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INTERNATIONAL CONFERENCE ON HARMONIZATION

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PUBLIC MEETING

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TUESDAY,
October 19, 2004

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The meeting was held in the Chesapeake Conference Room, 5600 Fishers Lane, Arlington, Virginia at 1:30 p.m.

PRESENT:

- JUSTINA MOLZON,
Associate Director for International Programs
- ANDREA FEIGHT,
Center for Drug Evaluation and Research/USFDA
- NORMAN SCHMUFF,
Center for Drug Evaluation and Research
- ROBERT YETTER,
Associate Director for Review Management CBER/FDA

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A-G-E-N-D-A

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P-R-O-C-E-E-D-I-N-G-S

1:33 p.m.

1
2
3 MS. MOLZON: Well for the transcript,
4 thank you to the transcriber for being here because
5 one of the things we try to do is make available
6 information at this meeting for people that aren't
7 able to attend because this is FDA's attempt to work
8 with stakeholders and be transparent. I think we're
9 one of the only regions in ICH that actually does
10 this, that allows some time before the ICH meetings
11 for people to come and have an update on what's going
12 to be presented so they're aware of various documents
13 that have been put up for comment and whatever.

14 So today, we're basically going to have
15 four topics discussed. There will be, it looks like
16 10 or 15-minute presentations on each of those topics.
17 We're going to hear about what's going on in MedDRA,
18 the Medical Dictionary for Regulatory Activities; an
19 update on the eCTD because what's happened is the past
20 four or five of these meetings I would give a
21 presentation on the statistics on the CTD and we've
22 progressed so far into the eCTD that that's going to
23 be the focus for this meeting. So I'm not really not
24 going to spend much time on the CTD. I put a
25 presentation in the *Backgrounder*, but it's just, you

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1 know, the statistics that I generally show. And then
2 Dr. Robert Yetter is going to give an update on new
3 and ongoing topics and I know that we have one public
4 presentation on CDISC from Art Gertel. And I think
5 that's it.

6 Do you have anything to add? Anyone else?
7 Bob?

8 (No audible response.)

9 MS. MOLZON: Okay. So our first
10 presentation is going to be by Andrea Feight. She is
11 our MedDRA management board representative and she's
12 just going to be talking about some recent activities
13 in MedDRA.

14 MS. FEIGHT: Good afternoon and thank you
15 for coming. I'm going to basically give you a status
16 of MedDRA and AERS, which is the FDA's Adverse Event
17 Report System for Drugs and Therapeutic Biologics.

18 And I'll touch on a couple of new topics.
19 There's actually my outline. I'll touch on a couple
20 of new topics towards the end, which will address some
21 things that are up before the management board.

22 As I discuss AERS, I'm going to give just
23 a brief history of AERS including the history of the
24 upversioning of the MedDRA dictionary within AERS.
25 I'll give you a very brief status update on electronic

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1 submissions. I will discuss MedDRA as a reporting
2 requirement, and as I said, I'll touch on some topics
3 in the works and then allow a little bit of time for
4 some questions.

5 And I do encourage you to ask questions
6 because I will not be asking for the rest of the
7 meeting this afternoon. So if you do have questions,
8 please ask me at the end of my presentation.

9 So, MedDRA implementation at the FDA. The
10 history of that is that in November of 1997 we began
11 using MedDRA and we were using version 1.9, which was
12 really a pre-official release of MedDRA.

13 in November of 1997 when we launched AERS,
14 we migrated about 1.5 million records from our old
15 Spontaneous Reporting System into the new Adverse
16 Event Report System. And in order to accomplish that,
17 we brought forward the terms that had been coded using
18 COSTART, which was our old coding dictionary. We
19 mapped those into MedDRA so that we wouldn't have to
20 maintain two separate databases and two separate
21 terminologies. So what we now have is
22 approximately a total of 3 million records within that
23 system because since November of '97 we've added about
24 1.5 million records.

25 We are entering data into the system using

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1 MedDRA at the preferred term level. We would have
2 preferred now in hindsight to have entered them at the
3 lowest level term level and we are moving in that
4 direction sometime in the near future.

5 As far as versioning goes, MedDRA is
6 released now twice a year and I'm happy to say that
7 for the last almost two years now we've kept up with
8 every change in MedDRA. Initially it was a very big
9 job for us to do and we had a lot of competing demands
10 from the AERS system itself, which meant that our
11 resources moved more towards updating the system and
12 providing fixes to the system. But now we do have
13 enough resources allocated towards keeping up with
14 MedDRA and this is very well accepted by the MedDRA
15 user community, industry users especially. So we are
16 actually on schedule to update our system to MedDRA
17 7.1 on November 1st.

18 Now as far as submissions into MedDRA go,
19 we're accepting them two ways; paper, which is the way
20 that we've always accepted mandatory submissions to
21 the Adverse Event Reporting System, but also we began
22 an electronic submission program back in August of
23 2000. And initially we had about three or four
24 companies submitting. Some of them were using MedDRA
25 as the reporting terminology. Others were not

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1 precoding their data into MedDRA. But now I'm happy
2 to say we have 13 U.S. companies that are submitting
3 their reports on a mandatory basis of course, but
4 they're voluntarily submitting them in an electronic
5 format. And so to date, we have 143,324 case reports
6 that we've received electronically and many of those
7 are precoded in MedDRA. If you caught my public
8 meeting presentation last May, you would have heard
9 that we had only received about 70,000. So we've
10 really had a ramp up over the last six months or so
11 and we're very happy to see this because of course
12 processing the reports that have been submitted
13 electronically is much less expensive than processing
14 a report from paper.

15 We are accepting, as far as the MedDRA
16 terminology goes, we're accepting data in either the
17 text string or using the MedDRA numeric code. Europe
18 currently is requiring only the numeric code; you
19 cannot submit text strings, so most companies are
20 actually submitting to both authorities using the
21 numeric code.

