

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ICH PUBLIC MEETING

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WEDNESDAY,
APRIL 20, 2005

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The meeting was held at 9:00 a.m. in the Plaza I Room of the DoubleTree Hotel and Executive Business Center, 1750 Rockville Pike, Rockville, Maryland, Dr. Justina Molzon, Associate Director for International Programs, presiding.

FDA PRESENTERS:

JUSTINA MOLZON, M.S., Pharm.D., J.D., CDER
JOAN WILMARTH BLAIR, M.A., CBER
LAURIE B. BURKE, R.Ph., M.P.H., CDER
RANDY LEVIN, M.D., CDER
TIM MAHONEY, CDER
PAUL SELIGMAN, CDER

OTHER PRESENTERS:

HALLE MAI GAWRYLEWSKI, M.A.
ARTHUR GERTEL
MEREDITH NAHM, M.S.
STEPHEN A. RAYMOND, Ph.D.
KRISTOFER SPAHR
BARBARA TARDIFF, M.D., M.B.A.

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

(9:01 a.m.)

1
2
3 ASSOCIATE DIRECTOR MOLZON: Good morning,
4 everyone. Let's get started, but before we do I
5 wanted to introduce Sema Hashemi. She's been helping
6 me put on this meeting, and she'll be in the back, you
7 know, so if you have issues about registration
8 information, the parking code to get out of the
9 garage, all that good stuff, just see Sema.

10 Everyone should have a packet of handouts,
11 and I've also passed out a survey on hotel - basically
12 hotel information. We are going to be moving to White
13 Oak in September, and there are no hotels near the new
14 campus. So we are trying to a demographic survey to
15 see what people look for in a hotel when they come to
16 one of our meetings. So if you could fill that out
17 that would be very helpful for future meetings.

18 Yes, Helle?

19 MS. GAWRYLEWSKI: Excuse me, I didn't get
20 a survey.

21 ASSOCIATE DIRECTOR MOLZON: You didn't get
22 one?

23 MS. GAWRYLEWSKI: No.

24 ASSOCIATE DIRECTOR MOLZON: Okay. Yeah,
25 we'll bring you a couple. They are at the front desk.

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1 I was talking with you guys too much. Okay.

2 So this morning, what I'm going to do is
3 just set the stage, and I always give a brief overview
4 of ICH because there's a lot of people that, you know,
5 are just starting out in the pharmaceutical industry,
6 have retired from various other capacities, and are
7 now working in new areas that they are not familiar
8 with. So I basically give an overview so there's a
9 basic understanding of how ICH works.

10 Unless you've gone to an ICH meeting it
11 might be difficult to actually understand how all of
12 these documents are created.

13 I'll also show you a graphic on something
14 that PhRMA and FDA have come up with to show how
15 guidelines should be implemented. We were asked to do
16 this by the ICH Steering Committee. It's still in
17 draft, but we are going to discuss the final form at
18 the meetings in Brussels, but, basically, once you
19 come up with - how you come up with a good topic for
20 harmonization, how do you go about harmonizing, how do
21 you get the word out, what's the roll out, and then
22 once you do that, how do you maintain these documents?

23 And this meeting, in particular, is the
24 focus of how we maintain those guidances and what we
25 need to do to get new topics, and I'll talk a little

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1 bit about that when I get to that point.

2 I'll also give very basic background on
3 the CTD and eCTD, because we have other speakers on
4 the program today, Randy Levin and Tim Mahoney, that
5 will discuss those in detail, and then I'm also going
6 to focus on the Global Cooperation Group, which is a
7 group of harmonizing - regional harmonization efforts
8 that we are starting to work with in ICH, so we can
9 work more globally.

10 So ICH -- I've used this joke for many
11 years, but ICH stands for the International Conference
12 on Harmonisation, and as I indicate here we've never
13 actually agreed on how to spell "harmonization." So
14 this just indicates that even though we are working
15 towards a harmonized guidance, there's still minor
16 differences, but that doesn't really dilute or defeat
17 the purpose of that guidance. So it's the
18 International Conference on Harmonisation of Technical
19 Requirements for the Registration of Pharmaceuticals
20 for Human Use.

21 And the ICH Secretariat is located in
22 IFPMA, the International Federation of Pharmaceutical
23 Manufacturers Association in Geneva, Switzerland, and
24 they have put together a wonderful web site that lists
25 all the guidances, talks about processes and

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1 procedures, has all the press releases from the
2 various meetings we've had, basic background
3 information. So if you are just starting out and
4 don't know that much about ICH, go to this web site
5 and it's got more than enough information.

6 So ICH was a unique approach that started
7 in 1990, and this is something I want to emphasize.
8 In 1990, we started working on these documents, and
9 some of the documents we are going to be talking about
10 this afternoon, especially E3, where we are going to
11 be hearing reports from different non-ICH and some ICH
12 initiatives, these documents were created in 1990,
13 when ICH started. This was before the CTD/eCTD were
14 even thought about, so we have some basic documents
15 that are the foundation of the CTD that might have to
16 be updated or clarified because they are being used in
17 a completely different context. So later this
18 afternoon we'll be hearing from a group of medical
19 writers that work with E3 on a daily basis, and they
20 have some suggestions on how this might be clarified
21 in the context that they are using it today.

22 ICH is an agreement between the European
23 Union, Japan and the U.S., to harmonize different
24 regional requirements for registration. This is
25 unique because it's a joint effort by regulators and

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1 associated pharmaceutical industry trade associations.
2 The best example I have of the impact of harmonizing
3 on a different regional requirement is the Q1A
4 document, which deals with stability studies. At one
5 point, each region, the EU, U.S. and Japan, required
6 stability studies at different temperatures and
7 humidity settings.

8 So if you picture a company having to
9 build buildings for their stability studies, they'd
10 have one for Europe, one for Japan, and one for U.S.
11 When we harmonized, they could do away with two of
12 those buildings, so harmonization really leads to a
13 saving of resources in terms of human capital, human
14 resources, so you don't have to spend so much time
15 duplicating efforts for registration information.

16 The objectives of ICH, as I just
17 mentioned, are to identify and eliminate the need to
18 duplicate studies to meet different regulatory
19 requirements, and so it leads to more efficient use of
20 resources in the research and development process, and
21 also quicker access for patients to safe and effective
22 new medicines.

23 In the example of the stability studies,
24 you might actually have your product held up for
25 release because you didn't have the stability

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1 information to back up the shelf life.

2 Now, ICH works through a series of expert
3 working groups. There is working groups focused on
4 safety, which is the pre-clinical aspect of R&D;
5 efficacy, that's the clinical aspect; quality, that's
6 the chemistry manufacturing control; and GMP; and
7 multi-disciplinary, and that's sort of a catch-all
8 category and basically has to do with electronic
9 submissions these days, and this is the category that
10 the CTD falls into.

11 These working groups report to the
12 Steering Committee, and the Steering Committee serves
13 to monitor and facilitate the expert working groups.
14 So there's an expert working group for each ICH topic,
15 and within that working group there's six topic
16 leaders, one from each ICH party, and they work to
17 develop consensus on technical issues. And these
18 consensus documents result - turn into the ICH
19 guidelines, and this is where you get this alphabet
20 soup. You have E documents, S documents, Q documents,
21 M documents associated with some number. So, like
22 Q1A, that has to do with drug stability. It was the
23 first document in the quality series. I think there
24 were several aspects of stability, so Q1A was the
25 first document that looked at this topic.

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1 If you are new to the ICH process, this is
2 probably the most confusing aspect of ICH. If you go
3 to the ICH Secretariat web site you can actually print
4 out all of the topics, and there's a blurb next to
5 each one of them, so you can become familiar with the
6 array of topics that are covered.

7 This is the schematic that I mentioned.
8 This describes what we think is a way to make sure
9 that you can implement the topics that are coming -
10 the guidelines that are coming out of ICH. So, the
11 most important part is topic selection. You know, is
12 it an appropriate topic? It must be value-added and
13 implementable. So, you want to pick something that
14 has the hope of reaching a consensus position.
15 There's been some topics that have been introduced.
16 We realized that it would just take too long, or we
17 would never agree on something, so there's some topics
18 that have never been introduced into ICH.

19 Dissemination, this has to do with the
20 communication process. Once you select a topic and you
21 come up with that document, you have to publish that
22 information and get the word out, and this, as I
23 mentioned, this is a draft schematic in order -
24 anticipating flipping the publication and the
25 dissemination. But there's actually a loop there,

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1 because when you look at the ICH step process, where
2 we come up with a consensus document, post it for
3 comments, take those comments and then republish it,
4 there's a little continuous loop here between the
5 dissemination and publication. You have to get the
6 word out. You want to hear from the stakeholders to
7 assess the accuracy of the document you've developed,
8 and then you would publish it again.

9 One thing that we haven't really focused
10 on is training. We really need to train on these
11 documents once they've been published, because
12 otherwise, you know, people don't understand and
13 there's not consistent - a consistent approach based
14 on these guidelines. We have done a lot of training
15 programs focused on the CTD and the eCTD, and, as a
16 matter of fact, on Friday we are having a free
17 tutorial on the eCTD. It's a half-day program from
18 8:30 until noon, I believe, and it's just an
19 opportunity for people to just come and learn about
20 this and have a lot of questions answered, because
21 when you are back home trying to implement these
22 things, you know, you'd have to send e-mails and phone
23 calls, and this would be a nice forum for people to
24 get a better understanding of the eCTD submission
25 process.

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1 This training has to be at all levels. It
2 has to be at industry for regulators, all areas of
3 industry, and, you know, this is something that we are
4 focusing on.

5 Implementation is really putting the
6 guideline theory into practice, and then management is
7 sort of what we are doing here at this meeting. You
8 have to monitor the documents that you worked on. So,
9 one of the main topics for this afternoon is looking
10 at all of the efficacy documents. These documents
11 have been in place since the early '90s. There's 13
12 of them. It's time to sit back and see if there's
13 something that we should be working on in the future,
14 sit back and look at all the documents that are
15 currently in place, how do they have to be improved,
16 what can we do to make sure people understand their
17 use in the current context.

18 So, this is one of the reasons we have a
19 public meeting. We are the only - the U.S. is the
20 only region that actually has public meetings prior to
21 ICH meetings. We want to meet with our stakeholders,
22 get input, and then go into ICH with this information
23 so that we can represent the U.S. region, you know,
24 much better than just doing things in a closed
25 situation.

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1 This is another reason that we have a
2 transcript of this program, and we always take the
3 transcript to ICH with us and share it with our ICH
4 partners so that they can see what's going on in this
5 region. So, we are trying to include as many
6 different groups as possible, be inclusive, talk to as
7 many different types of people to get input, and then
8 go to the ICH meetings with that information.

9 Now, in terms of harmonized guidelines,
10 there's probably about 50 of them, and as I've said
11 before, they fall into the efficacy, safety, quality
12 and multi-disciplinary categories.

13 In 1996, ICH industry representatives
14 proposed assembling this information into the same
15 order. So, if you think of these 50 or so guidances
16 as building blocks, what was happening was you'd have
17 these building blocks, and you'd have to put these
18 blocks in one order for Europe, another order for
19 Japan, another order for the U.S. So the goal here,
20 industry's goal, was to decrease the amount of time
21 and staff needed to assemble and disassemble the
22 documents for submission to ICH regions.

23 Industry did several surveys and looked at
24 the number of people that were actually needed to take
25 apart an application and put it back together again

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1 for another region, and how much time that took, and
2 that's really just down time. You are not submitting
3 something while you are taking it apart and
4 reassembling it.

5 This is just an example. This is a
6 listing of information you'd need for an NDA for the
7 U.S., how it would have to be taken apart and
8 reassembled for an EU Marketing Application.

9 This is just, you know, busy work. It,
10 basically, is what industry thought, and so we worked
11 with them to develop the common technical document.
12 Where the information would be assembled into the same
13 format - the common technical document is nothing more
14 than a common table of contents. You are just
15 submitting the information in the same table of
16 contents. It's not that everything in that submission
17 is exactly the same, as I said before, there's certain
18 topics that have never been presented to ICH for
19 harmonization because they were too contentious. So
20 the documents aren't exactly the same. It's just that
21 there's a place holder for all of the information and
22 it's a common technical document.

23 The benefits of the CTD from the FDA's
24 perspective is, this makes for more reviewable
25 applications. Before the common technical document,

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1 we would receive an application from, say, Lilly, and
2 then Pfizer, and then Rouche, and then other
3 companies. Each company would have their own format.
4 So a reviewer would spend, you know, a certain amount
5 of time working on one application and then write the
6 review and be finished with it. They would then pick
7 up the next application, and there would have to be a
8 certain amount of time getting used to where the
9 information was in that application. So he had to
10 erase whatever formatting he had from the previous
11 review and then get used to where this information was
12 in the next company. So this saves a lot of down time
13 between reviewers. They can start working right away
14 because they are familiar with where this information
15 is.

16 It also leads to - we are hoping it leads
17 to complete well-organized submissions, because
18 there's a common template for everyone now to follow
19 to submit that information. So this more predictable
20 format, we are hoping will lead to more consistent
21 reviews. And we've also written reviewer templates
22 for the various review disciplines that follows the
23 CTD.

24 So we are getting our reviews in a more
25 consistent format, and those reviews are now posted on

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1 our web at the end of the review process so that
2 people can read it. We are trying to make sure that
3 the consumer actually can understand how we've
4 evaluated this product, and this is becoming more and
5 more important as we are looking at a lot of different
6 safety issues. So we are trying to share this
7 information in an organized way.

8 This should also lead to easier analysis
9 across applications of various information. You need
10 to look for something, say, on hepatotoxicity, you
11 know exactly where to go. Before you'd have to figure
12 out where it is in the individual company's
13 submission.

14 And, most importantly, this facilitates
15 electronic submissions.

16 The eCTD, we are going to have several
17 speakers talk about this, but the eCTD is basically an
18 electronic version of this paper CTD, and we've listed
19 a lot of the specifications for this on our web site,
20 and it's been really helpful in trying to get the
21 submissions in to the Agency.

22 As I've mentioned, we are going to be
23 moving to White Oak in September. We have boxes, and
24 boxes, and buildings, filled with applications. All
25 of that information would have to be moved. If you

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1 put that on - submitted that electronically, you'd
2 have a little disk or something you'd take, and it
3 allows for reviewers to sign into an electronic
4 document room and just pull their information down
5 instead of having to go look for it.

6 So this also provides for efficiency,
7 because when I worked in the Office of Generic Drugs
8 I would have to go down to the document room on the
9 first floor, sign out my documents, take them up, you
10 know, and then I'd have to go find something that
11 wasn't in the packet. So it just - you save a lot of
12 time not having to, you know, hunt for the information
13 you have to review.

14 Information on the eCTD is, of course, on
15 the ICH web site, but we also have information on the
16 FDA web site, and I'm sure a lot of you are very
17 familiar with this information because if you are
18 working on applications hopefully you've switched to
19 the electronic format.

20 Now, something that's very interesting is
21 that there's actually been an extension of the eCTD
22 within FDA. FDA has a Data Standards Council, and
23 Randy Levin is our representative on that, and the
24 Data Standards Council is working on a common
25 application table of contents as an agency-wide

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1 standard. So, we are trying to harmonize the table of
2 contents in the various medical products in the
3 agency.

4 So, many of the applications received by
5 the Centers have similar and overlapping concepts,
6 there's an opportunity to harmonize this table of
7 contents across the agency. And, they are actually
8 using the common table of contents that was developed
9 by CDER and CBER for Module 1 and the CTD. So, now
10 you are seeing that the work that we've done in ICH is
11 being extended to devices and other medical products.
12 And, I don't know if this was anticipated, but you are
13 seeing how this is spreading.

14 Now, at the ICH meetings in Brussels,
15 which takes place the week of May 9th, we are going
16 to, as I mentioned, talk about maintenance process for
17 ICH. So, we are going to be reviewing existing
18 guidelines and have several - two plenary sessions to
19 do this.

20 As I mentioned, this is an important part
21 of this implementation process flow. We will actually
22 have to go back, take the time to sit and look back at
23 what you've done, picture the future and what might be
24 missing in all of the documents you've developed.

25 So, there's going to be a

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1 pharmacovigilance plenary that's going to be presented
2 by Doctor Paul Seligman in a little while. The
3 pharmacovigilance group has collected information on
4 regional pharmacovigilance guidelines, and they've
5 done a gap analysis to serve as background information
6 for this plenary. So, they'll be discussing, you
7 know, they'll be looking at what documents have
8 already been developed, what else might fit into this
9 mix, and just come up with, you know, a plan on how we
10 should approach this topic.

11 There's also going to be a plenary session
12 on all of the ICH efficacy topics, and because of that
13 I've become aware of a variety of activities that are
14 sort of related to the efficacy program in ICH, and
15 have invited a series of groups to come and give
16 presentations about what they are doing. And the
17 whole point of these presentations is to have the
18 groups speak for themselves, explain what the group
19 is, then have some ideas on things that, you know,
20 they might think would fit well with ICH, but the
21 whole point is to get these groups' background
22 information into our transcript so that I can then
23 take that to the Steering Committee in ICH and have
24 the groups explain in their own way how this might be
25 helpful to work through ICH. So we'll be hearing from

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1 a group of medical writers on E3, the clinical study
2 reports, structured product labeling -- we actually
3 had a workshop on Monday and Tuesday to sort of look
4 at the process of structured product labeling, and
5 we'll be hearing a report from that group today.

6 HL7, we'll be having some discussions on
7 that initiative; and then CDISC, the Clinical Data
8 Interchange Standards Consortium; and also clinical
9 development plan summaries. So these are topics that
10 sort of fit into the efficacy arena, and we want to
11 see how this might actually help promote what we are
12 doing in ICH.

13 I also wanted to mention a relatively new
14 initiative called the Global Cooperation Group. This
15 group was established in March of 1999 as a
16 subcommittee of the ICH Steering Committee, and it was
17 formed to respond to growing interest in ICH
18 guidelines by non-ICH regions. The name reflects the
19 desire to establish links with these non-ICH regions.
20 The membership are the six ICH parties, including the
21 two observers, World Health and Health Canada, and the
22 ICH Secretariat.

23 And initially, the focus of this group was
24 just information sharing. We had to put together
25 brochures and leaflets that explained how ICH worked,

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1 because unless you are part of the program it's very
2 difficult to understand the process. This
3 alphanumeric nomenclature makes it difficult to
4 understand exactly what people are talking about when
5 they are just saying E3, E5, E6, you know, you have to
6 come up with a whole new vocabulary.

7 And, it became clear when we were
8 developing these information packets that it would be
9 very helpful to have more active engagement with the
10 different regions. So, there's been an evolution in
11 Global Cooperation Group activities and thinking.
12 There's been a series of joint meetings with regional
13 representatives in preparation for the ICH6 meeting we
14 had in Osaka several years ago, and we basically
15 invited representatives from various regional
16 harmonization efforts to meet with us and present
17 information on their programs at the ICH meeting.

18 So, at Osaka in November of 2003, we
19 reached an important milestone because the ICH
20 Steering Committee recognized and endorsed a new
21 mandate in terms of reference that called for the
22 ongoing participation of regional harmonization
23 efforts and greater transparency with other regions of
24 the world. So, the regional initiatives that we are
25 working for are APEC, the Asia-Pacific Economic

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1 Cooperation group; the ASEAN, Association of Southeast
2 Asian Nations; the Global Cooperation Council - I
3 mean, the Gulf Cooperation Council; PANDRH, the Pan
4 American Network for Drug Regulatory Harmonisation;
5 and SADC, the South African Development Community.

6 At our last meeting, this group came up
7 with a draft mission statement, and it's to promote a
8 mutual understanding of regional initiatives in order
9 to facilitate harmonization processes related to ICH
10 guidelines, regionally and globally, and to strengthen
11 the capacity of drug regulatory authorities in
12 industry to implement them.

13 So, the Global Cooperation Group is
14 serving as a vehicle for promoting transparency and
15 openness. You know, we are actually interacting with
16 other regions of the world that did not participate in
17 the ICH process. It's not really a technical body.
18 We are not, you know, experts on all of the documents,
19 but it really helps to find priorities, work plans,
20 time lines, roles and responsibilities.

21 And, the way this group is evolving is, we
22 are actually this little think tank on how to best
23 harmonize various activities. All of these groups
24 have different ways of working. So, we are trying to
25 come up with, you know, a model that sort of explains

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1 the whole process. So, we've sort of donated the
2 implementation process that I've shown you in a
3 graphic, and we are talking to people to see how - if
4 you face a problem, how would you approach it, you
5 know, so we are sort of thinking about how we can work
6 towards better harmonization processes, recognizing
7 different capacities in the different regions,
8 different interests. So, it's really a very unique
9 opportunity to talk with representatives from all over
10 the world about how they work to harmonize things
11 within their region.

12 So, we are focusing on the technical
13 guidelines, of course, and as I've mentioned
14 harmonization and regulation in general, and there
15 will be some training in capacity building as a result
16 of having representatives from ICH go to some of these
17 regional meetings for their annual meetings or
18 training programs.

19 So, we are sort of - in terms of
20 harmonization and regulation, we are sort of moving
21 beyond the bounds of the original remit for ICH, and
22 the GCG serves as a unique forum for harmonization
23 initiatives to discuss best practices, lessons
24 learned, innovative approaches to harmonization and
25 regulation, as I've already mentioned, and then ICH

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1 topics of interest to these other regions, what would
2 they like to work on with us.

3 And, it may be that some of these
4 guidelines are beyond the scope of ICH, and we'll have
5 to figure out how to work on those topics.

6 Thank you for your attention, and I'd be
7 pleased to answer any questions. Does anyone have any
8 questions?

9 Yes, sir. There's a mic right there.

10 DOCTOR APOSTOLOU: Can you give us some
11 idea how far they have gone, or how far they intend to
12 go, with labeling, structured labeling? You mentioned
13 that.

14 ASSOCIATE DIRECTOR MOLZON: Oh.

15 DOCTOR APOSTOLOU: Particularly in
16 pregnancy and carcinogenicity.

17 ASSOCIATE DIRECTOR MOLZON: Okay.
18 Labeling is part of Module 1, and those - Module 1 is
19 actually not part of the common technical document.
20 Those are regional administrative information - that's
21 regional information. And so, labeling is still left
22 up to the various regions.

23 Structured product labeling is something
24 that we're doing at the FDA, but there may be ways to
25 link to the common technical document. For example,

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1 in the workshop that we had Monday and Tuesday, we
2 realized that we really have to come up with a way so
3 that the structured product labeling and the eCTD are
4 more compatible so they can all be submitted together.

5 And, we have some representatives from
6 that group, Kristofer Spahr, that will be discussing,
7 you know, that initiative, so people have a better
8 understanding of how that works.

9 Any other questions? Yes.

10 I forgot to mention that we need to have
11 people give their name for the transcriber.

12 MS. DHURUVAKUMAR: Sure. My name is Sadhana
13 Dhruvakumar, I'm with the International Council on
14 Animal Protection.

15 ASSOCIATE DIRECTOR MOLZON: Yes.

16 MS. DHURUVAKUMAR: I was just wondering, you
17 mentioned a couple of times topics that were too
18 contentious or where you thought getting consensus
19 would take too long, and I was wondering if you could
20 give us a couple of examples of topics like that that
21 hadn't been addressed.

22 ASSOCIATE DIRECTOR MOLZON: I knew someone
23 was going to ask that, and I don't remember any at
24 this point. But it's - because they've fallen by the
25 wayside. It might be very specific technical things,

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1 and it could be that most of them are in the quality
2 side, you know, like how many batches of something we
3 require, or different technical issues. But, I can try
4 and come up with - I'll brainstorm with some of my
5 colleagues and get back to you on some topics.

6 Anyone else?

7 Yes, sir. Please identify yourself.

8 DOCTOR APOSTOLOU: Alex Apostolou,
9 Toxicology Consultant.

10 ASSOCIATE DIRECTOR MOLZON: You might want
11 to also give the transcriber your card so she has the
12 correct spelling.

13 Okay, anyone else?

14 Okay, thank you very much.

15 Our next speaker is going to be Joan
16 Blair. She's my colleague in CBER.

17 While Joan is doing that, ICH is a joint
18 effort by the Center for Biologics and the Center for
19 Drugs, so Joan is the International Affairs Advisor
20 for the Center for Biologics, so we work in parallel
21 on a lot of these initiatives.

22 Joan is going to be talking about the new
23 and ongoing topics in ICH.

24 MS. BLAIR: She's like my sister.

25 You'll notice that I have ten minutes, so

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1 this is going to be a zooming, tree-top presentation.
2 I'm essentially tasked with giving you the inventory
3 of current work activities in ICH.

4 We have certain activities that are
5 ongoing from our last meeting in Yokohama in November;
6 certain things will be newly taken up in Brussels; and
7 then a few items have been deferred for the subsequent
8 meeting which will be taking place in Chicago. So,
9 I've broken my talk into those three pieces, and I
10 wasn't aware fully of everything that Justina was
11 going to speak to, so some of my slides I can just
12 brush over because she did, in fact, touch on them.

13 I'll start quickly with MedDRA, and I
14 promise to tell you what each acronym is as I go
15 through these slides. Some of us take it for granted.
16 MedDRA is Medical Dictionary for Regulatory Activities
17 Terminology. This was created some time ago. Its
18 little alphanumeric is M1. It is, in fact, just as a
19 little background, for maintenance purposes a separate
20 organization was contracted to maintain the
21 dictionary, that's the MSSO, which stands for, I've
22 got it written out here, Maintenance and Support
23 Service Organization. Its work is overseen by a
24 management board, which is composed of ICH members, as
25 well as a few other folks. They meet in conjunction

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1 with the run-of-the-mill ICH meetings, so, in fact,
2 the management board meets in advance of the ICH week.

3 There has been created an expert working
4 group that addresses clarification, usage, et cetera,
5 of the terminology. This is probably one of the very
6 first maintenance activities that ICH undertook. This
7 group actually generates points to consider documents,
8 that's the PTC.

9 I see in the room we have Janet Showalter,
10 so I'm not going to drill down on any of these topics.
11 If you have specific questions to any of these topics,
12 I see in the room a lot of different experts who could
13 be responsive to specific questions on this particular
14 topic. At a minimum, I know Janet Showalter could be
15 responsive.

16 Because we have a number of speakers who
17 are addressing the electronic data topics, again, I'm
18 only including them here just to be complete. In
19 Brussels, there will be discussions on M2, which is
20 electronic standards for the transmission of
21 regulatory information on the electronic CTD; M4, data
22 elements and standards for drug dictionaries; M5,
23 which is a new topic, electronic submission and
24 individual case safety reports. There's a lot of
25 cross talk between these groups, but, in fact, we have

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1 several speakers and they can go into greater detail.

2 This particular issue represents a
3 relatively unique set of circumstances for ICH. I
4 bring it up because it demonstrates that despite the
5 very formal processes that characterize ICH, on the
6 other hand ICH can adapt when need be. It really does
7 not want to overwork an issue.

8 Q3A(R), which the R stands for revised,
9 which means after the initial document was created at
10 some point in time it was opened up and revised. The
11 same is true of Q3B, these address impurities in new
12 drug substances and products. They were concluded,
13 but then on one portion of the documents there was a
14 need for clarification. It was raised by one of the
15 Steering Committee members.

16 Rather than opening up the documents all
17 over again, they had already been opened up and
18 revised, an approach was undertaken. The former
19 rapporteur for the groups was asked to dialogue with
20 the former EWG members to see if, in fact, this issue
21 was, in fact, a significant issue that required
22 opening up, or whether it could be resolved in a more
23 straightforward manner. E-mail and telecon
24 communications took place. It's been reported to the
25 Steering Committee members that a consensus has been

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1 reached. Because it actually was consensus, a sign-
2 off step will take place. I mean, it proceeded to
3 that degree. So, they will not meet in Brussels.
4 However, a postal sign-off will take place for the
5 consensus that was generated to respond to the
6 concern.

7 Q4B, a quick background. This is a fairly
8 recently created group, although the work that is the
9 foundation for it has been ongoing for some time.
10 This relates to the regulatory acceptance of
11 pharmacopoeial interchangeability. In the
12 pharmacopoeial world, they have a harmonization
13 effort, which is conducted through PDG, Pharmacopoeial
14 Discussion Group. The PDG has chosen to meet in
15 conjunction with the ICH meetings. They do their work
16 independently. However, there is an intersection of
17 that work. Originally, there was an expert working
18 group that helped facilitate harmonization in certain
19 topics in the pharmacopoeial area.

20 It became clear over time that in the
21 PDG's work that complete harmonization wasn't always
22 possible. They considered different approaches to
23 partial harmonization, which brings up the issue of
24 interchangeability. So, Q4B was created in order to
25 address the regulatory acceptance of some of these

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1 hybrid outcomes.

2 So, in fact, the Q4B group initially meets
3 separately during the ICH week, and then they join
4 with the PDG and have joint discussions. Some of the
5 issues that they will be discussing, I note here this
6 interchangeability document is proceeding, it probably
7 will not reach Step 2 until Chicago. There's some
8 general test chapters that are going to be discussed.

9 I don't know if we have any pharmacopoeial
10 people in the room who could answer anything.

11 Q8 is a relatively new topic. It did
12 reach Step 2. The intent of the Q8 is to actually to
13 fill out one of the boxes of the CTD, in essence, the
14 P2, that includes risk and quality by design
15 considerations. It is currently out for comment. The
16 group, the expert working group, will meet in
17 Brussels. They won't, at that point in time, have
18 sufficient time to have received the comments and
19 taken a look at them, but they are also going to
20 clarify the work plan and interface a scoping
21 discussion, which I'll discuss on quality systems.

22 There are an array of quality topics that
23 will be discussed in Brussels, and many of the experts
24 have overlapping expertise.

25 S7B and E14, I've linked them because, in

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1 fact, these two documents, although are separate
2 efforts, because they have overlapping topics, in the
3 sense that it concerns QT interval prolongation, on
4 the one hand the S7B piece is the non-clinical
5 evaluation, the E14 piece is the clinical evaluation.
6 S7B was undertaken earlier, as it progressed E14 was
7 taken up, and it became clear that, in fact, the
8 progress of the two documents should, in fact, be in
9 parallel. So, as they reach - they should not reach
10 Step 4 delinked, they should both reach Step 4 in a
11 harmonized fashion. So, there is a great deal of cross
12 talk between these two topics.

13 Both of them reached Step 2. They are
14 receiving comments. There was a public meeting just
15 last week, Justina can speak to that if there are any
16 questions, addressing some E14 considerations. The
17 goal is, in Brussels, to reach Step 4 on both
18 documents.

19 S8, immunotoxicology studies, just very
20 quickly. It has reached Step 2. There's a need for
21 some hard data to proceed. A survey was issued, data
22 is being gathered. The experts are meeting to take a
23 look at the data and discuss and make progress, but my
24 understanding is that Step 4 is actually a goal for
25 the Chicago meeting, not for the Brussels meeting. If

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1 anyone knows differently, they can speak up.

2 Justina mentioned the pharmacovigilance
3 brainstorming, and we have Paul Seligman who is going
4 to speak after me, so I'm not - I don't want to steal
5 his thunder. So, there was an initial brainstorming
6 session quickly in Yokohama, identified some potential
7 topics of interest to folks. There were such an array
8 of topics that were identified the Steering Committee
9 felt that a more substantive, lengthier opportunity
10 for discussion to develop one or more of these topics
11 for actually taking up an ICH would be worthwhile, so
12 that will be taking place in Brussels at discussion,
13 and Paul will be discussing it, I think, more fully.

