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FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
ELECTRONIC SUBMISSION OF ADVERSE EVENT REPORTS TO FDA
ADVERSE EVENT REPORTING SYSTEM (FAERS) USING
INTERNATIONAL COUNCIL FOR HARMONISATION (ICH) E2B(R3)
STANDARDS

Docket No. FDA-2018-N-4002

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Silver Spring, MD 20993

Reported by: Michael Farkas

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A P P E A R A N C E S

(Continued)

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

2 I N T R O D U C T I O N S

3 MR. DE: All right. Good morning, everybody.
4 So is the -- the Webex is on, right? Just want to
5 know. So good morning, everybody. My name is Suranjan
6 De. Welcome to the FDA. I'm the Deputy Director for
7 Regulatory Science and Office of Surveillance and
8 Epidemiology in CDER.

9 So today again -- we had the first session in
10 March, end of March. Today is the second session. So
11 before we start the session, I want -- I would ask
12 Gerald to come here and, you know, say a few words on
13 this whole project which we are doing of upgrading FDA
14 with E2B(R3).

15 MR. DAL PAN: Okay. So good morning. And I'm
16 Gerald Dal Pan. I'm the Director of the Office of
17 Surveillance and Epidemiology in CDER. I like to thank
18 you all for coming here today and tolerating the sticky
19 Washington heat of summer. And I think we have a lot
20 of people participating remotely too, so welcome to you
21 as well.

22 As you all probably know, the Adverse Event

1 Reporting System, FAERS, is really the backbone of our
2 drug safety surveillance system. We hear a lot today
3 about artificial intelligence and real-world data and
4 real-world evidence, and those things are very
5 important and we're using them and like many of your
6 companies we're interested in developing them further.

7 But adverse event reporting the old-fashioned
8 way, a 50-year-old system, is still a very critical
9 part of what we do. About half of our post-market
10 safety label changes come from these type of data. So
11 I don't see this as anything that's going away any time
12 soon, if ever, in a drug safety surveillance system.

13 And within that system, FAERS is the backbone
14 of that system. For those of you who have been
15 involved in this for a long time, you'll remember that
16 we had AERS in 2012. We switched over to FAERS, a new
17 system. Now we're switching over to what we're calling
18 FAERS II, a different underlying architecture that will
19 incorporate the changes we agreed to in ICH E2B(R3).
20 And we recognize that, yes, we're the last large
21 regulatory body to be implementing R3 and we wish it
22 could have happened sooner, but we are where we are.

1 So as Suranjan mentioned, this is the second
2 of three meetings and we're going to hear from a lot of
3 different people today about different aspects of this.
4 We're expanding FAERS to accommodate types of reports
5 that traditionally haven't been sent to FAERS.
6 Traditionally, it's been adverse event reports for
7 biologics and drugs for approved products and marketed
8 products.

9 And you'll hear today after Suranjan's
10 synopsis about incorporating IND safety reports.
11 Typically, IND safety reports are sent to the IND.
12 They're generally sent to FDA as PDFs in the electronic
13 common technical document. Now -- and that method of
14 submitting them does not allow for analysis, filtering,
15 searching. Here we're going to put them into FAERS and
16 it will allow the pre-market reviewers much better and
17 more efficient access to them. So Suranjan will be
18 talking about that this morning.

19 Then we'll hear from Karen Feibus from the
20 Office of Generic Drugs. Generic drug applicants for
21 the last 12 years or so had the requirement to submit
22 adverse event reports for serious adverse events that

1 occurred during bioavailability and bioequivalence
2 studies. Again, those have come in in a traditional
3 method. Now it will be coming in through FAERS. And
4 she'll explain that program as well.

5 Combination products have received a lot of
6 attention over the past few years. We have a
7 combination product safety reporting rule that I'm sure
8 many of you are familiar with. And you'll hear about
9 (sic) Melissa Burns about the regional requirements for
10 combination product safety reporting.

11 Later on, you'll hear from our colleague Craig
12 Zinderman on electronic safety reporting for vaccines.
13 That's a separate system. And then you'll hear from
14 Dr. Hans-Jorg Romming from Merck KgaA in Germany about
15 industry's experience implementing R3 with regulators
16 around the world.

17 So it's a busy day. We thank you for coming,
18 and we hope that these meetings will allow for a smooth
19 transition from R2 to R3 when we make that transition.

20 So with that, I'll turn over to Suranjan.

21 MR. DE: Okay.

22 MR. DAL PAN: Thank you.

1 SESSION 1: SYNOPSIS FROM PREVIOUS MEETING

2 MR. DE: All right. Thank you, Gerald. So as
3 you heard Gerald that we have our commitment to
4 implement R3 in FDA and we basically want to work
5 together with all your support to implement R3 within
6 FDA. Of course now as you have also heard that we have
7 so many different kind of reports that needs to be
8 implemented in part of R3. So with that, we will start
9 with the first topic.

10 So as I said, I'm Suranjan De. I'm Deputy
11 Director, Regulatory Science in OSE, CDER. So I'm
12 going to start with a little bit of synopsis from what
13 we talked about in the last meeting in -- on March
14 25th.

15 So we had a talk all about the FAERS II and
16 what was FAERS II, what are the -- what are we
17 implementing in FAERS II and we communicated the plans
18 of FAERS II and our plans of E2B(R3) upversioning. In
19 addition to that, we also talked about that we don't
20 have a current or a compliance date of when -- a
21 compliance date for the -- for industrial sponsors, but
22 FDA plans to implement R3 by March 2020. So that's

1 where FDAs plans is.

2 Now, after March 2020, there is no compliance
3 date that has been set, so -- and then finally, we
4 talked -- last time we talked a little bit about the
5 testing plan and the method. So once FDA is ready,
6 then what would -- how would industrial sponsors would
7 come and, you know, do their testing as they are
8 getting ready. So we talked a little bit of that
9 process and the method.

10 The second session we had in the first
11 meeting, Meredith (ph) actually talked about IND safety
12 reporting into FAERS. She talked about certain
13 scenarios, some data elements with some use case
14 examples. And then we also -- we had TJ, who came and
15 then talked about the IDMP part of things, explaining
16 what IDMP is and how -- in future how that probably
17 would get used or implemented.

18 Third session we did talk about the post-
19 market safety. So what are the specific data elements,
20 regional elements for post-market safety in R3. So we
21 are not going to go over those elements at this session
22 that we discussed in the first meeting. So this

1 session mostly we'll on the post-market side would
2 concentrate on the combination product data points.

3 And then we have updates to the electronic
4 submission routing mechanism. We talked about that.
5 We talked about that today we have one mechanism of
6 submitting the post-market report. In future, you're
7 going to have two separate paths, which means you're
8 going to have two separate routing IDs or two separate
9 ACEs, two headers, which you would use one on the pre-
10 market side, one on the post-market side. That would
11 help us to separate those reports and handle them
12 separately. Because as you know, the post-market
13 reports are also redacted and posted publicly and we
14 want to separate them out such that the pre-market
15 don't fall into those -- that bucket.

16 And then finally, we also talked about how
17 reports could be tested by sponsors, where FDA plans to
18 provide a website or a URL where sponsors can go in,
19 upload their file, test the file, validate their file,
20 see any errors which are showing up. These files
21 validation will be against the R3 core elements and the
22 regional elements. So that way, you would see if

1 you're testing -- if your vial passes through. And if
2 they do, then, you know, before you do your production
3 -- first production submission, I think, you know, this
4 testing would be important.

5 There is another testing which FDA plans to do
6 as we're getting ready. We are also -- since we are
7 part of ICH, we also plan to do across regional testing
8 with other regulators so that -- just making sure that
9 when a sponsor submits a report which is reportable to,
10 let's say, three countries, the idea is not to create
11 three different files. The idea is to create one file
12 so that it can be submitted to the different regulators
13 and it will be the regulators' responsibility to then,
14 you know, ignore the regional elements of the other
15 regulators.

16 So we want to do across regional testing so
17 that we know, understand what would happen if we get a
18 file from Europe and ingest that in FAERS.

19 So this was all summary which we talked about
20 in the last meeting. This summary, all the slides, the
21 presentation, the video, everything is available on the
22 meeting page, on the FDA's meeting page. So you can

1 visit them and look at them and download them.