22 I'm going to talk a little bit now about
23 how the coding is actually done. And for the paper
24 reports, the narrative provides the basis for coding.
25 The information is entered by data entry folks in an

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1 electronic format and then it has been coded using
2 both an autocoder as a tool and then the experience
3 and expertise of the human MedDRA coders to enter the
4 actual MedDRA terms into the database.

5 Now on the electronically submitted
6 reports, we are accepting the MedDRA terms as they
7 have been reported. But we're using the narrative as
8 the basis for quality control and we do do quality
9 checks on all reports.

10 Now when the MedDRA versions do not match,
11 as was the case when we first started using MedDRA,
12 that was fairly common, those reports would need to be
13 recoded. But we'll also do recoding if we find that
14 the quality of the coding of the report does not meet
15 our standards and we'll also work with the company on
16 these reports.

17 About a year ago we developed a quality
18 assurance plan and that has been communicated to
19 industry through the E*Prompt working group that is a
20 joint FDA/Pharma initiative.

21 So the evaluation plan that we are
22 currently working on was developed by our AERS coding
23 working group with oversight by the Office of
24 Pharmacoevidence and Statistical Sciences. We
25 asked their biostatistics office to develop a sampling

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1 plan and we now have a statically valid sampling plan
2 that we use to evaluate each manufacturer as they
3 begin to submit reports electronically. We also
4 continue to evaluate them on an ongoing basis once we
5 have determined that they have met our criteria for
6 accepting reports.

7 And we have a contract with PSI to data
8 enter and code our data and they're also serving under
9 the existing contract to perform evaluations of the
10 data using the sampling plan, using the criteria that
11 we had provided to them. I should say that the
12 criteria that we have provided to the contractor
13 include what should be in the report, but also
14 criteria for what we consider unacceptable errors and
15 there are two main unacceptable errors. One being
16 that a medical concept was entirely missed; it was
17 described in the narrative, but no codes relating to
18 that medical concept are included in the listing of
19 codes. Or we would consider it an unacceptable error
20 if a company does what we call "in house soft coding"
21 because we haven't really found a better term for
22 that. But this would be when the company reports the
23 event, but they use a term that doesn't really reflect
24 the severity or the specificity of the medical concept
25 that is included in the narrative.

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1 Now once a company has joined our
2 electronic submissions program and been evaluated for
3 the quality of their coding, the sampling percentage
4 can actually be decreased from 100 percent, where
5 we're looking at each and every report that comes in,
6 down to as low as 10 percent if the company is doing
7 very well with their coding. And we do this in order
8 to maximize the resources that we have, but yet
9 provide a level of quality in our database that we
10 feel is necessary.

11 I'm going to move now to the topic of the
12 proposed rule. I'm sure that you all have seen the
13 proposed rule out on the street for reporting of
14 Adverse Events for Drug and Biological Products. It
15 published on March 14th of 2003 and the comment closed
16 just about a year ago. And of course those comments
17 are public and they're available through the docket.

18
19 In that rule, we propose that each
20 suspected adverse drug reaction be coded at the
21 preferred term level in the individual case safety
22 report. And since the proposal also includes a
23 section on medication errors, the same criteria were
24 laid out for reporting medication errors.

25 In the rule, we also communicated

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1 information about the possibility that waivers would
2 be granted for the MedDRA requirement itself for small
3 companies and that would be on a case-by-case basis.
4 We're looking at some other possible alternatives to
5 that as well, perhaps having a publicly available tool
6 that would enable on-line reporting, but those are
7 still under evaluation and work.

8 Well, regarding the proposed rule, FDA
9 received 109 unique comments to that rule and many of
10 those did address the MedDRA requirement. The Agency
11 is still in the process of reviewing those comments
12 and is considering them as the final rule is being
13 prepared.

14 So I said that I would touch on a couple
15 of topics that are sort of new and in the works. I
16 should let you know that the FDA, regarding the
17 medication errors they worked with some other entities
18 both in the United States and outside the United
19 States on medication error terms and there is now a
20 proposal to add additional terms to the MedDRA
21 terminology and this is posted on the MedDRA MSSO
22 website for comment. And I believe the comment period
23 is open for another approximately month.

24 So if anybody is interested in commenting
25 on this, they should go to the MedDRA MSSO website at

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1 meddramsso.com.

2 The other topic that is underway right now
3 and is up for review at the next management board
4 meeting is the inclusion of terms that are related to
5 the causes of device failure. This would be a brand
6 new area for the MedDRA terminology. It was something
7 that was envisioned by the expert working group that
8 created MedDRA as a potential area for expansion as
9 MedDRA became utilized and became more stable. So I
10 think it's probably good timing now that this is being
11 considered and I understand that the proposal to begin
12 on this now actually came from several industry
13 groups, maybe from small manufacturers as well as the
14 industry group itself. And we have some people within
15 the Center for Devices working on this topic.

16 So these two topics, as well as
17 several other topics, are going to be up for
18 consideration at the next MedDRA management board
19 meeting during ICH.

20 So I would be happy to take questions at
21 this time, if you have any.

22 MR. GERTEL: I do have a question.

23 MS. MOLZON: I think you have to --

24 MR. GERTEL: Do I identify myself?

25 MS. MOLZON: Yes, you have to identify

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1 yourself.

2 MR. GERTEL: Okay. These are live?

3 MS. MOLZON: Yes.

4 MR. GERTEL: Is this good? Okay. Art
5 Gertel from Beardsworth Consulting Group. You had
6 mentioned earlier that there were advantages to
7 electronic MedDRA submissions. Do you have any
8 metrics on that in terms of time and dollars that we
9 might save?

10 MS. FEIGHT: There have been some
11 estimates made. I don't have the numbers right in
12 front of me now, but I believe a report that goes
13 through the system, a paper-based report from start to
14 finish runs around \$30 a report and a fully-electronic
15 pre-coded in MedDRA report, I'd be guessing right now,
16 I'm sure they went over this at the E*Prompt meeting
17 a week ago, but I was not at that meeting, it's
18 probably somewhere around a quarter of that.