14 Again, Justina spoke to the Global
15 Cooperation Group. I think the one action item,
16 specific action item for the Steering Committee, is to
17 accept the mission statement, which she already
18 discussed.

19 Gene Therapy Discussion Group is another
20 sort of unusual component of the ICH process. It's
21 the first taking up, I would say, of a new technology
22 topic. This is a situation of prospective
23 harmonization in the gene therapy world. In fact, we
24 don't have licensed products, so harmonizing the
25 technical requirements is premature. However, in

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1 anticipation that we will be seeing that, then there's
2 no point in having a disharmony develop in the
3 regions, so a discussion group was formed to, in fact,
4 keep the ICH parties abreast, have an opportunity for
5 information exchange, to share points of view, and,
6 perhaps, to develop prospective harmonization as this
7 field grows.

8 They weren't, in fact, intended to meet in
9 a face-to-face in Brussels. However, some of you may
10 know there were some recent adverse events associated
11 with a trial and event. So, the group decided to -
12 the Steering Committee decided that, in fact, it would
13 be of benefit for the group to meet. They will be
14 meeting and discuss these events. They'll also be
15 continuing their work in preparing for a symposium, I
16 call it a workshop here, workshop symposium, that will
17 take place in Chicago on gene therapy. It will be a
18 stand-alone symposium, so they will be working on
19 that, as well as considering some potential topics for
20 guidelines to be taken up in the gene therapy arena.

21 Again, I think Justina alluded to the
22 discussions that have been ongoing at the Steering
23 Committee level for the future of ICH. They began in
24 Washington in June, 2004, including administrative
25 pieces, process pieces, membership, transparency,

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1 streamlining, process for new topics, resource
2 implications, do we have too many face-to-face
3 meetings? This was broken into a three-part discussion
4 in Washington. The scope of the concerns were laid
5 out in Yokohama, greater depth was given to these
6 issues, and, hopefully, we will conclude in Brussels
7 on these matters and there will be a number of
8 documents that will be generated as a consequence.
9 These will be procedural documents possibly or just
10 decisions taken by the Steering Committee.

11 Again, Justina has already mentioned the
12 efficacy plenary. I'll just add that that actually is
13 an outgrowth of a Japanese proposal to take up a
14 multi-regional trial guideline, and in the discussion
15 of that proposal it became clear that it would be
16 useful to actually look at the universe of efficacy
17 guidelines, perhaps, an integration of these
18 guidelines would be helpful.

19 So, the discussion will not only be on the
20 efficacy guidelines, but it will also be considering
21 this concept for multi-regional trials, and we
22 understand, I've noted JPMA, but it may, in fact, be
23 JPMA and EFPIA, which are the Japanese and the
24 European pharmaceutical industry groups, have said
25 that they will also address the possibility of taking

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1 pharmacogenomics as an ICH topic, and they will do so
2 in the context of this efficacy plenary.

3 Oh, in fact, when we were thinking of
4 having this efficacy plenary, another Steering
5 Committee member had, the EFPIA, had raised concerns
6 about escalation of direct development costs, and the
7 need to explore potential value of better global
8 cooperation, and at one point we thought we'd throw
9 that into the efficacy plenary, and then we, in fact,
10 decided, no, we'll parse that off and have a
11 discussion at the Steering Committee level.

12 There will be a discussion, a plenary, a
13 brainstorming session, on what we are describing as a
14 potential Q10, quality topic. This has a bit of a
15 lengthy history. It goes back at least a year,
16 probably three Steering Committee meetings ago when
17 this was first raised as a potential topic. It was
18 raised and the Steering Committee asked for some
19 greater clarity, a scoping document, industry has
20 presented that, regulators signaled, essentially, that
21 there were resource limitations, our plate was full at
22 that point in time, and we deferred movement on this.
23 If the time is right, this is going to be discussed in
24 Brussels. It was linked to the completion of some of
25 the other, or at least to reaching Step 2 and some of

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1 the other Q topics.

2 And, I think we also have some speakers
3 today on this. Have we addressed this at all? In any
4 case, I do see a lot of folks in the audience who
5 could address any questions on this.

6 I raise this again as another case of
7 thinking outside the box, in terms of resolving
8 issues, separate from the formal ICH process. Q1F is
9 one of the quality documents. It's final, it's
10 closed, but it was recognized by various stakeholders
11 that there's been a divergence outside of the ICH
12 regions in some of the climate zones issues, since the
13 issuance of Q1F.

14 WHO has been playing a great role in
15 facilitating dialogue to produce a harmonized outcome.
16 This has been electronic, there have been meetings.
17 Currently, some options are under active discussion.
18 There will be an informal discussion in Brussels, in
19 some cases the experts aren't going to be there so
20 there will be attempts to have a telecon, as well as
21 face-to-face with those folks on site.

22 So, that's it for Brussels, and rather
23 than going in depth in terms of what might come up in
24 the future, I'm just going to talk about two topics
25 that, in fact, were deferred in certain respects.

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1 Q9 is one of three active Q topics, the
2 Q8, the Q9 and the potential Q10, addressing risk
3 management, application to quality requirements and
4 practices. This reached Step 2 postal sign-off, which
5 means that, in fact, on site at the least meeting they
6 weren't able to achieve a sign-off, but they continue
7 their work, they are very close, they know they can
8 reach closure via e-mail. They did so and sign-off
9 sheets are sent around via mail, and so it has reached
10 Step 2. It's out for comment. Clearly, we won't have
11 time to have enough comments until Chicago, so that
12 group will meet in Chicago in November.

13 On the plate potentially for Brussels was
14 a third plenary brainstorming session on biotech. The
15 Steering Committee deferred that to Chicago. There are
16 some ideas circulating in the biotech area for ICH to
17 take up. I'm just - I'm throwing out some of the
18 things we've heard, this does not mean we are doing
19 it. That's why the question marks. Process
20 validation for biotech drug substance, specifications,
21 maintenance for Q6B, perhaps it's time to open that
22 up. Classification of manufacturing process
23 variations. Again, we want to hear from stakeholders.
24 There's also mention of a potential for inclusion of
25 vaccines in ICH in the biotech area.

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1 And, that's my talk. I do note there's no
2 health break, as the Europeans say, are you going to
3 let people have a break at some point?

4 ASSOCIATE DIRECTOR MOLZON: A bio break, as
5 long as we are talking about biotech?

6 I would like to ask if anyone would have
7 any questions before we do that. Does anyone have any
8 questions?

9 Yes, please go to the mic and state your
10 name and your organization.

11 MS. GAWRYLEWSKI: Helle Gawrylewski,
12 J&JPRD. I was wondering when you mentioned the postal
13 sign-off, how is that then recorded? Is there an R
14 then after the name, or how is that documented that
15 there's been a revision?

16 MS. BLAIR: Oh, on the Q3A?

17 MS. GAWRYLEWSKI: Right.

18 MS. BLAIR: I think what we will do in that
19 case is simply make the change. In a situation like
20 that, it's very minor, it's a clarification, and I
21 don't think -

22 ASSOCIATE DIRECTOR MOLZON: It actually
23 just follows the - if you look at the listing on the
24 ICU Secretariat's web site, it details the history of
25 each of the topics. And, it will say updated with

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1 editorial - it lists the type of change.

2 MS. BLAIR: Actually, in terms of the
3 procedural streamlining and addressing the process
4 that's under the rubric of the future of ICH is a
5 document that clearly spells out the different types
6 of changes that can take place with the document.
7 And, there's a rationalization of the proliferation of
8 alpha numeric codes. We are going to abandon, or I
9 don't know, did we actually agree?

10 ASSOCIATE DIRECTOR MOLZON: Well, it's -

11 MS. BLAIR: I think we agreed or, perhaps,
12 it's all wrapped up. We are likely to adopt a more
13 uniform coding. We used to have R, we had M, we had,
14 you know, all these different nuances, and it's just
15 now going to be a simple letter that will indicate
16 that some change did occur, and there will be a
17 history on the web site, a short history, of the
18 history of that document, if it was opened and what
19 took place.

20 MS. GAWRYLEWSKI: Good.

21 I also wanted to know if we have an update
22 on the MedDRA and the fact that here in Health and
23 Human Services is using SNOMED, and is there any kind
24 of ICH effort?

25 MS. BLAIR: I will let Randy.

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1 ASSOCIATE DIRECTOR MOLZON: Yes, Randy will
2 be -

3 MS. BLAIR: Randy can address that when he
4 talks, how about that?

5 MS. GAWRYLEWSKI: Okay.

6 ASSOCIATE DIRECTOR MOLZON: Okay.

7 MS. GAWRYLEWSKI: And, I have a colleague
8 who works in the device area, has that come up as a
9 topic for ICH harmonization at all?

10 MS. BLAIR: There is a separate
11 harmonization effort for devices. It's the Global
12 Harmonisation Task Force, which actually operates a
13 bit differently in certain respects than ICH. There
14 had been some communication on the potential for
15 inclusion of combination products, which could have a
16 device component. I mean, there could be the world of
17 combinations can be drug biologic, drug biologic
18 device, whatever, and that's been communicated to us,
19 that there is an interest on the part of at least a
20 stakeholder. That's something, again, hasn't - that's
21 been between meetings, we haven't brought it forward
22 to discussion at the Steering Committee. In fact,
23 there's been communication at the Steering Committee
24 level via e-mail, it may come up as a discussion point
25 at the Steering Committee in Brussels.

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1 MS. GAWRYLEWSKI: Thank you.

2 ASSOCIATE DIRECTOR MOLZON: Anyone else?

3 I've written down the questions that were
4 asked of Randy, and I'll ask them again when he gives
5 his presentation.

6 We are going to next hear from Doctor Paul
7 Seligman, and why don't we hold off on the break and
8 let Paul give his presentation - I mean, Paul has an
9 appointment after this, so I'd prefer to have him give
10 the presentation and then we could take a small break.

11 While John is pulling up Doctor Seligman's
12 slides, Doctor Seligman is the Director of our Office
13 of Pharmacoepidemiology and Statistical Science, and
14 he's our lead at ICH on pharmacovigilance topics.

15 DOCTOR SELIGMAN: Good morning.

16 I want to recognize before I make my
17 presentation the contribution of the other
18 representative to this working group, Doctor Miles
19 Braun, from CDER, and also to start, of course, with
20 the standard spelling disclaimer, which is that we
21 favor the British s over the z or the zed, as well as
22 the combination ae over the e in my presentation. So,
23 you'll notice in my slides that I defer to that
24 spelling, this was by intent and not by accident.

25 I'm going to be talking today about the

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1 Pharmacovigilance Working Group. Some of you refer to
2 pharmacovigilance as post-marketing risk assessment,
3 or surveillance of adverse events in the conduct of
4 post-marketing studies, any of those synonyms will
5 work as well as some of the associated topics that
6 often come with pharmacovigilance, including safety
7 and communication.

8 I'm going to cover two things very briefly
9 today, one in the area of publication, and the other
10 in the area of topic selection. In the area of
11 publication, over the last the Pharmacovigilance
12 Working Group developed a guidance document which was
13 published on April 1st in the Federal Register on
14 Pharmacovigilance Planning, E2E. This document was
15 incorporated by reference as well into a recent FDA
16 guidance on good pharmacovigilance practice and
17 pharmacoepidemiologic assessment. This former
18 document, Pharmacovigilance Planning, is available on
19 the ICH web site.

20 It has two major features, for those of
21 you who are familiar with the document, one detailing
22 the safety specification and the second the
23 pharmacovigilance plan.

24 The intent of this document is really to
25 take the richness of the safety or risk information

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1 that's developed during the course of randomized
2 clinical trials, both clinical information as well as
3 non-clinical information, ensure that this information
4 is gathered, summarized and utilized in planning
5 subsequent post-marketing surveillance activities.

6 There is, in the safety specification, a
7 detailed outline of what should go into that with a
8 summary of the particular product, and then in the
9 pharmacovigilance plan talks about how to structure
10 such a plan to ensure that for at least in the United
11 States for certain products that there is a purposeful
12 activity following the launch of a product and
13 collecting additional surveillance information that
14 may go beyond just the reporting of spontaneous
15 adverse event reports.

16 This document has also, in sort of the CTD
17 and the ICH framework, been incorporated as part of
18 the common technical document by reference, as well as
19 in the question and answers section.

20 As Justina pointed out, in November of
21 2004 we conducted a brainstorming session at the last
22 meeting of the ICH in Yokohama. It included all of
23 the alphabet soup, the parties above, the European,
24 Japanese and American pharmaceutical associations, as
25 well as the regulators from those regions, including

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1 Public Health authorities from the World Health
2 Organization, Health Canada, as well as, I guess, the
3 European Free Trade Association.

4 At that time, we held a session where we
5 talked about, in sort of the broadest terms, potential
6 topics for future deliberations in the area of
7 pharmacovigilance, as well as the bridge between pre
8 and post-marketing safety assessment and risk
9 communication.

10 It was determined at that time, given all
11 of the activity going on in the three regions in this
12 particular area, that it was critical that we
13 summarize in some organized fashion all of the rules,
14 regulations, guidance documents, guidelines,
15 publications, in our three areas and determine where
16 there were potential gaps or areas that really needed
17 to either be addressed and/or harmonized across our
18 three areas.

19 The European Union took the leadership in
20 conducting this gap analysis. They sent out a survey,
21 both to the industry as well as to the regulators in
22 February, have gathered all this information together,
23 and that will be, basically, the basis for our
24 discussion in Brussels in, I guess, a couple, two,
25 three weeks.

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1 The survey, basically, covered five major
2 topics. One on adverse event reporting and safety
3 assessment during clinical trials. The second on
4 safety communication, a third topic on
5 pharmacovigilance pediatrics, a fourth on good
6 pharmacovigilance practice, and finally a topic
7 related to risk minimization.

8 We were asked in responding to this
9 request for a gaps analysis to, basically, focus on
10 certain sort of topic areas. In the area of safety
11 assessment and clinical trials, we were asked,
12 particularly, to focus on those areas in the United
13 States, or in our own particular region, where we, you
14 know, detail how annual safety reports are produced,
15 in either standardized or consistent fashion, what
16 guidance or guidelines we provide in terms of how
17 safety data are interpreted, how individual case
18 reports are reviewed, assessed and reported, and
19 finally, how groups like institutional review boards,
20 as well as data safety monitoring boards, operate in
21 our area.

22 In the area of safety communication, again
23 we were asked to provide information on standards of
24 the content of the various sections of the label, how
25 is it that we develop areas related to warnings,

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1 precautions, adverse events, contraindications, et
2 cetera, as well as a second topic, which is sort of
3 getting at what I consider to be sort of the frontier
4 of pharmacovigilance, which is any information we have
5 on how we develop consistent communication approaches
6 with patients and healthcare providers that go beyond
7 what is contained in the label or product information.
8 It would include things like your healthcare provider
9 letters and patient information.

10 The third area dealt with sort of what we
11 call pharmacovigilance and surveillance in selected or
12 vulnerable populations. The Europeans are
13 particularly interested because they are currently
14 drafting a note for guidance on the conduct of
15 pharmacovigilance for medicines in the pediatric
16 population, that we consider whether there might be
17 something that we should focus just on children.

18 As you know in the United States, we have
19 the Best Pharmaceuticals For Children's Act, which
20 provides legislatively a mandate for the collection of
21 data on adverse events for products that have been
22 granted exclusivity under that Act.

23 The fourth topic was in the area of good
24 pharmacovigilance practice. As I think most of you in
25 this room know, we have, the FDA published guidance on

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1 this topic in this past month in the - the web link is
2 noted there, which deals with not only case - good
3 quality case reporting, causality assessment, how we
4 manage adverse event reporting in terms of analytic
5 techniques, such as data mining, as well as good
6 practice in the conduct of observation and studies,
7 and there's guidance under consideration as well in
8 the European Union, as well as in Japan, on this
9 topic.

10 And finally, again in the U.S., we
11 published a guidance on the development and use of
12 risk minimization action plans, or risk maps.
13 Recently in the European Union again there's guidance
14 under consideration on this topic, so again, we are,
15 I think in large measure, when we get to Brussels in
16 May we are going to be focusing then on, basically,
17 all of the efforts that are being conducted, both in
18 pre and post-marketing risk assessment and risk
19 minimization, and trying to come to some consensus,
20 not only on where there are areas where we need to
21 harmonize our work, as well as areas where there may
22 be, you know, outstanding gaps or things that should
23 be attended to.

24 Clearly, I'm interested in any input that
25 any of you have in regards to topics that you think

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1 would be appropriate or important for us to consider
2 at ICH. Clearly, we've gotten, and we'll have, the
3 information and the opinions before us in Brussels
4 about what your regulators in industry thinks, but I
5 think it's absolutely vital that we have public input
6 as well as to what they think are important topics for
7 consideration in this area.

8 In addition to the gap analysis, a number
9 of parties to this discussion have begun to develop
10 concept papers on topics that they would like to see
11 discussed, and as I indicated we'll be spending two
12 full days in Brussels on May 9th and 10th discussing
13 future topics and, hopefully, narrowing the field in
14 trying to select topics we think are appropriate for
15 further harmonization activities.

16 With that, I'm happy to stop and take any
17 questions, comments, input, that anyone might have.

18 ASSOCIATE DIRECTOR MOLZON: If you have a
19 question or comment just go to the mic, and it looks
20 like you can start forming a line to ask them.

21 MR. GERTEL: Art Gertel, Beardsworth
22 Consulting Group.

23 The European clinical trial directives,
24 how is FDA and you going to work either harmony to
25 incorporate those concepts into ICH, or is there going

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1 to be a separate initiative on the part of FDA?

2 DOCTOR SELIGMAN: Justina, this is related
3 to the Clinical Trials Directive, the CTD, in terms of
4 harmonization on that, do you want to try to address
5 that? I've sort of not really been party to those
6 discussions.

7 ASSOCIATE DIRECTOR MOLZON: Well, I'm
8 assuming that that's part of the discussion, you know,
9 that we're having this brainstorming session about.
10 You know, you look at the efficacy topics, good
11 clinical practice, the concept of this multinational
12 clinical trial program that JPMA proposed, all of
13 that's up for discussion.

14 So, I don't have anything yet. That's the
15 purpose of the discussion.

16 DOCTOR SELIGMAN: That was sort of the
17 first topic that I mentioned, sort of the safety
18 assessment and clinical trials, and the question sort
19 of begged the point, which is that there are
20 differences throughout the regions in that area, and
21 I think the purpose of doing this gaps analysis was
22 also to collect information on where those differences
23 occur, which ones are particularly noisome, or
24 bothersome, or intrusive, or confusing, or
25 problematic, so that we can begin to address those.

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1 And again, if you have any particular
2 feelings as to regard as to which areas are
3 problematic or noisome, or however I described it,
4 we'd be happy to have that input.

5 DOCTOR RAYMOND: I am Doctor Stephen
6 Raymond with PHT Corporation, here representing CDISC,
7 and I realize that your appetite at the moment is
8 mostly focused on the harmonization issue, it may not
9 be tilted in the direction of innovation with respect
10 to adverse event detection and logging.

11 But, it is a topic that came up in the
12 recent DIA ePRO Conference that was held in Washington
13 a month ago, and it seems that regulators have a large
14 role in pushing a kind of conservatism into practice,
15 that this idea that adverse events need to be
16 spontaneously offered, for example, that you can't
17 represent a list. And, if you have a list, you can't
18 rate their severity or something, and that the
19 possibilities technically for discovery and tracking
20 of symptom severity and occurrence have really
21 developed recently, and I'm wondering if that is a
22 topic that people have broached and considered yet, or
23 is it something where it, basically, has to follow the
24 harmonization.

25 DOCTOR SELIGMAN: I think it's a perfectly

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1 legitimate topic to broach. Clearly, you know, we are
2 always, you know, prisoners to our ability to get at
3 the richness of the information that's contained in
4 the conduct of clinical trials, and clearly the CDISC
5 effort is just, from my sort of simplistic point of
6 view, one way of unlocking that richness and
7 organizing the information in a way that allows people
8 access to that information and to really use, you
9 know, the information that's contained in those kinds
10 of studies.

11 So, I think to my mind that's a perfectly
12 appropriate issue, you know, to broach at the ICH
13 level, because that's - those are, to my mind, the
14 kinds of things that should, you know, to the degree
15 that we can, standardize across regions, I think they
16 should be.

17 ASSOCIATE DIRECTOR MOLZON: Could I,
18 Stephen, I think - well, I know CDISC is on the
19 program this afternoon, and are you going to be
20 addressing some of these issues, because we could make
21 sure that you present this during your presentation so
22 that it's captured by the transcript.

23 DOCTOR RAYMOND: Oh, okay, I can add that
24 element to my presentation this afternoon. I'm mostly
25 talking about eSource, but in some sense the

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1 possibility for capturing information about symptom
2 severity comes from the use of eSource where patients
3 are supplying that information themselves using new
4 electronic technology, so I can mention that.

5 ASSOCIATE DIRECTOR MOLZON: Thank you.

6 Helle, state your name again.

7 MS. GAWRYLEWSKI: Helle Gawrylewski.

8 I was wondering, given the fact that in a
9 very short time about 25 percent of the population
10 will be elderly, instead of pediatric, I'm wondering
11 if the risk assessment and risk management for that
12 population would be an appropriate focus now, you
13 know, considering, you know, polypharmacy has a
14 different perspective from the pediatric concerns.

15 DOCTOR RAYMOND: I have a particular
16 preference for that issue myself.

17 MS. GAWRYLEWSKI: So do I.

18 DOCTOR RAYMOND: No, I think you are
19 absolutely right. I think, you know, collecting
20 information in that particular population,
21 particularly, because they are using, not only the
22 bulk of medicines, but there's a lot of polypharmacy
23 in that area, is of, you know, I think great interest
24 to all of the particular regions.

25 Just as an aside, you know, in the U.S.

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1 with the Medicare Modernization Act Part B, and the
2 fact that the Federal Government will be taking a
3 greater role in paying for the drugs in the elderly,
4 at least at the FDA side we've been, you know, in
5 close communication and discussions with the CMS on
6 how best to utilize the information that they will be
7 gathering in the course of administering this program.

8 But, you know, and that's why when I
9 described that topic as pharmacovigilance in practice
10 I really sort of prefaced it by talking about
11 vulnerable populations, and I think the elderly is a
12 perfectly - is clearly a vulnerable population in this
13 regard. And, I think it's certainly a legitimate
14 topic that's worth broaching with our colleagues in
15 Japan and Europe.

16 ASSOCIATE DIRECTOR MOLZON: Thank you.

17 Anymore questions?

18 Thank you, Doctor Seligman, I know you
19 have some other appointments, so thank you for taking
20 the time out to speak with us.

21 DOCTOR SELIGMAN: You are welcome.

22 ASSOCIATE DIRECTOR MOLZON: We are going to
23 take a short break, but then we'll hear from Randy
24 Levin and Tim Mahoney on Electronic Submissions.
25 Please turn in your surveys. The people that have

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1 gone to the microphone to ask questions, please give
2 your card to the transcriber, so that she has the
3 correct spelling of your name.

4 Thank you very much.

5 Ten-minute break, please.

6 (Whereupon, at 10:12 a.m., a recess until
7 10:26 a.m.)

8 ASSOCIATE DIRECTOR MOLZON: If I can have
9 your attention, we are going to start up again. If I
10 could have your attention, we are going to be
11 switching the order of the next two speakers. Tim
12 Mahoney has an appointment, so he's going to be going
13 before Randy Levin.

14 Tim Mahoney is our rapporteur for the M2
15 eCTD topics, so he'll be talking about the eCTD and
16 ICH M2.

17 Tim?

18 DOCTOR MAHONEY: Great, thank you, good
19 morning.

20 Actually, my presentation is fairly brief,
21 because the eCTD has been off and running for a couple
22 years now, so we've got to do some repositioning in M2
23 in terms of planning workout for the next two years,
24 and that's going to be a big topic at this month's, or
25 next month's meeting.

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1 So, what I'm going to cover today is the
2 agreements we made at the November meeting, as well as
3 the agenda for the meeting next month, an update on
4 FDA eCTD software, where we are headed, some initial
5 information, and I've encouraged folks to attend other
6 presentations to get the more updated information on
7 the software, and then where you can find additional
8 information after today.

9 So, in November we processed three new
10 change requests, if you look up on the ICH web we have
11 a pretty standard change control process. It resulted
12 in one new Q&A, as well as an updated style sheet.
13 Our previous style sheet was deficient, and we have a
14 new one that works in all regions.

15 We were working on something called
16 validation criteria, in order to help those providing
17 or creating eCTD tools, to help them know how to
18 validate, and we completed a draft. We did finally
19 post the final study tagging file, and that will
20 remain the same until the next eCTD spec. We created
21 a subgroup to evaluate all of our recommendations on
22 secure transmissions, and we agreed that we have to
23 map out our work for the next two years.

24 For the next meeting, we have our standard
25 eCTD change request. We want to finalize the

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1 validation Q&A. We want to look at what this subgroup
2 has done in between the meetings on our secure
3 recommendations, as well as listen to the M5 group
4 about their requirements for a new message, and then
5 work on our work plan.

6 So, it's pretty straightforward. The FDA
7 has been using a software package called the eCTD
8 Viewer System for the last few years. It was a
9 custom-developed system, still is, and it has not met
10 all of the requirements. We've talked about this in
11 previous public meetings, but we conducted an
12 alternative analysis and we found that the next step
13 for the FDA, the best step, is to procure a
14 commercially-available product.

15 I don't have a lot of information today
16 about which product, which partner, but I can tell you
17 that FDA management has decided to do this through a
18 cooperative research and development agreement,
19 working with a commercial partner, probably at the DIA
20 annual meeting, follow-up meetings when the official
21 documents are signed we'll be able to talk more about
22 that.

23 And, as promised, my presentation is brief
24 today, but again, there's always more information,
25 there's information posted. I'd be happy to answer

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1 any questions you may have this morning.

2 Of course, Joe, who I'll see next week, or
3 tomorrow.

4 MR. CIPOLLINA: I wasn't going to let you
5 get away that easily.

6 Joe Cipollina, Bristol-Myers Squibb.

7 Could you go into a little more detail
8 about the M5 discussion?

9 DOCTOR MAHONEY: It still hasn't come to
10 the M2 group yet, so at this meeting we plan to meet
11 with M5 business representatives to hear their
12 requirements. So, I don't - we don't have any plans
13 yet for how we are going to do the message, that's
14 something we have to do at this meeting.

15 MR. CIPOLLINA: Anymore perspective of the
16 business case for the message?

17 DOCTOR MAHONEY: I haven't even seen it.

18 MR. CIPOLLINA: Okay.

19 DOCTOR MAHONEY: To be honest with you. I
20 expect to see it in May, but that's a good question.

21 ASSOCIATE DIRECTOR MOLZON: Doctor Randy
22 Levin will be talking about the M5 group itself in the
23 next presentation.

24 Any other questions?

25 Is that it for Tim?

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1 DOCTOR MAHONEY: As always, please look
2 after the meeting, the M2 eCTD IWG we always have new
3 documents, because we always get change requests. So,
4 please look for an updated change request document.

5 And, thank you, Doctor Levin, for letting
6 us switch this morning. Hope you enjoy the rest of
7 the day, thank you.

8 ASSOCIATE DIRECTOR MOLZON: Okay. We'll
9 have questions we'll submit to you in writing after
10 the meeting then. Okay.

11 While Randy is bringing up his
12 presentation, during the break I talked to various
13 people that have been active in ICH to try and come up
14 with some of those issues that I said were contentious
15 and weren't discussed in ICH.

16 One of them was post approval changes and
17 variations, that was a topic early on, and it was just
18 decided that the systems are too different to actually
19 try to harmonize them. And, another one was
20 guidelines for clinical evaluation by therapeutic
21 category. We were going to do a whole bunch of
22 disease-specific guidances. We worked on E12A, which
23 is Principles for Clinical Evaluation of New Anti
24 Hypertensive Drugs, and found that that was so
25 difficult that we sort of sidelined that idea of

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1 working on disease-specific guidances. So, those were
2 some of the issues that were presented, and it was
3 decided that it would be too difficult to reach
4 agreement, and so they were sort of sidelined.

5 Okay, Randy, could you please give your
6 presentation?

7 DOCTOR LEVIN: All right.

8 When Tim said he was going to switch, I
9 thought he was going to give my talk, so I was going
10 to give his talk.

11 You'll notice that on my slide I have the
12 time there, that's in Eastern Standard Time, okay,
13 since we are a little bit late.

14 I'm going to be talking about two projects
15 going on in ICH regarding terminology standards. One
16 is M5, which are the data elements and standards for
17 drug dictionaries, and the other is a proposed M6, can
18 I call it that?

19 ASSOCIATE DIRECTOR MOLZON: Sure.

20 DOCTOR LEVIN: Okay, for a maintenance
21 process for ICH terminology lists.

22 M5 is the - originally, this was proposed
23 as an ICH drug dictionary, that ICH would have its own
24 drug dictionary, but it was decided that instead of
25 that the regulators would provide information on their

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1 medicinal products so that people can create drug
2 dictionaries, and that there would not be one drug
3 dictionary, but people could use this data and create
4 their own drug dictionaries.

5 Right now, the scope of the project has
6 been defined, and guidelines are being developed, as
7 Tim was just mentioning about the requirements for the
8 exchange standard, that's being worked out and being
9 developed, and will be discussed at this coming
10 meeting.

11 The scope of the project currently is
12 human drugs and biological medications used for
13 treatment or diagnostic purposes. There is talk about
14 future involvement with homeopathic medicinal products
15 and investigational medicinal products. This has not
16 been discussed fully, we'll be attempting to do these,
17 but right now it is the human drugs and biologics. It
18 also will include herbal preparations if they are
19 considered drugs.

20 The data elements that have been worked
21 out in the group are to have information about the
22 product itself, that would be the proprietary name,
23 and an identifier, a medicinal product identifier
24 called MedID. That would be a universal identifier
25 that would go across the different regions.

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1 Also, data elements on the active
2 ingredient. This would include the name of the active
3 ingredient, an identifier, a unique identifier, and
4 the strength of the active ingredient. And so, there
5 are the data elements on that. Data elements on the
6 dosage form, route of administration, and information
7 about the marketing authorization holder, including
8 the name, some identifier, and the country for the
9 marketing authorization holder. So, these are the
10 data elements that will be exchanged from M5.

11 There's also control terminology that's
12 being worked on in M5 for the active ingredient
13 identifier, the strength units, dosage form and route
14 of administration. So, those are the activities going
15 on in M5.

16 Then, as was discussed, there is an
17 exchange format, so you have these data elements, you
18 need a standard for exchanging this information, and
19 the requirements are being worked on, but, one, they
20 have to be non-proprietary standard, also, at least
21 from FDA perspective and PhRMA perspective, I can
22 speak for them, it has to be consistent with
23 healthcare system standards, and I think that we are
24 going to discuss this in various talks coming up,
25 where we need to have harmonization between the

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1 healthcare community and ICH. I think Justina brought
2 that out in the very beginning, and this is a theme
3 that's going to go through all the discussion, or many
4 of the discussions, that the ICH and the rest of the
5 healthcare communities need to be harmonized,
6 otherwise they are going to go on divergent paths,
7 just like for terminologies that the question was
8 brought up before.