2 So what did we do after we finished that first
3 meeting? So after we finished that first meeting, we
4 had asked for comments on the docket. So we did not
5 receive any comments from the docket. We also started
6 - went and updated our schema on the regional elements,
7 because we have all these combination products that
8 what we were supposed to work on. We started working
9 on that. And of course started preparing for some of
10 the IND and the combination products for today's
11 meeting. And as I said even the last time that once
12 you have -- the docket timeframe is over, you have this
13 e-mail address where you can always e-mail and we'll
14 respond back to you.

15 So before I start with -- okay, the third --
16 this one is again important. We updated the roadmap
17 based from what we talked about in -- when was that? --
18 March. So we are in July. So in July if you look at -
19 - we have our public meeting which is happening today.
20 As we are moving through, we are starting to update our
21 technical specification. And then the last time I
22 actually showed you that we're creating this one big

1 spreadsheet of all data elements, which includes all
2 the ICH core data elements and the regional elements.
3 And as we are creating that spreadsheet, we're also
4 trying to harmonize data elements between VAERS and
5 FAERS.

6 Now you will still see some data elements
7 which will purely eventually say -- will say VAERS, but
8 the idea is to harmonize. Eventually, that spreadsheet
9 should only say the source of the data element is
10 either ICH or FDA, not differentiate between FAERS,
11 VAERS and all that. So that spreadsheet is being
12 updated.

13 Last time actually I showed you what the data
14 element -- what the columns of that spreadsheet is
15 going to look like. And that spreadsheet, all the data
16 elements are basically picked up from the IG, the ICH
17 IG.

18 So today you will see some of that sections
19 when we talk about combination products. So we have
20 been updating the data elements, adding in, you know,
21 what the attributes of the data elements are going to
22 be, what new OIDs the data elements are going to have,

1 requesting for the appropriate OIDs to connect to those
2 data elements and making sure that all these data
3 elements eventually also comply with the HL7 model,
4 because it needs to have some home HL7 model eventually
5 so you have the right XPaths available.

6 So as you see in the slide, we still have the
7 date where we said our technical specification
8 eventually will be available by end of March. And the
9 whole idea is, once it is updated -- once it is
10 published, we hopefully will get, you know, very few or
11 minimal comments because we're having these meetings to
12 communicate our plans and communicate what we are
13 doing, what are regional requirements are. And
14 expecting that we will get a lot of comments during
15 these meetings or maybe right after this meeting so
16 that when we do our technical right specification
17 update, we have considered all these comments which
18 come from you all. And hopefully, once it is
19 published, we get few or hopefully no comments.

20 Another update which we have is, as I said, we
21 actually have just started now that -- now that the
22 first meeting happened, we just started our tools to

1 get updated to those data elements. And right after
2 March, you will then have the sponsor testing, which
3 you will have the opportunity to use our website to
4 test your files if you're ready or when you're ready.

5 All right. So with that, any questions on our
6 whole introduction of my -- the summary we had, the
7 timelines? Any questions? Anybody -- yeah.

8 So when we will -- when we publish this, I
9 think it will be a draft publication which will come
10 out and then we will finalize it. The idea would be
11 that all this data elements which we are talking about
12 in -- hopefully, we will be able to cover all the data
13 elements until today -- up to today's session.

14 We have another session in February. That
15 will be more like a finalization. So within that
16 timeframe, we will give -- just group out all the
17 documentation related to those data elements as they
18 are discussed. Yes.

19 Exactly. So this technical specification
20 today which we have for R3 only talks about post-
21 marketing. So there will be now a section for pre-
22 market and a section for combination products, maybe a

1 section for BA/BE. If it can be combined with --
2 together as pre-market, of course. But if not, then
3 there'll be two sections: one for IND, one for BA/BE.
4 But it will be one technical specification document.
5 We do not want to have a separate document.

6 So that's the idea. And as we go through the
7 data elements, the meeting page -- so keep an eye on
8 the meeting page of FDA. This meeting page today
9 actually has the first session, some data elements we
10 talked about in the first sessions. And then today's
11 session all those elements will be available there.

12 For R3? Yes, yes. So the idea would be that,
13 you know, when you are testing this -- so once -- let's
14 say, we are ready in March 2020. When you start
15 testing this, you would want to test an IND safety
16 report, right? You want to test combination products
17 post-market report. You want to do a non-combination
18 product post-market report. You may want to do a BA/BE
19 trial, you know, report. So yes.

20 Because the reason was that if we did this in
21 different timeframes, then what happens is whole cost
22 of testing that again, you know, making sure the

1 vendors are then ready. You know, it will come in
2 chunks. And just having in chunks sometimes just
3 creates a lot of dependency and makes things a little
4 difficult.

5 Yes. So we will have it -- our formal testing
6 -- as we come close to March, we will have -- a proper
7 testing process we will set. I just gave a little
8 brief last time on how testing is going to happen, but
9 we're going to have proper testing procedures. And
10 this URL or the site we're trying to -- we're going to
11 be publishing, it's basically a front-end UI and
12 there'll be some help instructions as to how you want
13 to test before you do your first production submission.

14 Yeah. The testing by the gateway process will
15 probably still stay the same. That's really not
16 changing, except that there'll be a routing ID for pre-
17 market and a routing ID for post-market. But the
18 process is still the same, right?

19 I think the more -- I mean, sponsors will be
20 probably more interested if their file would pass the
21 validation or not, right? So that will be the prime
22 focus. The way you are submitting post-market report,

1 I think the path would be -- basically, the routing ID
2 will be a different routing ID, one for pre-market and
3 one for post-market.

4 So vaccine is right now happening in a
5 different parallel route. So Craig will talk about
6 that. It's a separate guidance which they have.
7 Eventually, the whole idea is that sometime in future -
8 - I don't know when, if I'm still here -- but have one
9 safety database for FDA, right? So maybe it's vaccine
10 or, you know, tobacco product or device product or, you
11 know, drug product, whatever it is. I mean, thinking
12 is that. But right now it's separate.

13 Yes, yes. The guidelines will be separate,
14 yeah, yeah. Yeah, yeah. And you will actually see
15 that especially -- I think last time I presented that,
16 it shows the data elements as rows and the column says
17 which are the ones which are core, okay, which are the
18 ones which are specifically for post-market, which are
19 the ones -- and within the post-market, it tells you
20 what the conformance and all that is.

21 And then with -- then it gives you a column
22 for IND and then it gives you a column for I think

1 vaccine and post -- and combo. So there are separate
2 columns which kind of say -- so same data element, is
3 it used in all these four or this is only used here?
4 So you will know that.

5 But again, as I said, we want to make it in
6 such a way that it doesn't matter that data element is
7 for -- is in that schema. But when you submit it, let
8 the receiving -- the destination system decide on what
9 to take, what to ignore and -- so that the submissions
10 are passed.

11 One other thing, important thing is that, you
12 know, we are really not going to have any new specific
13 data checks. I mean, today we don't do much data
14 check. I mean, so four elements are to be there.
15 Whatever the schema today defines is what will be
16 there, okay? So we currently don't plan to have any
17 new data checks.

18 I mean, we take advantage of Europe actually.
19 Because there are so many data checks there that, if
20 they pass, then that means we are getting good data --
21 I mean, the same report. But we're not going to have
22 any special data checks except -- I think when we talk

1 about IND, I'm going to talk about there is just one,
2 because that specification is important for us to route
3 the report to the right reviewer to review, so. But
4 other than that -- yes.

5 All right. That's a very -- I knew -- yeah, I
6 was expecting that question because -- yes. So what I
7 would -- yeah, three. Yeah. So I would -- let's do
8 this. Let me answer that question when we talk in the
9 afternoon about combination product. So we'll have
10 Melissa, who will be here. So she will definitely
11 address this or at least I will address this during
12 that time. We had a question from there. Oh, you have
13 the same question.

14 So the specification document, the main
15 document with the -- yeah, the spreadsheet will
16 probably be available. We'll try to make it available
17 prior to March 2020. But the actual specification
18 document with all this FDA headers and all that, that
19 will only come after March 2020, because that has to go
20 through all these different clearances and all that.

21 But the actual data element points, I think as
22 we are going through these sessions, we are posting it.

1 I mean, our slides have it. So we will -- hopefully,
2 after this meeting, the second meeting, I think we will
3 be pretty much done with most of the data elements. So
4 by fall, we should be able to post those data elements.
5 We are just waiting for the OIDs to be requested and
6 put in this -- with these data elements. So hopefully,
7 by fall, we should be able to post the spreadsheet at
8 least. So you'll get a fair idea about what these data
9 elements are.