19 Any other questions?

20 (No audible response.)

21 MS. MOLZON: Okay. Well, I'm going to
22 poll the audience. How many people are familiar with
23 the way ICH works? Okay. That's why I didn't want to
24 give that basic introductory discussion on the CTD.

25 The way this is scheduled now, Norman's

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1 going to talk about the eCTD and I was going to talk
2 about the CTD. That order doesn't make sense because
3 you need a little bit of background for the eCTD. So
4 I could give some just preliminary slides by way of
5 introducing that topic, if that's okay. The CTD
6 itself was finalized in November of 2000, so it's now
7 four years later. I don't think we need to keep
8 harping on the number we get all this kind of stuff,
9 but I think there are some slides that I have that
10 could help introduce Norman and I can clear up maybe
11 the most general misunderstanding about the CTD,
12 because I think Art asked me this question --

13 Well, I'm Justina Molzon. I'm on the ICH
14 Steering Committee for CDER and I'm going to skip
15 through a bunch of these, which basically explain how
16 ICH works. But the whole point behind the CTD, after
17 ICH spent a lot of time generating guidances. MedDRA
18 is one that Andrea just talked about. We had over 50
19 documents that had focused on the technical
20 requirements for submission of information to the
21 regulatory authorities involved in ICH and in 1996,
22 industry proposed assembling this information; if you
23 think of it as building blocks, in the same order so
24 that companies could start putting submissions
25 together in the same order and submitting it to the

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1 various regions because they actually looked at what
2 had to be done to take a submission, and NDA, to the
3 U.S. and what they had to do to convert it to a
4 marketing application in the European Union and there
5 were a lot of people involved in this. A lot of
6 people manipulating paper, a lot of staff time and a
7 lot of time to do that. So some companies spent three
8 months to convert something. Other companies spent up
9 to 10 months. Some people had 20 people working on
10 this conversion. Others had up to 50 and this was
11 just a lot of time to shuffle paper around. So that's
12 where the concept of the CTD came about. Industry
13 wanted to put all of that information that we had
14 agreed upon in the same order so it could be
15 submitted.

16 The most common misunderstood point about
17 the CTD from the U.S. viewpoint is that we say this is
18 highly recommended. It became mandatory in the
19 European Union and in Japan on July 1st of last year.
20 It's highly recommended in the U.S. and this is
21 because ICH documents have always been considered
22 guidance. They're not mandatory in the U.S. and there
23 was a rule promulgated in fact that talked about
24 guidances. At one point, we had guidances, point to
25 consider guidelines, all these documents out there.

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1 Companies didn't know what to follow so we instituted
2 good guidance practice, which became a regulation on
3 September 19th of 2000. And this rule requires that
4 the CTD in essence not be mandatory. So this is due
5 to a regulation. It's not an indication of lack of
6 commitment to ICH or the CTD. It's just this little
7 quirk that we have in our regulations. We have to
8 follow good guidance practices. And the resubmission
9 meetings that we're going to, most companies are
10 following this recommendation to a very high degree.

11
12 Okay. This just gives you an idea after
13 July 2003 many companies were submitting information
14 in CTD format.

15 Now to get ready for the last ICH meeting,
16 what I started to do was to look at the number of
17 submissions that were coming in in CTD format. And if
18 you look at May, in May we had one NME in come in and
19 that NME was in CTD format. So it's the ratio. One
20 application, CTD format. April nothing came in CTD
21 format. March, one came in out of three. And, you
22 know, we're starting to track this information, but
23 there's a time lag because we're only allowed to
24 release the information on the number of NMEs that
25 have been submitted at a certain time. So I have to

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1 wait for that information to be submitted to update
2 these statistics. But we're starting to track that
3 because we're most interested in the ratio. Most
4 things should be coming in in CTD format. And last
5 Friday I actually spoke to a group of new reviewers
6 that were going through new reviewer training in one
7 of our programs that our Office of Training and
8 Communication puts on. And I realize I'm talking
9 about this big transition from the NDA to the CTD, I
10 mean from the NDA to the CTD, and most of the people
11 that were sitting there were receiving CTDs. Their
12 very first application to review was a CTD and that's
13 when I realized I had to change my talk because we're
14 not going to have a conversion anymore. Most of these
15 people are starting out with them. And so I believe
16 that this is a very nice trend. You know, there were
17 50 people at this new reviewers workshop and most of
18 them were working on NDAs for their first application.

19 The thing that I wanted to mention to
20 preface Dr. Norman Schmuff's presentation on the eCTD
21 is that we've spent a lot of time working on eCTD
22 guidance documents. So at one point we had a general
23 considerations document on how to submit things in
24 paper format. We're putting our energy into the eCTD
25 documents. So you should make sure that you have

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1 those documents because what we've done in the eCTD is
2 actually update the specifications for module one.
3 The documents that are related to the eCTD actually
4 list all of the information that should be included in
5 module one. That's the regional-specific information
6 for the U.S. Then we have the specifications for
7 module 2 and 5, but I think the most important piece
8 of information in these documents is a complete table
9 of contents from top to bottom, headings in hierarchy
10 in a CTD. So this does what the paper documents have
11 not done. The paper documents list this information
12 in clumps. The quality documents, the efficacy
13 documents and the safety documents. The eCTD
14 documents are providing information which would be
15 very helpful to companies that are now assembling
16 these documents of a top-to-bottom listing of how
17 these documents interleaf and fit together. Norman's
18 going to talk more about this.

19 We do a lot to make sure that we answer
20 questions from companies that are submitting these
21 documents. We've established two e-mail addresses.
22 One is ctd@cderr.fda.gov and then esub@cderr.fad.gov.
23 Both of these e-mail addresses are answered by the
24 same person for consistency. That person's located in
25 the Office of Information Management, which at the

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1 beginning of the CTD was just a small group of people,
2 but now is a complete office that deals with
3 implementation of these documents, creation of the
4 software necessary to deal with the information that's
5 coming in.