9 So, one of the areas that we are looking
10 at for exchange standards would be the structured
11 product labeling, and Chris will talk about that
12 later, about how the drug modeling and structured
13 product labeling could handle the information that's
14 brought out in the M5 data elements, and also when
15 Barbara is going to talk about HL7 and how to
16 harmonize those things because structured product
17 labeling is an HL7 standard, she'll also tie - you'll
18 see in her discussion a tie in with this as an example
19 of where healthcare and ICH should be harmonizing.

20 The other standard - the other group is
21 the maintenance process for ICH terminology lists, and
22 where this came about were specifically from Tim's
23 group when they were working on the eCTD and their
24 appendices on E3, or their terminologies for the CTD
25 of how to group different studies, and people wanted

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1 different - more appendices or different appendices,
2 or different grouping variables, and what was the
3 process of doing that.

4 The guidelines, many times the people
5 working on those guidelines have long disbanded and
6 the guideline is out there, and as Justina and Joan
7 were talking about, some of these things have been in
8 existence for quite some time, and need a way to
9 maintain them.

10 So, this group is taking the lists, all
11 these terminology lists that are embedded in this
12 guidance, and trying to develop a process, a
13 maintenance process, to keep them up to date so people
14 can say, well, we want to add something to this
15 terminology list, and now there's a process to go
16 about and do it.

17 A concept paper was presented to the
18 Steering Committee and accepted, and standard
19 operating procedures are being developed to work on
20 this maintenance process with a pilot planned this
21 year.

22 So, the basic ideas that change requests
23 would be collected, that there will be a facilitator
24 from each regulatory authority to take on these change
25 requests, then a group of ad hoc experts would be

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1 gathered to look at the change requests. These are
2 people that were involved with the original
3 guidelines, bring them out back on, look at this
4 issue, and to make a decision on whether they think
5 that this should be included or not. Then a decision-
6 making process involving these experts, the
7 facilitators at the Steering Committee to update that
8 list, and then to post them on the ICH web site and
9 propose, we are also looking into the possibility of
10 using a vocabulary, the Enterprise Vocabulary Service
11 from the National Institute of Health, so that these
12 terminology lists can be - not only be accessible on
13 the web page, but could be accessible through computer
14 systems and programs.

15 So, that is the proposed M6 that we'll be
16 talking about in the upcoming meeting.

17 Those are - that's what I had to present
18 on these two topics. I did hear my name brought up
19 that I have certain questions that I'm supposed to
20 answer about MedDRA and SNOMED?

21 ASSOCIATE DIRECTOR MOLZON: Yes, MedDRA and
22 SNOMED, an update.

23 DOCTOR LEVIN: So, one, there is - we had
24 proposed at MedDRA is going to be required for post-
25 marketing safety reports from industry. That proposal

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1 went out, we had comments coming back. Because we are
2 in the midst of this rulemaking process we really
3 can't talk about the details of what the comments
4 were. They are posted, you can look at them, and what
5 the process is from here, but we will address those
6 comments and then propose a - then post a final rule
7 on that. But, we did propose that MedDRA be required
8 for post-marketing safety reports.

9 But, as far as the MedDRA SNOMED, again,
10 this is just an example of where we have healthcare is
11 going in one direction and the ICH or regulators are
12 in a different direction. We need harmonization
13 between the two, so that they are discussing these
14 things. I think that was something already brought up
15 that Justina was already talking about, and we need
16 that discussion.

17 Healthcare is a much larger part of - is
18 a big driver for standards. There's an electronic
19 health records standard that's being developed.
20 There's going to be terminology that's going to be
21 developed for the electronic health record. They are
22 already working on it. The United States Government
23 is working in a Consolidated Health Informatics
24 Initiative, to try to set standards for U.S.
25 Government. There's a lot of activity going on in the

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1 healthcare community, and ICH needs to be a part of
2 that, but needs to work with the healthcare community.
3 Otherwise, we will go and have these divergences, and
4 terminology is just one example, but there are many
5 other examples, and I think that you'll hear some of
6 those examples talked about when Barbara talks about
7 the HL7 process, which is a healthcare - which is a
8 standards development organization really focusing on
9 healthcare standards, and maybe Chris will talk about
10 that with the structured product labeling, which is an
11 HL7 healthcare standard.

12 And again, the labeling is a conduit
13 between the regulators and the healthcare community,
14 and if we are not having the same standards it's not
15 going to be helpful. I mean, it's not going to be -
16 it's not going to work. So, we need to have these
17 standards together.

18 That doesn't give you the direct answer
19 about SNOMED or MedDRA, but it does, you know, talk
20 where we have to go, what direction we have to go
21 toward.

22 There was another?

23 ASSOCIATE DIRECTOR MOLZON: A question
24 about devices, and if we are - Helle asked this
25 question, I believe, if we were working with devices,

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1 and you had - I know in my presentation I mentioned
2 how the Data Council is sort of extending the CTD into
3 a common table of contents for medical products in the
4 agency, and if you had anything else to mention about
5 that.

6 DOCTOR LEVIN: Right. With the common
7 table of contents, we first - a project we did earlier
8 was the individual case safety report. We took the
9 E2B elements and we looked at the E2B elements, and we
10 want to have a standard that will go across our
11 regulated products, not just be with drugs and
12 therapeutic biologics, but go and be involved with
13 devices and other products.

14 The E2B data elements were not sufficient,
15 because they are focused on just the drugs and
16 therapeutic biologics, so we took those data elements,
17 we took them to Health Level 7, and we developed a
18 standard that would be involving more than just those
19 products, and Lise Stevens was our lead on that and
20 developed a standard that's now an HL7 standard, will
21 be ANSI-accredited, it includes both new drugs,
22 vaccines, and devices, so it's all based on the E2B,
23 and that's an example where there was - where you are
24 trying to harmonize what work is going on in ICH with
25 the healthcare community and with other products.

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1 So, we are doing the same thing with the
2 table of contents, so we have the common technical
3 document. That's very specific for drugs and
4 biologics, and so what we are doing is taking that,
5 that table of contents, starting with that, and going
6 to our other centers, the Devices, Veterinary
7 Medicine, Food, and to say how can we harmonize this,
8 how can we work together, so that we have one
9 standard.

10 And, the ICH eCTD, which Tim just brought
11 up, is very specific for drugs and biologics, and when
12 you look at it the whole table of contents is built in
13 to the standard. And, when you talk with the other
14 centers, that doesn't meet with their needs, and
15 basically it's the square hole and round peg or
16 whatever you want - whatever analogy you want to use,
17 and so they are - what we are trying to do is work on
18 a standard that will be more flexible, that would meet
19 all the requirements that we already have for the
20 eCTD, but also meet the requirements for these other
21 regulated products, and do it in a place that's
22 dealing with Health Level 7 that would allow us to be
23 harmonized again with the standards that are going out
24 and being developed in other areas.

25 So, that's - does that address your

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1 question?

2 MS. GAWRYLEWSKI: Will that be in the RCRIM
3 area?

4 DOCTOR LEVIN: It hasn't been proposed yet,
5 but it will be in the RCRIM area.

6 ASSOCIATE DIRECTOR MOLZON: Could you
7 explain what that is?

8 DOCTOR LEVIN: RCRIM is a Health Level 7,
9 I don't know, Barbara, are you going to be talking
10 about this? Okay. Health Level 7 again is a
11 standards development organization that's for
12 healthcare. When CDISC and FDA were looking for moving
13 forward with the standards that were being developed
14 for clinical research, and seeing that in HL7 there
15 was not a good representation for clinical research,
16 which we think is part of healthcare. So, we lobbied
17 for a technical committee, a group to work on clinical
18 research issues, and that was formed, the Regulated
19 Clinical Research Information Management Technical
20 Committee, and that is - Barbara Tardiff is one of the
21 co-chairs for that committee, and she is involved with
22 CDISC and the pharmaceutical industry, and I'm another
23 co-chair, along with Linda Quade, also from the
24 pharmaceutical industry. So, that's where we deal
25 with the clinical research issues, including CDISC

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1 standards and these other standards.

2 And, there's a special interest group off
3 that committee that deals with patient safety issues,
4 that's where Lise is co-chair of that committee, that
5 special interest group, and working on the individual
6 case safety report.

7 ASSOCIATE DIRECTOR MOLZON: Okay.

8 Any other questions?

9 Yes, sir.

10 DOCTOR APOSTOLOU: Alex Apostolou, again.

11 Is the terminology in English only, or it
12 will be translated to other languages, too?

13 DOCTOR LEVIN: It is in English. I don't
14 know what the policy is for ICH as far as the other
15 languages.

16 ASSOCIATE DIRECTOR MOLZON: The working
17 meetings are conducted in English. There is - and
18 once the documents are finalized and implemented the
19 region then does what they need to implement it in
20 their country. So, in Japan the documents are
21 translated into Japanese, in Europe I'm not sure if
22 the documents are translated into all the European
23 languages. But, the working groups work in English,
24 and then the documents at Step 5, when they are
25 finalized and implemented into the region, that's

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1 where they would be translated.

2 DOCTOR LEVIN: And, when we were working on
3 mapping the different terminologies for dosage form,
4 route of administration, the Japanese did send us
5 both. So, that was good, because we couldn't read the
6 Kanji characters.

7 ASSOCIATE DIRECTOR MOLZON: Yes, Art?

8 MR. GERTEL: Art Gertel, Beardsworth
9 Consulting.

10 Do you plan to incorporate the CDISC HL7
11 glossary terminology into your terminology lists and
12 codes as well?

13 DOCTOR LEVIN: For the M6 group, what we
14 are doing is just taking the terminology lists that
15 are in the guidelines, so it's just the lists that are
16 in the guidelines. So, if that's not in the
17 guideline, the guidelines for ICH, it won't be
18 included in M6.

19 MR. GERTEL: Okay, because a lot of the
20 terminology that we've incorporated into the glossary
21 is derived from ICH guidance. So, and in some cases
22 there might be discrepancies in terms of use or
23 definition. I'm wondering whether there might be
24 consideration given to the glossary that has been
25 developed and published in the formulation of your

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1 final work?

2 DOCTOR LEVIN: A glossary is an excellent
3 idea, but right now the scope is for the ICH
4 guidelines. Maybe we can have an ICH guideline on for
5 glossary, you know, but it would be - that's a very
6 good idea, but right now the scope was to take all the
7 lists that are in these documents, even bring them out
8 is a chore, just to show all the lists that we have,
9 and then here's the process for updating the list.

10 ASSOCIATE DIRECTOR MOLZON: Yes, another
11 question?

12 MS. GAWRYLEWSKI: Helle Gawrylewski.
13 Perhaps I didn't understand M5, but you said that
14 after the development people can create their own
15 dictionaries. Could you expand on - that kind of
16 concerns me if people are going to be creating their
17 own drug dictionaries, and maybe I just didn't
18 understand that.

19 DOCTOR LEVIN: A drug dictionary, in that
20 situation you want to have a list of all the different
21 medications, and you want to use that in your systems
22 for adverse event reporting, or any other function.
23 You are going to create a database or a dictionary,
24 which should have all the medications, and the
25 synonyms and things along those lines. That's what

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1 you are going to create. That's what I'm talking
2 about with a drug dictionary.

3 The things that we are providing are the
4 things, the data that you would put in your drug
5 dictionary, in your database. It could be just what
6 we provide you, it could be additional things, but we
7 are going to provide this information, it will be up-
8 to-date information about products, so that you can
9 keep your drug dictionary up to date.

10 Now, there are a number of companies out
11 there that create their own drug dictionaries and sell
12 them, and they put some value added in there. They
13 might put in new identifiers or different identifiers,
14 or something to meet their customers' needs, and they
15 will continue to do that. We will just provide the
16 data that they could use to update their dictionary.

17 We didn't want to create a dictionary on
18 its own, because that means that we would have to have
19 an organization to handle that dictionary, and so what
20 you would have to do, and we didn't want to go down
21 that route, instead you have the data elements from
22 these different places, you bring them together, put
23 them in the one location, and create your own
24 localized or local dictionary to meet your needs.

25 And, we expect all the commercial vendors

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1 to utilize this, to create and use in their
2 dictionaries to make their dictionaries better and
3 more up to date, more complete.

4 So, does that answer your question?

5 ASSOCIATE DIRECTOR MOLZON: Anyone else?

6 Okay, Randy, you are going to be hanging
7 around for most of the meeting, so if you have other
8 questions, you know, just go up to Randy and ask them,
9 and we'll be having a lot of interactions during the
10 second half of the program.

11 So, what I want to do at this point, we
12 are a little ahead of schedule, but I think that's
13 good because it will allow for more discussion in the
14 afternoon, is to hear from the groups that are not
15 actually members of ICH, but that are working on
16 efficacy-related topics.

17 And, the way I've broken down this section
18 is, I know that there's a group of medical writers
19 working on E3, which is Clinical Study Reports, so
20 here's a group that's actually working with a document
21 that was created in 1994, I believe, and they are
22 working with it in the context of the common technical
23 document and other updates, and so they have some
24 suggestions on that particular topic. So, we are
25 going to look at suggestions for topics on how they

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1 can be updated, and then we'll be hearing from a
2 variety of groups on specific activities, some of
3 which Randy has already mentioned, about how we might
4 consider using some of those activities in the ICH
5 venue.

6 Sema, did you have a question? Okay.

7 Helle Gawrylewski is the representative
8 from the Medical Writers Group that will be discussing
9 Clinical Study Reports.

10 MS. GAWRYLEWSKI: Good morning, I'm Helle
11 Gawrylewski. I want to thank and express appreciation
12 for being able to be here this morning, and just a
13 little bit of a background on the slides.

14 These were kind of compiled by the DIA
15 Medical Writing Special Interest Area Community, the
16 SAIC, but I need to express a disclaimer. DIA
17 provides the forum and the mechanism to have
18 discussions, but they don't endorse any position,
19 being a neutral party. These are industry medical
20 writers that have gotten together, had discussions,
21 and this presentation is a compilation of the concerns
22 that have bubbled up to us. It doesn't necessarily
23 represent an official opinion of the SIAC, but just a
24 compilation of issues over the years and concerns.

25 This is an area, the ICH E3 guidance is an

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1 area with a lot of interest, and every roundtable,
2 every presentation we have, inevitably, someone from
3 the audience comes up and says, well, how do you
4 implement this, and how do you interpret that, so it
5 is an area that has a lot of interest in the medical
6 writing community.

7 The achievement of this guidance is that
8 it was the first major effort to harmonize
9 applications. Since then, 50 guidances have been
10 harmonized, and they have added measurably to the time
11 saving and cost saving effects in drug development.
12 And actually, no one could have anticipated that this
13 guidance would have been so successfully used all
14 these years, since its adoption in 1995, so this is
15 the 10-year anniversary of this guidance. We should
16 have a celebration. And, it forms the foundation of
17 CTD, and as Justina alluded to the fact that no one
18 anticipated at the time that this guidance was
19 prepared that that would be the case ten years later.

20 And, we certainly commend the group, the
21 Expert Working Group, that came up with these
22 guidances.

23 But, a lot has happened since then. The
24 regulatory context has changed, and the questions that
25 existed at that time now some electronic elements have

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1 come into the play, and actually when we went to -
2 Barbara Kamm and I went to put some example TOCs on
3 the SIAC web site, just to be an assistance to medical
4 writers, we found that every table of contents that we
5 got was different and represented a different
6 interpretation of the guidance. So, that peaked our
7 interest, and we started to have discussions, and we
8 were surprised at the level of kind of agony that was
9 out there. It wasn't my particular point of view, but
10 there were a lot of people who were searching for
11 answers.

12 But, we do not propose that the guidance
13 be opened and revised, because a lot of companies have
14 built expensive libraries of templates based on this
15 guidance, but we do like, we would like to have
16 certain aspects clarified that we think need
17 clarification and at least discussion.

18 The main area that seems to be causing
19 consternation and is contentious is, is this E3 a
20 guidance or is it a template? And, an official
21 opinion from the ICH would be very useful.

22 The trend in the guidances seems to be to
23 specify a structure, but allow flexibility in the
24 content of the information within that structure. So,
25 that is a reasonable approach, and we support that.

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1 The E3 guidance preceded the FDA Good
2 Guidance Practices document that clearly states that
3 this is a guidance and it's non-mandatory, but it
4 hasn't been clear to many people out there. Those who
5 see the guidance as a guidance have successfully
6 designed templates to accommodate most study types,
7 including abbreviated reports. Others, however,
8 interpret the E3 as a rigid template, including
9 recently software vendors who are designing
10 applications, QA auditors, who are constantly having
11 this come up as an issue internally and externally,
12 and a proportion of U.S. companies.

13 As a personal aside, I work for a company
14 who interprets the E3 as a guidance, but our
15 development partners are constantly saying that our
16 reports are not in compliance with E3.

17 Our colleagues in the Asia-Pacific area
18 often interpret this guidance literally.

19 Mentioning the abbreviated reports, some
20 sponsors are concerned that E3 allows that structure,
21 an abbreviated report or a synopsis, based on a
22 subsequent FDA guidance, but they are concerned that
23 these might not be acceptable to authorities in Europe
24 and the Asia-Pacific area.

25 So, the study tagging file documents refer

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1 to and recommend, and appear to recommend, E3
2 numbering, and there's no reference at the time
3 specifically linked to the actual official E3 copy,
4 and I just heard today that that will be changed in
5 the ICH web site. But, the point I need to make is
6 that new - there's some of us who, you know, know
7 where to look, and where these things are, and keep up
8 with it, but there are no biotech companies, new
9 staff, new writers, who go to the original ICH E3
10 document and really are not aware of what
11 modifications have come subsequently and what
12 modifications are allowed, because there has really
13 been no forum for getting an official answer, and
14 that's what we discovered in our discussion, that we
15 hesitated to say, oh, this is the way we do it, and
16 it's been fine, you really can't rely on that hearsay
17 when you are putting together an application. And, I
18 would hate to give that recommendation to a sponsor
19 and have problems arise because of a different
20 reviewer. So, a public forum for getting an official
21 ICH position would be very useful.

22 And actually, originally the guidance was
23 designed to specify minimum required content and
24 actually minimum required content for Phase 2 and 3
25 studies. As a template, it is really not user

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1 friendly. I think it breaks down kind of in the
2 middle, where there's a whole discussion about
3 statistical assumptions, and all of a sudden it's very
4 difficult to start using it as a template.

5 Questions arise, and most of the questions
6 that will follow in this presentation arise when
7 sponsors attempt to force a report into an E3 used as
8 a template. So, a clear and publicly available
9 position from ICH on this issue would be useful.

10 So, one case in point that might seem
11 minor on the face of it, the CTD and eCTD allow and
12 recommend the synopsis as a separate document, and
13 some see that as a conflict with the E3 guidance and
14 want to have a synopsis externally and then repeat the
15 synopsis within the document, and, really, this
16 defeats the purpose of tagging and reusing elements.
17 But, at the time of the E3 guidance, who could have
18 anticipated the concept of CTD or the submission life-
19 cycle management could not have been anticipated that
20 we're building toward now. And, even though the
21 guidance does have argumentation for a reasonable
22 approach, this is not really getting through, it's not
23 allaying the concerns. I know a lot of our working
24 group in developing these slides came and said, well,
25 these aren't really issues, these are not problems,

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1 but what I'm telling you today is that, that they are
2 problems for certain people out there, writers and
3 authors, who are looking at the guidance very
4 literally.

5 So, just some general questions. The E3
6 at times appears incompatible with the rigidity of
7 electronic requirements. The overall structure and
8 numbering is sometimes confusing. People ask how to
9 best adapt the E3 to Phase 1 reports, and how to
10 submit synoptic reports and abbreviated reports in
11 eCTD format.

12 Questions arise in other areas, specific
13 questions about the actual appendix content, wording
14 of the headings, signatures, and within the text of
15 the document, which is one unit in an electronic
16 submission, and this has nothing to do with the
17 electronic submissions at all, is within the text
18 people are asking about what to do about duplication
19 of information, missing variables and sections, what
20 are the possible ways to insert these, what about
21 reordering sections.

22 At my company, we've actually added a
23 dosing section before - that precedes efficacy,
24 because we felt that in order to put the efficacy
25 discussion in context you need to know what doses were

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1 received and the duration of that, and waiting to get
2 to the safety section with exposure was just not doing
3 the job. So, we have taken the liberty of making this
4 change, but the other sponsors are agonizing with
5 these changes and are not able to convince their
6 companies that this is a possibility.

7 So, just some specific examples. I just
8 wanted to present this and include this for the
9 record. The perceived incompatibility with ICH E3 and
10 eCTD is that for the paper submissions you can add an
11 entire report, you can append a report on microarray
12 data, health outcomes, special studies. It's not as
13 clear as to how you go about doing that in an eCTD.
14 The numbering corresponds with the study tagging file
15 recommendations, but the location of information,
16 there's uncertainty about the placement of this
17 additional information, and I know that many issues
18 have been solved at Yokohama, but I'm telling you that
19 these are not well understood and they are not getting
20 out there, and people are just not understanding how
21 to apply that.

22 If you are lay reader, and you go to this
23 document, it's very difficult to see how it applies to
24 a paper submission, if at all, and how to kind of
25 migrate from paper to an electronic submission.

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1 This is just kind of an overview of the
2 kinds of discrepancies people see. Can we - they are
3 asking, can we combine these sections, can we reorder
4 within the text, and admittedly the authors are
5 wanting assurance that this is okay, and this arises
6 from the use of the guidance as a template.

7 Also things of, what are the, you know,
8 acceptable additions, and what are the ramifications
9 of a sponsor straying from an E3 structure, and it's
10 not so much, you know, permission to include these
11 data, because these are vital data, it's how to do it,
12 and what would be the appropriate location. So,
13 allowing flexibility within this type of text
14 situation will allow the writer to streamline and make
15 the discussions more concise.

16 There's always a lot of questioning around
17 protocol deviations, how much detail, and the content
18 question, the common ones are, protocol, is it the
19 final protocol or all versions of the protocol, IC, or
20 is it the IC, the informed consent, from all the
21 sites, or just the main site, or the sample IC, and
22 CVs, principal investigator or sub-investigators, and
23 some regional guidances have been developed but this
24 could lead to divergent views. And, I think this
25 point has been made before. If we handle an issue

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1 locally, what does that mean globally, and this would
2 be an opportunity for ICH to have an official position
3 on some of these content issues.

4 And, there was something else, oh, there
5 was a lot of anxiety about the laboratory validation
6 piece, and some people are putting in all of their
7 entire routine laboratory manuals, incredible amount
8 of data that may or may not be necessary, and some
9 people do not submit. So, there's really a widespread
10 view on what to include here.

11 Some other minor things, table of
12 contents, we don't put authors on the table of
13 contents, we put the regulatory department head, and
14 we handle signatures a certain way, there are
15 questions around that. What are the allowable
16 modifications for Phase 1, and how do you reconcile
17 the FDA guidance on abbreviated CSRs to the fixed
18 format of eCTD, and I think this is an opportunity to
19 develop some global agreements for recommendations to
20 provide less than full reports. What circumstances
21 are allowable for abbreviated reports, what
22 circumstances support synopses, the FDA guidance has
23 some good arguments there, and it may be a good idea
24 for ICH to consider this because we are doing global
25 submissions.

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1 We've alluded terms and different
2 questions that have come up from the Japanese Medical
3 Linguistics Institute. They asked about selection
4 criteria and inclusion criteria, is this the same or
5 is this a different concept, and non-English speaking
6 people ask these very perceptive questions that some
7 of us, you know, take for granted, and are really an
8 opportunity for us to expand on this in a good
9 glossary.

10 In the synopsis, there's a section on
11 methodology, what is that, study design,
12 investigational plan, rationale, and also the test
13 product mentioned in the synopsis is referred to as
14 treatment study, test drug, investigational product,
15 medicinal product, you know, the terms are all over
16 the place in the guidance, and these terms in the
17 guidance itself are really not consistent across later
18 guidances.

19 So, we very much support this activity
20 that Randy mentioned on a change control process for
21 ICH terms, the maintenance process for ICH terminology
22 lists, and encourage this to be linked to the HL7/
23 CDISC/RCRIM group that, you know, was mentioned, and
24 the Protocol Representation Group with a glossary
25 effort. As a member of that Protocol Representation

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1 Group myself, I can tell you how important it is to
2 know that many other initiatives exist, and these
3 efforts use the ICH e guidances quite heavily as a
4 basis for terms and terminology, E3, E6, E7, E9, just
5 to name a few, and these serve, actually, as a field
6 source for the protocol data elements in our modeling
7 and glossary activities, so it's very important for us
8 to be harmonized and in sync and be clear, not about
9 the actual term we use, but what is the underlying
10 concept, are we agreeing on that concept.

11 So, the current situation is that we have
12 varied interpretations and widely varying CSR content
13 and location of information. And, as I mentioned
14 before, many companies spend a lot of time and effort
15 collecting, processing and submitting, perhaps,
16 unnecessary documents, and we need to remember that
17 there is a large segment still requiring and
18 submitting paper documents, and will be doing so in
19 the future. Not everyone is capable of doing the
20 electronic submissions now, and I'm sure that
21 reviewers of paper submissions certainly might
22 appreciate not receiving some of this unnecessary
23 information, and also electronically. I mean, your
24 servers could explode if we were to put in every lab
25 manual that ever came across our desks.

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1 So, the common goals for guidelines for
2 the CSRs are that they allow adequate and concise
3 reporting of data, just not reporting of every piece
4 of information you ever knew about to study, to allow
5 consistent and predictable locations for information,
6 and that that be compatible with other formats, but
7 that the guidance remains flexible enough to
8 accommodate devices, Phase 1 studies, oncology MTD
9 studies, which is a stretch right now, and other types
10 of studies.

11 And, we need a win/win solution, and
12 consistency really assists the reviewers, and also
13 streamlines compilation for sponsors, and there is a
14 lot of discussion about what we can do for time and
15 cost savings in effective drug development.

16 So, here's the bottom line. We recommend,
17 as a SIAC, and, of course, that doesn't mean that it
18 has any weight whatsoever, but we recommend an
19 official Q&A process for E3, and recommend that an
20 expert working group be reconstituted to provide
21 official responses, and is E3 intended to offer
22 guidance or be a template, because we see that
23 template used out there. We want these answers posted
24 on a central location, and as a medical writing SIAC
25 we have detailed lists of all the questions that

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1 people are asking out there that we would be willing
2 to share.

3 And, we would also like medical writers to
4 be included in this expert working group, people who
5 are preparing these reports as part of their function.

6 These are the people who have contributed
7 to this presentation. I hope I haven't forgotten
8 anyone, but I think I have because we did get some
9 late comments that I wasn't able to incorporate. We
10 have within this group different opinions about the
11 importance of the listed concerns. I certainly have
12 no problems with some of the issues I presented, so
13 it's not that I was, you know, giving you my own
14 personal opinion, it was really kind of a group
15 opinion. But, all of us support the opportunity to
16 have an official Q&A available, because I can
17 appreciate a new writer coming into the field, or a
18 new company, and just not knowing where to get the
19 official answers.

20 You know, at a big pharmo we sometimes
21 forget that we have people looking at all the
22 guidances, and I get a little blurb and update every
23 day, and I don't have to worry about that, but other
24 people do not have that capability or that resource
25 available to them, to be able to read and find these

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1 web sites, and even find the location of all the
2 updates. So, that's the message I want to leave with
3 you.

4 So, thank you for your attention and
5 consideration, and a special thanks to Justina who
6 participates on our SIAC and has been very helpful in
7 bringing these issues forward. Thank you very much.

8 ASSOCIATE DIRECTOR MOLZON: Thank you,
9 Helle.

10 Are there any questions?

11 Well, I want to thank Helle for, you know,
12 clearly articulating the issues and laying out the
13 concerns, and one thing I learned when I was trying to
14 help implement the CTD is that you actually have to
15 actively participate with the end users, the people
16 that are actually going to be putting these documents
17 together. So, that's how I started to get involved
18 with the medical writers, through the DIA Medical
19 Records SIAC, and also the American Medical Writers
20 Association. These are the people that are actually
21 going to be taking these documents, they didn't
22 participate in the ICH process, their representatives
23 come back and just give them the assignment, okay, you
24 are going to start doing this. So, I think one of the
25 reasons the CTD was fairly successfully rolled out was

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1 that we started working with the people that actually
2 had to do this work.

3 And, as Helle said, we really want to
4 prevent divergent use of these documents, and the E3
5 document is, you know, ten years old, it was developed
6 in a completely different context, it's time to start
7 evaluating what we can do to update it.

8 There has been a Q&A process established
9 during the implementation of this CTD and it's been
10 successful in addressing a lot of the concerns. So,
11 we didn't have - we are trying to prevent, once again,
12 divergent implementation of this topic.

13 I think that's - and that's one of the
14 points of this meeting. It's very important to gather
15 this information and go into the ICH process, and then
16 let people know what's actually going on with the
17 documents that were created in ICH.

18 Yes, Michael.

19 DOCTOR UMEN: Michael Umen, Michael Umen &
20 Company.

21 I want to just add something for, perhaps,
22 the benefit of the Steering Committee and others with
23 whom you'll be sharing the transcripts.

24 One of the things that exacerbated, I
25 think, some of the concerns that Helle raised amongst

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1 the medical writers about template versus guidance,
2 actually occurred when the eCTD and CTD implementation
3 really reinforced how important it is in the eCTD and
4 CTD to use the numbering scheme precisely, as put
5 forth in the CTD guidance documents, especially, for
6 example, within Module 2. And, the granularity and
7 the numbering system there led a lot of folks in the
8 medical writing realm and in the QA realm who saw the
9 way the CTD and eCTD numbering scheme were being very
10 rigorously enforced and adhered to as an ICH
11 recommendation, thinking that the E3, which has a
12 numbering scheme of its own, and which numbering
13 scheme was embraced in the study tagging file for some
14 of the appendices in Section 16 of the E3, led to, I
15 think, some of the challenging diversity of
16 interpretations amongst the users of the E3 guidance
17 document and the corresponding M series of CTD
18 implementation guidances.

19 So, that is some perspective that may help
20 in the record to clarify the deliberations as ICH
21 addresses this issue, and I think Helle gave a very,
22 very good, and you also, Justina, gave a very good
23 assessment of the current diversity of challenges that
24 are out there in implementing E3.

25 MS. GAWRYLEWSKI: Thanks, Michael, and

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1 that was just my point, that it isn't that we are
2 saying this is the true or correct interpretation,
3 it's just making you aware that those are the
4 interpretations out there.

5 DOCTOR ROGERS: Hi, I'm Chris Rogers with
6 RPS.

7 I just want to emphasize, in addition to
8 supporting that, I guess it's sort of a don't throw
9 the baby out with the bath water comment, from a
10 perspective of providing contract services.

11 I can tell you that there are an enormous
12 number of companies that have religiously implemented
13 the ICH guidelines, even though they struggle with
14 knowing what goes in these various sections.

15 But, I think that there is some value to
16 that rigor. While we can see it in the CTD, that
17 navigability for reviewers, for development partners,
18 while within the eCTD the study report itself is a
19 single element, a single element, a single study
20 report body at least.