10 Yeah, on the meeting page. Yeah. Okay. All
11 right. So there's one thing which I realized on the
12 agenda, that for the IND safety reports -- I don't
13 know. For some reason I have put up to 11:00 o'clock.
14 I don't have that much of content to go up to 11:00
15 o'clock. But let's see how we go about...

16 SESSION 2: E2B R3 REGIONAL REQUIREMENTS FOR
17 IND SAFETY REPORTING

18 MR. DE: All right. So next is we're going to
19 be talking about -- just before that. Okay. So this
20 session 2, we're going to start talking about regional
21 requirements for pre-market safety reporting, all
22 right. Now this pre-market safety reporting, some of

1 the data elements we're going to be talking about is
2 going to apply for both IND and BA/BE trials, all
3 right. So these elements are common.

4 So there are a few data elements which -- of
5 course all the core data elements stays at the core
6 data elements, but there are a few data elements which
7 either has a specific value you need to submit. And we
8 have I think two data elements which are new.

9 All right. Let's go with the first data
10 element. So we have the batch receiver identifier. So
11 this is what we are suggesting for the batch receiver
12 identifier. Where the value is -- we've used this
13 value called ZZFDA. Okay. This -- again, the ZZFDA is
14 something I don't know who came up with, but it was
15 before my time. Okay. And probably I can blame it on
16 Roger (ph) there. Okay. He's our veteran -- he's our
17 veteran -- yeah.

18 So to differentiate between pre and post-
19 market -- so we are saying that if that can be sent as
20 ZZFDA pre-market. And of course we have the test
21 environment, we all know. So that becomes a
22 ZZFDATST_Pre-market. And for post-market, it stays the

1 same. There's no change to that. We're going to still
2 use the way we are using it today.

3 Then you have the ICSR message. So here is
4 the interesting thing about ICSR message. Because we
5 have trial INDs for CDER and CBER -- now this is again
6 a suggestion we're trying to give out here. We want to
7 hear from you all is: with the message receiver
8 identifier, do you all think that if we can have a
9 value saying CDER pre-market and CBER pre-market? Then
10 it actually supports FDA to route the report to the
11 right center because the gateway is not differentiating
12 that.

13 But once it comes to FAERS, when we read this
14 message, we will be able to then say, "Hey, yeah, this
15 is a pre-market report for CDER IND or this is a pre-
16 market report for a CBER IND." Then their regulatory
17 systems, these case numbers can be sent to them.

18 So that is a suggestion which we have. I'm
19 not going to ask for your opinion now. But to the
20 docket or to the eprompt e-mail address if you have --
21 if you guys have any thought about this, please let us
22 know. If not, then we will go with -- we will go with

1 this. So this is the second element where we want to
2 identify which center this needs to be routed to.

3 Because third -- the other option was: we have
4 another routing ID, right? That was third option. And
5 we just said, "You know, another routing ID, then" --
6 you know, there's always confusion: "Okay, now this
7 report, I sent it to this routing ID and this to that
8 and this to that." Okay. Anyway, you have two routing
9 IDs. That's still -- probably sometimes, you know,
10 could confuse. But the two routing IDs are now set up
11 in such a way that they're very clearly defined: one is
12 for pre-market and one is for post-market. So think
13 about it and provide your comments. We'll really
14 appreciate that.

15 All right. So the next data element is now
16 the opposite side. That acknowledgment has been sent
17 out. So you may want to know where it is coming from.
18 And if you're trying to update your pre-market, your
19 IND safety report with their acknowledgment and -- or
20 the post-market report with the acknowledgment -- this
21 was -- when -- and the reason why we did this is -- you
22 will all know that -- I think last time Meredith talked

1 about that we're doing a pilot program with some
2 sponsors for the pre-market, the IND safety reporting.

3 While we were doing that, one of the sponsors
4 kind of suggested that if we could do this, then it
5 just makes our safety database easy to know what --
6 where it is coming from, what it is about, so we can
7 actually update our safety database with that
8 acknowledgment appropriately.

9 So with that, today we have post-market stays
10 the same and just pre-market we are saying that just to
11 have these -- these values. Okay?

12 Then this is a very important data element.
13 This is actually a new data element. So any new data
14 element if you see a prefix, it's starting with a FDA
15 dot, those are regional data elements. So when
16 eventually we publish that big spreadsheet, when you
17 see any element which says source as FDA, you will see
18 that element actually starts with the element number
19 starting with an FDA. So which means -- so that is a
20 regional data element.

21 So FDA report type. Now this is very
22 important for us on many fronts. One is because you

1 have all these different types of report. And as you
2 were -- we were talking about the different columns --
3 I think we were talking about that where -- how do you
4 define for what element for what. So the spreadsheet -
5 - this is a snippet of the spreadsheet. You see these
6 columns "post-market, IND, combo." That's how it's
7 been defined.

8 So you have a data element which will say
9 FDA.C.1.7.1 and the name of the element is FDA Report
10 Type that identifies the report FDA classifies based on
11 the reporting timelines. It's length of 1. The
12 conformance is mandatory. And then you see the allowed
13 values.

14 Now these allowed values are again based on
15 the type of report. So if you have a post-market, we
16 have the 15-day and a periodic. If you have the IND,
17 you have the 15-day and the 7-day. And then for combo
18 product, you will still have 15-day, the periodic, the
19 5-day, and the 30-day.

20 So that is -- those are the allowable values.
21 And we're going to have a new OID. So that's what I'm
22 waiting for. Once I get -- we finally get the OID,

1 that's when we're going to -- we can post that
2 spreadsheet. Yes?

3 Yeah. We can keep that into -- yeah, yeah. I
4 think we're almost there getting the OIDs. We already
5 have requested it. So I think it should be -- TJ, TJ,
6 who is providing the OIDs? So it's the -- the whole
7 mechanism of OIDs the last time we talked about, where
8 TJ explained how this whole OIDs come through. So
9 every number and dot represents some entity. And then
10 eventually, we said FDA's entity will be -- the last
11 digit will be this -- sorry, the second last digit will
12 be this. Then the last digit will say it's CDER or
13 eventually it may say FAERS. And so that becomes the
14 OID.

15 So it's applicable to FAERS or applicable --
16 because there are some data elements just applicable to
17 vaccines, right? Or some -- so there's a whole
18 mechanism. And then we come kind of at the end "dot
19 this, dot this, and dot that."

20 Yes? No, no, no. The reason I put combo
21 products is just because -- is just because the combo
22 products versus the non-combo products, I was trying to

1 differentiate there. And if it's a confusion, then we
2 can -- definitely we'll update this, because -- I mean,
3 end of the day, the combo products are also post-
4 markets products, right, are also post-market products.

5 So -- yeah, are also -- so if -- I mean, if we
6 all think that it makes sense to have everything in
7 post-market, but the problem comes is that we have
8 special fees for combo products that doesn't apply to
9 all other products. So when we go in the -- we talk in
10 the afternoon about all this other set of data elements
11 that truly doesn't apply to non-combo products.

12 So that's the reason we had separated out
13 combo products. I mean, combo products -- again, we
14 will of course say this -- we'll have to update this.
15 I realized this actually a week back that we should say
16 "post-market combo products" so that you know they are
17 still post-market.

18 Yes, yes. Because -- the reason being that if
19 you look at the regulations, post-market is serious and
20 unexpected. Pre-market is serious, unexpected and
21 suspected, right? So you can have a serious and
22 unexpected. That will now be required to submit post-

1 market, right? But then it became suspected, then you
2 have to submit the pre-market. And one is on the IND,
3 one is on the NDA.

4 So it has to be -- and then we have to make
5 sure that all the information which has come in the
6 IND, they don't get published, right? For the post--
7 market, we'll redact certain data points and then
8 publish. Especially, like the reporter, patient
9 identifications and all that, they all get redacted
10 before it gets -- narrative doesn't get published.
11 Some basic things get published. So that's why it's
12 important that we have -- we have two reports.

13 Now, in IND, you have to note that if you have
14 such a -- when you have such a situation, what we have
15 done -- and we want to hear that from you all also, how
16 would you manage or, you know, have a report in your
17 system. Like we're asking for two, but how would you
18 do that in your system. Because -- and the reason I'm
19 asking this question -- is it going to be one report in
20 your system or is it going to be two reports in your
21 system?

22 And the reason why I'm asking this is, we

1 assume that it -- if it is one report in the sponsor's
2 system, then our follow-up algorithm works based on the
3 safety report ID number, okay? So if you -- if the
4 sponsor sends us two reports, both have the same safety
5 report ID, then in FAERS it will automatically try to
6 create a follow up. We don't want that.