6 Dr. Robert Yetter is going to be talking
7 about the new topics we're discussing in ICH and as
8 each new topic in ICH is introduced, you have to be
9 mindful that we have to go back and make sure that it
10 doesn't affect the CTD somehow and we've done that for
11 the topics that have been listed and there's actually
12 place holders in the CTD for this information, so we
13 didn't have to revise anything. But that's something
14 to remember. Every time we introduce a new topic, we
15 have to go back and see if the CTD would have to be
16 adjusted.

17 So in terms of next steps, we're still,
18 you know, looking forward to all these submissions
19 that are coming in. The increased submissions will
20 help determine if there is any effect on the review
21 process. I don't think there has been one except in
22 a positive sense and that applications are coming in
23 in the same format and people can just pick one up,
24 review it and as that one's finished, go to the next
25 one that's in the same format. Our Office of

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1 Information Management is providing training to our
2 reviewers when this information comes in. A lot of
3 that is focusing now on the eCTD because people have
4 to have an understanding of how this all fits together
5 and our Office of Information Management provides
6 something called over-the-shoulder training where they
7 actually take one of their people and they sit with
8 the reviewer and explain how you can navigate through
9 the different documents.

10 This is just an indication on, you know,
11 back in July of 2001. When we started talking about
12 this, we really had no submissions and now we're up
13 to, you know, well over 100, probably 113 for various
14 submissions and I know that Norman has some statistics
15 on eCTD submissions, which is the trend we're finding.
16 Most people have put a lot of effort into just getting
17 up and running and they're switching to the eCTD,
18 which we highly appreciate.

19 Thank you for your attention and, you
20 know, if there's any questions, I just thought I'd try
21 and preface what Norman was going to say by giving
22 some background.

23 Yes, Art?

24 MR. GERTEL: Art Gertel again, Beardsworth
25 Consulting.

1 Do you anticipate any sort of a NDA
2 rewrite-type of a consolidation of all the new
3 guidance similar to what happened in July of '88? Is
4 there going to be a total revamping or is guidance
5 going to come out as it has been, sort of piece-by-
6 piece?

7 MS. MOLZON: Well, when we had to
8 determine if we had to rewrite the regulations for the
9 CTD, we actually went back and analyzed it. And
10 because it didn't say anything about format, we didn't
11 have to rewrite it. It's just a very general
12 document. Most people would just follow the way it
13 was laid out in the CFR, but they didn't have to.
14 There wasn't anything that said they had to do that.
15 We haven't actually changed much, except reorder the
16 information. You know, at some point it would be good
17 to go in and clean up some things, but we have lots
18 going on and I don't anticipate that. Okay?

19 MR. GERTEL: Yes.

20 MS. MOLZON: Okay. Next, I'd like to
21 introduce Dr. Norman Schmuft. Norman's been involved
22 with ICH probably from pretty early in the beginning
23 and he's going to be talking about the exciting things
24 we're doing in the world of the eCTD, which is really
25 the innovative aspect of the common technical

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1 document.

2 DR. SCHMUFF: Okay. Thanks, Justina.

3 I had occasion recently to be an acting
4 team leader in a division where a reviewer was
5 reviewing his first CTD submission and he said he was
6 having some concerns about it and he said to me, "Boy,
7 who are those boneheads that came up with this CTD
8 format?" Well, he didn't actually say "boneheads."
9 I'm paraphrasing. But, I had to admit, Ernie, I was
10 among that group.

11 And so just to give you an idea of the
12 human element, here is actually just a part of the
13 people who were involved in the CTD. It's the people
14 who happened to be around for the picture. And as an
15 exercise for the audience, where is Bob Temple? So
16 you can think about that for a minute.

17 And I'll just point out that in the center
18 is Alex Giaguinto from Pharma who really was the
19 father of ICH and who retired from being chair of the
20 Steering Committee. I guess it's two years ago or so.

21 Now the eCTD group formed immediately in
22 2000, well not immediately, but at the next ICH
23 meeting, which would have been 2001 after the CTD was
24 finalized in step four. And two years later, we
25 managed to come up with a step four document here in

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1 Tysons Corner and just to, you know, put the human
2 element in, Greg Brolund from FDA was the original
3 rapporteur, so FDA is the rapporteur for the eCTD.

4 This is Joe Montgomery who runs the
5 electronic document room in CBER, you know, kind of a
6 hard job really.

7 Tom Selenekovic does the same thing for
8 CDER and as you'll see you've gotten quite a number of
9 submissions. I'll mention that we got one eCTD
10 submission with 16,000 files. I think nobody
11 anticipated that. So Tom has to deal with those
12 issues.

13 John Clark actually was responsible for
14 the STF for drafting a study tagging file.

15 And last, but not least, Tim Mahoney who
16 is the current rapporteur for the eCTD. And I just
17 have to say it's been a great pleasure to be involved
18 with Tim because, you know, he's a very personable
19 guy. He's worked hard. He's a good organizer and a
20 good manager. And it gives me a good feeling to be
21 associated with FDA when we have people like Tim
22 representing us. He would have been here today had he
23 not had some other commitments.

24 So, here's the overview of what I plan to
25 talk about today. Of course we'll take some comments,

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1 give you some numbers.

2 Tim initially set out this concept that we
3 should have a change control process and the change
4 control process at the last meeting was I would say
5 refined a bit and the idea that we should freeze any
6 major changes for two years really I think also
7 probably came from Tim, but I think generally it was
8 -- well, it was supported by the other parties.

9 Minor releases and bug fixes would occur
10 in between, but particularly for the -- well, I guess
11 it's for everybody's benefit that we're intending to
12 freeze the major revisions to a two-year cycle. I
13 think we are driving the vendors crazy by making all
14 these changes.

15 The study tagging file, still there's some
16 discussion about that and really we signed off on step
17 four of the eCTD document with sort of an implicit
18 understanding that there would be this study tagging
19 file that captures the kind of clinical trial data
20 that we need here at FDA, but it was generally agreed
21 also by the other parties.