21 And so, there isn't the need, as Michael
22 just said, to really follow the numbering system
23 precisely. Given the fact that that is off the table,
24 I do think that there is some value to, perhaps, being
25 able to come to a consensus of maybe Level 1 and Level

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1 2 headings, that maybe don't carry the weight of a CTD
2 standard, but could be maybe an annex, or a
3 recommended, like a default without, you know, as some
4 sort of a template for the many organizations that are
5 struggling with this.

6 I think that a Level 1 and Level 2
7 consensus may be, you know, by way of the Q&A,
8 inserting homes for some of these pieces that don't
9 have a home right now.

10 I think, you mentioned, Helle, that, you
11 know, some of your development partners are concerned
12 that your reports aren't ICH compliant. I think maybe
13 one other message to hear from that is that they are
14 struggling with navigability, and if that's true among
15 development partners, then it's true among reviewers
16 throughout the world. And so, I think that, you know,
17 I'd like to suggest that at least we keep maybe as a
18 goal some level of standardization that would
19 facilitate reviewability, communication, I understand
20 it may take forever to get that agreement, but, you
21 know, if we keep it at a high enough level it might at
22 least assist those regions.

23 You know, again, from a - perspective, I
24 work with a lot of small companies who want to know
25 that the report they produce is going to be easily

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1 recognized by whoever they might partner with down the
2 line, and, you know, this just might be a way of
3 meeting that need.

4 MS. GAWRYLEWSKI: Yeah, that's a good
5 comment, and we struggled with that, too, because
6 companies who have already developed numerous
7 templates are worried that now all their templates
8 will be invalid, but there is definitely a need for
9 people just starting out or who don't have templates
10 developed to get some advice on how to do that in a
11 reasonable way, you know. So, I think that both
12 concerns need to be balanced.

13 ASSOCIATE DIRECTOR MOLZON: Any other
14 comments?

15 Randy?

16 DOCTOR LEVIN: It's a very interesting
17 discussion, but some of the things I see as confusing
18 is that the E3 documents were all written for paper
19 submissions, and we're in an electronic world.

20 When we are working on the electronic
21 ideas, it's a totally different way of looking at it,
22 a different approach, and so the numbering was not
23 something that the technical people are thinking
24 about, it's only just to point to as this is a
25 concept. And, that is when you are taking the

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1 numbering as very specific, it's not the way the
2 technical people are looking at that.

3 If you look at it in a way that this is
4 terminology, this is just controlled terminology, we
5 want to identify what the subject matter is of these
6 documents, that's what these headings are for, to try
7 to say what the subject matter is, we need controlled
8 terminology for that, not numbers, just, you know, the
9 concepts of what these documents are for.

10 And, that's what we are working on with
11 the other groups, to try to come up with this
12 controlled terminology. That's why they went to E3,
13 to look for a controlled terminology for what these
14 different topics are, and it sounds like there we need
15 more terms, and that's to try to define what these
16 topics are.

17 On the other hand, so when you go to
18 electronic you are forced to be more specific, to try
19 to harmonize, you can't just come up with your own new
20 heading, or, I mean, new topic, or revise some topic
21 that's already there, you have to use what's
22 available. So, it sort of limits you.

23 But, if we are allowed a process to add
24 these new terms to the list, then that might address
25 those issues. But, it's really - the way I look at it

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1 is, it's terminology, controlled terminology, that is
2 going to the subject matter for those documents.

3 MS. GAWRYLEWSKI: Exactly. We always get
4 push back from people who don't understand that
5 concept by saying, well just add this file, and we
6 say, well, you can add all the files you want, but the
7 reviewer will not see those files, and will not know
8 that they are there.

9 DOCTOR LEVIN: Yeah.

10 MS. GAWRYLEWSKI: And, I think that that's,
11 you know, something that is not being understood.

12 DOCTOR LEVIN: So, the idea that whether
13 it's a guideline or a template, when you do the paper
14 it's a guideline, and people are supposed to follow
15 this, but if you didn't follow exactly what's going to
16 happen. I mean, you are trying to follow so everyone
17 knows where to get the documents.

18 But, when you go to the electronic, the
19 computer is looking for that specific thing, and if
20 you don't have it, then it's going to be a problem.

21 MS. GAWRYLEWSKI: So, Randy, if you are
22 looking for the four month safety update, or the seven
23 month safety update, where would you look? I'm going
24 to take this opportunity to ask you, because, you
25 know, we've been wrestling with where - what to do

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1 with those documents.

2 DOCTOR LEVIN: Again, and look, it's a
3 document we want to know something about - the heading
4 is really the subject matter, we want to know
5 something about the subject matter. We want to know,
6 we have to decide whether the information there is
7 already covered by another subject matter, that we
8 don't have to make up a new title, that we can already
9 fit it into terms that we already have. Those are
10 some of the decisions you have to make.

11 And then, identify that when you put in
12 this type of document, this is the headings that you
13 place it under to define the subject matter.

14 It has nothing to do with the order. It
15 has nothing to do with - it's just trying to say what
16 the subject matter of that document is, so now the
17 reviewer, when they want to look for something, they
18 know where it is.

19 So, we have to go through, what is that
20 three month safety update, a lot of that information
21 is already submitted under - there are already topics,
22 there are already subject headings or terminology for
23 those, that information, so you don't need to make up
24 new topics for that, and that's where you need
25 controlled terminology people to look that over and

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1 have the terminology just for those.

2 MS. GAWRYLEWSKI: So, the terminology
3 linked to the content in that certain section.

4 DOCTOR LEVIN: That's right, what's the
5 content, and that's what that is, instead of that this
6 is the order of the way the document is, this is just
7 exactly how we have to put it together.

8 And then starting out maybe with less
9 granularity, and as we get more familiarity you can
10 add more granularity, because in the body of the study
11 report we don't have everything - you don't know
12 exactly what to do, if you have very specific
13 granularity there we are going to be in a lot of
14 trouble. So, in the body of the study report there is
15 no granularity you can really have a lot of
16 flexibility, but the more - the better, like in the
17 labeling, if you know what every section is supposed
18 to be then you can divide it up and that's more
19 helpful.

20 So, these different types of reports, we
21 need to work on the terminology, then you have to
22 write out some sort of implementation guide or
23 something to tell people how to tag those documents
24 with the information.

25 MS. GAWRYLEWSKI: Thank you.

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1 ASSOCIATE DIRECTOR MOLZON: But, I think
2 this is exactly what Michael was talking about.
3 There's this concern about, you know, the very rigid
4 construct, and people are trying to do this, and Randy
5 is articulating this ability to have flexibility, but
6 it's very difficult for people to get this, and I
7 think that's what Michael - isn't that what you were
8 talking about?

9 DOCTOR UMEN: Within the context of the
10 study report, for example, the body of the study
11 report is, even at the study tagging file level, a
12 granule, and within that granule there is a lot of
13 control, opportunity for controlling terminology, but
14 the numbering scheme within it is only - as long as
15 the granule is still the body of the report has a lot
16 of flexibility. And, I think it would be an over
17 interpretation of the E3 guidance, as Randy said
18 originally made for paper, to try and superimpose upon
19 that the granularity within it and the numbering
20 scheme within it, when it's just in the eCTD just
21 going to be body of a study report. That's the only
22 granule.

23 There are other things that have more
24 granularity, identified within the study tagging file,
25 but that's a - there are still challenges there.

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1 ASSOCIATE DIRECTOR MOLZON: One thing I
2 know from working with the medical writers is that
3 they are very focused on helping the reviewer. They
4 are very concerned about writing documents in a way
5 that it will help the reviewer, you know, take this
6 information and to make a decision, so I think the
7 intent of the group is to actually try and come up
8 with consistent information in E3 so that there is
9 consistency.

10 And, once again, you go to read these -
11 the CSRs, which are the basis for the efficacy module,
12 and it would be helpful if the reviewer kept seeing a
13 more or less consistent approach to this. And, I
14 think that's the bottom line here.

15 And so, the questions that have been posed
16 are very helpful. We'll take this into ICH. I don't
17 think it would be difficult to recommend a Q&A
18 process. We've realized through our work with
19 implementation of the CTD and eCTD that this is a very
20 valuable way to help clarify issues that will just
21 help people have a better understanding of the actual
22 intent.

23 So, you know, thank you for your time, and
24 I know there's a large group of people that helped put
25 this document together, so thank you.

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1 We are a little ahead of schedule, but our
2 next speaker is going to talk about Structured Product
3 Labeling, and that speaker is Kristofer Sphar.

4 MR. SPAHR: Good morning. I've always known
5 that there's two things you don't want to do in life,
6 one is the last speaker before lunch and the first
7 speaker after lunch, so if you'll indulge me a little
8 bit.

9 My name is Kristopher Spahr. I'm with
10 Wyeth Pharmaceuticals, and I'm also the Chair of the
11 SPL Working Group, and I'm delighted to have the
12 opportunity to talk this morning.

13 The ground I want to cover this morning is
14 really to give you a little bit of background in terms
15 of the work that's been done in the SPL Working Group,
16 define at a very high level the SPL concept, talk
17 about the different drivers or motivations that led
18 towards moving towards structured labeling content,
19 speak also to some of the harmonization challenges and
20 opportunities that I think exist between SPL and the
21 initiative in Europe with PIM, and then finally some
22 recommendations.

23 The SPL Working Group was initially formed
24 within the PhRMA Industry Group. We now function
25 within Health Level 7 as an RCRIM project team, being

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1 the part that Doctor Levin talked about earlier.

2 The working group has 88 members,
3 including a good representation, a very good
4 representation, of a number of different perspectives.
5 We have within our group an HL7 modeler, which is very
6 important in the Health Level 7 world. We have the
7 very good representation of PhRMAs, approximately 30
8 or so of different sizes, small, medium and large. We
9 have a number of individuals from the FDA representing
10 different departments and centers, and we also have
11 about approximately 15 commercial vendors who are a
12 part of our working group as well.

13 The way that the group has evolved is into
14 three primary work streams or teams, if you will.
15 There's a technical team whose focus has been largely
16 on the development and extension of the SPL model.
17 This group is responsible for developing the SPL
18 standard. They are also responsible for extending it
19 in its various releases, and they've also authored an
20 XSL style sheet which was important. This is a
21 structured document put into an XML format, but it's
22 important that both the agency and industry have a
23 common view of what that looks like when presented,
24 and that was part of the work of that technical team.

25 There's also a process team, whose focus

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1 is really on resolution of the process issues, or in
2 other words taking the standard and putting it into
3 practical application. That group, their primary
4 deliverable is an implementation guide. We are also
5 about to author some FAQs as an additional way to
6 understand some of the process issues around this
7 standard as well.

8 And then finally, we have a testing team,
9 and their job was to work in collaboration with the
10 FDA to develop a test plan and then test the SPL
11 exchange. That we anticipate will occur in August of
12 this year.

13 Kind of the last piece that the working
14 group also tries to address is raising industry
15 awareness concerning SPL, so through a variety of web
16 casts, and telecasts, and public meetings we've tried
17 to bring the SPL story and an understanding to the
18 industry as well.

19 To give you kind of a brief history of SPL
20 and where it started from, motivated by some internal
21 government recommendations, some initiatives and legal
22 mandates, the agency sought a more sophisticated way
23 to exchange the content of labeling. The SPL standard
24 was originally developed by a small group within
25 Health Level 7, within the RCRIM technical committee,

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1 and it was originally based on a concept called the
2 Clinical Document Architecture. It came to be known
3 more as a sibling than a child. The important
4 takeaway there is simply to understand that what we
5 are doing is we are taking a document that's in a
6 structured format and translating it into a format
7 that can then be transmitted as an XML message.

8 The HL7 Task Group was formed - of, I'm
9 sorry, the PhRMA HL7 Task Group then formed the SPL
10 Working Group, and this was in January of 2004, to
11 kind of further the work of that initial development
12 group with RCRIM. And again, as I said, we now
13 function as an RCRIM project team.

14 In May, 2004, the SPL passed the Health
15 Level 7 Committee ballot process, and what that then
16 makes it eligible to be is an ANSI standard, and it
17 became an ANSI standard in its first version in August
18 of 2004.

19 In 2005, in January, the SPL Version 2
20 passed the committee ballot. It's now up for a
21 membership ballot, and actually going through the
22 ballot process as we speak.

23 So, the question is, what exactly is SPL?
24 It is a standard for describing the content of
25 prescription drug labeling in an XML document form.

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1 Or, if you want it in a little bit more specific
2 definition it's an extensible document specification
3 that does define both the semantics and the structure
4 constraints necessary to represent a product label in
5 an XML format. Again, that's based on the HL7
6 Clinical Document Architecture, and it's intended to
7 be used as a basis for regulatory guidance documents
8 and tooling applications for the exchange of that
9 product labeling information. Important to note there
10 that it's a basis for regulatory guidance. It doesn't
11 necessarily mean that the current version that's out
12 there would be adopted in total in a regulatory
13 guidance, and, in fact, I think we'll see that in
14 October of this year, where we may well have a more
15 far-reaching standard and a subset of that will be
16 defined within the guidance.

17 It's important also to understand what SPL
18 is not. As I mentioned, it does model the structure
19 and the semantics of labeling content, but it's not
20 geared towards the presentation that you might find in
21 printed labeling or promotional labeling. And again,
22 it's a specification for information exchange, it does
23 not specify a system for creating or managing those
24 documents, that's largely left up to the cleverness of
25 commercial vendors and sponsors, to be able to come up

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1 with those systems. It is a format that allows for
2 the storage and exchange of that information.

3 At a very high level, if you wanted to
4 understand SPL from a conceptual standpoint, it is a
5 structured document, as I've said several times. The
6 main portion of it is header information, which is
7 sort of meta data about the document itself, who did
8 it come from, what's their organizational ID, that
9 type of thing.

10 There are the different sections within
11 the label, the actual body, that's the part that you
12 see, that's the part we are all familiar with in a
13 product label, and there is structured data about the
14 product that exists also within the standard. The
15 structure is flexible, in other words it allows for
16 room to grow. The human readable elements is kind of
17 a characteristic of XML, they are preserved within the
18 document. The semantics of the mark-up come from the
19 RIM, not important to understand that unless you are
20 very involved in Health Level 7, but just understand
21 that what that means is that, in this case the
22 standard is defined within larger overarching
23 information models, and a limited set of data elements
24 that were in the original version can be expanded over
25 time. And, in fact, as we move towards Release 2 of

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1 the SPL standard, largely the top half represents a
2 portion of the model that was Version 1, which dealt
3 with the document, the sections, the product
4 descriptions and the drug listing information, some of
5 that drug listing information. The bottom portion is
6 the bulk of Release 2, which brings the standard in
7 alignment with the soon-to-be anticipated Physician
8 Labeling Rule. It allows for prescribing information
9 as you see, it also allows for pharmacovigilance
10 information, such as adverse events, to be included
11 within the labeling standard as well.

12 And, if anyone can read that
13 representation, or understand what it says, I'm very
14 impressed.

15 The drivers for structured labeling in the
16 U.S., important to understand, the real motivation was
17 to improve patient care through better information
18 management, and it's driven by some larger initiatives
19 as well. The Medicare Modernization Act, always fun
20 for me to try to say that, e-health records, e-
21 prescribing, the daily meta initiative of the National
22 Library of Medicine, decision support within the FDA
23 as well. Important to note that these patient care
24 oriented initiatives, SPL becomes the point of origin
25 for a lot of that information which flows into those

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1 initiatives as well.

2 There are also challenges with the
3 existing format of the labeling content. It was - it
4 can be, at times, difficult to read, if you are an
5 elderly person or a person who has trouble with vision
6 some of the formats, some of the fonts in the existing
7 labeling can be difficult to read and understand.

8 The distribution is limited. The text
9 again, in a PDF format, is not something that
10 computers can much use of. PDF often being referred
11 to as electric paper, as opposed to breaking the data
12 down into a more data centric representation.

13 Terminology and code sets are not
14 standardized, and it's sometimes difficult to ensure
15 that the end users or the health care community does
16 actually have the latest information, because in some
17 cases it doesn't directly flow from the sponsor of the
18 drug product in the first place. There can be other
19 parties involved who may not have the most recent
20 information.

21 Because what we are also addressing is the
22 harmonization of structured labeling, important to
23 note that in Europe there's another initiative that I
24 don't mean to speak for, other than to outline their
25 particular objective called PIM in Europe. The focus

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1 there, and the motivation, is different than it was in
2 the U.S. The motivation in Europe was, number one, to
3 focus initially on the centralized procedure, and
4 subsequently then see if it can be extended to mutual
5 recognition or national procedures. But, it was more
6 of a shared problem, and the situation in Europe is a
7 bit different from the U.S. In this particular case,
8 if you envision a change to a product label, in the
9 different formats that it might have in Europe, the
10 summary of product characteristics, the package
11 leaflet, other labeling contents such as carton
12 information, foils, and then add to it the different
13 languages in Europe as well, then also compound that
14 problem by considering that for each drug product
15 you've got a different presentation, a different pack
16 size, different trade names, different strengths, you
17 can see that any change to a product label has a
18 multiplier effect. In some cases, it's - I think the
19 average can run into the neighborhood of 400 to 600
20 documents that can be affected, with a ceiling of
21 sometimes as high as 1,600 documents.

22 That's a problem for the sponsor who has
23 to prepare those documents, it's a problem for the
24 agency that has to review those documents. So, in
25 this particular case, more of a shared problem was the

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1 driver in Europe than in the U.S.

2 But, for many of us there are global
3 pharmaceutical companies, this presents a bit of a
4 dilemma, because we've got two different standards for
5 structured labeling content, coming at it really from
6 two different motivations.

7 But, as a result, the standards that came
8 out of those two efforts have a different sense of
9 granularity, and what I mean by that is, you can
10 almost get a tip of the focus of each initiative by
11 their names. In the U.S. we call it structured
12 product labeling, and it's addressed from that
13 structured document paradigm. In Europe, it's product
14 information, and it's much more granular, much more
15 data centric, with the idea of generating, not just
16 one label type, but multiple label types.

17 If you looked across both standards you'd
18 see an inconsistent use of vocabularies, external
19 vocabularies, SPL being a bit more leveraging in
20 external vocabularies that PIM as a generality. In
21 the U.S. we have a single language to deal with, in
22 Europe there is multiple languages to deal with, but
23 I think in all fairness, in terms of the maturity of
24 both standards you could say in Europe a little bit
25 more mature in terms of its application to the full

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1 label negotiation process, as opposed to some of that
2 is a bit more formative in SPL currently.

3 But, those challenges also bring with them
4 certain opportunities for harmonization. The first
5 one bears a little of explaining. What do we mean by
6 semantic and syntactic interoperability? This may be
7 something that Barbara speaks a little bit to, I don't
8 know, in her talk later today. In Health Level 7 this
9 is one of the themes of the value proposition of
10 Health Level 7. Not only do you need to define and
11 get agreement within a larger domain, in terms of what
12 something means, but also in terms of how it is used.
13 And, the operative thing there is that you are doing
14 that within a larger domain space.

15 There's also, between the two standards,
16 ample opportunity for the difficult discussions around
17 vocabulary harmonization to occur. Clearly, from a
18 sponsor's perspective, there's the opportunity for
19 reduced costs and increased process efficiency with
20 one harmonized standard that leads to one process, one
21 tool set, makes that a much more efficient, much more
22 consistent process.

23 Consistent application to eCTD
24 submissions, simply stated, with a harmonized label
25 standard it makes it easier to then define those

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1 situations in which they would become submissions
2 through the eCTD format, as opposed to two different
3 standards.

4 And then, just to kind of expand a little
5 bit on what Randy had said earlier, if you remember
6 back to the slide where the SPL has within its
7 structured data that talks to the product information,
8 and within PIM that's certainly a big portion of that
9 particular standard, there's ample opportunity for
10 harmonization of those product information models
11 within M5, for instance, in the ICH.

12 So finally, in terms of recommendations,
13 what I would suggest is that, while structured
14 labeling certainly appears to fit within the ICH both
15 efficacy and multi-disciplinary topics, I would
16 strongly suggest that the ICH also consider utilizing
17 a formal standards development organization for the
18 development of the standard. I can certainly see a
19 scenario where the ICH would champion the
20 harmonization of this effort. I can certainly see a
21 scenario where the ICH would sponsor this type of
22 activity, and I think this is an appropriate forum for
23 that to occur.

24 However, I would also suggest that
25 development of the actual standard itself might be

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1 taken to a formal standards development organization
2 such as HL7 for the following reasons. Number one,
3 being able to ensure this interoperability within a
4 broader information domain. By example, Health Level
5 7, the domain is all of health care, patient care, as
6 well as the clinical and pharmaceutical side of the
7 business.

8 Secondly, there is a rigorous methodical
9 approach to standards development, which again is not
10 to suggest that within ICH that that's not a part of
11 the process also, but again, the operative portion of
12 that is that it's developed within a much larger
13 domain. Now, that adds a little bit of pain to the
14 standards development process. Truthfully, it adds a
15 lot of pain to the standards development process, but
16 I think within a situation like structured labeling,
17 which ultimately feeds into patient care initiatives
18 such as e-prescribing and e-health records, it's
19 important to keep that domain clearly in mind.

20 I think it's also important to have a
21 forum in which all perspectives are required to
22 implement a standard. One of the things that I think
23 is important within the working group is that we do
24 have commercial vendors represented. I think that's
25 important, because they become the enablers of that

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1 standards and its practical application.

2 And, I think it's also important to have
3 a complete standard, a more complete standard tends to
4 evolve from a more complete end-to-end process vision.
5 And again, ultimately, the goal being to increase the
6 accessibility of both useful to humans and computers,
7 and accurate medication information worldwide.

8 Any questions?

9 ASSOCIATE DIRECTOR MOLZON: Thank you,
10 Kris.

11 Any questions? Any comments? You don't
12 have to actually have a question.

13 Helle.

14 MS. GAWRYLEWSKI: Sorry, I can't help
15 myself. I just have a comment about that very good
16 point about the health care and broader applicability
17 of the standards, and I think we'll be hearing from
18 this later, but the caBIG, the bioinformatics grid
19 activity in cancer centers underscores the need for
20 these centers to be able to share information, which
21 they can't do now. So, it's not just a matter of
22 submitting, you know, documents to health authorities,
23 it's about health care in general, and how do we do
24 risk management at a broader perspective, or how do we
25 find signals earlier from a safety point of view, or

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1 efficacy signals earlier, and that really goes beyond
2 just drug development, because in drug development we
3 have a very limited population that we may be focusing
4 on initially, that really needs to be broadened. But,
5 if all the pockets of information is non-standard in
6 all of these various research centers we have no
7 possibility of looking across the larger database.
8 So, I think that's a really good point to bring
9 across.

10 MR. SPAHR: I concur with your point, and
11 I think it's always been very important in a working
12 group to keep in mind that the point of the effort is
13 better patient care.

14 And, we've been fortunate enough to have
15 speakers come to our working groups from organizations
16 like the VA, who kind of point out the ultimate end
17 game and how these things can be used.

18 DOCTOR UMEN: Michael Umen, Michael Umen &
19 Company.

20 One of the challenges, I think, for
21 worldwide, at least in the three major regions, full
22 adoption of eCTD has been some of the challenges to
23 quickly get viewers that are functional at health
24 authorities worldwide. And, I'm not sure the extent to
25 which there has been harmonization from the health

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1 authority side for the enabling viewers to receive and
2 able review of eCTD.

3 I'm curious if there's any learning from
4 that challenge from the eCTD that can be applied to
5 the structured labeling or PIM, because there must be
6 something going on in Europe that is the equivalent of
7 ELIPS here in the U.S. So, perhaps somebody here
8 could comment, or, perhaps, it might be worthwhile for
9 discussion at ICH to see what the current status is
10 and the implementation plans within the health
11 authorities for receiving and processing the
12 structured label information, and whether there's an
13 opportunity for harmonization there, as well as the
14 production of the documents, the messages themselves.

15 MR. SPAHR: Yes, again, I won't choose to
16 speak on behalf of the PIM group, and I'll defer to
17 anyone who has better knowledge thereof, but I think
18 to your fundamental point, as we began our work one of
19 the common grounds that we had to establish was a
20 generic XSL style sheet that we can both refer to, so
21 that we were both having - all sides would have a
22 common view.

23 We've made that simple style sheet
24 publicly available, and it is considered to be a
25 deliverable of the group, along with the standard

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1 implementation guide and other tools.

2 As for PIM, I'll defer to anyone in the
3 room who might want to tackle that one.

4 DOCTOR UMEN: How about the equivalent of
5 an ELIPS and the status of ELIPS here in the States
6 and the potential harmonization?

7 ASSOCIATE DIRECTOR MOLZON: I'll have to
8 defer to Randy, or Laurie, or anyone else that can
9 answer that question.

10 DOCTOR LEVIN: As Kris was noting, that PIM
11 addresses somewhat of a different problem that the
12 Europeans have than we have with so many different
13 versions of the labeling that need to reuse pieces,
14 where our goal was more of processing labeling changes
15 and getting the information out to the health care
16 community through the DailyMed.

17 As far as the tool - so our tool is geared
18 to meeting our needs at the FDA, ELIPS, which is, I
19 think right now the plan is to implement that end of
20 October.

21 ASSOCIATE DIRECTOR MOLZON: I think it's
22 Halloween.

23 DOCTOR LEVIN: Halloween, and then for PIM
24 I know that they are working on their tool, again,
25 it's very much geared to meet their needs, so it's -

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1 and I know they are on a very - it's actually a fairly
2 similar time line.

3 MR. SPAHR: Yes. Their position at present
4 is to do a pilot by year end, and at that point that
5 system will be piloted.

6 Any other questions?

7 ASSOCIATE DIRECTOR MOLZON: Since we have
8 - any other questions?

9 Okay, thank you, Kris, for your
10 presentation.

11 What I want to do now is, we have about 15
12 minutes before we break for lunch, to get back here by
13 1:30, and the Federal Register notice mentioned that
14 we were going to have a presentation on, I think it's
15 Clinical Development Plan Summaries, also referred to
16 as TPP, and the industry speaker was unable to provide
17 a presentation on this topic, so I've asked Laurie
18 Burke, who has been involved in this, to just provide
19 some background, because in the Q topics, Q8 is the
20 Pharmaceutical Development Plan, and so there's an
21 analogy here to have a summary of the Clinical
22 Development Plan. So, Laurie is just going to explain
23 that, because I think it's an important initiative and
24 it would be good to get it into the record, so when we
25 go to ICH for the efficacy topics this has been at

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1 least mentioned at this meeting.

2 Laurie, if you could introduce yourself.

3 MS. BURKE: Hi, I'm Laurie Burke, and I am
4 the Director of the Study Endpoints and Label
5 Development Team, which is a part of the immediate
6 office of the Director in the Office of New Drugs.

7 Development Plan Summaries I will discuss
8 in the context of Target Product Profile, an
9 initiative that is a fledgling initiative, but yet
10 certainly has been around for longer than most people
11 realize, and it has been developed by a working group
12 comprised of members of PhRMA, as well as FDA.

13 Target Product Profile, or TPP, is a tool
14 for building efficiency in the drug development
15 process by beginning with the end in mind. Something
16 that most people believe is a good thing to do, but
17 it's hard to actually do it in practice. It's related
18 - this initiative is really - the tool is related to
19 almost every ICH advocacy initiative, as well as to
20 the other topics that have been presented today, and
21 it's a bridge between development and labeling. A TPP
22 is a format for a summary of the Drug Development
23 Program, described in terms of labeling concepts, and
24 it is an evolving document that is updated before each
25 FDA sponsor interaction to summarize the work that's

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1 been completed to date, and the plan development
2 activities that are the focus of current or future
3 discussions. And, it summarizes all of that
4 information into a single document that then can be
5 reviewed and is expected to create order to this huge
6 development plan underway. So, it's not limited to
7 efficacy, it's much broader than that. It's in the
8 context of the entire label, so it crosses every
9 discipline in product development.

10 A TPP can contribute to an advisory
11 meeting and can provide review efficiency when it is
12 a component of a briefing document. So, therefore, we
13 are talking about briefing documents from the earliest
14 stages of development, clear through to the pre-NDA
15 meeting.

16 It reduces sponsor surprise, is what we
17 have found, about how FDA will eventually review and
18 make its decisions about final labeling.

19 It can facilitate a risk-based product
20 development atmosphere, by engaging FDA in a
21 discussion about the following at these advisory
22 meetings, does FDA agree that a proposed development
23 activity, for example, a proposed adequate multiple
24 trial, if completed successfully will comprise
25 appropriate evidence to support the labeling concept

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1 specified in the TPP. That is, when FDA is providing
2 advice about the protocols that are planned by the
3 sponsors, how does that - how would FDA view that if,
4 in fact, the protocol as described is successful.

5 A TPP is not a required component of any
6 regulatory submission. It is not an obligation to
7 complete development activities on the part of the
8 sponsor. It is not a guarantee for language in
9 labeling or promotion on the part of the FDA. It is
10 not a substitute for FDA review of the NDA, which many
11 people think, oh, my gosh, are we making these
12 agreements up front, how can this be.

13 There was an informal PhRMA survey that
14 was - from 2003, and they found they got responses
15 from ten sponsors concerning their interaction with
16 six different Office of New Drugs Division, and most
17 sponsors that responded used the TPP in conjunction
18 with their end-of-Phase 2 meetings. They also did
19 state that it would be more useful to use even earlier
20 product development and to follow it through to the
21 end-of-Phase 2 meetings. Sponsors found the TPP to
22 focus discussions and aid - it was an aid to
23 explanation of the development plan, and all the
24 sponsors that responded said that they would use the
25 TPP again, with another development plan. In fact, we

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1 know that almost every sponsor already has a document
2 that's internal that they use for their development
3 process. It's this - the TPP is just taking that
4 document and turning it into something that they are
5 going to share with FDA for their discussion.

6 So, this initiative is going to be linked
7 with many other FDA initiatives that are underway.
8 There are many guidances in draft form listed here,
9 good review practices for IND applications, IND
10 process guidance, there's an OND labeling review
11 process guidance under development, there's an end-of-
12 Phase 2A meeting guidance under development, and we've
13 been talking with the pharmacogenomics and
14 pharmacokinetics folks about how it could be
15 incorporated into the guidance that they are giving
16 during drug development.

17 And, as Justina mentioned, it has a lot of
18 similarity to the ICH Q8 Pharmaceutical Development
19 Guideline. It represents a risk-based approach to
20 drug development, and you can imagine that what this
21 TPP does is define the design space somewhat like the
22 Q8 document does, and let's there be clarity in the
23 discussion between the two parties about that design
24 space, which represents the target of drug
25 development.

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1 There are several communication activities
2 underway. We are working on a draft guidance,
3 specifically, addressing the TPP initiative. We are
4 also building a web site. Currently, there is an old
5 web site. This initiative was first conceived of in
6 the early 1990s actually, and it was called targeted
7 product information at that point in time, and there
8 is a web site that you'll find on CDER's web page
9 under TPI, that will be transformed into TPP once the
10 draft guidance is made public for comment.

11 There are two panels that are organized by
12 the work group that I told you about for the June DIA
13 annual meeting. We do have a web site in EIO for any
14 questions concerning TPP or anything else having to do
15 with OND activities that I've listed here, and there
16 is a publication on this on the TPP that was fairly
17 recent, in January, that I referenced here as well.