7 So we have found a mechanism how to keep that
8 separate. Because we're coming from two separate
9 routing IDs, so we know how to now keep that separate.
10 But especially, in the sponsor's safety PV databases,
11 we want to hear from you all how would you create those
12 reports and how would you store and how would you
13 manage those reports. Are they managed separately?
14 Are they managed as one case in your safety database?
15 And then when it's sent out, if it's sent out
16 separately. We want to hear from you just because -- I
17 mean, you're submitting that to Europe today. So we
18 definitely want to hear something on the docket or on
19 the eprompt e-mail address. So we'll definitely want
20 to hear...

21 Right. Okay. Right. So typically today is
22 it managed as two separate cases or it's just one case?

1 One case. Okay. And then when you -- especially, when
2 you're submitting to Europe then -- because they have
3 EVCT and EVPMM, right? So then they're separated out.
4 All right. Okay. Yeah. Okay. So yeah. So that's
5 typically on the post-market study report. Suppose --
6 it's submitted in two different routes. And again, as
7 we all realize that this whole IND concept is a U.S.
8 concept, right?

9 All right. Yeah, this was -- I think this was
10 -- I talked about this -- I talked about this the last
11 time. So this is an element which was not there, which
12 is reporter's e-mail. And this is a regional element
13 we added.

14 Okay. Next item, study identification. Now
15 this is -- the next two elements are new elements. And
16 the purpose of this element is basically routing the
17 report to the appropriate reviewer. Now this is a very
18 important field for us and this field is mandatory for
19 study reports.

20 And the business rule -- this is now what our
21 thinking is on that business rule that might change a
22 little bit, but this is right now what our thinking is.

1 So this particular data element is especially when you
2 have -- we're trying to eliminate cross-trial
3 reporting, right? So which means you don't have to
4 submit to all the other INDs.

5 So the way to do that, first, is that we have
6 to know the primary IND on which the adverse event
7 occurred, right? So this field will help us in
8 actually routing the report appropriately and applies
9 for both IND and for BA/BE safety reports. So we have
10 the number.

11 The reason why I am saying the business rule
12 might change, because we are trying to just figure out
13 here the numbering system so that the numbers don't
14 collide or coincide. And if it does, if we know if it
15 does, then we may have to have a prefix to that as
16 PANDA and then NDA -- and IND.

17 But so far what we think is we can probably
18 manage this having unique numbers. So if it is unique
19 numbers, then this number is looked into our FAERS
20 database and then the appropriate reviewer is actually
21 assigned to that application number, the report shows
22 up on their alerts.

1 So that is one field. The second field is
2 that, because cross-reporting we're trying to
3 eliminate, but the agency still wants to know what are
4 the cross-reporting IND numbers. You don't have -- no
5 reports have to be submitted, but to know the cross IND
6 reporting -- the IND numbers.

7 So typically in this -- then what we are
8 seeing that this is a C-5R, means repeating. And you
9 just -- this field needs to be repeated with all the
10 other IND numbers which is not the primary on which the
11 adverse event occurred. And will have the same format.
12 And what it does also is it also helps us in routing.
13 Because today when a cross-reporting happens, the
14 primary IND on which the adverse event occurred is sent
15 to a reviewer. And the other reviewers are like an
16 FYI, just letting them know that the reports have come.

17 So we want to do the same thing. So in our
18 system there'll be only one report, right? And maybe
19 five reviewers are looking at it. One is a primary;
20 the other ones are like FYI-ed on that. So that's that
21 two data elements which we plan to add into our
22 specification.

1 Okay. So we will have Karen, who will speak
2 next on and give some introduction -- because the next
3 one is BA/BE study trial. So she's going to speak a
4 little more on those concepts and what they will be.
5 All right. Yes.

6 No, we're talking about prefix with IND or
7 PANDA. So we have to basically figure out -- find out
8 that if these numbers can start from a different
9 series. Then we don't have to do that. Because once
10 these reports come in, I still have to now split the
11 numbers with the prefix. I don't want to do that.
12 Just if I can have the number and the number is
13 directly assigned to a reviewer, it just goes to the
14 reviewer, so.

15 All right. All right, next. So with patient
16 identifier. So I think in the last session you have
17 heard from Meredith about a concept of aggregate
18 reports. So she had mentioned about the different
19 types of reports, of which two types of reports which
20 would be submitted through the gateway -- through an
21 E2B message was: one is the pure IND report which you
22 have and then you have an aggregate report. And the

1 aggregate report concept is, it's still an ICSR, in
2 that in the linked report IDs, you're just mentioning
3 about your case series of, let's say, all the
4 pancreatitis cases because you have created -- and then
5 your narrative is writing about that series or that
6 aggregate.

7 Now how do we identify that it's an aggregate
8 report? So our first initial thought was we have an
9 observation type, right? We thought that if we go to
10 observation type and we add a new value called
11 aggregate -- this whole observation type from ICH
12 perspective has its own OID and list of values. So
13 that's going to be a big change.

14 So rather we decided that we will have a
15 conditional mandatory on the patient ID or the initials
16 where -- in this case, there is no single patient,
17 right? So if the patient ID is submitted as aggregate
18 and that will define as how we'll do aggregate. And
19 similar talk you will hear in the afternoon about the
20 summary report in combination products, where we'll be
21 using the same -- basically, overloading the same
22 patient name initial with the word summary.

1 So that will define what -- that will give us
2 or tell us that these are aggregate reports coming from
3 the IND. So with that -- yeah.

4 Basically, it has those names. Because
5 tomorrow -- yeah. Right. It was coming through eCTD
6 submission, which was summary, yeah. But -- so that
7 aggregate what we found out, it was also a MedWatch
8 form which was being submitted as an aggregate. So if
9 it is that, then it could be submitted as an ICSR,
10 where you -- we could use the attributes of that ICSR
11 to submit that aggregate.

12 So when we started looking at what kind of
13 information is coming in that aggregate, we did see
14 that it just fits into as an ICSR. And in future when
15 you have these aggregates done -- submitted and now you
16 are submitting a follow up on that aggregate, it's
17 still an ICSR, so the follow ups also hopefully will
18 just fit in correctly or appropriately in its place.
19 And the narrative is basically filled up, yeah.

20 Yeah. Fitted into the narrative and that will
21 come in there. Patient identifier, as I said, you
22 would just say aggregate for patient identifier.

1 Reporter. Probably we'll still have a reporter, which
2 will say who is reporting this aggregate. And then --
3 I mean, we got the four data elements.

4 That is true. That is true. We can -- yeah,
5 we can define that as to some value, because the four
6 elements kind of -- maybe we can release -- reduce the
7 rule for aggregates and say that "if you're sending an
8 aggregate, then just make sure that your patient
9 identifier has aggregate. And then of course you have
10 these -- these -- it will still be considered at a 1 or
11 6. I think they have -- the aggregate also has a 15-
12 day requirement. So that will still say the IND --
13 it's an IND report. It will be 1. And it will still
14 say this is pre-market, so we will know it's a pre-
15 market.

16 And we can -- we can -- I think we can -- we
17 should be able to reduce the rule to not asking for a
18 reporter, because that in the post-market side it does
19 ask for a reporter, so.

20 What the volumes are? I mean, it's not like
21 the individual case safety reports because it's
22 aggregating. I do not have a number of what kind of

1 volume we get for aggregate. I think I should be able
2 to get something from Meredith. I can ask her and I
3 can definitely -- during the break, I can just get you
4 some numbers. But that's -- it's not many, it's not
5 many.

6 Yeah, it happens, it does happen. Yeah, we
7 still have aggregate reports. Yeah, it's part of the
8 submission that aggregate reports does come -- now
9 today it comes through eCTD as a PDF and it comes as a
10 MedWatch form actually. So then if you see the
11 MedWatch form of an aggregate report, I mean many of
12 the information is left out. I mean, yeah, the product
13 will be there and then they will have the narrative
14 filled in. They'll have additional pages for the
15 narrative, because that is how much you can fit in, so.
16 But it comes like -- it looks like a MedWatch.

17 No, no, no. It's -- as I said, it's again
18 aggregate, so. They have to see what conclusion they
19 come to. There could be so many events that has
20 occurred, and then based on that, they're aggregating
21 it and then sending it.

22 Correct. Yeah, exactly. Yes. No, no, no,

1 no. I think they have -- they have like four or five
2 different types of reports you're submitting for that
3 IND. And one of them are submitting the individual
4 case safety reports, which you submit. One of them is
5 aggregate. One of them is like non-clinical. One of
6 them is that -- some are descriptive, very descriptive.
7 And they're submitted through eCTD today. Okay?