22 At the last meeting we also discussed some
23 M2 recommendations, which are consolidated in a
24 notebook which is on the ICH website and these include
25 things like media, what are acceptable media?

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1 Initially we had MS DOS, floppy disks. Then then
2 there was CDR and JOLIET format. JOLIET just gives
3 you the longer names. And the most recent inclusion
4 was DVD RAM. And, you know, the kind of discussion
5 was, "Well DVD RAM is not that well supported, but on
6 the other hand, DVD RAM has a lot of error checking
7 that's important." So the data validation was an
8 important reason for selecting DVD RAM. So that's the
9 kinds of things that you can find, although you can
10 also find some older perhaps outdated standards in
11 this notebook.

12 So we have change requests in. I was just
13 looking through my e-mail. We have a number that
14 we'll deal with at this upcoming November meeting.
15 One concern is validation of the applications, that an
16 application that validates in one vendor's pool does
17 not necessarily pass in vendor two's pools. So we
18 have to work on that problem.

19 And, you know, well the specification is
20 huge and it has stuff like all the file names should
21 be in lower case. So some validator's saying, "No,
22 you got some upper case forbidden characters in your
23 file names. This is not good." At least in the SGML
24 world, the validation basically checks for conformance
25 with the DTD, which is essentially the hierarchy and

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1 the heading and subheading things. So that's one
2 level of validation. But now we're seeing this other
3 thing, you know, including the file names and
4 including these things called check sums, which also
5 relate to data validation.

6 We'd like to finalize the study tagging
7 file specification. There also has been some
8 discussion about whether study tagging files should be
9 separate or it should be in the main body as a
10 specification. And really there are pluses and
11 minuses of doing both. One plus is that you can
12 maintain it separately without messing with the
13 specification and the minus is that you have to deal
14 with these two separate things and maybe it would make
15 sense to have them in one piece.

16 We're going to talk about the next major
17 release, the two-year-later release and talk a little
18 bit about secure communication recommendations. So at
19 least from the FDA point, all of this will also be in
20 the context of FDA standards and initiatives, HHS
21 standards and initiatives and Government-wide
22 initiatives that relate to secure communication issue.
23 So at least from Tim's viewpoint, he's thinking about
24 all those things.

25 Here are the numbers. Yes, over 100 as

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1 Justina indicated. Ten NDAs with 101 submissions so
2 that just means that there were amendments and/or
3 supplements, ANDAs, DMFs; that would be type-two DMFs
4 that deal with drug substance, IND and one application
5 had what's referred to here as 49 life cycle
6 submissions, which really means 41 amendments plus
7 supplements. And CBER also has received BLA and IND
8 submissions and actually since some products that CBER
9 formerly regulated and on CDER Bob was telling me that
10 some of the BLAs that we have received are actually
11 CDER BLAs, whereas typically we're thinking of BLAs as
12 a CBER thing and we didn't have to worry about then,
13 but now we do.

14 I think probably most people know that the
15 eCTD, which is the M2 topic, can be found at the ICH
16 -- much information can be found at the ICH website,
17 including the big specification document and that
18 change request form and that we actually have this
19 page, which is Electronic Regulatory Submission and
20 Review, that's what ERSR stands for, on our website
21 and as Justina indicated we're accepting eCTD
22 questions at this particular address. I think at one
23 time ICH was accepting questions at an ICH address,
24 but I think that lapsed. So don't submit questions to
25 the ICH e-mail account. You'll have to submit them to

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1 us and to other regions.

2 So that's about all I had to say, but if
3 there are any questions, I'd be glad to entertain
4 those. Yes?

5 MR. HOGAN: Alan Hogan, Booz Allen
6 Hamilton. One of the goals of the eCTD was to
7 facilitate two-way communication. Is that on the
8 radar for this release that's going to be in 2006
9 since that's come up since you talked about business
10 requirements?

11 DR. SCHMUFF: Yes. We had yesterday a
12 telecon with our other partners, which for us it
13 started at 4:45 a.m., and that topic did come up. But
14 not much was discussed about it and I think it's safe
15 to say that that's somewhere down the line, the two-
16 way communication. Also we have gotten some Q&As in
17 the Q&A thing. I don't know if we actually put that
18 in there, but we did get some questions about that and
19 so yes, certainly some time in the future, but not in
20 the immediate future.

21 MS. MOLZON: Anyone else?

22 (No audible response.)

23 MS. MOLZON: Well, Norman mentioned that
24 the Q&A process for CTD has sort of lapsed because we
25 in fact have sort of -- we used to have an

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1 implementation working group that met at every ICH
2 meeting, implementation working group from the CTD,
3 and this meeting coming up in November, the week of
4 November 15th, well in fact we're not going to have a
5 meeting of that group anymore because we've gotten to
6 the point where we think we've ironed out most of the
7 problems and the questions. So that's the first
8 meeting that that group's not going to be meeting at,
9 which I think is indicative of how this has just
10 rolled out very nicely.

11 You're next, Bob.

12 DR. YETTER: Okay.

13 MS. MOLZON: I'd like to introduce Dr.
14 Robert Yetter. He and I are both on the ICH Steering
15 Committee. Bob represents CBER; I represent CDER.
16 He's the associate director for review management at
17 CBER and he's going to be giving us an update on the
18 new topics and some of the ongoing ones that are
19 outside of the CTD and eCTD.

20 Thank you, Bob.

21 DR. YETTER: Boy, I hope these are the
22 same slides that I was looking at before.

23 Good afternoon. What I'm going to be
24 talking about is the non-CTD topics, immunotoxicology,
25 which is safety topic 8; pharmacovigilance, E2E,

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1 that's Efficacy 2E; quality systems, pharmaceutical
2 development and risk management, which actually have
3 their own numbers distributed in there; the drug
4 dictionary in M5; pharmacopoeial interchangeability;
5 biocomparability and we'll come down to the future of
6 ICH, always an interesting topic.