18 I just want to end by saying that
19 Justina's slide this morning about the benefits of the
20 CTD from FDA perspective could actually be a slide for
21 the benefits of TPP from FDA perspective. It makes
22 for more reviewable applications. It makes complete,
23 it makes for complete and well-organized submissions,
24 and more predictable formats with complete data, more
25 consistent reviews, easier advice, and we are talking

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1 about reviews of these submissions in the development
2 pre-NDA period.

3 Easier advice can be given, because it's
4 focused on the intended use of the information under
5 development. You don't have to review a submission
6 for every possible use. You can focus your comments on
7 what the sponsor's goals are.

8 There's easier exchange of information.
9 It facilitates electronic submissions, and a more
10 efficient drug development process.

11 Companies already prepare these documents,
12 as I've said. Many want to share them with FDA and
13 other regulators to streamline their development
14 processes, and so we are attempting to make - to
15 provide guidance on how to do this.

16 ASSOCIATE DIRECTOR MOLZON: Thank you,
17 Laurie.

18 Any questions? Any comments?

19 So, we have a little -

20 MS. BURKE: Justina?

21 ASSOCIATE DIRECTOR MOLZON: Yes, Laurie.

22 Oh, I'm sorry, yes, go ahead.

23 DOCTOR RAYMOND: You mentioned that this
24 would be a TPP or the plan that you are talking about,
25 that would be prepared by the sponsor, would start

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1 with the end in mind, it would mainly focus on the
2 intended label. Yet, in the discussion, pre-
3 discussion to the NDA, it appears to me that there may
4 be elements of methodology to be used in the trial.
5 Would that be something that ought to be part of the
6 plan, the methodology, is that part of the label? I'm
7 sorry, my ignorance is very large here, and I'm just
8 interested to know.

9 MS. BURKE: Oh, absolutely, the methodology
10 is critical for being able to plan a successful result
11 in your label. So, my favorite, as you well know, my
12 favorite example of this is, is to discuss the
13 methodology for development of your measurement in a
14 clinical trial.

15 DOCTOR RAYMOND: So, the endpoints labels,
16 that's partly why you are interested in it,
17 qualification of the questionnaires, patient measures,
18 et cetera.

19 MS. BURKE: Right.

20 DOCTOR RAYMOND: Great, sounds like a good
21 idea.

22 ASSOCIATE DIRECTOR MOLZON: Okay, thank
23 you, Laurie.

24 MS. BURKE: Thank you.

25 ASSOCIATE DIRECTOR MOLZON: So, this gives

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1 you five extra minutes for lunch. There is a variety
2 of eating facilities across the street, all different
3 types of food in that little shopping center, you just
4 have to walk right across the pike. There is, you
5 know, just a variety of different places you can go.
6 It's probably very nice outside, you might want to get
7 out of the hotel.

8 We'll start up at 1:30. In every public
9 meeting we have a specific hour set aside to hear from
10 people that want to make public presentations on
11 whatever they would like also to get into the record.

12 So, please be back at 1:30.

13 Thank you very much.

14 (Whereupon, the meeting was recessed at
15 12:10 p.m., to reconvene at 1:30 p.m., this same day.)
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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 1:37 p.m.

3 ASSOCIATE DIRECTOR MOLZON: Hello,
4 everyone. I'd like to start, get started for this
5 afternoon's session. Would you please have your
6 seats?

7 Okay, thank you. Welcome back. I thought
8 I would just sort of make a few announcements. We've
9 now been joined by Michelle Limoli. She is the ICH
10 Coordinator for FDA, and Mike Garvin, if Mike could
11 stand up, Mike Garvin is the ICH Coordinator for
12 PhRMA. On the ICH web site there's contact
13 information for the coordinators. They are, in fact,
14 the only people that do have contact information. So,
15 if you have questions you can actually get their phone
16 numbers and e-mails and send them questions, and then
17 they would bring the questions into the ICH process.

18 I've also been asked to announce that the
19 Power Point presentations that were presented today
20 will be posted on the web, on the CDER web site.
21 We'll put that up shortly after this meeting, because
22 I know some of the presentations were not in the
23 packet, but all of the presentations will be posted.

24 As I've already mentioned, this is a
25 graphic that explains what we are doing in ICH to make

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1 sure that the documents that we work hard on are
2 implemented correctly, and part of that is
3 disseminating the information and gathering
4 information in time for the ICH meetings.

5 And, this morning we spent a lot of time
6 focusing on efficacy guidelines. I have this slide in
7 your packet, it just goes through the list of all of
8 the efficacy guidelines we've worked on since 1990,
9 and there's a fair number. We do have one request for
10 a presentation during the public meeting part of this
11 - the public session part of this public meeting, but
12 after Sadhana Dhruvakumar, from the International
13 Council for Animal Protection, gives her presentation,
14 if anyone else has comments they want to make about
15 the efficacy guidelines, or ICH in general, you know,
16 just feel free to participate in this part, because I
17 know we focused on several ICH, non-ICH parties that
18 are sort of focused on ICH topics, and we've included
19 them in the agenda, but, you know, there is - there
20 will be time for other people that just have general
21 comments, questions, or concerns, just to, you know,
22 go up to the mic and mention those so they get into
23 the transcript.

24 So, we did have one request for a
25 presentation during the public session part of this

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1 public meeting, and that request came from Sadhana
2 Dhruvakumar, from the International Council for Animal
3 Protection, so could you please come up and give us
4 your presentation?

5 MS. DHRUVAKUMAR: Hi, I just want to begin
6 by thanking the organizers for the opportunity to
7 present to you today.

8 The International Council on Animal
9 Protection is a coalition of animal protection groups
10 from Asia, Europe and North America, so the same
11 regions represented by the ICH, and we represent 30
12 million supporters worldwide. I'll just leave the
13 names up so you can take a look at who we are. We've
14 been working together for three years on international
15 animal testing issues.

16 We really formed around working with the
17 OECD on some of their animal testing guidelines and
18 programs. At OECD, we work as ICAPO, and we have
19 invited expert status at the OECD meetings on test
20 guidelines. These are mostly for industrial chemicals
21 when it comes to the OECD. They have 100 test
22 guidelines, of which nearly half are animal tests, so
23 that was something we were very concerned about. And,
24 they also have programs to test chemicals for
25 endocrine disruption and to retest, actually, a lot of

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1 high production volume chemicals using thousands of
2 animals, and we've been trying to get them to use
3 validated alternative tests for those programs.

4 We have also requested admission to the
5 OECD joint meeting, and at the OECD we work under
6 confidentiality, such as other observers.

7 We've been working with the OECD, which if
8 you are aware is an economic alliance of 30
9 industrialized nations, including the same people
10 again as the ICH, and we've had a lot of very positive
11 feedback and developed very good relationships there.

12 Just to give you a little bit more
13 background more specifically into things that we've
14 done at the OECD, we've requested NGO status at the
15 OECD in April of 2001, and then we started interacting
16 by submitting comments on their draft guidelines,
17 participating in meetings, and it was about a year
18 later that we were formally recognized as invited
19 experts.

20 And then since then, they've kept us very
21 busy submitting technical comments on draft
22 guidelines, helping to draft guidelines for tests that
23 either replace or reduce animal use, and participating
24 in different meetings all over the world.

25 So, we have also become interested in the

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1 ICH, in terms of, you know, it being another
2 international harmonization body that does have
3 guidelines that pertain to animal testing. What we
4 would like is to participate in the ICH, become
5 involved, and we are looking for, you know, a
6 relatively limited interaction where we want to
7 participate in anything that relates to animal testing
8 issues, participating in steering committee meetings
9 during the portions when safety or other animal
10 testing guidelines are being discussed at Step 2 and
11 Step 4 points, more importantly even perhaps, attend
12 the Expert Working Group meetings for guidelines
13 containing animal tests, and have the opportunity to,
14 perhaps, present to them opportunities for refinement
15 and replacement and that kind of thing.

16 So, our main goal would be to support the
17 incorporation of what they call the three Rs, of
18 reduction, refinement and replacement of animal
19 testing into ICH guidelines. We would be in a good
20 position to bring validated models to light, and also
21 to help get access to the data that would be required
22 for consensus at the ICH.

23 We work with a lot of other international
24 and national regulatory bodies, OECD, as well as
25 ECCVAM and ICCVAM and other groups, who are validating

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1 these models, so we are very aware of what's the
2 latest state of the art out there and who has the
3 data, and also with procedures for validating and that
4 kind of thing that ICH has not really kind of gotten
5 involved with yet.

6 And, I apologize that things are running
7 off the page, but, you know, and then we would, you
8 know, we would kind of instigate all this, and then
9 also give our technical comments.

10 We realize - well, when it comes to the
11 ICH there are some precedents for, you know, non-
12 regulator - sorry, there are some precedents for non-
13 ICH members to be involved, such as OTC and generics
14 industry involvement, regulators from other regions.
15 We realize that it has not happened that non-industry,
16 non-regulators participants have been involved, but we
17 are an international group, a fully international
18 group, and so we do want involvement on the
19 international level, and we do think that it's very
20 timely that we would become involved for reasons that
21 I will be explaining to you in a little bit, and just,
22 you know, this issue is on the agenda for the May
23 meeting in Brussels.

24 So, the ICH's mission is actually very
25 consistent with some of - you know, there's overlap

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1 with our mission. The ICH is interested in reducing
2 redundancy, which it already has done and which has
3 resulted in less animal testing for, you know,
4 duplicative pre-clinical submissions, and, you know,
5 we think this is a very good result. But, the ICH is
6 also interested in transitioning to technically
7 improved testing procedures, especially ICH4 and
8 comments on the future of the ICH said that the focus
9 should shift from the redundancy to harmonizing new
10 technologies, incorporating scientific progress, and
11 preventing disharmony, so in this way a lot of the
12 alternatives that are out there, the animal tests are
13 the old ways of doing things, the alternatives are
14 usually high-tech, hopefully, human-based methods, and
15 that transition does need to happen. ICH could be a
16 part of that.

17 When you look at the ICH guidelines, there
18 are a few examples of in vitro tests being
19 incorporated or an animal test being deleted, but it
20 hasn't gone a long way towards the three Rs that I was
21 talking about. There are a lot of opportunities for
22 improving them. Most of the guidelines, the safety
23 guidelines, are based on the old animal tests, and
24 improving them is an opportunity to improve the
25 science behind drug development. For example, the

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1 carcinogenicity studies that are done, our rodent two-
2 year bioassays that call for extremely high exposure
3 level that result in over prediction of
4 carcinogenicity, this assay is, in general, I was the
5 Tox meeting earlier this year, and in general it's
6 just almost - it's very discounted, but it's still the
7 tests that are on the books.

8 Similarly, when it comes to reproductive
9 studies, actually, the ICH guideline itself says that
10 histopathological examination of reproduction organs
11 and the repeated-dose tox tests are more sensitive
12 than male fertility studies, and so when things like
13 this are redundant it's an opportunity to delete one
14 of the tests, the male fertility study.

15 When it comes to the safety in the pre-
16 clinical tests, more of the human-based, early human
17 clinical trials, such as microdosing and experimental
18 guidelines are needed, and the FDA just came out with
19 an exploratory IND studies guideline, this type of
20 thing should also be incorporated at the ICH, and just
21 more guidelines addressing some of the other
22 alternatives, such as alternatives to phototoxicity
23 and pyrogenicity that have already been developed
24 could be incorporated to let companies know that they
25 can definitely do these tests and that they would be

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1 accepted.

2 So, I just wanted to move to animal
3 testing and why we do believe that moving away from
4 animal testing will better protect human health. When
5 you look at animal tests, especially safety tests,
6 they are mostly decades-old tests that could not
7 necessarily be validated today. Usually, I don't
8 think they would be. They are not reliably predictive
9 of human responses, especially for any given species.
10 You do the tests, and then you see whether it
11 corresponds to the human response, and you don't
12 really understand why or why not.

13 The species variation is a problem, the
14 fact that a lot of the disease models that we have are
15 sometimes very poor, and we study these diseases
16 thinking that we are studying the human disease, when
17 we are not.

18 The confounding effects of the fact that
19 these animals are held in laboratory cages, fed lab
20 chow, they are - they have distress or stress every
21 time they are handled, that affects their physiology,
22 and so that makes these animal tests not as
23 predictive.

24 And lastly, most of these animal tests
25 have problems with repeatability or reproducibility,

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1 they are just not very consistent from lab to lab and
2 from day to day. Furthermore, they are expensive,
3 they are time consuming, and they are not amenable to
4 high throughput, they are really an old way of doing
5 things, and pharmaceutical companies need to
6 transition to, you know, to the new way, which they
7 are, I think they are doing, but the regulations
8 aren't really keeping up, so then they have to go back
9 and do the old animal tests.

10 And so, basically, the overall picture is
11 that there's, you know, a paradigm that was the old
12 paradigm of using animals as surrogates for humans,
13 trying to do all the research in the animals, figure
14 out the disease in animals, cure the animals, and then
15 see whether that applies to the humans, and it's just
16 not as effective as studying humans directly, which we
17 now have the technology to do, and that transition
18 really needs to happen.

19 And, I just wanted to quickly read to you
20 a quick quote from the Boston Globes, as I was reading
21 on the plane on the way here yesterday, there's a
22 quote from a biologist at Tufts that said, "Most
23 cancers don't look like human tumors. They don't
24 behave like the actual breast cancer. We can cure
25 most breast cancers, but that can't always translate

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1 to the clinic," and it's just I feel like more and
2 more I kind of hear this being said, people are
3 recognizing that an animal is not a human, and it's
4 not the best way to go about these things.

5 The FDA put out a Critical Path document
6 that actually echos a lot of the sentiments that I
7 just said. When it comes to assessing safety, the
8 document said that animal toxicology is laborious,
9 time consuming, requires large quantities of product,
10 and may fail to predict the specific safety problem
11 that ultimately halts development.

12 When it comes to demonstrating utility,
13 they said currently available animal models have
14 limited predictive value in many disease states. I
15 think that the FDA recognizes this. I've gotten a lot
16 of good feedback from the FDA that they do see
17 transitioning away from animal tests to more modern
18 technologies that are usually not animal tests, to be
19 a critical part of the Critical Path Initiative, which
20 is all about modernizing research technologies and
21 improving pre-clinical technologies so that we don't
22 have as many failures in the clinic that we've been
23 having, which are, of course, more costly for drug
24 companies.

25 The problem with using these models is

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1 that it results in, for example, when an animal test
2 predicts that a drug that would have been good for
3 humans, if it's toxic in animals we might never get to
4 use that drug, we have missed opportunities, for
5 example, penicillin, you may be aware that penicillin
6 is toxic to guinea pigs, has no effect whatsoever on
7 rabbits, because it is excreted too quickly, and, of
8 course, is one of the biggest booms to human medicine.
9 So, this is an example of, you know, there's many
10 other drugs out there that we might be missing out on
11 today.

12 And, in terms of missed problems, what it
13 says down there is, animal studies found that COX-2
14 inhibitors, such as Vioxx, were actually protective of
15 cardiovascular health, so when an animal tests, also
16 just because of species differences misses a problem
17 in the pre-clinical stage, we go further and further
18 without understanding the true risks of that drug, and
19 if it fails later, if it fails in clinical trials it's
20 more expensive, if it fails after that it's a scandal.
21 We need better pre-clinical systems to be able to
22 catch these things early.

23 And, actually, at a Science Board meeting,
24 the FDA Science Board meeting last week, and Janet
25 Woodcock, who runs the Critical Path Initiative, gave

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1 another great example that I want to share. She said
2 that 15 years ago problems with metabolism were the
3 number one cause of late stage clinical trial
4 failures, and what switched from 15 years ago to now
5 is that they used to use animal models to try to
6 detect problems with metabolism, and animals are
7 especially divergent in metabolism when it comes to
8 drug metabolism away from humans.

9 And so, what they had to switch to doing
10 is looking at human enzyme, specifically, human P450
11 enzymes, and using human cell lines, and looking at
12 that they have been able to almost prevent these kinds
13 of failures based on metabolism.

14 So, what is the alternative if we move
15 away from this animal testing? There's human-based
16 research, you can do target discovery, and actually
17 some drug companies have told us that almost all of
18 their target discovery now is genomics and proteomics
19 profiling of human tissues, looking at disease versus
20 normal, early versus late stage, and you can work out
21 a map, you know, of what's actually going on in a
22 human disease, and pick your targets that way, they
23 are much more likely to be relevant, instead of
24 studying an animal disease model that, you know, where
25 the target that you come up with may not relate to

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1 humans.

2 And, of course, there's epidemiology, that
3 type of thing.

4 When it comes to the safety and efficacy
5 testing, that's a little bit more of the regulatory
6 side, there's a lot of in vitro technologies that are
7 currently developed and that could be developed,
8 especially human-based tissue cultures, physiochemical
9 systems, and, of course, as we are talking about going
10 more quickly into humans in terms of microdosing and
11 experimental medicine trials, which is enabled by some
12 of the technologies such as the imaging technologies,
13 genocis and proteomics where you can have biomarkers,
14 and study humans directly without compromising their
15 safety.

16 And lastly, of course, predictive
17 computer-based methods, computer modeling, you know,
18 based on databases and things like that, and -
19 experimentation, that's really kind of the way we need
20 to move, especially because we need to move towards
21 pharmacogenomics, that's what everyone keeps saying,
22 you know, targeted therapies, understanding if there
23 are certain populations that are more at risk or would
24 more benefit from different drugs, and we can only do
25 that if we study humans. If we are studying - I just

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1 find it interesting that with pharmacogenomics we are
2 saying that the differences between individual humans
3 could be responsible for whether the drug would be
4 effective or risky to them, and then we are trying to
5 extrapolate between species, which is a much larger
6 gap. So, we just can't do that if we need to get
7 towards the personalized medicine and the higher level
8 of medicine that we are going to have in the future.

9 When you look at these alternatives, these
10 non-animal alternatives, the advantages are numerous.
11 Basically, I think across the board they are better.
12 They are faster, they are quicker, they are more
13 consistent. They can be high throughput. They can be
14 species relevant. Across the board, there's only
15 advantages. Pharmaceutical companies would benefit
16 greatly, I think, from using this, and I think most of
17 them do see that.

18 All these reasons are the drivers for the
19 development of in vitro technologies, and the
20 technologies have been getting there, but the
21 regulations, as I said, have not kept up.

22 The only disadvantage of these
23 alternatives is that they are not a whole animal, that
24 seems to be the main thing that people say, well,
25 that's just not a whole animal, you need to throw it

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1 into a whole animal and see, but I would argue that if
2 you use a whole animal and it's not a human, you don't
3 really understand what you've gotten out, it's kind of
4 a black box exercise. What you really need to get to
5 is a mechanistic understanding of where your drug is
6 interacting, what are the potential problems. Once we
7 get there, once you have the mechanisms, you can do
8 something fully with a battery of in vitro tests,
9 understand what you are doing, and not necessarily
10 need that kind of whole animal, you know, kind of
11 check.

12 So, I just wanted to conclude by talking
13 about going back in time the animal testing issues
14 back into the harmonization, animal testing is
15 actually about to become a very big issue for
16 harmonization, the reason is, well, one reason is that
17 the EU has legislation that requires the use of non-
18 animal tests whenever validated alternatives are
19 available. The corresponding animal test will not be
20 accepted. That means that if a company, you know, has
21 to do a certain test for Europe it will be the non-
22 animal test, if the U.S. and Japan do not accept that
23 test they are going to end up doing duplicative
24 testing of different types for the same endpoints.

25 There's also the Seventh Amendment to the

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1 Cosmetics Directive, I'm not sure if you've heard of
2 that, but the EU is banning animal testing of all
3 cosmetics ingredients, and that's phasing in between
4 2009 and 2013. Because of that, the cosmetics
5 industry has been rapidly developing many new non-
6 animal tests, and they are just - they are being
7 turned out for a lot of the same endpoints as affects
8 drug testing, and because they are going to be
9 available, because of the previous point that I made,
10 pharmaceutical companies will be having to use them in
11 the EU. So, basically, this creates a major
12 harmonization issue for every industry that conducts
13 animal testing, and it needs to be dealt with very
14 soon. The EU is leading the way, but if Japan and the
15 U.S. don't keep up it's going to be a big
16 harmonization issue.

17 So, basically, this is what we think the
18 ICH - why the ICH should be working on these issues,
19 and why we think that we would be able to help them in
20 getting there quicker.

21 Thank you.

22 ASSOCIATE DIRECTOR MOLZON: Thank you very
23 much.

24 Does anyone have any questions?

25 One thing I would request is, we are going

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1 to be posting your slides on the web with the rest of
2 the presentation, if you could adjust it so the bottom
3 line moves back up so we can make sure the public can
4 read it.

5 I'd like to point out that we do have two
6 safety topics out for comment right now, it's a Step
7 2 process. One is S7B, it's the non-clinical
8 evaluation of the potential for delayed ventricular
9 repolarization, it's part of the QT prolongation work
10 in E14, and along with S8, which is immunotoxicology
11 studies, so you are welcome to view those documents
12 and send in comments.

13 And, we will, you know, of course, take
14 your requests along with the other requests that we've
15 gotten at this meeting, along with the transcript, and
16 take that to ICH, because this is - these meetings are
17 to involve stakeholders at the regional level, and
18 then to take information into the ICH process.

19 So, thank you for your presentation.

20 MS. DHARUVAKUMAR: Thank you.

21 ASSOCIATE DIRECTOR MOLZON: So now, let's
22 see, is Barbara here? Okay. We are remarkably on
23 time.

24 We've heard a lot about Health Level 7
25 today, and what I'd ask is that someone from the HL7

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1 group to, basically, give us a presentation on the
2 background and we can have a thorough discussion of
3 what this actually is, because this very well could be
4 an important way for regulatory authorities to
5 interact with the health care community.

6 At the Pharmacogenomics meeting that DIA
7 offered last week, Doctor Woodcock opened the session
8 and pointed out that our labeling, for example, is the
9 - that is the foundation for the health care system,
10 really, that's how we get our work into the health
11 care system. So, HL7 may be a way to take our efforts
12 even further.

13 Did you want to make - Joan, I'm sorry.

14 MS. BLAIR: Joan Blair, Center for
15 Biologics. I just wanted to clarify one of my
16 responses in the morning. There was a question on
17 devices, and as I was speaking during the break with
18 someone, and it was raised in further detail, I
19 realized that I had crossed some wires. In fact, the
20 management board of MedDRA was considering expanding
21 their terminology into the device world. There is a
22 Device Harmonization Initiative, the management board
23 was directed to engage with the GHTF to determine
24 whether, in fact, that would be an encroachment or an
25 overlap, or duplication of effort.

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1 Communications have been going on between
2 the two initiatives, and they will be reporting back,
3 the management board will be reporting back to the
4 Steering Committee this coming meeting on what they
5 learned in terms of taking and addressing device
6 terminology in MedDRA, and that was related to there
7 was a combination, reference combination product, that
8 was the driver behind the interest of industry in
9 having device terms brought to MedDRA because of
10 combination products.

11 ASSOCIATE DIRECTOR MOLZON: Okay, thank
12 you.

13 We, basically, have two presentations
14 left, one from HL7 and one from CDISC, and at the end
15 we will have some time, if anyone has questions, or
16 things that they want clarification on, we'll have
17 time at the end of the afternoon to get all that into
18 the record. So, you know, just write your questions
19 down, and we can take care of them later.

20 Okay, Barbara, if you could introduce
21 yourself?

22 MS. TARDIFF: Yes, yes, thank you very much
23 for this opportunity to be here.

24 My name is Barbara Tardiff, and as Randy
25 mentioned this morning, I am one of the Co-Chairs of

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1 the HL7 Regulated Clinical Research Information
2 Management Technical Committee.

3 I also, in my day job, I oversee clinical
4 and regulatory information services at Merck.

5 I'm coming to this group and putting
6 forward this proposal really from an understanding
7 that stems from both of those perspectives. One is a
8 recognition of the issues that are faced by
9 pharmaceutical companies in implementing and
10 maintaining information systems in support of drug
11 development, and secondly, based on my familiarity
12 with the standards development process, and what it
13 really takes to develop robust standards that are
14 truly interoperable.

15 I'm not going to tell you everything about
16 HL7 in this forum, that would, obviously, take a great
17 deal of time, and I have a pretty focused message that
18 I wanted to get out there, recognizing that if there
19 was - where there was more detail we could drill in,
20 or I could respond to questions.

21 But, first, really, going to, to put
22 forward a proposal and cover the key elements of what
23 that proposal would be, to secondly go into why the
24 proposal is being surfaced at this time, what are the
25 issues that are out there, give you a little bit of

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1 background on HL7, and then finally discuss or
2 highlight some of the benefits that could be
3 recognized if ICH chose to move forward and act on the
4 proposal.

5 So, first, really, what's proposed, that
6 ICH use the Health Level 7 methodology and framework
7 to create and maintain technical specifications for
8 data interchange messages and structured documents.
9 And, what this really would mean is that requirements,
10 reports and submissions would be provided based on ICH
11 guidances, would be provided to the appropriate HL7
12 technical committee. In most cases, this would be the
13 Regulated Clinical Research Information Management
14 Technical Committee.

15 And, these requirements will be provided
16 as they are as guidances for reports, or documents, or
17 submissions, will be provided as the guidances are
18 defined.

19 Technical experts from the ICH community,
20 including the M2 Expert Working Group, would
21 participate in HL7 working group meetings, and in the
22 development of the technical specification. And,
23 similarly, HL7 RCRIM representatives would also
24 participate as observers in the M2 Expert Working
25 Group.

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1 So, I'd next kind of like to say, why is
2 this proposal surfacing, and surfacing at this time?
3 And, I think it's helpful, actually, to back up to the
4 root of why there's an interest in standards in the
5 first place. And, I'm actually going to echo some
6 messages that were articulated this morning. It's
7 really, the end game for all of us is an improved
8 availability of effective medical therapy, so reduced
9 time to market, increased patient safety, reduced
10 cost.

11 And, in order to get to this goal we focus
12 on the areas where a lot of resources get consumed in
13 non-value-added activity. And, that is - and one of
14 these areas is the preparing and processing of data
15 for use associated when it gets transferred from one
16 entity to another, or one system to another.

17 And so, it's recognized that the use of
18 standards to enable the efficient transfer in a way -
19 in a reliable, secure way, in a manner that specifies
20 the data that's being transferred, i.e., it can be
21 automated machine process, it is an important tactic
22 to achieve a strategy of more efficient transfers of
23 data interchanges across the drug development life
24 cycle.

25 So, the reality is that drug development

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1 is an exceedingly complex business - process in
2 business systems, and that many of the processes, if
3 we look from beginning to end, cross organizational
4 and functional boundaries, and that there are lots of
5 stakeholders in these data, and that extend beyond the
6 regulatory authorities and the pharmaceutical
7 industry. There are lots of - and you are going to
8 hear, I think, more about some of those stakeholders
9 in the afternoon, and that information exchanges play
10 very important roles in maintaining relationships
11 beyond the relationship between pharmaceutical
12 sponsors and the regulatory authorities.

13 And so, it's not as simple as the exchange
14 between a pharmaceutical sponsor and the regulatory
15 authority, that's only one component of this whole
16 environment, this whole landscape out there, of
17 stakeholders that share and are vested in the
18 information that is ultimately incorporated into
19 submissions and used to support the prescribing of a
20 therapeutic.

21 So, there's already a bit of a problem.
22 The messages and structure documents that are created
23 by ICH are typically not in alignment with established
24 regional or national standards that may go through a
25 different process. And, this leads to several

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1 limitations. First of all, because they are developed
2 in isolation, they are different from those
3 interchange standards that are used by other
4 organizations, and that may be actually widely
5 supported by technology used across the clinical
6 research life science and health care industry.
7 Having a very focused set of use cases reduces the
8 market that technologies are actually available in, so
9 there is a larger set of technologies, and software,
10 and tools out there that serve standards that are
11 widely used.

12 That ICH organizations, including the
13 regulatory authorities such as the FDA and
14 pharmaceutical companies have limited ability to use
15 and reuse electronic data acquired or maintained or
16 received by computer systems, other than those that
17 are specifically developed to deliver ICH
18 requirements.

19 And, the data that is in messages and
20 structure documents developed to support one guideline
21 may not be easily reused in a report or submission
22 defined by a different guideline. And, this is the
23 issue that Randy and others alluded to this morning
24 around the relationship between the structured data
25 that's in the structured product label and data that's

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1 in the electronic CTD.

2 So, the other part of this problem is that
3 ICH really is currently limited to a relatively small
4 pool of resources to advance its mission and vision,
5 that participation in the creation of the technical
6 specifications is limited to representatives from the
7 pharmaceutical organizations and regulators in the
8 United States, Europe and Japan, and this means that
9 ICH doesn't have the advantage of a broad and relevant
10 set of expertise, and also must pull from a very
11 limited resource pool.

12 And, there are some very important
13 expertises and stakeholders that are not included in
14 this process. Specifically, health care and solution
15 providers, who often have a great deal of experience
16 in creating and implementing technical standards.

17 In addition, outside technical experts who
18 might be able to bring their talents to bear, data
19 modelers, architects, system analysts, also do not
20 participate in the process, unless they are
21 specifically invited.

22 And, even for participant organizations,
23 such as the FDA, representation may be limited to a
24 subset of key stakeholders.

25 There is - divergence is already having

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1 its consequences, that under the current model
2 regulatory authorities and pharmaceutical companies
3 that receive and transmit messages and structure
4 documents based on both HL7 and ICH standards, for
5 example, the individual case safety report, where it
6 may be received based upon the ICH E2B, and may
7 receive or have to generate based upon the HL7 ICSR to
8 cover devices and vaccines, must invest in systems
9 that are able to accommodate and support translation
10 between the format.

11 And, this is a redundancy and duplication
12 of resources and greater business value would be
13 gained if the required resources could actually be
14 invested in more value-added activities.

15 The fact that there's a limited market
16 does slow the development and availability of new and
17 additional technologies, and the part of the solution
18 is standardizing to a common reference information
19 model, and incorporating the relationship between data
20 components across a domain of interest, and that would
21 eliminate the need for much of this activity in
22 transferring standards from one format to another.

23 So, the bottom line is that ICH really
24 could benefit by taking advantage of what is a very
25 important resource in HL7, and look at HL7 as a

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1 resource instead of as a competitive standards
2 development organization, that this HL7 is
3 specifically dedicated to the definition of messages,
4 documents, structures and terminology, so not the
5 requirements around the information exchanges, but
6 really the generation of a technical specification for
7 those messages, and to support not just the collection
8 storage and distribution, integration and analysis of
9 research and health care information, and that in
10 addition the HL7 standards are developed according to
11 a well-defined accredited methodology and founded in
12 that sort of common information model that I mentioned
13 earlier that's referenced by all the areas of
14 interest.

15 And, what this does is, it ensures that
16 the standards are interoperable, and that's a word
17 that came up a couple times in the presentations this
18 morning. And, what that means is the data that's
19 received by one computer's system for one purpose can
20 be exchanged and used by any other computer system
21 that's compliant with that standard.