8 Today everything is submitted through eCTD.
9 There are like five or six different types of
10 submissions which happen that are submitted, of which
11 we are just picking two of them where we think are
12 going to fit into an ICSR.

13 If you actually go to the FDA meeting page and
14 you look at the slides, there's a whole -- session 1 or
15 2 you will find on IND safety reporting which was done.
16 And there's a table there very nicely defined, where it
17 gives you all the different kind of submission based on
18 which CFR and then it tells you which ones we are
19 trying to tackle as part of FAERS. You will see that
20 there. Okay? Oh, yes.

21 That's what we are saying. So we're saying
22 that -- yeah. Yeah, I think the people on the web are

1 unable to hear, so if you use the microphone or you can
2 -- yeah. So same. The idea or the concept is that if
3 we have that as an ICSR the aggregate report, then we
4 will be able to, you know, manage like a case. And any
5 follow up comes on that, we will be able to track those
6 follow ups.

7 And in the follow up -- now if you have a new
8 case series you have created on those cases you may
9 have already submitted, they becomes like link cases,
10 because you have a whole concept of link cases in the
11 ICSR. So we -- so the idea would be to use those link
12 cases to link your case series.

13 So let's say you have 10 cases and now you are
14 able to find five on which you are building your
15 aggregate. So which means you have the 11th case,
16 which is your aggregate, and in which you are
17 mentioning in the link cases those five and then you're
18 writing about those five.

19 Yeah. Correct. So February will be -- or
20 that idea on February will be like finalizing certain
21 things and also showing some of those features which we
22 have on how do you want to test, going through the

1 website. You know, we'll have -- basically, have it
2 pretty much live showing you how you're going to do
3 that. Maybe we can show an example of an aggregate
4 report. We can show you some sample files of how the
5 aggregate report in R3 is going to look like. And then
6 of course the sample files and of all the different
7 types of reports.

8 UNIDENTIFIED SPEAKER: And would it be
9 mandatory to send the aggregate reports also through an
10 electronic format? Or could that also continue to be
11 sent as the -- in the eCTD file (ph)?

12 MR. DE: So right now, as I said, that when we
13 do R3, the mandatory -- there is no mandatory rule
14 currently. I mean, the idea is to eventually make it
15 mandatory. I mean, the good part about when you're
16 submitting these types of -- this ICS -- the single
17 ICSR and the aggregate, you are basically skipping not
18 creating a cover letter, you're skipping not creating
19 the 1571. All those things are eliminated, okay?
20 Because what we have heard during the pilot is that
21 adds to the time, that adds to of course the cost. And
22 now you're basically trying to send it directly from

1 your safety databases.

2 So to answer that, yes, it's -- there's no
3 compliance date which has been set, as I said in the
4 start. But as we see how companies are doing or how
5 sponsors are doing, we get some vibes from them, then
6 we will start looking at, you know, when do we want to
7 make this...

8 Yeah, yeah. If they started doing R3, then
9 they don't have to submit to the eCTD, right? I mean,
10 there are other documents which you still have to
11 submit to the eCTD, because it's a whole set of
12 documents we have. Only the single individual case
13 safety report -- as you start submitting through the
14 gateway -- you have moved on to the gateway now. I
15 mean, gateway meaning to the ICH standard, if you moved
16 on to that. Because -- I don't want to say gateway
17 because everything else come -- all comes through
18 gateway.

19 But if you have moved on to -- if somebody
20 moves on to submitting through the safety reporting
21 portal or somebody moves on to submitting individual
22 ICSRs through this R3 standard or R2 standard, they

1 have moved, so they don't have to go through -- so I
2 think for them, right away the saving is no cover
3 letters, no 1571. All that things basically is gone.

4 Oh, yeah, yeah. Correct. Use cases we are
5 trying to. Because we used to never -- I mean, our
6 technical spec used to never have use cases. But what
7 we're trying to do is, instead of putting the use cases
8 and the technical spec on the FDA electronic submission
9 webpage, we want to put those use cases. Because
10 technical spec the problem is, if I open a technical
11 spec, it has to go through clearance. But on the
12 website we can always put those use cases going
13 through, you know, major clearance.

14 So we will do that in that. And then with
15 Q&As and all that, we want to put that on to -- and the
16 February meeting you will actually see all these things
17 have happened, so that we can point you to the right
18 locations to start looking at things. Okay. Yeah. Is
19 it on?

20 UNIDENTIFIED SPEAKER: And in terms of the
21 guidance, would you also be providing some information
22 in terms of transition? So what happens when you go

1 from an IND paper submission to an ICSR for pre-market
2 in terms of follow ups. So how would that work? And
3 less so for ICSR from E2B(R2) to E2B(R3) as well.

4 MR. DE: Right. So that is something -- we
5 are actually working on more like a transition plan to
6 show -- if you have already been submitting through the
7 eCTD, okay, so can you start -- can you jump into
8 submitting an electronic -- you know, an XML
9 submission? Or should it be that any new trial when
10 you're starting is when you want to be submitting there
11 and finish that through eCTD on an existing trial?

12 So that is something we're discussing because
13 we want to just also make sure that how this data is
14 going to show up for the reviewers. Most probably what
15 is going -- I think the path we probably will be taking
16 is that, if you can move over, you just move over.

17 So if you have already submitted a few through
18 eCTD as MedWatch forms and now you're ready for an XML
19 submission, you just get into an XML submission. It
20 comes into FAERS. It goes through our data analytics.
21 The reviewer looks at it. But we do have a regulatory
22 system where all the list -- against that IND all the

1 list of safety reports are attached. So the idea would
2 be that the old reports are already there. The ones
3 which has come electronically, they'll be a link
4 provided to them against that IND there. So if they're
5 looking at all the reports, if they click on there,
6 that data analytics opens up and shows them the case --
7 versus in the old one, they click on that, it opens a
8 PDF to show them the case.

9 So -- but if -- the thinking is going as -- if
10 you're ready, you could start submitting. And I think
11 also now that this final phase of our pilot is going
12 on, we have learned a lot from this phase. So there's
13 a lot of Q&A which we have started -- we have prepared.
14 Meredith has been talking about use cases of --
15 different types of use cases.

16 And we have also told this pilot sponsors
17 that, "As you go through this, try submitting an
18 aggregate report. Even though it's in R2, still submit
19 an aggregate report. Let's see how it comes up and how
20 it shows up. And follow up to that aggregate report.
21 You know, make one and follow up to that aggregate
22 report. And then we'll see how." So this pilot is

1 actually giving us a lot of information.

2 All right. Okay. So -- sorry. Yeah. I
3 mean, again, as I said, when it comes to -- even though
4 it's an -- yeah, so we have a flag in R3 which
5 differentiates between that, yeah.

6 Adverse event on which the AE occurred, that
7 becomes the -- yeah. And then IND number for other
8 INDs with the same suspect product.

9 Starting this October R2 only, because we will
10 be ready R3 in March 2020. Yes. So R2 technical
11 specification, I think our target is to -- it's in
12 clearance actually right now. So our idea hopefully is
13 by September we get that. So by the end of September,
14 we are able to post that. Now the thing about that is,
15 once it is posted, okay -- I think it's a draft and
16 then we'll have the final, and then from final, 2
17 years. But at least if you can post the draft and
18 companies can start looking at all these data elements.

19 Okay. So right now we are at 10:20. So as I
20 said, my agenda got a little messed up because I had a
21 break at 11:00. If you have any -- no more questions.
22 So we have two options: either we can take a break or

1 we can then start with Karen. We'll take a break?
2 Okay. So let's take a 15 -- 20 minutes break and then
3 we come back and then we have -- we will have Karen
4 presenting on BA/BE safety reporting.

5 BREAK

6 SESSION 3: GENERIC DRUGS - BA/BE TRIALS SAFETY
7 REPORTING

8 MR. DE: All right. So we'll start with our
9 session 3, which is on Generic Drugs - BA/BE Safety --
10 Trial Safety Reporting. So I welcome Karen Feibus.
11 She's Acting Director with Clinical Safety Surveillance
12 Staff in Office of Generic Drug in CDER. So Karen, the
13 stage is all yours.

14 MS. FEIBUS: Good morning. So I'm going to
15 take you on a little journey into the world of generic
16 drugs. So I don't know how many of you here in the
17 room and online work with or for the generic drug
18 industry. But generic drug safety is what I've been
19 eating, breathing and sleeping for the last couple of
20 years and wanted to talk about it with regards to
21 trying to facilitate electronic reporting in the pre-
22 market space.