7 S8 is immunotoxicology studies. There is
8 a harmonized guideline on non-clinical assessment for
9 unintended immunosuppression. It was published in
10 October of 2002. That guideline requires immune
11 function testing when immunotoxicological findings are
12 observed in the course of the regular repeat dose
13 toxicity studies.

14 The guideline gives people information on
15 the type of pharmaceuticals that need to be tested and
16 the immune function assays that should be used to
17 determine the unintended immunosuppression. It also
18 speaks to the time of conducting the immune function
19 assays. It was determined that in order to make that
20 guidance document really more useful, we needed more
21 information. So the ICH decided that they would
22 sponsor a survey on immunotoxicity data. They figured
23 that the auspices of the ICH would enhance the ability
24 to collect immunotoxicity data from the three
25 pharmaceutical industry parties. The idea here is to

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1 really get more information that will let us get a
2 better grasp on the correlation between pathological
3 and hematological findings and the immune functions
4 that are determined by nine clinical studies and
5 relate all of that to the clinical situation. In
6 other words, to really better evaluate the clinical
7 relevance of these studies. That would allow us to
8 establish the procedure for immunotoxicity assessment
9 of pharmaceuticals. We expect that the discussions
10 will lead to a publication of a document for comment
11 in Yokohama.

12 Pharmacovigilance, E2E. E2E is actually
13 pharmacovigilance planning. This deals with
14 specifications for pharmacovigilance that is adverse
15 advent reporting and other aspects of oversight of the
16 use of pharmaceuticals in the post-approval phase.

17 This actually stemmed or was developed
18 around an original concept from the MHLW, their Early
19 Post-Marketing Phase Vigilance plan, or EPPV.
20 Subsequently, the PADUFA-3 legislation here in the
21 United States mandated certain risk management
22 components which had a heavy hand, had a great effect
23 on how we view pharmacovigilance. It also provided us
24 a way to use PADUFA funds for certain
25 pharmacovigilance activities and so all of that went

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1 into the development of this document which is
2 expected to reach step four in Yokohama.

3 Quality systems, pharmaceutical
4 development and risk management. FDA has put out a
5 report that talks about the specific steps that the
6 agency has taken and intends to take to develop and
7 implement quality systems in terms of management of
8 the review practice and in terms of our interaction
9 with respect to regulation of pharmaceutical products.
10 It really relies very heavily on a risk-based product
11 quality regulatory system. It describes the
12 accomplishments that we've made already and our plans
13 for the future. And really what it has to do with is
14 an assessment that we completed on current good
15 manufacturing practice regulations, the current
16 practices and some new tools in manufacturing science
17 that enable a different way of approaching controls
18 based on quality systems and risk management.

19 There are two sub-groups under this in
20 quality. Q8, which is pharmaceutical development.
21 Now earlier Justina told you about every time we have
22 a new topic, we have to go back and look to the CTD to
23 see if we need to change the CTD. This in fact is a
24 topic where we had something in the CTD that needed to
25 be explained so we developed this, the tripartite

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1 guideline that will describe and describe at a very
2 high level the harmonized contents of Section 3.2.p.2.
3 That's a pharmaceutical development. It's in the
4 quality module of the common technical document.
5 There was a lot of concern about what should go in
6 there. That's what this is aimed at. The guideline
7 will focus on principles of quality by design and
8 incorporates concepts from parallel discussions of
9 risk management under Q9. Funny I should mention
10 that.

11 Q9, risk management. This is a harmonized
12 guideline that defines principles of risk management
13 and how they can be applied and integrated into
14 decisions both by regulators and industry as regards
15 the quality of the products across the product's life
16 cycle and it also touches on BMP compliance. The
17 guideline is intended to include a framework of risk
18 management for pharmaceutical quality and it should or
19 it is expected to contribute to more consistent
20 science-based decision making and it should support
21 the revision of our quality-related practices,
22 guidelines, requirements and standards in a positive
23 manner. We expect both of these documents, Q8 and Q9,
24 to reach step two by Yokohama. They will be published
25 for comment.

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1 M5 is a drug dictionary. Two years ago
2 this November a concept paper for the development of
3 a guideline defining data elements and standards for
4 drug dictionaries was approved by the Steering
5 Committee. The guideline is supposed to support or
6 the drug dictionary supports pre and post-approval
7 pharmacovigilance activities and the communication of
8 regulatory information.

9 The objectives were not to replace
10 anything, but to build on what's currently available
11 in the regions and support the population of existing
12 systems or applications with reliable regulatory
13 medical product information. It was not intended to
14 build or maintain a full-fledged drug dictionary.
15 That's a very important distinction. This was not
16 replacing existing drug dictionaries. It was intended
17 to support the existing ones.

18 The development of data elements and field
19 attributes for the electronic submission of medical
20 product identifiers, MedID, was one of the first
21 objectives of this drug dictionary. I'm not going to
22 through all of the data sets that these are on. You
23 have handouts and that's more small words than I can
24 deal with with these glasses.

25 The other or another objective was to

1 develop a control vocabulary as a standard for the
2 electronic transmission of this MedID for relative
3 data elements and it is expected that this drug
4 dictionary or the standards for the drug dictionary,
5 more accurately, may reach step two in Yokohama.
6 Maybe.

7 Pharmacopoeial interchangeability is Q4B.
8 There is a pharmacopoeial discussion group wherein
9 representatives of the pharmacopoeias from each of the
10 three regions discuss the differences between the
11 monographs in their pharmacopoeias and attempt to
12 reach harmonization of those.