22 I just want to give a little bit of brief
23 background on what HL7 is, and I won't go into too
24 much detail because some of this has already been
25 surfaced in earlier presentations, but I kind of

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1 wanted to pull it all together in one place. This is
2 not a new - Health Level 7, or HL7, is not a new
3 organization at all, it was founded in 1987 as an not-
4 for-profit organization, and the initial scope really
5 was focused on the health care setting. Its current
6 scope involves both research and health care, and
7 really fairly broadly life sciences.

8 It uses, as I mentioned earlier, a defined
9 formal methodology, that's an ANSI-accredited
10 methodology to develop and approve standards, and what
11 this methodology is all about is a set of operating
12 procedures that are designed to ensure consensus,
13 openness, and balance of interest. And, having
14 consensus, openness and balance of interest assures
15 you of getting standards that are robust,
16 interoperable and can be widely used across many
17 different systems and settings.

18 It is open to all interested parties, and
19 thus it is able to tap into extensive expertise and
20 resources.

21 Over the last number of years, HL7 has
22 established formal relationships with a number of
23 other standard-setting organizations, such as CDISC,
24 DICOM, and what these organizations do is that they
25 use HL7 processes for creating and maintaining the

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1 messages. They still have an identity in and of
2 themselves for defining the requirements and really
3 mapping out the domain, but they use HL7 for what HL7
4 is really good at, is creating interoperable messages,
5 structured document standards.

6 The way that HL7 is organized is in terms
7 of technical committees and special interest groups,
8 and it's the technical committees that are really
9 responsible for - directly responsible for generating
10 the content of standards, and they sponsor standards,
11 they sponsor the validating of standards. In
12 addition, there are also special interest groups, and
13 special interest groups are formed around areas which
14 may not - areas for exploration that may not be yet
15 involved in creating and developing specific
16 standards, but there is an area where people want to
17 form a community and want to work together to define
18 the standards and messages that might be used in that.

19 The Regulated Clinical Information
20 Management Technical Committee, specifically focuses
21 on standards needed to improve or enhance information
22 management during research and regulatory evaluation
23 of the safety and efficacy of therapeutic products or
24 procedures. There are two special interest groups
25 that RCRIM has a relationship with, the Patient Safety

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1 Special Interest Group is actually sponsored by RCRIM
2 and is actually the author of the individual case
3 safety report and other reports used for reporting to
4 a central authority.

5 In addition, RCRIM has a relationship with
6 the Clinical Genomics Special Interest Group and is
7 specifically working with that special interest group
8 around messages related to pharmacogenomics.

9 The participation within the technical
10 committee includes not just international regulatory
11 agencies and other government agencies, but PhRMA,
12 CDISC, academic research organizations, vendors and
13 other service providers who operate in this industry.
14 Specifically, what the products of this technical
15 committee are, are messages, document structures and
16 terminology, all related to the systems and processes
17 used in managing data in drug development.

18 And, all of these message and standards
19 not only have to conform to the HL7 reference
20 information model, but most importantly they actually
21 have to conform to the business requirements. That's
22 really the starting place. So, using HL7 doesn't mean
23 that HL7 defines what the requirements of the business
24 are, rather it means that HL7 uses those as raw
25 materials, you know, clarifies them where they are

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1 needed, and then turns those in to technical
2 specifications that can execute those business
3 requirements.

4 So, I just want to summarize with a couple
5 of the high-level benefits of the ICH taking advantage
6 of HL7 as a forum for developing standards. I think
7 the first, and, perhaps, most important is that ICH is
8 able to focus on its mission in advancing human
9 pharmaceutical drug products, and takes better
10 advantage of - and take advantage of HL7 resources and
11 expertise, specifically, for the development of
12 technical specifications, while being assured that the
13 regulatory data standards that are used to support HL7
14 processes will be harmonized with health care
15 standards and standards used in other settings.

16 Using HL7 for this purpose doesn't
17 interfere with the autonomy of ICH and the ICH process
18 for requirements gathering and specification of
19 guidances. And ICH, in addition to being able to
20 focus on its core business, actually also gains
21 standards that both meet their requirements and are
22 robust enough to be widely supported in the industry,
23 and that HL7 is an international organization with
24 extensive international participation and membership,
25 that would get technical standards that would be based

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1 on a collective input of industry experts.

2 The fact that, although as Kris mentioned
3 this morning, by having a large number of stakeholders
4 involved it does add complexity, but the other thing
5 that happens by having a large number of stakeholders
6 is it becomes very difficult for one interest or one
7 party to dominate, which really does ensure that you
8 have standards that ultimately are more robust and
9 more flexible.

10 And, the balloting process within HL7
11 specifically requires, although no one stakeholder can
12 dominate, the balloting process does require the
13 technical committee to address and resolve all
14 negative comments and ballots. So, even though one
15 entity cannot dominate, if there are significant
16 issues with a proposed standard those issues have to
17 be addressed before the standard gets finalized.

18 So, I'd like to just go back to - I don't
19 have the slide here, go back to the actions requested
20 here or proposed, is really the bottom line is that
21 this is - ICH really does need to recognize what's
22 going on in the industry, that there's a need for
23 interoperability, and that HL7 has become somewhat of
24 a clearinghouse for a lot of the standards efforts in
25 life sciences, and that at a minimum there really is

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1 a need to initiate a dialog or a brainstorming
2 session, that ICH needs to be informed about these
3 related activities, and needs to be positioned so that
4 it can act and respond from a position of leadership,
5 because these standards are going to continue to
6 develop, I think as you'll hear in subsequent
7 presentations, there's a real drive to have
8 interoperable health care information that can be
9 repurposed across multiple systems and organizations,
10 and, you know, it's in ICH's interest to be informed
11 and be aware, to be a participant in those efforts.

12 Thank you.

13 ASSOCIATE DIRECTOR MOLZON: Thank you,
14 Barbara.

15 Are there any questions?

16 Before Helle gets up there, I've had a
17 question that I wondered about for a long time. What
18 are HL1 through 6?

19 MS. TARDIFF: Let's see, actually, I always
20 have to keep looking this up, because it refers to
21 different levels of, sort of like 1 is like the base
22 machine level, and 7 is at the application level or
23 something. I'll find it and get an answer to you.

24 ASSOCIATE DIRECTOR MOLZON: No, because,
25 you know -

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1 MS. TARDIFF: There isn't a Health Level 1,
2 2, 3, 4, 5, 6, but the Level 7 really refers to where
3 it is in terms of information management.

4 ASSOCIATE DIRECTOR MOLZON: - okay,
5 because I think, you know, part of understanding
6 different approaches is to have a thorough
7 understanding.

8 MS. TARDIFF: Yes, and I should know that,
9 and I've known it, but it's one of those things -

10 ASSOCIATE DIRECTOR MOLZON: Okay, Helle,
11 did you have a question? Go to the mic.

12 MS. GAWRYLEWSKI: Perhaps you can say a few
13 words about the messaging concept, because that's
14 something that it took me a while to understand about
15 that, because messaging means something different in
16 other areas, and it might not be clear, you know, as
17 a concept.

18 And, the other thing is that, you said
19 something about the no one stakeholder can dominate,
20 but I think that maybe we need to consider that it
21 takes a lot of resources and support to be
22 participating in HL7, and the people who are
23 participating are, you know, large companies who have
24 the staff and the money to spare, and vendors who have
25 an interest, regulators who have an interest, but I'm

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1 just concerned about the concept that HL7 has more
2 participation than ICH. I really kind of take
3 objection to that, because it takes a lot of effort
4 and support to participate in HL7, and it's not an
5 easy thing to do.

6 And, I think that maybe if we can make it
7 more widespread that it might be more effective in
8 some smaller companies, you know, smaller groups.

9 MS. TARDIFF: Okay, good question. Let me
10 respond to the first one around the messages.

11 First of all, what HL7 concerns itself
12 with is data interchanges, so data that merely is
13 collected and stored with a system is outside of the
14 scope of HL7. HL7 is concerned with when information
15 goes from one system to another or one organization to
16 another, those are the use cases.

17 And so, that usually - that transfer of
18 information is what is called a message, and the way
19 that most of the HL7 messages are constructed is that
20 they are actually are carriers of the content, and
21 they are transitory in the sense that once the content
22 gets processed and used the message, you know, can get
23 saved, but doesn't need to get saved.

24 Now, that works really well for structured
25 data, where you are going to process and put it in its

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1 place. But, there are some data that you actually
2 want to preserve in context, which is what we usually
3 think of as a document, which is the relationship of
4 different data elements to each other.

5 So, HL7 also has a structured document
6 standard, which is what SPL is, which actually does
7 preserve all of that data in the context of
8 interrelated data.

9 Now, still in order to send that document
10 you would incorporate it into a message. You would
11 put a wrapper around it that would actually tell you
12 how to process that document, but store it as an
13 object instead of as individual data elements.

14 Does that answer your question? So,
15 that's really what - that's what messages means in HL7
16 terms.

17 Now, the second question related to the
18 participation, and there's no question that standards
19 development is a time-consuming activity, and it is
20 also not - it also is very true that those who have a
21 stake in it are those who actually are willing to
22 invest their time. And, that does - but that isn't
23 necessarily limited just to big companies, because
24 certainly in the vendor arena there are a lot of small
25 vendors who actually have a really big stake in the

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1 standards, because they aren't Oracle, and they are
2 not IBM, or they are not Microsoft, and they can't go
3 out and get into a market by dominating it, they have
4 to have standards in order to get their foot in the
5 door.

6 So, I don't think it's quite - now, it's
7 a little bit different in the PhRMA industry, where I
8 think a small biotech probably doesn't - has a stake
9 in their mean standards, but probably doesn't have as
10 much stake in what those standards, you know, look
11 like.

12 And so, yes, it's true that bigger
13 companies have more resources, but I can say that
14 there's also a lot of small companies who seek
15 standards as being important for their success who
16 invest in it as well.

17 What I do think is, perhaps, also true,
18 though, is that the breadth of expertises that's
19 involved in HL7 is broader than ICH, in that it does
20 have, not just representatives from pharmaceutical
21 companies and regulatory authorities, but also has
22 vendors, has service providers, has academic research
23 organizations, has other government agencies like the
24 CDC and the Veterans Administration, and other
25 government agencies internationally. So, it is a

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1 broader set of perspectives. It's not the whole
2 world, but I think it is broader.

3 ASSOCIATE DIRECTOR MOLZON: Any other
4 questions, comments?

5 Janet.

6 MS. JENKINS-SHOWALTER: Janet Jenkins-
7 Showalter from Roche.

8 My question is, taking the next step and
9 assuming maybe that there would be ICH participation,
10 I'm assuming you have to pay dues to be a member of
11 the HL7, so how would you envision that working for
12 ICH when you are talking about every member of the
13 Expert Working Group being in, would every single
14 company that has an expert then have to pay dues?
15 Would ICH pay the dues? Would PhRMA pay the dues?

16 MS. TARDIFF: Okay.

17 MS. JENKINS-SHOWALTER: Financial
18 arrangements, I think I'd like to know.

19 MS. TARDIFF: All right, this is a good
20 question. There's a number of ways it could be worked
21 out, and let me actually first of all make - you don't
22 actually have to be a member of HL7 to participate in
23 working group activities, and to vote and to actually
24 come to working groups, and to vote at those working
25 groups, to participate in teleconferences.

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1 You do have to be a member in order to
2 participate in the formal balloting that takes place.
3 Now, but one can contribute, one can, you know, give
4 a lot of ideas, give a lot of feedback, actually be
5 very actively involved and very responsible without
6 actually ever being a member.

7 There is a cost, you know, really a modest
8 cost of attending a working group meeting, it's really
9 to cover expenses, the meal, you know, food and use of
10 the rooms and things like that. It's, you know,
11 roughly \$100 a day or something.

12 Now, there is - there are several
13 categories of membership, there are individual
14 memberships, and there's organizational memberships,
15 and then there is a benefactor status that gives you,
16 and you have different numbers of votes depending on
17 the category of membership. The cost of the
18 membership is scaled to the sort of size and revenue
19 status of the organization, so there's some adjustment
20 based upon whether or not it's a not-for-profit or a
21 for-profit organization.

22 So, organizations like CDISC actually have
23 an organizational membership, and they FDA has an
24 organizational membership, so they are members as
25 organizations and they can have votes as

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1 organizations.

2 Now, one of ANSI's rules, though, is that
3 organizations - members - votes have to be cast by
4 individuals, they can't be cast as a block. So, even
5 if Merck had an organizational membership and had ten
6 votes, I couldn't go and cast ten votes, there has to
7 be ten individuals that cast those votes. You can
8 discuss about how you are going to vote, but they have
9 to be cast and assigned to individuals. So, ICH could
10 have an organizational membership and assign its votes
11 to particular individuals who would vote.

12 Alternatively, those individuals could
13 also be individual members, or they could be members
14 through their - you know, through their organization,
15 through their sponsoring pharmaceutical company.

16 In addition, one of the things that has
17 been established between CDISC and HL7 is this
18 particular joint arrangement, such that if you are a
19 member of CDISC you get a reduction in the cost of
20 your HL7 membership and vice versa, so there's, you
21 know, an encouraging of collaboration.

22 So, there's a number of strategies that
23 could be worked out to give individual participants in
24 ICH a voice, as well as ICH as a whole voice.

25 ASSOCIATE DIRECTOR MOLZON: Any other

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1 questions?

2 Did you put a web site in your -

3 MS. TARDIFF: I didn't put a web site in,
4 I'm sorry, the web site, though, is pretty simple,
5 it's www.HL7.org.

6 ASSOCIATE DIRECTOR MOLZON: Okay, thank you
7 very much.

8 Our final presentations will have to do
9 with CDISC, the Clinical Data Interchange Standards
10 Consortium, and I know that Art Gertel and Steve
11 Raymond are here, but is Meredith Nahm or Cara
12 Willoughby? Cara is not presenting, so you are
13 Meredith, okay, I just wanted to make sure everyone
14 was here.

15 Would people like to take a ten-minute
16 break, because I think - do we have to make sure
17 everyone is presentations are in the - okay, we'll
18 take a ten-minute break, thank you.

19 (Whereupon, at 2:36 p.m., a recess until
20 2:59 p.m.)

21 ASSOCIATE DIRECTOR MOLZON: If we could get
22 started, please. As I mentioned before the break, the
23 rest of the afternoon is going to be spent learning
24 about Clinical Data Interchange Standards Consortium,
25 or CDISC, and Art Gertel is our first speaker. He's

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1 going to be discussing glossary and protocol
2 representation standards.

3 MR. GERTEL: Everybody is all juiced up on
4 your - maybe I shouldn't use that term, motivated from
5 your caffeine and your sugar.

6 I'd like to first say that I'm here
7 representing a whole consortium of people who are
8 involved in the protocol representation and glossary
9 groups, many of whom are here today, so if you are
10 going to throw objects throw them over there as well
11 as over here. I'm going to be talking about both the
12 structure protocol model and the glossary, which are
13 really two operating paradigms that work hand in
14 glove. They are part and parcel of the same package.

15 A little bit of history, the Protocol
16 Representation Group was initiated in 2003, and we've
17 been working together to develop a standard
18 representation model for clinical trial protocols, and
19 we have brought together representatives, as Barbara
20 mentioned with HL7, very similar type of a concept,
21 bringing together people with different perspectives,
22 different experiences, and different degrees of
23 stakeholding, both from service providers, PhRMA
24 companies and regulators. And, we tried to identify
25 those common elements that apply across any protocol,

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1 try to define those elements within the context of
2 regulatory guidance, and then develop a glossary which
3 I'll deal with in the latter half of the presentation
4 that would provide information so that we have a
5 common understanding of what the terminology means.

6 If you thought Barbara's Tardiff's
7 organizational structure was confusing, well this
8 probably is pretty darn close. There are many
9 different points of etiology for standards in the
10 world of clinical trials, and that's the schematic
11 that represents some of them. I'm not going to go
12 into any detail, but just to show you that we have
13 many masters that we must serve, and it's hard to
14 satisfy everybody, but we do our best. And, that's
15 why we have a very cross disciplinary representation
16 on the Protocol Representation Task Force.

17 These are some of the structured clinical
18 trial protocol, the SCTP, another acronym for you,
19 shows the interrelationship between the data layer,
20 the full text protocol, and the database, so that when
21 data are being transmitted from the point fo
22 collection, and are migrating their way into a
23 database you've got to think of the main driver for
24 the context and the operational units of collection of
25 data as being the clinical trial protocol. So, you

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1 design the protocol with the final result in mind, and
2 as we heard earlier the final result in this case, of
3 course, is the labeling, but in the case of a, you
4 know, more direct application for clinical trial
5 conduct it's really the database that you then
6 analyze, interpret and report upon.

7 So, the approach was, how do we tackle
8 this monumental task, how do we come up with a common
9 and acceptable standard for clinical trial protocols.
10 Well, the first thing we tried to do was to define the
11 set of elements that appear in a protocol. Now, there
12 are, obviously, esoteric terms and esoteric items that
13 occur in a range of protocols. We tried to take the
14 80/20 rule into account, pick the most common, most
15 universal concepts and incorporate them into our
16 model, with the idea that that would serve as the core
17 foundation for more idiosyncratic protocols that may
18 be a derivative to that standard model.

19 So, we met with key parties interested,
20 involved in developing the machine-readable protocols
21 and standard databases, because ultimately we have to
22 provide a model that is not just human readable and
23 comprehensible, comprehensible, but also machine
24 readable within the context that it's being used for.

25 So, here's another schematic showing many

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1 of the steps that have to be followed in order to get
2 from point A to point B, starting with the group of
3 reviewers, and then modeling the actual context and
4 concepts of the protocol, ballot within HL7, and then
5 create the implementation tools to actually migrate
6 that model out into the user groups. The user groups
7 in this case being, primarily, the pharmaceutical
8 industry and service providers to that industry, and
9 then ultimately the regulators.

10 This was the hierarchy of the information
11 that was contained in the protocol model structure,
12 and what we tried to do after identifying the terms
13 was to categorize them according to these particular
14 baskets of information. So, we have the document-type
15 general information, background information, purpose,
16 objectives, trial design, very similar to the kind of
17 a structural element that you would see in a journal
18 article, for example. You want to lay the ground
19 work, you want to give the rationale, you want to give
20 this the organizational elements, and then how the
21 patients are treated, how the data are collected, and
22 then how they are analyzed, and then moving through
23 to, ultimately, the use of the document, which is
24 either a regulatory submission to a regulatory
25 authority, or a publication in a peer review journal,

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1 for example, or as we are moving towards publicly-
2 accessible databases on to a web site.

3 So, we completed a spreadsheet and we used
4 specific headers, and I'll be showing you a snapshot
5 of a couple of samples of spreadsheet pages, we used
6 Excel, because it's a commonly-understood and well, I
7 think, familiar to most of the users, both the people
8 developing the protocol model, as well as in our
9 ultimate customers, and we created a number of names
10 for each of the columns to contain critical
11 information about each of these items in the protocol.

12 And, it defined major sections of the
13 protocol using the ICH guidance, primarily, but we
14 also used FDA guidance, we used publications,
15 recognized journal sources, anything we could find
16 that represented a universally-accepted or as close as
17 we could get to that universally-accepted standard for
18 terminology, and definitions.

19 When the guidance did not include
20 particular elements, or a category of elements, we had
21 to sort of rely on the expertise that was represented
22 among the members of the committee and come up with
23 our own, and so we added two more hierarchical levels,
24 subsections and protocol elements within these
25 subsections.

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1 And then, we created, as represented
2 earlier, these were the content data elements. Again,
3 we followed the ICH guidance as closely as possible,
4 so that we were not going either contrary to standards
5 that had already been developed, and so that we could
6 have some regulatory teeth, if you will, being able to
7 point to our sources and say, look, you know, this is
8 a recognized standard, it's an enforceable standard
9 according to the regulatory authorities, we are not
10 just making something up out of whole cloth, you know,
11 we are basing this on something that's been accepted.

12 We came up, and I think we are actually
13 above 354 elements now, but that's a fairly
14 considerable set of specific protocol elements that we
15 will be addressing in any clinical trial.

16 Again, there are two levels, the protocol
17 representation, an example schematically of how the
18 information was categorized.

19 That's a view of the spreadsheet, and you
20 can see the columns as named earlier, and we tried to
21 provide as much information as possible, considering
22 the name itself, the attributes of the name, the field
23 name explanation, the field name definition and
24 citation, the source, which is in most cases ICH
25 guidance, the EudraCT information, and then any

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1 ancillary information that had to do with comments.

2 Now, you'll notice a glossary reference as
3 well in there. As we were building the database, we
4 tried to cross fertilize the glossary, so that as we
5 ran through the protocol representation model we would
6 try to identify terms that required definition.

7 So, if you look at the protocol elements,
8 those that apply to protocol identification would
9 include the title, a short title, a number, relevant
10 dates, amendments if they apply, and a confidentiality
11 statement. All of those elements, considered as a
12 body, go towards the identification of a particular
13 protocol and should be unique to that protocol.

14 Contact information, the sponsor, who to
15 contact in case there's an issue, the central labs,
16 the number of sites, trial sites, so it's providing,
17 as you drill down, we were very familiar with the
18 concept of granularity by now, we've heard it said
19 many, many times, as you drill down to that level of
20 granularity you are going to find defining
21 characteristics for each of these protocol elements.

22 More examples, I'm not going to go into
23 detail here, but just to show you the kinds of
24 information that are being provided to support each of
25 these elements within the protocol.

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1 We then had to think about where
2 information was going to go to, and where it was going
3 to come from. So, that's part of the modeling and the
4 mapping exercise, and so when you look at where a
5 protocol title, for example, goes to, well, it goes to
6 a clinical study report, goes to a table of studies,
7 goes to the synopsis. That information is being
8 reused, and reused, and reused, and that's the
9 significant advantage that electronic documentation
10 and context-specific tagging has for the process of
11 taking information from cradle to grave. So, as
12 information is being collected at the source of care,
13 the point of care, it's then being migrated to various
14 other documents that are associated, not just with the
15 clinical trial, but also with the registration
16 activities that are going to occur with respect to the
17 drug regulators.

18 And, those are specific examples of where
19 this information ends up, and that has a significant
20 advantage over the old paper world, where you had to,
21 basically, recreate sections of documents for every
22 subsidiary document.

23 And, there's just a schematic again
24 showing where protocol title information would go,
25 where protocol identifying number would go, and so we

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1 created this spreadsheet, which has been vetted, not
2 just within the protocol representation group, but
3 also to a broader community within HL7, and I know
4 that we - I'm not sure if it's posted yet for public
5 comment, I don't believe it has. I know it's sort of
6 leaked out in a few places, but I don't think it's -

7 MS. WILLOUGHBY: The original version was
8 posted a year ago.

9 MR. GERTEL: Was balloted, yeah.

10 MS. WILLOUGHBY: The original version was
11 posted a year ago.

12 MR. GERTEL: Right.

13 MS. WILLOUGHBY: But, the updated version
14 will be posted in the near future.

15 MR. GERTEL: Okay, so for those of you who
16 couldn't hear that, the original version was posted
17 about a year ago, the updated version will be posted
18 in the near future.

19 DOCTOR RAYMOND: Posted to the CDISC web
20 site.

21 MR. GERTEL: Posted to the CDISC web site,
22 yes, thank you, Steve.

23 Segueing into the glossary group
24 activities, again, we've incorporated many terms into
25 the protocol representation model. Once you've

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1 incorporated those terms you have to define them, and
2 you have to define them in a way that's consistent
3 with what we believe to be the intent of the guidance,
4 and also that makes sense in terms of the utility of
5 the product for people who actually have to use it.
6 So, we considered the perspective of medical writers,
7 we considered the perspective of care givers, we
8 considered the perspective of technology providers,
9 and, of course, the regulators. So, all of these
10 people who are using these documents as models need to
11 have a common understanding of what these terms mean.

12 So, we had this mission, which was to put
13 together a standard glossary of terms related to the
14 acquisition and exchange of clinical trial
15 information, which, of course, is consistent with the
16 HL7 CDISC mandate, to create interoperability of
17 information. And, you know, hopefully this will
18 contribute to a broader standard of use among the
19 entire community.

20 So, we needed to define terms, we needed
21 to define acronyms, of which there's no shortage in
22 this business, and abbreviations, and I know that, you
23 know, as someone who has moved around within the
24 pharma industry, any time you go to a new company you
25 have to have the secret decoder ring for every new

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1 term and every new acronym that's used in a meeting,
2 and if you don't have that secret decoder ring you are
3 lost. So, hopefully, this will provide that key index
4 to terms that we all use in this industry.

5 The initial format was a spreadsheet, and
6 they've now been moved into a separate document. We
7 published the most recent version in Applied Clinical
8 Trials in December of 2004. It is available on the
9 CDISC web site, and it is also, of course, published
10 and I guess if ACT has a web site it's on there as
11 well.

12 And, we've structured our glossary
13 spreadsheet according to this model. We give an
14 example of the term assessment, and we give a context
15 within which that term would be used, as well as a
16 definition, and then we also provide information on
17 alternative terminology that may be used in a,
18 perhaps, different context. So, variable is sometimes
19 thought of as an assessment and vice versa, so we
20 cross reference, and then, of course, we have a
21 definition for the term variable as well.

22 There's also a separate list of
23 abbreviations and acronyms that were also published
24 with the glossary, so we took, not just terms, but
25 also the definitions of the acronyms and

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1 abbreviations. As I mentioned, they were published in
2 ACT.

3 So, the process for going through and
4 establishing these as standard definitions and terms
5 was to first solicit within the group and through
6 connections of colleagues of members of the group,
7 terms that they felt would be important to have, and,
8 perhaps, those that needed to be better defined than
9 they were in the common dictionaries or the common
10 guidance, and so we selected terms to be included, we
11 set aside terms that we thought were not in scope. We
12 wanted to be able to have a digestible chunk of terms,
13 we didn't want to try to define every single term in
14 this business, we decided to triage and define those
15 that were the most relevant to our business.

16 We created sub teams within the glossary
17 group to suggest term definitions, either gleaning
18 them from the available terminology in the guidance or
19 other published sources, or else coming up with a
20 definition that they felt was appropriate to the term,
21 and as a group we then reviewed and amended often
22 multiple iterations, and come up with an accepted
23 definition.

24 We would then send the proposed defined
25 terms out to the CDISC Industry Advisory Board, the

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1 Board of Directors, and selected review committees,
2 which included the American Medical Writers
3 Association, the European Medical Writers Association,
4 FDA and PhRMA, for comment within 30 days, and we felt
5 that that would give us the opportunity to get
6 different perspectives on these terms and their
7 definitions.

8 We would then review the comments from
9 each of these reviewing groups, and go through another
10 iteration, and then finally add them to the published
11 glossary.

12 We tried to provide definitions in terms
13 of context, both national geographic and geopolitical.
14 Obviously, there are differences in the guidance,
15 there are different regulatory authorities, and there
16 are different cultural applications of these terms.
17 Ethics committees are not ethics committees, are not
18 ethics committee, they vary from country to country in
19 terms of their scope, their authority, and their
20 definitions, so we had to very careful that as much as
21 possible when we created definitions for these, or
22 applied definitions for these terms, that they were
23 far reaching and global.

24 We also had to consider the clinical, the
25 technical, the regulatory context as well. So, what

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1 is true of the definition in a regulatory context is
2 not necessarily true of a definition in a clinical
3 context, and so we had to be very careful again, and
4 in some cases this required us to develop multiple
5 definitions, depending upon context. It's not a one-
6 size-fits-all business, so we had to be very careful
7 that we weren't eschewing a particular definition
8 because it didn't fit the clinical model, we had to
9 provide models for both.

10 And then, of course, there's always an
11 exception to every rule, so we would sometimes find
12 that there was something somewhat specialized that we
13 wouldn't consider in our normal course of the world,
14 but we had to deal with anyway.

15 These are the sources, the primary
16 sources, which were the ICH guidance and the FDA
17 guidance, and we looked at various sources as well as
18 published resources.

19 Sometimes - well, we often had to make
20 decisions, that's the toughest part of these things.
21 You have to come to consensus as much as possible.
22 The easy ones were when we found a definition that was
23 perfectly acceptable and universally applicable, and
24 then we could just say, it looks good to us, we are
25 going to put that in the glossary, we are done with

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1 that term.

2 An example of that would be one definition
3 of raw data, records and original observations,
4 measurements, activities, without conclusions or
5 interpretations, so that was one that we felt fit the
6 bill in terms of a definition for raw data, and that
7 was based on a definition that was published in
8 Applied Clinical Trials.

9 Sometimes we had to revise an existing
10 term or definition because of what existed wasn't
11 quite what we were looking for. An example of that is
12 clinical data, and we had to - we added clarifying
13 parts of the definition.

14 Sometimes there were multiple existing
15 terms and definitions, and we had to select the most
16 appropriate of those, or revise a selected term or
17 definition and then reconcile those with legacy
18 definitions and concepts. This was particularly
19 challenging in the world of the movement from paper to
20 electronics, and we found that there were a whole
21 litany of new terms that had e in front of them,
22 because everybody wants, you know, eCRF, eCRA, EDC,
23 lots of new terms that didn't exist ten years ago,
24 that we then had to come up with a contextual
25 definition that didn't obviate the old definition,

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1 because the old definition still applies, in a world
2 where we are in transition from paper to electronic,
3 so we had to consider those as well.

4 Here's an example of a definition for
5 clinical trial, and there's another definition for
6 clinical trial, both within regulatory guidance.
7 There's the 21 CFR 50.3, and there's the ICH GCP
8 guidance, so within two of our source providers of
9 definitions we have radically different definitions
10 for the same term.

11 Examples of discrepancies, we came up with
12 a number of them, and I know Helle has been looking
13 very diligently at E3, but we came up with some
14 examples, the old subjects versus patients conundrum,
15 it depends who you talk to, and even when you look
16 within the guidance there are differences. If you
17 look at E.6.4.3, Medical Care of Trial Subjects,
18 E.6.4.8, Informed Consent With Trial Subjects, and a
19 selection withdrawal of subjects in E.6.6.5, whereas,
20 E3 seems to like patients. So, ICH is not ICH, is not
21 ICH, is not ICH, so you have differences in the use in
22 terminology.

23 And, from pharma company to pharma company
24 you have differences, and even within pharma companies
25 you have differences, so these are the kinds of

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1 consistent use that we'd like to drive towards, and
2 we'd like to make a decision, let's go for it.

3 Now, in our glossary, subjects is the
4 preferred term, that's what we've - you know, we voted
5 on, but there will still be differences, and we hope
6 to get some sort of a consensus there.

7 The use of the term generic in E6, Section
8 7.2.1, well in the pharma context the term generic
9 means something completely different and sometimes is
10 the enemy, so you've got to think about the context
11 that the term is being used in, and we suggest maybe
12 using non-proprietary name instead of generic name for
13 a product.

14 So, these are the things you run into in
15 terms of trying to come up with a definition that will
16 satisfy all the use cases, and sometimes you can. You
17 have to develop multiple definitions.

18 So, that was, basically - right on time,
19 right?

20 ASSOCIATE DIRECTOR MOLZON: I know.

21 MR. GERTEL: You didn't think it could be
22 done.

23 ASSOCIATE DIRECTOR MOLZON: I've been on
24 the program with Art for a very long time, for many
25 programs, and it always amazes me that he has all this

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1 material and always comes in on time.