1 So I'd like to start off with a brief overview
2 of generic drug pharmacovigilance and how it's similar
3 and different from new drug pharmacovigilance. Talk
4 about bioavailability and bioequivalence studies and
5 the safety reporting requirements. What our staff's
6 current processes are for receiving, tracking and
7 reviewing expedited reports from BA/BE studies. And
8 take a look at what some of the opportunities are
9 provided by electronic submission when this becomes
10 feasible on the pre-market side. And what the steps
11 are that we're trying to take to make sure that this is
12 going to work.

13 So generic drug pharmacovigilance is actually
14 kind of complex because it involves so many different
15 groups and parties within the Center for Drugs. We're
16 dealing with three time periods, the pre-ANDA phase,
17 the ANDA review phase, and the post-approval phase.
18 And it involves the Office of Generic Drugs.

19 But because we are dealing both with generic
20 drugs for active pharmaceutical ingredients that have
21 already been out on the market as brand named products,
22 it also can involve the Office of Surveillance and

1 Epidemiology that is responsible for ongoing
2 surveillance of everything related to the active
3 pharmaceutical ingredient and its safety; the Office of
4 New Drugs, because if there is an emerging safety
5 signal for a particular active pharmaceutical
6 ingredient, the Office of New Drugs is going to be
7 involved; and also the Office of Pharmaceutical
8 Quality, our chemistry colleagues, because when you're
9 looking at generic drugs and acceptable differences and
10 how they are behaving in the marketplace compared to
11 the reference list of product, you really cannot
12 divorce those clinical considerations from the
13 underlying chemistry and those differences.

14 Within OGD, our Clinical Safety Surveillance
15 Staff is a small group that lives in the immediate
16 office. And while we are looking at pre-market safety
17 reports and post-market safety reports, we have other
18 groups in OGD who are looking at safety during other
19 parts of the lifecycle.

20 So our Office of Bioequivalence colleagues,
21 the Office of -- the bioequivalence reviewers are
22 seeing the safety data coming in with the

1 bioequivalence studies and determining whether our
2 clinical colleagues in the Division of Clinical Review
3 need to take a look at various serious adverse events
4 or the balance of different kinds of adverse events
5 between reference and test.

6 We have colleagues in the Office of Research
7 and Standards who are responsible for developing our
8 product specific guidances that are guiding how
9 bioequivalence studies are actually conducted and
10 designed and also they are overseeing the pre-ANDA
11 meetings that are now being made available for complex
12 product development.

13 Our lawyers and OGD policy are wonderful and
14 accessible and they help us when we have all sorts of
15 questions about regulatory authorities or odd
16 situations that have come up and it's not clear how
17 they relate to our regulations.

18 And then our Division of Labeling sits in yet
19 another sub-office, the Office of Regulatory
20 Operations. And because they are so intricately tied
21 to the safety labeling changes that may be coming from
22 the reference list to drug side, they are also part of

1 our safety data review and concern.

2 And as you can see, my structure that's being
3 built here is really built on a foundation of sameness
4 and really understanding and thinking about what
5 sameness to brand really means.

6 So as I mentioned, new drug and generic drug
7 pharmacovigilance look a little bit different because
8 the development processes for a new drug and generic
9 drugs are different. And what I mostly want to point
10 out is, on the generic drug side, everything's really
11 based on choosing that reference listed drug, finding
12 your product specific guidance based on that, designing
13 a bioequivalence study that meets those requirements,
14 pulling all that data together into your ANDA and
15 submitting it. And then we have various reviewers
16 reviewing it.

17 And potential safety concerns can emerge
18 during ANDA review related to differences in
19 formulation, various allowable differences and whether
20 or not they're going to make a difference in clinical
21 use. And if the ANDA is approved, we're then
22 continuing to watch for that. When the generic drug

1 gets out there? When it starts to become the majority
2 of the market? Are there emerging safety signals just
3 because the drug may be getting used in a broader
4 population than initially it was when only the brand
5 was on the market?

6 And is there any evidence emerging that a
7 safety profile for one particular generic drug looks
8 different than all the others for some reason? For
9 some unanticipated reason that the formulations
10 behaving differently? Or the drug device combination
11 that was approved as a drug is behaving differently
12 when it's in the hands of a patient or unexpectedly
13 getting substituted in the pharmacy?

14 So when it comes to adverse events -- I want
15 to briefly touch on post-market right now, because our
16 post-marketing process is a lot more fluid at this
17 point. Our post-market adverse events are submitted
18 electronically since June of 2015. They come in
19 through either the E2B method, database-to-database, or
20 through the safety reporting portal. And they go into
21 the FDA adverse event reporting system.

22 Our data team on a regular monthly basis is

1 doing pharmacovigilance using primarily the drug
2 quality reporting system right now, which is a subset
3 of these adverse events that focus on quality-related
4 issues to see whether any of these products are showing
5 a higher rate of reports than others. And if they're
6 popping up as having higher rates of reporting, we take
7 a closer look at what might be going on.

8 On the pre-market side by comparison, the
9 serious adverse event comes in through an e-mail box as
10 a PDF of the required reporting 3500A form with all of
11 its various PDF attachments, a cover letter, usually a
12 protocol summary, sometimes something else as well.

13 And when we receive them, they have to be
14 manually entered into our project tracking system.
15 Follow-up reports that come in for the same event have
16 to be manually linked to the original. And ultimately,
17 even though we're able to link the original to the
18 follow-up reports in an awkward kind of way in our
19 project tracking system, we can't link it to the ANDA
20 when it comes in.

21 And so ultimately, we have our bioequivalence
22 reviewers and our clinical reviewers actually calling

1 us up and saying, "Hey, did you receive and review this
2 serious adverse event," because they can't see it, they
3 can't find it.

4 And so we're hoping to leverage these
5 opportunities for electronic reporting to help make
6 this whole process of tracking and reviewing pre-market
7 serious adverse events from bioequivalence studies a
8 lot more quick and efficient.

9 And that's today's focus. So let's see what
10 kinds of opportunities electronic submission may offer
11 on the pre-market side of the house for generic drugs.
12 We have two scenarios when it comes to bioequivalence
13 studies. There are bioequivalence studies that are
14 conducted under IND and somehow they got a nickname of
15 Bio-IND because they're attached to a bioequivalence
16 study.

17 And the regulations require bioequivalence
18 studies to be conducted under IND for radioactively
19 labeled drugs and for cytotoxic drugs. But otherwise,
20 all other generic drugs being developed that do not
21 meet the requirements to be exempt from an in vivo
22 bioequivalence study, do not need to be conducted under

1 an IND. So they have no application number associated
2 with them at all.

3 And this slide just summarizes what those
4 governing regulations are. For the bioequivalence
5 studies conducted under IND, the safety reporting
6 requirements are exactly the same as for any other IND
7 and an IND safety report needs to be submitted for any
8 event that is serious and unexpected and there is some
9 evidence to suggest a causal relationship. And both
10 individual cases have to come in as well as those
11 prickly aggregate reports that have been getting
12 discussed this morning.

13 For bioequivalence studies being conducted
14 without IND, there is a different regulation that
15 describes the reporting that has to occur and you can
16 see that here. And these reports are any serious
17 adverse events that occur regardless of whether it's
18 considered drug-related. And they have to come in at
19 either 7 or 15 days depending on whether it's a death
20 or other serious adverse event as defined elsewhere in
21 regulation.

22 So this slide I actually borrowed from

1 Meredith Chuk, who presented at the March meeting and
2 was really focusing on what's going on in the world of
3 INDs. And she talked about the December 2015 draft
4 guidance that describes safety assessments for IND
5 safety and talked about compliance with what will be in
6 the final guidance occurring 24 months after that final
7 guidance is published. And that at that point, all IND
8 safety reporting will have to come in as either E2B
9 reports or through the safety reporting portal.

10 And the goal, as mentioned, is that there's
11 voluntary submission starting in October of this year
12 to try to start using the system that's going to be
13 stood up and is being worked on through the pilot right
14 now.

15 So safety reporting, as I mentioned, for
16 bioequivalence studies without an IND. While 7 to 15-
17 day reports have to be submitted, there is no
18 regulatory requirement and no planned regulatory
19 requirement at this point for them to have to come in
20 electronically. But all the other reporting is being
21 done electronically.

22 And submitting these reports electronically

1 may offer benefits if you're having to submit pre-
2 market bioequivalence reporting electronically to other
3 agencies for other applications, other studies.