13 What pharmacopoeial interchangeability is
14 intended to address is the regulatory acceptance of
15 PDG-harmonized text. PDG is the Pharmacopoeial
16 Discussion Group. The idea is to indicate the
17 regulatory interchangeability status of harmonized
18 texts for each of the regulatory regions. It's also
19 going to indicate the effective date that you can use
20 the filings that you can use these harmonized texts
21 for filings and for laboratory analysis references.
22 And it's also intended to ensure that the
23 interchangeability is based on sound science from a
24 regulatory perspective as well as from the laboratory
25 perspective. It's also intended to facilitate

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1 regulatory and industry easy access to benchmarked
2 harmonized texts so that everybody is sure of what
3 text has been reviewed and what the status of
4 interchangeability for that text is. It does not good
5 for you to know that a text is harmonized if in fact
6 its interchangeability is in question. And that's why
7 this should expedite implementation for
8 interchangeability. We expect this not to reach step
9 two in Yokohama, but to reach step two in spring of
10 2005. There is considerable work yet to be done on
11 this.

12 Bio-comparability is quality topic 5E.
13 This is actually to assess, to help people assess
14 comparability of biotech or biological products before
15 and after changes in the manufacturing process and to
16 provide guidance in design and conduct of studies that
17 will allow industry to collect data, to establish
18 comparability of the pre and post-change products, the
19 idea being that with this you can confirm that the
20 manufacturing changes don't impact the safety and
21 efficacy of the product. This document is expected to
22 reach step four in Yokohama in November.

23 Finally, we reach the future of ICH. We
24 started talking about this in the Washington meeting
25 this year. We discussed it to some extent and framed

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1 several issues surrounding maintenance of existing
2 documents and where we might wish to go from here. We
3 expect to further refine these discussions in Yokohama
4 and in Brussels in 2005 we should reach agreement and
5 finalize a document on our view of the future of ICH.

6
7 Part of that or part of the things that
8 may feed into that is the pharmacovigilance plenary.
9 We brought up pharmacovigilance at ICH and developed
10 a work plan and that work plan is almost completed.
11 In Yokohama we need to discuss the work load, what is
12 still to be done and there will be a plenary session
13 to discuss future topics in this area.

14 Just in closing for this presentation, you
15 may notice that the current number of active expert
16 working groups is smaller than in the early years of
17 ICH. You'll certainly notice that we had fewer
18 topics on the agenda today than we have had in the
19 past. Many of the discussions in Yokohama are going
20 to revolve around scoping potential future work; there
21 is much yet to be done. And with that, I will leave
22 you to, who's next?

23 MS. MOLZON: Any questions?

24 DR. SCHMUFF: Questions?

25 (No audible response.)

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1 DR. SCHMUFF: No questions.

2 MS. MOLZON: No questions. Well, now
3 we're at the part of the program where the public can
4 make presentations and we had one request for a
5 presentation and Art Gertel from Beardsworth Services
6 is going to be talking about CDISC I believe. So he
7 has a prepared statement.

8 You can either give it from your seat or
9 give it up here.

10 MR. GERTEL: I don't know if you have it
11 on the screen. I know it's on the handouts. Either
12 way.

13 MS. MOLZON: For the transcriber, where is
14 the sound better for you, here or -- can you do it in
15 the seat? Up here? Okay.

16 COURT REPORTER: It really doesn't matter.

17 MS. MOLZON: Okay.

18 MR. GERTEL: Okay. Thank you, Justina.
19 I'm here today along with Cara Willoughby who's over
20 in the corner there on behalf of the Protocol
21 Representation Group for CDISC and as sort of a
22 preamble before my prepared statement I'll give you
23 just a little bit of a context. CDISC is the Clinical
24 Data Interchange Standards Consortium and it's a
25 collaborative and cooperative group among regulators,

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1 service providers, pharma companies and others sort of
2 loosely affiliated with that group to create a
3 standard of both data structure and content and
4 context. And so some of the remarks that we heard
5 today are very encouraging because we're all moving in
6 the same direction in terms of standardization and
7 creating common goals, common interchangeability of
8 documents. Dr. Yetter mentioned interchangeability
9 and that's certainly a key element to our attempts to
10 create standards for the industry. So I will now read
11 our prepared statement into the record and if there
12 are any questions, feel free to ask afterwards. And
13 that should all be in your handouts.

14 The following is submitted on behalf of
15 the Protocol Representation Group. We'd like to take
16 this opportunity to introduce our group to the public,
17 to the FDA and to the ICH Committee.

18 The Protocol Representation Group is a
19 volunteer organization of domain experts with specific
20 expertise in developing and/or conducting regulated
21 clinical trial protocols. The PR Group was initiated
22 in early 2003 and includes approximately 20 to 30
23 active members from Government agencies, regulatory
24 agencies, biopharmaceutical companies, industry
25 service providers and technology providers. The PR

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1 Group actively participates in the development of
2 standards for clinical protocols as a project team of
3 the Clinical Data Interchange Standards Consortium,
4 known as CDISC, and as a project team of the health
5 level 7, HL7, Regulated Clinical Research Information
6 Management, known as RCRIM, Technical Committee. Our
7 objective is to develop a standard structured protocol
8 representation that supports the entire life cycle of
9 clinical research protocols to achieve semantic
10 interoperability, by which we mean the exchange of
11 both content and meaning, amongst systems and
12 stakeholders. This includes the development of a
13 human and machine-readable model that enables
14 interchange of protocol data. The focus of the PR
15 Group to date has been to identify and define the key
16 elements of clinical protocols based on the ICH
17 guidance for good clinical practice with special
18 emphasis on ICH E6, E3 and E9. In this process we
19 have identified discrepancies and terminology across
20 these guidelines, as well as the opportunities for
21 further harmonization.

22 While we are still in the process of
23 formulating specific proposals, at this time we would
24 like to request a contact for future interactions with
25 the ICH Committee.

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1 Thank you for your time and consideration.

2

3 That's the end of the prepared statement.

4

5 In essence what we'd like to do here today
6 is to establish a vehicle for communicating what we
7 find in our activities to represent standard clinical
8 protocols where we have identified potential
9 discrepancies or differences in the guidance from ICH.
10 We believe that much of the changes that will have to
11 come out of the addressing of these is based on a
12 transition from what had been a paper-based system to
13 what will become much more electronic. So we look at
14 the guidances. We see if the guidance was promulgated
15 based on paper. Now we're moving into the electronic
16 world and we see opportunities to encapsulate the e-
17 concept into the guidance. So we're looking forward
18 to working with and providing insights into the ICH
19 process.