2 Any questions for Art?

3 MR. GERTEL: Everybody is stunned into a
4 stupor.

5 ASSOCIATE DIRECTOR MOLZON: No, no
6 questions.

7 Okay, our next presentation will be by
8 Meredith, Meredith Namh, and I'm not actually sure
9 what you are talking - what you are going to be
10 discussing - eSource, thank you. Okay.

11 MS. NAHM: Hi, I'm Meredith Nahm. I am
12 from Duke Clinical Research Institute, and I'm also
13 the Co-Chair of the CDISC Industry Advisory Board, and
14 because of that I also have a disclaimer with my
15 presentation. The recommendations and information
16 that I am presenting are my personal opinions, and
17 have not been through a consensus development process,
18 and do not necessarily represent the views or opinions
19 of the CDISC organization or of its sponsor
20 organizations.

21 There are several main ideas with my
22 presentation today, and I'd like to go over those in
23 the beginning. The first is that with eSource and
24 medical records there are several major national
25 efforts underway to improve U.S. health care through

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1 electronic medical records, and interoperability. The
2 second is that data standards at the data element
3 level, and controlled terminology, are seen as very
4 critical to bridging the gaps that exist between
5 patient care and research. And, the third is that our
6 industry, and ICH's involvement and harmonization with
7 these efforts, is very critical to end the chasm
8 between patient care and clinical research. So, I
9 hope that the presentation will help to bring these
10 main themes out, and if not, please ask questions.

11 First, the definition of eSource, which is
12 source data captured initially into a permanent
13 electronic record. The collection of research-
14 oriented data must be integrated with the process of
15 clinical care as manifested in clinical information
16 systems. This is a statement that came out of the
17 National Health Infrastructure Initiative White Paper
18 from 2004, from their annual meeting, and some of the
19 things that were brought out was that even though a
20 tremendous achievement has come about in the United
21 States with electronic medical record implementation,
22 one of the things that has occurred with that is that
23 these EMRs are limited in their ability to support
24 clinical research, and as a result of that a lot of
25 parallel systems have developed, not just with EMRs,

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1 but within clinical research in general. And, we see
2 that every day in clinical research, because as Landon
3 Bain has so beautifully illustrated in the clinical
4 research world an investigator will say, hi, I'd like
5 some data, and over in the health care environment
6 they would say, sure, and send it over, and the
7 clinical research environment says, oh, wait, that
8 data is dirty. Here, let me design you a form to fill
9 out, and from the first time that happened clinical
10 research and health care have existed in two separate
11 worlds, represented by Landon's two circles on the
12 slide. So, clinical research, as we all know it,
13 collects data in a completely parallel process that
14 the NHII White Paper talks about.

15 And, this is where the NIH roadmap, in
16 Zarhouni's Roadmap document talks about, in bridging
17 the gap between research and health care.

18 So, what the solution or region of
19 interest looks like is interoperability and sharing of
20 data between clinical research and health care, and
21 this is what eSource could do.

22 So, in the United States as a whole, with
23 several national efforts, we really could be at a
24 tipping point. The National Health Information
25 Infrastructure, the President's IT Advisory Committee,

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1 the NIH through the Roadmap, industry-supported
2 standards development organizations like CDISC, like
3 HL7, and academic health centers are all saying very
4 much the same thing right now, the quote at the bottom
5 of the slide by the President's IT Advisory Committee
6 really sums it up, and that's that electronic health
7 systems are critical for improving patient care in the
8 health care environment, and also can help accelerate
9 clinical research, and clinical research's impact on
10 patient care.

11 There are some data-driven reasons, aside
12 from improving patient care in general, and bridging
13 that gap between health care and research, why we
14 might want to consider eSource. One is that eSource
15 is a much richer data source. It connects the data
16 that's connected to the data in general that's
17 collected to the date and time, because they are
18 collected in the same instrument, so that stream of
19 data is time stamped. The other is that it
20 facilitates the capture of raw data, i.e., non-reduced
21 data. It captures data that's otherwise
22 uncollectible, higher sampling rates than you can get
23 with human data collection, you can greater than 3D
24 data collection, and it enables the use of signal
25 processing to collect more data, if the data that's

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1 collected now is exactly like the data that was
2 collected two nanoseconds ago, it doesn't collect it,
3 it just counts it, and you know it looks the same.
4 You can collect an immense amount of data that way.

5 eSource builds in quality checks, it
6 eliminates transcription errors, no source document
7 verification is needed because you have one single
8 stream of data, the electronic data is the source.

9 There are also some bigger reasons why we
10 might consider eSource. For several reasons, clinical
11 research is losing investigators. It's becoming
12 harder to do clinical research in the United States.
13 There are a limited number of U.S. sites willing and
14 able to execute a trial in any given therapeutic area,
15 and cardiovascular research, that my organization does
16 quite a bit of, has about 500 U.S. sites. If you want
17 to do more than three or four mega trials at one time
18 in cardiology, you can forget it if they are over
19 8,000 patients.

20 Increasing the number of trials that are
21 turning to other countries for international sites to
22 meet enrollment, all of these are driving up drug
23 development costs.

24 So, if you want to put many of these
25 bigger reasons all on one slide and sort of categorize

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1 in a fishbone quality improvement diagram, the reasons
2 why it's becoming more difficult to do clinical
3 research, it might look something like this, and most
4 of you in this room do clinical research for a living,
5 so you can probably add additional reasons. And, some
6 of the main areas are high research entrance and
7 start-up cost, number of qualified experienced
8 investigators decreasing, rising health care costs in
9 general, and disparate data collections.

10 I got this slide from Chuck Jaffe, from an
11 investigational site, I believe this was actually his
12 site, and when folks were sending out laptops and
13 computers for data collection this site had a total of
14 six PCs at the site. This could be an issue.

15 And, I don't think any of these were
16 actually the electronic medical record at that site
17 used for health care data collection. These were just
18 trial computers.

19 This is a graph from the AMA of the number
20 of physicians in research careers, which shows it
21 decreasing from 1980 to 2000.

22 And, this is data from a nine-question
23 survey sent to 122 medical school deans, where they
24 prioritized the change needed to facilitate clinical
25 research, and in the top six two of those were

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1 regulatory requirements and appropriate IT systems to
2 facilitate clinical research.

3 And then, there are other problems that
4 specifically the FDA Critical Path is targeted at
5 addressing, and that's facilitating the drug
6 development piece of the clinical research process, to
7 make some of those things easier.

8 Three of the major national efforts
9 underway to address some of the bigger problem issues
10 are the National Health Information Infrastructure,
11 the NIH Roadmap, which has three pieces to it,
12 reengineering the clinical research enterprise, the
13 pathways to drug discovery component, and also
14 research teams of the future, and then there's the FDA
15 Critical Pathway, which the three components to that
16 are safety assessment, evaluation of medical utility,
17 and product industrialization.

18 This particular slide has some information
19 about the NHII, and then some of you may be familiar
20 with railer's RFI that went out, and this summarizes
21 some key trends from the responses back that he got
22 from his RFI. He received over 500 responses.

23 This slide discusses some statistics on
24 electronic medical use in the United States, and the
25 percentages are rising of electronic medical record

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1 use, both in the ambulatory setting and in the in-
2 patient setting, but one thing that is critical with
3 this is that even though the number of EMRs
4 implemented in the United States are increasing, those
5 electronic medical records are stand-alone systems,
6 and without data standards, both at the data element
7 level and at the control terminology level, we are
8 unable to get data from those systems, to exchange
9 data between those systems, and to pull data from
10 those systems to use for research in an effective way.

11 Specifically, the President's IT Advisory
12 Committee said current health care standards lack
13 specificity required for interoperability. They
14 mentioned specifically standardized data definitions
15 necessary for medical research, as well as controlled
16 terminology. They specifically recommend developing
17 a single set of data standards for the most common
18 forms of clinical information for the health care
19 setting, and recommend also developing those within
20 HL7.

21 One of the other recommendations that is
22 coming out of the President's IT Advisory Committee is
23 around standardized clinical terminology, which is
24 something that the CDISC controlled terminology team
25 is working on for clinical research, and controlled

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1 terminology is a very key area for ICH to work on and
2 address, because having internationally harmonized
3 terminology sets is critical to being able to pool
4 data, especially as pharmaceuticals are doing trials
5 that involve international data, having terminology
6 sets that are internationally harmonized are critical,
7 because that data crosses international boundaries.

8 One of the things that the President's IT
9 Advisory Committee pointed out was a lack of health
10 care authentication standards, which is also critical
11 for, not only the health care environment, but also
12 for the research environment as we interface with
13 electronic health care.

14 And, as we get into making
15 recommendations, a good number of my recommendations
16 are on the ICH documents, and I've also noted things
17 where the underlying regulations that are related to
18 the ICH documents are affected or have similar
19 language as well.

20 The first is Part 50, and the ICH also
21 acknowledges informed consent, and here the language
22 deals with written informed consent, and with dealing
23 with eSource the recommendation would be to use a
24 phrase similar to documentation of informed consent,
25 removing the word written, and then relax the

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1 electronic signature certification requirement in 21
2 CFR Part 11, even though that's not involved in ICH,
3 but that would be an overwhelming regulatory burden on
4 sites in the U.S., if they had to file certification
5 for patients for the e signature.

6 In ICH E6.4.9, Records and Reports, the
7 recommendation would be for the punctuation in the
8 4.9.2, in the underlying segment, that the underlying
9 part can perpetuate the perception that there must
10 continue to be a CRF and a source, which may
11 discourage sponsors and others from single source or
12 eSource approaches, pulling data directly from
13 electronic medical records where the source was
14 captured onto the CRF that wouldn't apply.

15 And then, in 4.9.3, the statement, the
16 investigator should retain records of the changes and
17 corrections, a clarification of retain to mean store
18 in a location or system to which the investigator
19 institution has authority to prepare and maintain
20 data.

21 This one in 3.12, and there is similar
22 language in the ICH, for case histories and
23 specifically in 4.9.4, in ICH E6, the investigator
24 institution should maintain trial documents, the word
25 maintain, interpret, maintain and direct access, as

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1 indicated, and I put just the dictionary definition of
2 maintain, but be clear that it would not be on site,
3 and then the direct access portion, a more clear
4 definition of direct access.

5 In the source data definition, there's a
6 series of several slides about statements that refer
7 to actually keeping source data on location at the
8 investigator institution, and the gist of these, this
9 is the ICH E6 essential document section, that
10 actually lists them as located at the investigator
11 institution, the gist is that, not just for source
12 documents, but even as the sites fall under HIPPA
13 security, under a business associate agreement the
14 sites can even out source the keeping of their whole
15 electronic medical record system to a separate
16 organization, so the whole source can reside on a
17 server farm somewhere else. And, that's perfectly
18 fine under HIPPA security, so I would, as a
19 recommendation, maybe utilize the earlier suggestion
20 for a definition of maintain, and recognize as
21 sufficient for maintaining source documents that the
22 site should maintain authority to prepare and maintain
23 the data, and that the investigator institution or
24 site staff have appropriate access and policies to the
25 system in accordance with HIPPA security.

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1 5.18, under the monitoring, the statement
2 of verifiable from source documents, maybe a text
3 acknowledgment that the source data and the trial data
4 are the same in an eSource situation.

5 Again, under the monitoring
6 responsibilities, two of the sections had to do with
7 documenting visits that subjects failed to make or
8 withdrawals or dropouts, in general, a significant
9 amount of the charting or documentation in the medical
10 record is by exception, abnormalities that exist, so
11 maybe acknowledging that in that text for things that
12 are pulled from the medical record.

13 5.7 is more of a cautionary thing with
14 eSource. Until there are data standards at the dat
15 element level of specificity, and until controlled
16 terminology is there to support true interoperability
17 with electronic medical record systems, we are still
18 going to be in the situation where sponsors and
19 vendors are shipping equipment to sites, and I've got
20 some examples further in the slide set of that, but
21 the table here sort of shows the different logic
22 scenarios that we fall under, and some of those
23 scenarios where we are shipping equipment to a site
24 could put the site in a situation where the site is
25 using someone else's equipment, not the site's

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1 equipment, and that can put the site in the situation
2 where the site is - when they are not using their own
3 equipment, when they may not have access to the data,
4 or may feel that they don't, for example, if they are
5 using an ECG machine, and that ECG, electronic ECG, is
6 not in their central management system, they may not
7 have continuity of care in some situations, because
8 that data is not in their electronic medical record.

9 So, it is precautionary in that the
10 investigator may still need to be made very clearly
11 aware that the investigator's obligations under 312.60
12 don't change for their responsibility for patient
13 safety, and the sponsors may need to be aware that
14 they need to be very careful what the investigator has
15 access to and need to make sure that they have access
16 to all the data.

17 The next is a graph that we need to
18 consider exactly where the source is and where the
19 data is reported. One size does not fit all in
20 eSource and there are lots of different varieties,
21 patients report over the web, patient can report on
22 paper, and it can be entered, which would make it
23 really not eSource, where the cite can report data
24 initially in the EMR, which is eSource, and then
25 direct electronic measurement insight systems or

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1 sponsor systems, which is eSource.

2 And then, some data in the source is not
3 so clean, and I've listed some examples, and here's
4 where the President's IT Advisory Committee actually
5 suggested maybe putting a warning label on paper
6 documents, because of the dirtiness of data in paper
7 source.

8 Other data in the source is much cleaner
9 with electronic source than with paper, and here are
10 some examples.

11 And then recommendations for eSource, if
12 you are using eSource now, before there are
13 interoperability standards that exist, and some are to
14 stick with biological measures that are captured in
15 raw data, by definition of it being raw data and
16 biological measures there's less opportunity for that
17 to be ambiguous. So, that's a little easier for data
18 that's pooled, non-reduced data is easier to pool.

19 Where there are clinical interpretations,
20 where those interpretations need to be captured,
21 capture them separately from the raw data, and having
22 the clinician make those interpretations in the
23 context of the clinical care.

24 Remove the constraint of maintaining
25 source in the investigator files.

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1 The concept of monitoring changes when the
2 trial and the source files, when the data in the
3 source files are the same. Sending a monitor to the
4 site to verify informed consent, drug accountability,
5 the subjects exist, samples are stored appropriately,
6 that cultures are stored appropriately, all those
7 things completely still need to be done, matching up
8 case report forms to source documents, not necessarily
9 that work is very different in an electronic eSource
10 type data capture situation.

11 In eSource, cleaning eSource data is very
12 different. You are looking for noise segments up
13 front. You are looking for noise during data capture,
14 and you are thinking of how in the eSource data stream
15 you are going to label those, and when in the stream
16 and in the processing of the data you are going to
17 label those noise segments, if a patient falls off the
18 table, if the patient has moved or breathed wrong,
19 when and how you are going to label those so when that
20 data goes through to the statistical analysis the code
21 will know that that's been identified as a noise
22 segment. So, the whole cleaning concept is different.

23 With eSource, you are also going to be
24 more concentrated on statistically monitoring the data
25 for measures of central tendency and dispersion that

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1 are going to indicate that some sites are behaving
2 abnormally, different from the rest, i.e., you are
3 looking for things like cases of misunderstanding, or
4 maybe training issues, or maybe even fraud, but you
5 are going to be spending your time on monitoring the
6 data and trying to catch issues sooner or trying to
7 catch issues where measurements need to be retaken.

8 If there are standards for data you are
9 collecting, for goodness sake, use them. If not, try
10 to collect the data anyway. Just the fact that you
11 are collecting the data will probably help move the
12 standards forward. Use the site's equipment when you
13 can, and calibrate it with centrally-designated
14 protocols, traveling phantoms, simulators, whatever.
15 Calibrated equipment is just as important to patient
16 safety and data quality as lab certification is, and
17 this is a very big deal with the eSource data.

18 A recommendation is to mentioned
19 calibration of equipment along with lab certification,
20 and then another recommendation would be to cover site
21 systems under HIPPA security, instead of Part 11. I
22 understand that's not an ICH thing, but just a
23 suggestion.

24 HIPPA security does cover system
25 evaluation and certification, that's HIPPA security

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1 information.

2 So, in conclusion, what a solution might
3 look like, and this is a slide from the CDISC single-
4 source project, it's actually a demonstration pilot
5 project, where there's a single stream of data that's
6 peeled off for both patient care and data collection,
7 so an HL7 CDA goes to the medical record after the
8 patient visit, and then the CDISC ODM file with the
9 CDISC, at that time it was SDS not SDTM, went to the
10 study database, with the idea that for submission it
11 would then go into Janus.

12 Another example, some perioperative
13 studies, we need to collect Continuous Hemodynamic
14 Monitoring data. We want to think of the drug
15 administration during the procedure with time, so we
16 need very tight time resolution on that data. It's
17 very difficult to accomplish that in the OR, so we
18 want to collect that with the Continuous Hemodynamic
19 Monitoring System. Currently, in trials that's either
20 done with manual data collection or that's done by
21 shipping actually the Hemodynamic Monitoring System
22 shown in the slide out to the sites. When we did it,
23 it was about a year and a half ago, we actually got 30
24 Continuous Hemodynamic Monitoring Systems, programmed
25 them, validated them, shipped the things out to the

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1 site. It's a computer monitor and a box, CPU, with a
2 CD writer in it, and we mailed them out to the sites.
3 We brought all the sites in house to the Duke
4 Simulation Lab and trained them in house on how to use
5 the system.

6 We would rather not do that, we would
7 rather have a standard for that data. So, in the
8 future, in the beautiful world, we would use the
9 site's system and send the data in VA standard.

10 The last example, electronic ECG
11 collection through the HL7 waveform standard. There
12 is a standard out there for this. People are doing
13 this today, and some people are using site's
14 equipment, other people are still shipping equipment
15 out to sites.

16 So, are we there yet? Not exactly. Are
17 we getting there? Little by little, like the NIH
18 Roadmap says, part of reengineering the clinical
19 research enterprise is bridging the gap between
20 research and patient care, eliminating the redundancy
21 of capturing data twice, having the medical record
22 available electronically, standardizing the medical
23 record, clinical trials, collecting closer to standard
24 of care. And, we very much would like to see ICH help
25 push this forward.

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1 Collecting what we can in eSource,
2 currently gives each trial on which it is implemented
3 benefits, it also helps us move closer to single-
4 source data capture.

5 And, what will it take to get there?
6 General recognition that streamlining clinical
7 research benefits everyone who interacts with the
8 health care system, bridging the gap between health
9 care and research, health care and research industry
10 endorsement of an involvement in standards efforts
11 like ECG waveform standard, enterprise in the clinical
12 research industry, experience in the clinical research
13 industry, and equipment-based data capture, which is
14 not easy. It's like data management turbo plus.

15 We tried to merge the data from the three
16 ECG vendors, we ended up doing fast Fourier.

17 Willingness to tackle the details,
18 continued standards development, even the President's
19 IT Advisory Committee and others in NHII recognize
20 that funding is needed for pilot efforts, like the
21 HIMSS Interoperability Demo, and single source, so
22 that people can see some of these pilot projects
23 demonstrated and see them in action, and also funding
24 for standards development.

25 And then, we need people to implement

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1 standards.

2 Thank you.

3 ASSOCIATE DIRECTOR MOLZON: Thank you very
4 much.

5 Any questions for Meredith?

6 Yes, Art.

7 MR. GERTEL: Art Gertel.

8 Because we have the technological
9 capability to collect data, are we running into a
10 situation where we are collecting so much data that it
11 presents an analysis and interpretation burden that we
12 didn't have to face when we couldn't collect so much
13 data? And, you know, knowing, as a medical writer,
14 when you have to go through individual data points you
15 can sometimes be overwhelmed by the noise, there's so
16 much there that it no longer becomes relevant
17 information.

18 So, from your perspective, you know,
19 feedback that you've had, or maybe from someone like
20 Steve, from the statistical side, Steve Wilson from
21 the statistical side, is there an imposed burden that
22 may be unnecessary because we've collected so many
23 data points?

24 MS. NAHM: I haven't run into that one yet.
25 I think that we may be collecting more data, for

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1 example, the Continuous Hemodynamic Monitoring
2 example, it certainly is a huge volume of data points,
3 or Continuous ST Monitoring in the ECG, it's a huge
4 volume of data, but when that data is analyzed
5 properly and displayed properly, that huge volume of
6 data is condensed down into one graph, where it
7 becomes information to a reviewer, so that that huge
8 volume in that one graph becomes an answer.

9 MR. GERTEL: So, the algorithms that are in
10 place to represent those data provide a meaningful
11 representation of those data?

12 MS. NAHM: Uh-huh.

13 MR. GERTEL: Okay.

14 Another question, and again it's based on
15 feedback you may have had. Having been in the EDC
16 business a while ago, one of the big concerns among
17 the regulatory authorities was acceptability of
18 eSource, and how do you go out and do an audit against
19 source documents that can't compare A to B? So, have
20 you had a greater level of acceptability now?

21 MS. NAHM: That's one of the reasons why I
22 was very excited about coming here to talk, because
23 we've been doing eSource probably for about two years,
24 two and a half years, I haven't gotten a lot of
25 questions about it, and that's why I'm here, to put it

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1 on the table and to bring it up for discussion,
2 because we do put the systems out there, we validate
3 those systems that are in our control, like the
4 Continuous Hemodynamic Monitoring System, the systems
5 that are at the site that we pull data from, those are
6 the site systems, and the sites do their testing when
7 they put those into production, but their processes
8 are different from Part 11, and that's what I'm
9 putting up and, thus, the recommendation, to hold the
10 sites to HIPPA instead of Part 11, because that's the
11 regulation that the sites are held accountable to.

12 So, I haven't gotten a lot of questions.
13 I know that a lot of sponsors are concerned about it,
14 because if we did move more full scale to eSource that
15 is very different. However, in order to remove the
16 burden to the sites, aside from a lot of logistical
17 issues, working out data interoperability, that small
18 concern there, there is a really big regulatory
19 question that we have to answer, and we have to put it
20 up on the table and deal with it.

21 So, it's a very good question. Thank you.

22 ASSOCIATE DIRECTOR MOLZON: Anyone else
23 have a question?

24 Steve, are you getting up to give your
25 talk, or do you have a question?

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1 DOCTOR RAYMOND: No.

2 ASSOCIATE DIRECTOR MOLZON: Okay.

3 Yes, please, your name?

4 DOCTOR ROGERS: Chris Rogers, RPS.

5 This is sort of anecdotal information, but
6 I have heard that some sponsors who are looking at
7 their EDC data find higher error rates than in sort of
8 the traditional monitored double data entry level.

9 And, I noticed that you did have a slide
10 that said that, you know, in here in the case it's a
11 single source, so maybe the implication is that that's
12 a transcription error at the site, if there's a
13 transcription error into EDC, again, that's an
14 anecdotal report, and I'm not saying that there's, you
15 know, but there's some element of sense there that if
16 somebody is doing a transcription error into an EDC as
17 opposed to a paper record that's being monitored,
18 that's going to have a double data entry, and I just
19 wondered whether you thought that might be true,
20 whether there might be error rates that were, perhaps,
21 more acceptable in clinical practice than in clinical
22 research?

23 MS. NAHM: Yeah, I have - there's actually
24 two slides in your packet, because of time I deleted
25 them out of here, and one shows, I'm actually working

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1 on a literature review paper with Kay Fendt, and one
2 slide is source to CRF/database audits that people
3 have done, and those are from all models. Some are
4 double entry, some are single entry, some are single
5 entry with visual verification, all models.

6 And, the error rates from the source to
7 the CRF/database range from anywhere from, I think
8 it's 3,240 errors per 10,000 fields, all the way down
9 to about 100.

10 And, the second graph shows two processes
11 split out from data that was processed, it's split
12 between data that's processed at the site and data
13 that was processed in house, and those are
14 specifically from systems that are like EDC systems.
15 They are single-entry systems with on-screen error
16 checks, and I saw something on the graph that I
17 completely did not expect to see, that was that the
18 data that was processed at sites had a lower error
19 rate on average than data that was processed
20 internally.

21 I completely did not expect to see that.
22 I can take a guess as to why that's so, when people
23 are entering data at the site they have the records
24 there, and when the, you know, the error check pops up
25 and it says, hey, the blood pressure can't be 1,000

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1 over 80, you know, maybe they can fix that quickly
2 right there. That's what the literature base has to
3 say on it.

4 It surprised me, too.

5 ASSOCIATE DIRECTOR MOLZON: Okay, any other
6 questions?

7 Okay, thank you very much, Meredith.

8 MS. NAHM: You are welcome.

9 ASSOCIATE DIRECTOR MOLZON: Our last
10 speaker for the day is Steve Raymond, and he's going
11 to be speaking about eSource with respect to ePatient-
12 Reported Outcome data.

13 DOCTOR RAYMOND: Great. Thanks.

14 Well, good afternoon, everybody. I know
15 it's stretching a little into the later part of the
16 afternoon. It felt awfully good to me to actually
17 stand up. I certainly wouldn't be offended if other
18 people just stood up for a brief moment here, and I
19 don't like you walking out the door, but if you just
20 stand up that would be all right with me.

21 I want to thank Meredith for what I think
22 was a really, really insightful set of
23 recommendations. The talk I'm going to give, I hope
24 you paid careful attention to hers, because I would
25 like to build mine on top of what she had to say, and

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1 mine is a little bit more vetted in the sense that it
2 represents a work in progress by CDISC to deal with
3 electronic source questions.

4 And, the area that I want to focus on is
5 an area which is probably of greatest regulatory
6 importance, and represents a lot of data, because when
7 patients begin making reports themselves into an
8 electronic device, a phone, or a hand-held device, or
9 something, and then sending it directly as electronic
10 source into a record, they might do that two, three
11 times a day for a year, so that the total amount of
12 data represented in the database that is pertinent for
13 clinical research and analysis might consist of, the
14 bulk of it, really, might be electronic source data,
15 if ePRO, e-Patient Reported Outcomes, are used.

16 So, CDISC is very interested in the topic.
17 They've formed an expert advisory panel within CDISC
18 called the Electronic Source Data Interchange Group,
19 and it's definitely a work in progress. So, while
20 there's a draft paper, there is no set of vetted
21 recommendations yet, so as with Meredith I'm going to
22 be giving, when I talk about a recommendation, give a
23 recommendation that is possibly my own, but it
24 certainly would be reflective of a group of people who
25 would think the same way. And, what I'm going to try

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1 and do, through the talk, is also present both sides
2 of a discussion, so I'm going to try and be like
3 attorneys who are arguing a case in front of a supreme
4 court. First the one attorney goes, then the next one
5 goes, and I'll be both of those, but I'm going to try
6 and capture, like Helle did in the morning, it's one
7 thing for Meredith to be doing eSource and doing it in
8 a context which is primarily with respect to health
9 care, it's quite another in terms of the intensity
10 over the regulatory side of the equation that occurs
11 when you are doing eSource for primary efficacy and
12 safety variables that are going into new drug
13 applications.

14 So, I work on the Protocol Representation
15 Group in CDISC, also in the Glossary Group, and I am
16 part of this Electronic Source Data Interchange
17 Advisory Panel. And, my other work is with PHT
18 Corporation, and that is a company that makes what are
19 called sometimes electronic patient diaries, that are
20 used to harvest patient reported outcomes often on a
21 daily basis. So, that's where I'm coming from.

22 CDISC is undertaking an analysis of
23 eSource, including ePRO, electronic Patient Reported
24 Outcomes, just a little bit bigger concept than
25 diaries, any patient reported outcome, whether it's in

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1 a daily diary or not would be potentially captured
2 initially or originally as an electronic record
3 without a paper record.

4 And, it's already in use in hundreds of
5 trials worldwide, so it's not just in the United
6 States, it's in use in Europe, in Japan, in China,
7 literally, 50 or more countries currently have sites
8 that are using electronic patient diary records and
9 ePRO.

10 And, it's shown, as Meredith had said for
11 the electronic health record, very substantial
12 benefits in the quality of the data and in the amount
13 of data. If you look at a paper diary, you might get
14 all 100 pages that you give to a patient back, but 90
15 of them would be empty, and then of the 90 that are
16 filled in, they are not filled in right, so fields are
17 illegible, missing, illogical, or in the wrong format.

18 So, when you get down to how much you can
19 actually put into your analysis, it might be as little
20 as 50 percent of the total available fields. When you
21 go to an electronic methodology, you still get 90
22 pages, but because the internal completion checks,
23 legibility and logic checks are operating,
24 essentially, all of those fields are both timely and
25 analyzable, which gives you, in essence, a much better

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1 picture of what's happening with the patient, at least
2 in terms of the patient's self-reported data stream.

3 Now, so that's an important potential
4 benefit, and that's why ePRO is in use, increasing in
5 breadth of use.

6 Like the SDTM, that's the, what is it, the
7 Study Data Tabulation Model for submission, and the
8 Protocol Representation, eSource is embedded in a
9 regulatory and GCP context. There have been some
10 questions about why CDISC be speaking to this
11 regulatory authorities? Well, it always has, it
12 probably always will, it's a clinical research
13 enterprise looking for standards, and it's, I think,
14 an appropriate neutral forum. Now, neutral doesn't
15 mean that everybody is asleep, there's quite a lot of
16 controversy, there's a lot of different positions
17 represented, but they are very broadly represented.
18 So, we have people who are physicians at sites, who
19 mainly do clinical care on the ESDI team, on the
20 Source Data Team, we have people who are from PhRMA,
21 we have technology providers who sell into that space,
22 we have technology providers who don't sell in that
23 space, and we have regulators.

24 So, as mentioned earlier this morning,
25 it's a precious moment when there's an opportunity for

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1 the people who write the regulations, including ICH,
2 to have an interaction with the people that are going
3 to try to put them into use. So, my talk will try and
4 focus on a couple of key issues that keep coming up
5 again and again, that we see primarily as inspired by
6 the laser-like focus that's brought on to regulations
7 when you apply them and try to ease the anxiety that
8 sponsors might have in adopting a new technology.

9 So, I'm going to highlight issues that
10 have to do with the word location and with the concept
11 of investigator authority and responsibility, and I
12 want to present a diagram to explain how that can be
13 understood, and how the people who are engaged in
14 electronic Patient Reported Outcomes and eSource now
15 think they conform to the existing regulations. So,
16 while there may be a debate about, in some quarters,
17 whether they do or not, certainly the people who are
18 engaged in it aren't engaging in it knowingly in
19 violation of those regulations.

20 And then I conclude with a couple of
21 familiar statements and questions that will bring it
22 back down to earth, you know, like where is the source
23 document, things like that, and I'm going to talk a
24 little bit about that. But first, we have to go
25 through a little educational foray.

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1 So, in the age of paper, which in some
2 ways is drawing to a close, and yet, as we see, it's
3 also very much with us. It's a proven technology
4 which is very familiar, and as a result it's often
5 presented as if it was simple. It isn't simple, but
6 it is familiar, and it's often easier to teach.

7 And, in the age of paper, when you had
8 physical possession of a paper, you also had access to
9 read that paper and to possibly make marks on it, so
10 you could enter data, you could change data, and you
11 could do all of the things that we're used to doing
12 with paper case report forms and paper source
13 documents.

14 And, it was important where that paper
15 was, because the key to having access to the
16 information was to have access to the paper. So, in
17 the age of paper location takes on a meaning which is
18 related to the technological properties of paper.