4 So this only applies to bioequivalence studies
5 conducted in the United States. And the majority of
6 our bioequivalence studies are actually being submitted
7 outside the United States and that safety data does not
8 have to come in prior to the abbreviated new drug
9 application coming in. So we're only talking about the
10 studies conducted in the United States for which
11 expedited reporting is required.

12 So I mentioned the pre-market process before
13 and this is just summarized again at the bottom, this
14 sort of manual PDF process that we're currently working
15 with.

16 So why even consider doing voluntary
17 electronic reporting for bioequivalence studies? It
18 would give you one method of submitting generic drug
19 safety reporting for BA/BE studies that are conducted
20 under IND, for those conducted without an IND, as well
21 as post-marketing adverse event reporting.

22 All of the pre-market adverse event reports

1 are going to remain in a non-public space, as described
2 by Suranjan earlier, that there will be various
3 required fields filled that will indicate that these
4 are pre-market reports and we'll separate them and
5 sequester them from the post-marketing reports, where
6 some of that data ends up being posted on the public
7 site.

8 In addition, you do receive automatic
9 confirmation of receipt. And so once you've pushed the
10 button and you've sent that electronic report and
11 receive confirmation that it's been received, you're
12 done with it, there's nothing else to do.

13 How will this work? Because right now when
14 you send in bioequivalence study adverse event reports,
15 you have no application number. And without an
16 application number, we can't route this anywhere.

17 So there's already a process in place when
18 complex products are requesting pre-ANDA meetings with
19 the Office of Generic Drugs. These companies are going
20 to this website that's pictured here and they're
21 obtaining a preassigned ANDA number. This is the same
22 exact number that's used when the application is

1 ultimately submitted.

2 The agency has found this acceptable for
3 complex products to request this ANDA number long
4 before a bioequivalence study has even been designed.
5 And so they've also found -- the agency has also found
6 it acceptable to request this ANDA number at or around
7 the time a bioequivalence study is going to be started.

8 And so this is just doing the same stuff that
9 you would normally follow when you request an ANDA
10 number. Only you would be doing it at the beginning of
11 your bioequivalence study rather than waiting until it
12 was complete.

13 You could wait until a serious adverse event
14 actually occurs and do it at that time. But as it
15 states on this website, there may be up to a 3-day
16 delay between the time that you make the request for
17 the number and the time you receive it. And if you
18 were dealing with a report that needed to be submitted
19 in 7 days, that might be a little bit nerve-wracking
20 and a little tight. So requesting the number at the
21 time that recruitment begins or at the time that
22 patients are starting to actually be assessed in a

1 bioequivalence study is probably a good way to do it.

2 Questions came up about the PANDA number or
3 pre-ANDA number. Depending on what the agency finally
4 settles on about whether they think a pre-market
5 indicator field can be used for both INDs and
6 bioequivalence studies that don't have an IND, either
7 there will be an IND indicator for studies done under
8 IND and a PANDA indicator for bioequivalence studies
9 not done under IND, or they will all be pre-market and
10 then further distinguished and routed based on the
11 actual 6 digit number.

12 But either way, there will be two fields that
13 basically route your report to the correct office and
14 the correct part of FAERS, whether it be the portion
15 that can be public or the portion that is kept
16 proprietary and private. And then this can be
17 submitted through E2B or the safety reporting portal.

18 And again, the benefits are: we, on our side,
19 look forward to being able to link the initial and
20 follow-up report so that we can evaluate the important
21 information that you're sending to us in as timely way
22 as possible, because we do follow-up and we will

1 request additional information, whether it's full
2 protocols, hospital records. Because we want to be
3 looking for drug-associated concerns, but we're also
4 trying to make sure that the subjects that are enrolled
5 in these bioequivalence studies are safe and that all
6 of the right safety monitoring is in place for them to
7 get through these healthy volunteer studies without
8 experiencing unnecessary serious adverse events.

9 And this will make it all easier that we have
10 a good way to review them, link them, document any
11 concerns that we might have or document our lack of
12 concern and then ultimately have the reviewers who are
13 reviewing the ANDA package as a whole able to see that
14 information and move through their review process more
15 quickly, leading to more quick action on that ANDA.

16 So electronic submission will reduce errors,
17 it will improve the amount of information coming to us
18 because of the mandatory and standardization of fields,
19 and will hopefully help us do a better job of subject
20 safety monitoring.

21 So just very briefly I wanted to just sort of
22 link together and come back full circle to how all of

1 this relates to efforts that we're making on the post-
2 market generic drug pharmacovigilance side. One of our
3 staff members has been working with the MedWatch form
4 team that meets every few years to evaluate whether
5 updates are needed to that required 3500A reporting
6 form. And over time, there's been increased prominence
7 and clarity for manufacturer fields, which become very,
8 very important for us on the generic drug side when
9 we're trying to look across all of the products that
10 exist for a particular active pharmaceutical ingredient
11 dosage form.

12 What is happening this time around is that
13 there's going to be a box added that actually says
14 "pre-ANDA." So that for companies that don't request
15 an ANDA number, they can at least check that off, and
16 we know that is a pre-ANDA associated adverse event and
17 it will get routed to us. And also it facilitates
18 datamining of those cases later.

19 And the other thing that will happen is when
20 this is done electronically, it will happen
21 automatically. But at least when it's not done
22 electronically, we're going to have a way to

1 distinguish these pre-ANDA cases through the MedWatch
2 form.

3 The other things that are going on is that
4 Suranjan and his staff have really been very inclusive
5 and it's been very reassuring to us and hopefully to
6 all of you that there's been a tremendous effort as
7 this system has been getting built to connect with all
8 of the various offices within CDER and the review
9 division needs to really make sure that the
10 enhancements that are going to occur with FAERS II are
11 going to improve drug signal detection both on the new
12 drug and the generic drug side. And we've really been
13 very grateful to that because our generic drug
14 pharmacovigilance process and our framework is really
15 still in a rapid growth phase with the development of
16 the Office of Generic Drug Super Office.

17 And so we're hoping this is going to help us
18 track signals and identify signals more effectively
19 over time and just have better visualization as far as
20 what is going on across all of the generics and trying
21 to ensure that patients really can have a seamless
22 experience at the pharmacy level when drugs are being

1 substituted.

2 We feel that electronic submission and this
3 opportunity to do this both on the pre-market and post-
4 market side for generic drugs really will enhance the
5 Office of Generic Drugs' ability to meet our mission,
6 as well as all the generic drug companies and the
7 Association of Accessible Medicine to meet their
8 mission, which, as you can see, are very, very similar
9 and really trying to make high-quality, affordable
10 medicines accessible to the public.

11 I would just like to acknowledge all of my
12 staff mates. Howard Chazin was the Director of this
13 staff until he took on this acting position. And then
14 you can see all of my staff mates down below. And it's
15 really the work that we do all together that has
16 brought this information together for today. So I just
17 want to extend my thanks and open it up to any
18 questions that you may have for me or Suranjan. Thank
19 you.

20 MR. DE: So any specifics on -- any questions
21 on the generic drug? As you saw that the previous
22 presentation which I gave -- I mean, some of the data

1 points are included. And I noted down one item, which
2 I think I have a question on, we have to go back and
3 evaluate, is the application number on which the
4 adverse event occurred. How do we want to approach
5 this? Do you want to approach this with a prefix? Do
6 you want to approach this as two separate data points
7 identifying IND and a number or a pre-ANDA and a
8 number? Or it should be one field with a prefix?

9 Because as soon as you have prefix, then you
10 have all these situations of concatenating it and then
11 extracting out, which all becomes a hassle on both the
12 source and the destination side. So this is something
13 we'll -- I think my team will have to talk about.

14 Right. That's why we have to have this prefix
15 or some kind of indicator to say, "Even though whatever
16 the number is, it's for the IND. Or whatever" -- "if
17 the number turns out to be the same, but it's for
18 ANDA." So they kind of go together, which then makes
19 it unique, right?

20 But even with that, how do we want to store
21 that and how do you want to use it? Do we want to
22 store that as IND space and a number or IND as a

1 separate field and number as a separate field data
2 element. So that way, if any time you have to
3 concatenate it, you can easily concatenate it and put
4 it into one. If you want to use it separately, you
5 still have -- separately you can...

6 UNIDENTIFIED SPEAKER: Well, how is it stored
7 in DARTs. I think we -- you know, because you get all
8 your stuff from DARTs, right?

