additional issue.

We monitor it. We obviously participate in it and encourage others to do so. We've got roughly 11 ongoing discussion areas right now. This is just a quick screen shot, gives you actually the link to the site, as well.

With that, I can take any questions you might have regarding MedDRA or the MSSO.

Thank you.

QUESTION FROM THE AUDIENCE: I have one for Justina. One of the discussions I see in Osaka has to do with the ISS and IA document. What is going to be FDA's presentation there? What is it going to consist of?

MS. MOLZON: I believe it's going to be-- the answer will be question number ten in the ECTD process and basically an ISS/ISB remain a

requirement for submission for an MBA. A CTD is nothing more than an MBA in a CTD format. Then it is up to the person submitting the document to determine the best way to present the information.

If the information, for some reason, doesn't fit into the overview, which is about 50 pages, there will be a summary which goes up to a couple hundred, then they are welcome to do that. If not, they're going to have to figure out how to split the information and provide the bulk of the data in Module 5.

We've been looking at some of the documents that have come in and there are some variety of ways for people to do this and they're all accessible, which is that a company has to decide how it wants to do it. But it is still a requirement. Nothing has changed that requirement.

In question number ten, it is going to explain various options.

QUESTION FROM THE AUDIENCE: Thank you.

MS. LIMOLI: Okay. The meeting is adjourned. I thank you very much for your

participation today.

[Whereupon, at 3:00 p.m., the meeting was concluded.]

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CERTIFICATE

I, **SONIA GONZALEZ**, 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.

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