19 Location in an electronic age has maybe
20 functionally or logically very similar importances to
21 regulations, but not so much to physically possessing
22 the disk drive on which the record is stored. It's
23 much more important possibly to have access to your
24 particular file with your name, your site number, and
25 that particular patient record, you know where it is,

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1 that's a location, but it's a logical location, not a
2 location in Afghanistan where the server is. It
3 doesn't matter where the server is, what matters is,
4 where is your file located?

5 So, I think it's a kind of a key incite,
6 it's certainly something that keeps coming up again
7 and again, when people talk about, well, is the
8 database the source document, or is the device on
9 which the record was captured the source document?
10 Well, in the days of documentation, it was the
11 physical paper, you could say that was the source
12 document, but what you really meant was it was the key
13 to the information. The electronic record is the
14 record, it's the data, where is it? Well, it's in my
15 files. Well, where are those files stored, that's a
16 slightly different question, if that's what the
17 regulations are about when they are talking about
18 location, then they are talking about something which
19 is maybe of academic interest rather than true
20 importance. But, it's still - it's very important if
21 that argument exists to the extent that it might
22 retard adoption of electronic source or its proper
23 operation.

24 So, with eSource the key operations that
25 you get by having physical possession of the paper,

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1 preparing, that means entering, reading, or changing
2 data, are conferred by authorization processes and
3 permission rules, which are established and built into
4 the software systems. They are built into the
5 computerized systems that give you access. We are all
6 familiar with this now, and then that's validated so
7 that it operates properly, and that's the equivalent
8 of the locking up of the paper. You can't get into
9 the system, even if you have physical possession of
10 the disk, if you are locked out of it logically.

11 So, FDA authors of Part 11 knew that they
12 were then just moving things into the electronic
13 record, and they made sure that there were certain
14 controls to ensure that the ease of, let's say,
15 porting an electronic record versus ten tons of paper
16 from one place to another, you might be able to do one
17 with a press of a button, and you'd have to have a
18 truck to do the other, so they wanted to make sure
19 that there were certain controls in place in Part 11
20 that would ensure that electronic records would be as
21 trustworthy, and the standard was no worse than paper
22 records. A very helpful standard, and, essentially,
23 the intent of Part 11 was to enable technology
24 providers and industry to move to electronic
25 methodologies with some confidence that if the Part 11

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1 audit was passed, if the system had the necessary
2 controls, then the records would be acceptable. And,
3 it has really, I think, achieved that objective in
4 clinical research. I think the authors were so
5 focused on clinical research applications that they
6 might not have considered what the same regulation
7 applied to drug manufacture might mean for people who
8 were engaged in that activity. But, for clinical
9 research and data capturing, data processing people,
10 it's a very sensible rule.

11 So, here's the promised diagram. There's
12 a light blue shading, you see the physician there at
13 the site managing the various patients, each of whom
14 has a little portable unit in which to record
15 symptoms. It could be a cell phone, it could be
16 something, but generically it's something that's
17 theirs, and on which they can regularly report symptom
18 level, medication consumption and the like, important
19 stuff for clinical research.

20 You notice that the blue shaded area
21 includes all of the patients, the physician, the site,
22 the site hardware is in that little circle, the
23 hardware that gets into the web to take a look at the
24 information, and then each of the patients has some
25 way of directly porting the data that they are

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1 recording into a centralized server.

2 Now, the centralized server has this
3 property that I mentioned, it's logically - the data
4 belongs logically to the site, it's located in files
5 of the site, but physically it's maybe not even in the
6 same country that the patients are. And, people who
7 think they are complying with the regulations believe
8 that it doesn't matter, what the regulations talk
9 about is the location of the file in the sense of
10 authority over its content, and the passthrough to
11 prepare and maintain the data in the file.

12 And, you see that maybe a CRO and some
13 technology services people are also looking at the
14 data using the web to access it, each with his or her
15 own particular privileges on the data. So, the
16 sponsor maybe has only read only privileges, to make
17 sure that the trial is underway, that the recruitment
18 and enrollment is happening, but they don't see any of
19 the personally identifying health information, the
20 private protective fields are eliminated, and they
21 can't change any data. So, the system is designed so
22 that the change, the access of authority is within
23 that blue shaded area.

24 And, this diagram then indicates where
25 this preparing and maintaining that's mentioned in

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1 both ICH and in the Part 11, and what Meredith has in
2 her presentation, is a location that is established by
3 its software, where logical proximity matters, but
4 proximity in distance in the physical sense doesn't.

5 Okay, so I've already explained it, and
6 this is sort of more for the record in case I'm not
7 around to explain it when you look at it again. The
8 argument, though, is that the idea of location is it
9 notes where the system provides ready access and
10 control of record content with solid trail and
11 protection against loss or destruction, and it's
12 basically for the site to use.

13 The key points are that the system is
14 designed and validated to ensure that a sponsor cannot
15 prepare or maintain a record. That is an assurance
16 which used to be given because the location of the
17 record was at the site, that prevented the sponsor
18 from easily running to the site and nefariously
19 altering the record.

20 Well, the location of the record logically
21 is in the site's files, the sponsor can't get into
22 those files. It seems homeomorphic both functionally
23 and regulatorially, and so that's the position taken
24 by the people who are using that idea.

25 At one point in the history of argument

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1 over this base, and I want to emphasize to the
2 regulators that there is a broad level of argument and
3 concern over this issue, if it's files in the
4 institution, well, gee, I've got to have a source
5 document in the institution. Maybe I ought to keep
6 all of those electronic devices that the patient is
7 using in some box, so that, you know, they can stay at
8 the site, and then later somebody can maybe, what, go
9 back and turn them on and they've all run out of
10 batteries or whatever, and, you know, maybe make sure
11 that the data that was originally on them is still
12 there or something?

13 So, there are people who think that that's
14 the only viable method in terms of the regulatory
15 process, even if it doesn't make any sense
16 technically.

17 So, and one of the issues was, well, if
18 the sponsors pay the sites, or pay the providers to
19 help - pay the providers, so, therefore, the
20 providers, technology providers, the people who do
21 this infrastructure provision, are the slaves of the
22 sponsor, and they'll do anything they say. But, that
23 would be a kind of a Peter Jennings reading of the
24 nature of the pharmaceutical industry. We've never
25 seen anything like that. The pharmaceutical industry

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1 tells us that they don't want to have access to those
2 records, that they want the sites to, in conformance
3 with the regulations, have full authority over the
4 records to be able to prepare and maintain them.

5 So, the sponsors really then pay the sites
6 to fulfill site duties, that's well accepted. They
7 pay the sites to have their patients and execute some
8 sort of medical control over the patients, and then
9 they pay the infrastructure providers to help the
10 sites fulfill, not necessarily the nefarious desires
11 of the sponsor, but the regulatory requirements that
12 are needed in order to accomplish the trial.

13 Okay. I find myself doing what Helle did,
14 I get passionate about this, because - and I feel that
15 other people, they haven't been in the same shoes,
16 they don't necessarily see the arguments that take
17 place and how unnecessary they are in some ways. If
18 we could just get a little bit of clarity, so I don't
19 think that in any sense CDISC is prepared, nor am I,
20 to ask that the guidance or the existing regulations
21 or Part 11 be rewritten, but that issues associated
22 with it be clarified. And, when Helle suggested this
23 morning that it would be very helpful, in the context
24 of the electronic common technical document, to have
25 an authoritative place that you could submit a

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1 question, where the agency or the ICH could then come
2 back with an authoritative answer on which the
3 sponsors or others could depend, that would be an
4 extremely helpful capacity in this area, too. What
5 does location mean? Here's one side, here's the
6 other. If there were a supreme court, it wouldn't
7 mean that you had to come out and audit every
8 technology provider, it would mean all you had to do
9 was make a ruling, and you can appeal it or something
10 if it turned out to be wrong.

11 So, CDISC is analyzing what the
12 regulations that currently reflect the age of paper
13 really mean around how to keep the data trustworthy.
14 And, there has been a draft white paper, some of you
15 may have seen it, authored by David Iberson-Hurst, who
16 is serving as a free and unpaid consultant to CDISC,
17 and while he may not have everything right yet,
18 there's quite a lot of controversy over the nature of
19 the comments that are in the paper, it's as genuine,
20 spirited discussion at this point.

21 And, as I say, the panel has quite a broad
22 variety of representation, and the hope is to have a
23 new draft for circulation possibly reflecting more of
24 our vetted and single position by CDISC available for
25 the DIA meeting in 2005.

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1 And, the implications of the diagram are,
2 if we have the logical understanding of location, then
3 the system, having the diagramed architecture,
4 probably does conform to the letter and spirit of the
5 existing regulations, but a clarification around the
6 meaning of location would be very helpful.

7 What do the regulations actually say? The
8 predicate rules, an investigator is required to
9 prepare and maintain accurate and adequate case
10 histories, including all supporting data. It goes on
11 a little bit more, but that's the essence of it, and
12 then retain it, and protect it against premature loss
13 and destruction, and then allow an FDA or regulatory
14 person to be able to audit it, have access to it.

15 Well, that can be provided by either a CD
16 at the site, or it can be provided by dynamic
17 connection to files of the institution, possibly with
18 role and privilege that is unique to the auditor, and
19 can be expanded only with the permission of the
20 investigator.

21 In the GCPs, the regulations pertain to
22 source documents, they define source documents,
23 include subject diaries in E6. The data on the CRF,
24 which are - and this is the same - it's interesting,
25 Meredith and I had different views of what this

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1 particular sentence said, data on the CRF, which are
2 derived from source documents, should be consistent
3 with the source documents. So, I thought that that
4 meant that it's perfectly okay for there to be some
5 data on the CRF that isn't derived from source
6 documents, and, of course, that would be consistent
7 with the source documents because that already was the
8 source. And so, it's fascinating how you can read
9 things the same way.

10 But, that is not a property - when you are
11 transcribing information from paper source documents
12 to a paper CRF, and from a paper CRF into an
13 electronic database, each of those transcriptions is
14 a potential source of error. Because of the
15 limitations of that technology, you have to do some
16 manual work to make sure that the individual fields
17 have been transcribed properly, and one of the
18 standards that's in place is to do 100 percent source,
19 field-by-field source document verification, or source
20 data verification.

21 Arguably, that's not necessary, and I
22 think that's what Meredith was trying to say, when you
23 have already validated the system accurately
24 represents the data that is captured on it by the
25 patient, reported patient outcome information is

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1 captured on a mobile device of some kind, and it is
2 validated to send whatever that data is back to the
3 central database, you don't have to look each time to
4 repeat that validation. Manual work would be
5 unnecessary, so the burden of source document
6 verification field by field goes away and is replaced
7 by the burden of validating that the system works as
8 intended, or as designed.

9 And then, the wording in GCP E6 8.3.13, is
10 that the source documents, and in the top of that
11 table is located the files of the investigator
12 institution, not at the investigator institution, and
13 not in the investigator institution. So again, we
14 take English as I learned it, that could mean they
15 belong to or of the institution, it doesn't
16 necessarily mean that they are literally located in
17 the physical position of the institution. So, the
18 existing regulation, subject to a little bit of
19 clarification, might work just fine.

20 Okay. So, how does it really work? Well,
21 during the trial the investigators prepare and
22 maintain eDiary data by what, well, they are not going
23 to enter the data themselves, but they are going to
24 instruct the patients how to understand the questions,
25 and how to enter the data. And, they are going to

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1 supervise the patients in terms of the visits, and
2 then the patients are going to go and enter that data
3 at home, or in the hospital, or wherever they happen
4 to be when they are engaged in the trial.

5 Then the investigators are going to review
6 the eDiary data and they are going to manage the
7 compliance of the patients with medication, with the
8 protocol, and with completion of the eDiaries
9 themselves by looking at the data stream that comes in
10 over the web.

11 And then the system, which are those
12 little dots there, that provides the access, the files
13 of the investigator, defines that the files belong to
14 the investigator, it makes sure that they are
15 accessible to site personnel and not other people, and
16 then the providers, that's us, validate that the
17 authority and security requirements concerning entry
18 access and change to data are met, and those
19 requirements would be consistent with Part 11 and with
20 the particular individual privileges that need to be
21 in place for a particular trial, and that each of
22 those requirements would now be stipulated in a
23 requirements document, they would be proven to be
24 fulfilled by the system, by testing, and then the test
25 document validation could be inspected and audited to

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1 make sure that the system was working as it should,
2 and that's what the monitor would look at when they
3 went to the site to make sure that the system was
4 behaving properly, that the data was correct, and that
5 the investigator had the necessary authority to
6 prepare and maintain the data.

7 And then, after the trial investigators
8 would retain the eDiary data by probably having some
9 kind of physical disk, the system would be turned off
10 and they'd have some kind of storage media at the site
11 that would live for 20 years, and one of the reasons
12 for using the CDISC ODM model for archive storage is
13 that it's all character based, it's all XML, it's
14 going to be readable in one form or another, maybe
15 conveniently if the XML viewer continues to run on the
16 operating system 20 years later, but even if it
17 doesn't the characters will still be legible and you
18 can certainly rebuild a viewer within a couple of days
19 by, you know, moderate - a person of moderate skill,
20 if they still exist. Twenty years a long time, you
21 know.

22 So, the interpretation now is that an
23 electronic Reported Outcome System, the providers of
24 such systems address the existing regulations by
25 understanding that the files in the ePRO system, which

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1 are electronic records, qualify as files of the
2 institution. I'm being very explicit here, because I
3 hope that this issue is one that is so easy to resolve
4 in some ways by ICH and by FDA, or by having somebody
5 who makes a clarification as an authoritative
6 spokesperson for either organization, I just want to
7 be clear, try to make sure that people understand what
8 people are arguing about. It literally comes down to
9 meanings of words like of, and I've made the
10 capitalization there of OF, that's my highlight.

11 And then, I mentioned this before, that
12 the features ensuring the investigator can use the
13 system to prepare and maintain the source records are
14 typically specified in detailed requirements
15 documents, validated by testing, and confirmed by
16 inspection of validation documents at audit, which is
17 inspectable, those documents are inspectable at the
18 site.

19 And then, this is the key final paragraph,
20 the sponsor orders the technology providers and the
21 site to use a system that conforms to these
22 requirements, so the sponsor audits the providers to
23 make sure that the providers conform to the
24 regulations. The sponsor has that obligation, and
25 makes sure that the technology providers fulfill it.

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1 But, in the paper age, the obligation of
2 maintaining and caring for the physical paper was
3 really entirely that of the investigator, and some did
4 and some didn't do - some did a good job, and some
5 didn't. But, there is an important sort of shift
6 here, in that the sponsor is really saying to the
7 investigator, I'm sure because I have the resources to
8 audit this system, that it works pretty well, it won't
9 lose your data, nobody else is going to be able to see
10 it, it has the necessary privacy protections and the
11 like, and I'm kind of warranting to you that on the
12 basis of my auditing of this system, as a sponsor,
13 it's okay for you to use it to fulfill your regulatory
14 obligations to prepare and maintain the records.

15 So now, we'll get to some of those
16 familiar questions, you are all prepared, this was the
17 educational foray now complete. So, where's the
18 source document? Well, these are the two answers that
19 could be given. The one lawyer says, well, physically
20 they are on a server, they are simultaneously on a
21 back-up tape, they may be also simultaneously on a co-
22 located server, and, by the way, they may still be on
23 the device that the patient used to record the
24 original outcomes. So, that's where the records are,
25 and the source document is all of those things, all

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1 those physical things, or it's only one of them. It
2 may be the device, but if it's the device, and the
3 data is not in the device any longer, then is the
4 device the source document, or is it in the database?
5 Well, if it's in the database, it's been changed,
6 because now it's in a representational configuration.
7 Logically, the different parts of any particular form
8 have been pulled apart, and they are now in different
9 columns and different fields that are represented in
10 the database. So, I don't think it's in the database.

11 But, if you have the same source document,
12 all of those fields tied together now electronically,
13 but in the old days tied together by a physical piece
14 of paper, all those fields were presented at the same
15 time, they were signed, they were entered, that
16 property, the physical properties of paper, acted much
17 in the way that the electronic system does today, to
18 hold the various fields together and present them
19 together, if that record is present simultaneously in
20 all those places, and the only people who can get to
21 them are people at the site and maintaining them, that
22 prepared them, then that seems to be the second item.

23 Now, the lawyer in the second position,
24 because that's the one I agree with, he got more --

25 Well, let's move on, what about the thin

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1 versus thick client, electronic data capture and
2 eSource? Meredith, correctly I think, identifies
3 electronic data capture nowadays as one where the
4 sites typically keep the paper source. Okay. And so,
5 we are really thinking here of electronic data capture
6 in the sense of, well, suppose you captured that data
7 electronically at its origin, that the data you were
8 going to refer to in your submission, that's what I
9 think of as original, that that data was originally
10 captured electronically and, therefore, there is no
11 paper source.

12 Well, people will argue that if the data
13 is on the remote server how can it be at the site?
14 And, that comes up a lot. The main purveyor of EDC
15 systems, Phase Forward, has the position that they
16 have to support paper source because the regulators
17 wouldn't accept electronic source. That's a position
18 that I don't agree with, but it might be true, but how
19 do we find out? How do we get this clarification? I
20 don't think we have to rewrite the regulations, we
21 just have to clarify what they mean.

22 And, is the eSource data on the server, a
23 so-called "certified" copy? Well, what was a
24 certified copy with paper? Somebody took a piece of
25 paper, and they Xeroxed it or something, and then they

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1 signed that they inspected it, and they said that the
2 Xerox copy was known to be exactly the same, and they
3 signed it, and manually processed, they verified that
4 the two were identical, had the same information on
5 them.

6 In the electronic world, a copy is made by
7 transmission, if the original device still holds the
8 data and the receiving device receives that data, and
9 the messaging process, as we called it this morning,
10 is proven by validation to be accurate, then
11 validation is asserting that the two now records of
12 data have identical information in them.

13 Well, that's not certification in the
14 usual meaning of manual certification of each copy,
15 but there is a manual certification by the person who
16 did the software quality engineering on the system,
17 who said that that's how the system operated and that
18 the copies were always identical, because every test
19 they run shows that the copies are identical, that the
20 copying utility is validated to work properly.

21 So, I don't know, interesting question,
22 whether it's a certified copy or not. Functionally
23 and operationally, I think it is, but, you know, would
24 we be held up on the regulation? Some people will not
25 do a trial with eSource, because they are concerned

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1 that FDA would be - or ICH, would be so focused on
2 this issue of certified copy that maybe it wouldn't
3 work.

4 Well, if the device is the source
5 document, we've done that maybe enough times, as you
6 already get it, and the unfortunate territory is that
7 you imagine the monitor coming to the site and trying
8 to figure out what to do with a little SD card that
9 had the records in non-volatile memory of a particular
10 patient's diary, that they are going to try and check
11 against a database.

12 Well, what about trusted third parties?
13 These are not part of present regulations, they are
14 introduced into the dialogue out in the real world by
15 people that are trying to implement the existing
16 regulations. The concept might be that the holder,
17 this server farm that Meredith talked about, that the
18 holder of the data is acting as a third party on
19 behalf of the site, but is that third party, does it
20 need to be discussed in the context of how trustworthy
21 is that party? Maybe not, because the other side of
22 the equation, now taking lawyer number two's position,
23 is that the sponsor has the full legal responsibility
24 for conducting the trial properly. If the sponsor has
25 vetted that the party holding the data is holding it

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1 properly, has built a system that isn't going to lose
2 it, and has inspected and assured that by audit, then
3 the sponsor has fulfilled their responsibility, there
4 is no separate responsibility for the trusted third
5 party. So, maybe you don't need to worry about the
6 trusted third party as a concept.

7 And finally, the clues about, you know,
8 all the people who worry so much about the FDA getting
9 it wrong, from the FDA draft guidance on "Computerized
10 Systems Used in Clinical Trials," which Joanne Roades,
11 bless her heart, calls CSUCT, which is what I call it,
12 that it talks about original observations are entered
13 directly into a computerized system, the electronic
14 record is the source document. It doesn't say the
15 system on which that record is stored is the source
16 document, it says the record, meaning, I think, the
17 informational content of the record. That's very - I
18 mean, that fills me with optimism. I think people get
19 it, and I'm hopeful that the new guidance will be
20 great.

21 The monitors in the paper process, they go
22 out and they do this field-by-field checking, because
23 paper had errors in it that electronic methodologies
24 simply don't have. They have them, but they are
25 weeded out by validation and testing, they are not

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1 weeded out by manual drudgery of each piece of paper
2 being compared against its origin, and that's why we
3 highlight that, does not require manual field-by-field
4 verification, there is still a process of source
5 document verification, that would go to make sure that
6 the originators of the source documents, the patients
7 themselves or the physicians making comments, are real
8 people, and that the people by other records that
9 might exist, either an electronic health record, or
10 maybe a paper health record, are consistent with the
11 diagnosis and the treatment, the therapy that the
12 person received.

13 And then, FDA investigators, what do they
14 do with electronic source? Well, if they show up at
15 the site during the trial, they should have access to
16 whatever records they ask for. That's what the rule
17 says. Well, they could get such access if they had a
18 secure log-in, if the site let them in the door, and
19 if the system made some sort of provision for them to
20 take a look at the site - that particular site's data,
21 because that's what they should see if they were there
22 in the old days of paper. They shouldn't be able to
23 inspect at site A the records that pertain to patients
24 that are managed by site B. So, if the system does
25 that, then that seems to be reasonable.

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1 And, if the trial is over, and they are
2 inspecting after the trial, then the FDA inspector
3 should be able to see a protected record that
4 supports, in the existing guidance, reconstruction of
5 the trial, which means that they should be able to
6 understand how the trial was done, how the electronic
7 system used in the trial for eSource functioned, what
8 was the regulatory environment at the time that the
9 trial was done, sufficient context to understand the
10 meaning of the data and to be able to establish
11 whether that data can be trusted to serve as the basis
12 for public policy and to protect people who are going
13 to take the new medication, or engage in the new
14 practice, or possibly have a therapeutic event as a
15 result of a new device.

16 So, here's our current thinking, and I
17 think work is continuing, I don't want to say that
18 this hodgepodge of positions that I'm reflecting, the
19 arguments that I'm taking up, are stable, but
20 everybody engaged in that discussion is trying to
21 focus on the objective, how do you get good science,
22 how do you get better information about what's really
23 happening to patients in a way that you can depend on,
24 so that you can know what's happening to the patients
25 and know that the source of information that you are

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1 getting about those patients is trustworthy?

2 Well, we know that the eSource and ePRO is
3 very helpful. The standard deviations look like they
4 are lower. You can use fewer patients and achieve the
5 same level of efficacy. People cooperate well, they
6 like it, and so it's useful.

7 The risks of electronic methods were
8 foreseen and addressed in Part 11 and in the security
9 provisions of CFR 45.164 in HIPPA, and they lead to
10 the necessary requirements that a system should have
11 in order for the data in that system to be
12 trustworthy.

13 And, sponsors are selecting and endorsing
14 the suitability of the systems that are made to those
15 requirements, they are literally traceability
16 matrices, with every aspect of the regulation listed
17 in a long column, an approach to how is that going to
18 be fulfilled by this particular system, the tests that
19 are done against each of those, individual granular
20 requirements, and then the documentation that the
21 tests were successful.

22 Well, if the sites use the system
23 providers for eSource are there useful clarifications
24 and guidance and GCP that ought to be made? And, here
25 are the recommendations. I believe that these verge

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1 on personal recommendations, but I think they get a
2 lot of endorsement. I just didn't have a chance to go
3 and make sure before I gave this talk.

4 So, sites should probably understand how
5 the systems safeguard the records. They have the
6 responsibility for preparing and maintaining the
7 records. They probably ought to know enough to, at
8 least on a common sense level, say, yeah, they know
9 how the system works, the sponsor validated that I was
10 the only one who was going to be able to see the data,
11 I didn't have any indication as I used the system that
12 anybody else was poaching on that data, and I'm pretty
13 comfortable because of the information sheets, or the
14 training, or whatever would be the necessary standard,
15 but I think that a guidance ought to require that an
16 explanation be provided, so that the old meaning of
17 the investigator having authority over this data could
18 be preserved in the electronic age. That's an
19 expansion, possibly, but I think it's a useful one.

20 And then, I think the disputes on the
21 location of physical storage devices, and also another
22 one that you hear a lot is, if it isn't the first
23 instance where, let's say, somebody's birthday was
24 recorded, it can't possibly be the source data. Well,
25 that's, I think, also fairly dumb, it's not - the

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1 important part is, is your original source that you
2 are relying on to be the accurate piece of information
3 that you are going to include in your report, that you
4 are using for deciding whether the drug effect that a
5 person of that age properly, is that age accurate and
6 right, and where did it come from? If it came from an
7 interview with the patient, and you were recording
8 that interview electronically, that isn't the first
9 time that patient has recorded possibly into a system
10 of some sort how old they are, but it is the original
11 recording with respect to that trial and the context
12 of that trial, and I think that could be made a little
13 clearer so we don't have silly arguments about, well,
14 a millisecond before the pen hits the paper the camera
15 that's looking at the position of the pen on the paper
16 is recording a digital event, and that digital event
17 comes second, so, therefore, the source document, even
18 though it's only a millisecond earlier, has to be the
19 handwritten thing.

20 Part 11 does a pretty good job on that
21 with respect to laboratory data.

22 And then, the disputes on location of
23 physical source devices, I've covered that, I hope the
24 guidance will clarify that.

25 Thank you.

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1 ASSOCIATE DIRECTOR MOLZON: Thank you,
2 Steve.

3 Are there any questions?

4 Helle, one last shot?

5 MS. GAWRYLEWSKI: Somebody asked about the
6 accuracy, and I think they were thinking like I was
7 thinking, how do you prevent a patient from making an
8 error, a transcription error, so we are comparing
9 maybe a CRF recorded at the site with an intercession
10 of, you know, somebody asking questions, versus
11 something that the patient takes away. But, we have
12 to compare what the patient takes away on paper, and
13 how that's a worse scenario. So, we shouldn't be
14 comparing, you know, what you are recording at the
15 site versus something that the patient takes away. I
16 mean, there's no comparison. So, when I was kind of
17 thinking about it, I think that's an important point,
18 the ePRO is much more accurate than, you know, than a
19 paper version of that, because you don't have those
20 checks built in.

21 DOCTOR RAYMOND: It's definitely more
22 accurate in that sense. It's also of great interest
23 to know whether the question represented on a portable
24 device or in telephone is answered in the same way if
25 it's presented electronically, as it was answered in

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1 the past on paper, the sort of psychometric validation
2 issue, and we've had a nice conference on that, that
3 indicated that in the main, as long as you don't
4 really change the semantic meaning of the question, it
5 works okay.

6 I was also asked earlier about adverse
7 event reporting, I think you mentioned it. And, one
8 of the - there are two brief points I would make, if
9 that's all right.

10 ASSOCIATE DIRECTOR MOLZON: Go ahead.

11 DOCTOR RAYMOND: Okay.

12 So, one is that new tools for harvesting
13 adverse event information from patients, maybe it
14 better be called symptom information, did you have a
15 headache, you know, did you sleep well, were you able
16 to be active, could you fulfill the activities of
17 daily living, kinds of questions like that, that you
18 might be able to have a check box, you know, headache,
19 muddled thinking, you know, constipation, various
20 things that might happen.

21 Well, the argument against having check
22 boxes is that you'll illicit additional adverse
23 events, which might not be such a great thing if you
24 are wanting to compete on the basis that your drug has
25 fewer adverse events than somebody else's.

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1 On the other hand, getting information
2 that patients routinely experience a mild headache is
3 really an important factor in deciding how the drug
4 should be administered, or in learning what the
5 patient's experience is.

6 So, I want to at least bring out the
7 possibility that the data capture methodologies, with
8 a check box and then a rating score, are very easy to
9 do, might work really well in terms of capturing
10 symptom information, not necessarily the serious
11 adverse events of hospitalization and the like, but if
12 you are looking for Patient Reported Outcomes and
13 eSource data, there is a data stream that can be both
14 dense and, I think, quite interpretable, and if you
15 are comparing against an arm that is a placebo or an
16 arm that's another drug under identical conditions for
17 collecting these adverse events, maybe you don't have
18 to worry that much about the fact that you arguably
19 might have more of them reported, they wouldn't be
20 differentially greater.

21 And then the second point is one that came
22 from Meredith Nahm's presentation, which is, if we
23 have electronic source in a medical record, with a
24 standardized meaning to the various kinds of adverse
25 events, the migraine headache grade II is always

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1 migraine headache grade II, and Randy Levin's
2 standardized terminology supports that consistent
3 usage in Europe, Japan and the U.S., we have a
4 tremendous possibility of getting reliable post-market
5 information out of electronic medical records that
6 could constitute the equivalent of a very large, very
7 reliable safety study, so that conceivably you could
8 imagine with the eSource medical record you could
9 imagine a world where the electronic - the study is
10 done for Phase III could be relatively small efficacy
11 and safety studies to make sure that nobody is really
12 in trouble, obviously, and then you do a high-level
13 statistical observation in the post-market, and you
14 wind up better off than you are now with less money
15 spent.

16 ASSOCIATE DIRECTOR MOLZON: Thank you.

17 Anyone else?

18 Well, you know, I went back and looked at
19 my papers, and E6 was signed off in 1996. I don't
20 think there were any PDAs, there was no HIPPA, so you
21 really have to evaluate, you know, how we gather data
22 in a new context. So, I think our assignment from
23 Steve is to go back and have a big discussion about
24 OF, right?

25 DOCTOR RAYMOND: Better than IS.

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1 ASSOCIATE DIRECTOR MOLZON: OF and E,
2 right, yeah, right.

3 So, before we close, I want to thank Sema
4 Hashema for helping me with the logistics, Laurie
5 Burke for helping me pull a lot of these groups in
6 here at the last minute. We took advantage of an
7 opportunity that we had, and I think we've done a lot
8 today, to get a lot of these things that have been
9 going on in their own little groups into one document,
10 into the transcript, so that we have a record of all
11 these different activities.

12 And, I forgot to mention that I'm actually
13 on the Steering Committee for ICH, so I'll be taking
14 this with me when we go to Brussels. And, I think
15 that's it.

16 So, I think we owe all the speakers a
17 round of applause, and all of us for staying here.

18 (Applause.)

19 ASSOCIATE DIRECTOR MOLZON: Yes, Barbara,
20 I'm sorry.

21 MS. TARDIFF: I'd like to respond to the
22 one question of yours that I was unable to answer.

23 ASSOCIATE DIRECTOR MOLZON: Oh.

24 MS. TARDIFF: Very quickly.

25 But, Level 7 refers to the highest level

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1 of the International Standards Organization, ISO,
2 communication model for Open Systems Interconnection,
3 or OSI, and the seventh level is the application
4 level, as I mentioned. That part I remembered.

5 And, it actually addresses the definition
6 of the data to be exchanged, the timing of those
7 interchanges, and supports related functions, like
8 security checks, participant identification,
9 availability checks, exchange mechanism, negotiations,
10 and, of course, most importantly, data exchange
11 structuring.

12 ASSOCIATE DIRECTOR MOLZON: Thank you,
13 Barbara.

14 So now the record is complete, so I think
15 we can call it a day, and thank you everybody.

16 (Whereupon, the above-entitled matter was
17 concluded at 4:56 p.m.)

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