20 Yes?

21 UNIDENTIFIED SPEAKER: (Off microphone.)

22 MR. GERTEL: Team members? Yes. This is
23 a global group. We have members from the EMA, as well
24 as from FDA. So we do have representation at least
25 from the European Union and I don't know, Cara, do we

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1 have any MLHW?

2 MS. WILLOUGHBY: I believe not.

3 No.

4 MR. GERTEL: I don't believe we do. At
5 this point it is limited to EU and FDA.

6 MS. MOLZON: But this is also part of HL7.

7 MR. GERTEL: This is part of HL7.

8 MS. MOLZON: Right.

9 MR. GERTEL: It's a joint effort between
10 CDISC and HL7.

11 MS. MOLZON: Right. And I know that Dr.
12 Randy Levin, I believe is part of your group.

13 MR. GERTEL: Right. Randy is I guess the
14 liaison with FDA with respect to our activities and he
15 has been in attendance at a number of our meeting and
16 has given his feedback and coaching, moving forward.

17
18 Cara, I don't know if you have any
19 comments on that?

20 MS. WILLOUGHBY: (Off microphone.)

21 MR. GERTEL: Who are actively members?

22 MS. WILLOUGHBY: Who are actively
23 participating at this point in time. We are seeking
24 an objective as we address the gap with Japan right
25 now because we do certainly want to make this as

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1 global as possible as we look at standards and
2 development.

3 MS. MOLZON: And I know that Dr. Levin is
4 working with HL7 and we're trying to make some links
5 and the meeting after the one in Yokohama will be in
6 Brussels in May. And I know that that's also sort of
7 right after some HL7 meetings in the Netherlands. So
8 I think Dr. Levin is envisioning. But I'm glad that
9 this is typed out so nicely because I will take this
10 to ICH and make sure that it's submitted with your
11 request for interactions. You know, the whole point
12 of this meeting today is to hear from other groups in
13 the U.S. that are interested in what's going on with
14 ICH and to provide feedback and information, so I can
15 present that so we could either do it that way. But
16 we could also give this information to the ICH
17 secretary at --

18 MS. WILLOUGHBY: Isn't Ms. Stevens one of
19 the FDA people?

20 UNIDENTIFIED SPEAKER: No.

21 UNIDENTIFIED SPEAKER: No.

22 MS. WILLOUGHBY: From CBER?

23 UNIDENTIFIED SPEAKER: She's with HL7.

24 MS. MOLZON: She's one of the HL7 --

25 UNIDENTIFIED SPEAKER: HL7 yeah. Because

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1 she's involved with the --

2 MR. GERTEL: We're in sort of a unique
3 perspective stance because we're looking at the
4 integration of a number of the guidances coming out of
5 ICH as they apply specifically to clinical trials. A
6 set component of this effort has been the development
7 of a glossary as well so that when the terminology
8 that we use is implemented as part of the protocol
9 representation, we also include definitions and cross
10 references to the guidance, whether that guidance is
11 ICH, whether it's 21 C.F.R. or whether it's a
12 recognized authority. So we try to bring all of those
13 things into a harmonized representation and where
14 there are discrepancies we do identify them.

15 MS. MOLZON: (Off microphone.)

16 UNIDENTIFIED SPEAKER: And ultimately
17 we're the users.

18 MR. GERTEL: Because we're the people that
19 are, you know, initiating, designing, developing and
20 conducting the clinical trial. So if we can harmonize
21 the clinical trial protocol with the guidance and
22 hopefully be in, if not lock step, at least reasonably
23 close proximity to that as we move forward together.
24 Then we don't have to reinvent the wheel.

25 MS. MOLZON: And I know that many of your

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1 representatives are from pharma companies and Mike
2 Garvin, the Pharma-ICH coordinator, is here, so he's
3 also been notified because of this presentation.

4 MR. GERTEL: Right.

5 MS. MOLZON: Okay.

6 MR. GERTEL: And again, we look forward to
7 interchange and communication and --

8 MS. BLAIR: (Off microphone.)

9 MR. GERTEL: Yes?

10 MS. BLAIR: Just funding. How are you all
11 funded in terms of --

12 MR. GERTEL: We are funded by members, so
13 the membership which comprises pharma companies here,
14 all the parties that were included in the statement
15 pay a membership fee based on degree of voting
16 participation and degree of, I guess, monetary size so
17 that depending upon its scale, membership rates are
18 scaled according to number of employees and your
19 annual income. You can belong as an individual, as an
20 institution, as a corporation, so it's all comers.

21 Any other questions?

22 MS. MOLZON: Anyone else?

23 (No audible response.)

24 MR. GERTEL: Thank you.

25 MS. MOLZON: As I said at the

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1 introduction, these meetings are an opportunity for
2 people to come and learn about ICH that normally would
3 not get to attend the meetings, to ask questions, to
4 let us know exactly, like Art did, about things that
5 are going on that might be of interest to ICH and as
6 I did mention before, I think we're the only region
7 that actually does this, you know.

8 Our next meeting will be in Yokohama the
9 week of November 15th and the meeting after that will
10 be in Brussels in May. So we'll be putting on another
11 one of these meetings at the end of April next year,
12 so you can mark that down. So we do try to include as
13 many different types of groups that are not in the ICH
14 structure specifically. Okay?

15 I'd like to thank the transcriber. And I
16 think that's it for the day and thank you very much
17 attending.

18 (Whereupon, the meeting was concluded at
19 2:42 p.m.)
20
21
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23
24
25

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CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: Public Meeting

Before: FDA

Date: Oct. 19, 2004

Place: Arlington, VA

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

A handwritten signature in black ink, appearing to be "K. W. [unclear]", is written over a horizontal line.