9 MS. FEIBUS: No.

10 UNIDENTIFIED SPEAKER: So you don't and that's
11 the whole problem.

12 MS. FEIBUS: So this is where it gets really
13 interesting. So right now -- so DARTs was -- when -- I
14 was here when DARTs came online, it was the hot new
15 thing. But it was really built to be used by the
16 Office of New Drugs and by other offices. But at the
17 time, the Office of Generic Drugs, which was much
18 smaller and primarily was a bunch of chemists and
19 clinical pharmacologists, they actually built their own
20 sort of internal archival system.

21 And a few years ago, back in the fall of 2014,
22 a new sort of work management tracking system and

1 archival system was launched called Panorama. And so
2 the Office of Generic Drugs and some of the other sub-
3 offices within CDER actually worked within Panorama.

4 Within generic drugs, you have much higher
5 numbers of applications that are being dealt with at
6 any one particular time and you don't have a review
7 team that is necessarily sort of housed and run out of
8 a particular division. So the workflow structure is
9 very different than it is in the Office of New Drugs.

10 And just the sheer numbers of applications
11 that are moving at the same time -- I mean, we're
12 talking I think 997 application approvals last year or
13 something like that -- required a workflow and work
14 management and work tracking system that had
15 capabilities that DARTs just doesn't have it.

16 DARTs is a fantastic archiving system and way
17 to find things. And Panorama has been improved and
18 modified over its first 2, 2-1/2 years of use to sort
19 of link with an interface with DARTs and be able to
20 show and access all of the documents that have been
21 submitted to a particular application and as well as to
22 show all of the reviews associated with that much as

1 DARTs does. But we work in a completely different
2 interface.

3 And so the importance of being able to both
4 route these -- being able to route these reports is one
5 problem, but the other problem is making sure that you
6 can still carve out that application number so that you
7 can associate work that's being done for that
8 application and associate it with the other documents
9 in that application whether it be in DARTs or Panorama.
10 So it's sort of this twofold challenge, as I see it.

11 MR. DE: Yeah, so -- so that's -- I mean, that
12 -- definitely we have a challenge. So we'll have to
13 figure out how do we want to do this. I mean, the --
14 and then of course we'll communicate that to the
15 sponsors.

16 MR. IYER: Hey, hi. Hi, Suranjan. Anand Iyer
17 from AstraZeneca. I have just a quick comment on the
18 approval numbers, right? So for vaccine submissions
19 that happens today that goes to CBER, GK31 that's the
20 tag for the E2B(R3). So they mandate the use of NDA or
21 BLA prefix before the approval number. So they maybe -
22 - they probably have a mechanism of splitting them or...

1 MR. DE: Separating out.

2 MR. IYER: Yeah.

3 MR. DE: Yeah, yeah, yeah. So I mean, that's
4 how we went with, but -- so as we are harmonizing those
5 data elements with ours trying to see -- because one
6 is, any new data elements which we have added to
7 harmonize that receiver or any data elements that CBER
8 has already in vaccine are -- sorry, elements which are
9 already in ICH, but the values they are applying on
10 those data elements, we're also looking at that to see
11 we harmonize that.

12 So that's why I said we have to go back to our
13 team. We actually -- every Friday the CDER and CBER
14 electronic submission team meet up to do this
15 harmonization. So we will be talking about this to
16 make sure that we harmonize so that it doesn't have two
17 separate method of putting the data element.

18 MR. IYER: Since that is already established
19 with CBER, I would think maybe take advantage of that
20 and harmonize with that.

21 MR. DE: Oh.

22 MR. IYER: Otherwise, we're -- you are also

1 talking about the N1-4, right? You're talking about
2 the identifiers also to be (cross talk)?

3 MR. DE: Right, right, right. With IND the --
4 see the problem happened was, in the drugs section, the
5 way that is set up, it's very difficult to know which
6 IND is a primary.

7 MR. IYER: Yeah.

8 MR. DE: Right? Because you're going to have
9 multiple drugs repeated, repeated and you could have --
10 you know, sometimes you have a parent IND and then you
11 have a child IND and -- so all that. So that's why it
12 was very difficult. That's why we had to have this
13 separate new feel where AE occurred, okay, to identify
14 that so it can be routed appropriately.

15 But I think if -- we will talk to CBER and
16 hopefully we can, you know, take advantage of what they
17 have done and maybe use the same method.

18 MR. IYER: I have another question in relation
19 to changes to the MedWatch and what you had in your
20 presentation. Just interested to know if there will be
21 an update to the MedWatch so that it will be in line
22 with what's proposed in the DDT in terms of how you

1 identify cases being expedited.

2 And you've added a new option in the code list
3 so that you can mark it as 7 day if it's fatal or life
4 threatening. However, in the MedWatch form and the
5 instructions, it still states that 7 days should only
6 be checked off for blood products. And whether or not
7 there will be some kind of harmonization between those
8 two definitions?

9 MR. DE: No, that's a good question. I think
10 for the 7-day report, I think it was -- I'll have to
11 look back actually. I think for the 7-day report is --
12 especially in the pre-market side, it's centered (ph)
13 for death and life threatening, right? And so then
14 when you're submitting a MedWatch form for a pre-market
15 report or an IND report, you would check that box, no?

16 MR. IYER: No, if you follow the instructions
17 for the MedWatch, it mentioned that you won't check the
18 7-day box. Yeah. Sorry. If look at the published
19 instructions for how to complete form 3500A for the 7-
20 day checkbox, it clearly states it's intended for blood
21 products. And we regularly have questions from
22 customers about that field.

1 MR. DE: Oh.

2 MR. IYER: They would very much like to check
3 it off for 7-day fatal and life threatening cases.
4 However, if we follow the instructions, it doesn't
5 apply. And so it would be good if there could be some
6 clarity for that particular point.

7 MS. FEIBUS: I just want to thank you for
8 bringing that to our attention and I will certainly
9 mention that to the person on our team who sits on that
10 committee as well, because that really sounds like a --

11 MR. DE: Yeah.

12 MS. FEIBUS: -- incredible disconnect.

13 MR. DE: Okay. We have written it down. So
14 yeah, we have to take it to the MedWatch council. All
15 right.

16 MS. FEIBUS: So I'm going to...

17 MR. IYER: So the -- sorry, just one last...

18 MS. FEIBUS: I was going to say I'm going to
19 fish for some information. I was having a very nice
20 break conversation and heard some concerns being raised
21 about the timing between what might be available
22 information-wise between now and the next meeting in

1 February and the short timeline between February and
2 the end of March 2020 as far as access to things that
3 would help companies get up and running, the electronic
4 submission in as timely way as possible. And I just
5 wanted to encourage you to ask any questions you have
6 about that -- because if you don't ask, we can't find
7 ways to help you out.

8 UNIDENTIFIED SPEAKER: Thank you for your
9 presentation. I have a question. If a certain drug is
10 the same with the -- it's a branded drug, I think it is
11 possible to use for detecting significant signal for --
12 signal about like their substance. How does USFDA use
13 AE data over generic drug to detecting significant
14 signal -- our (ph) signal?

15 MS. FEIBUS: So right now, we have a data team
16 that is part of our clinical safety surveillance staff
17 that is comprised of a team leader, who is a clinical
18 pharmacologist by training, and two data analysts, who
19 have backgrounds in pharmacy and epidemiology. And
20 each month they are running a particular search within
21 a portion of FAERS to look at primarily quality issues,
22 reports of lack of effect, reports of certain types of

1 side effects, and sort of seeing what bubbles up as
2 occurring at a particular frequency.

3 We're actually discussing now how to improve
4 that to use more data. So when FAERS II launches and
5 we're able to use the analytics that will be available
6 to us, our data team will be using all of FAERS' data
7 to look across generic drugs. We are in active
8 internal discussions talking about the best ways to
9 leverage all of the data that we have available.

10 In my mind, one of the things that I would
11 like to do is for particular drugs that we think may be
12 higher risk products, whether they be complex products,
13 whether they be drugs that are known to have higher
14 rates of side effects and more serious side effects,
15 cardioactive drugs, neuroactive drugs, we may be
16 setting up paradigms to take a deeper dive and actually
17 actively looking at adverse event reports that have
18 been submitted for all of -- all products for a
19 particular active pharmaceutical ingredient and dosage
20 form to see if we're seeing very similar patterns of
21 serious adverse events across the group and compare
22 that to the references to drug or whether there is a

1 standout, a product that really looks very different,
2 so that we can pay more attention and take a closer
3 look as to what may be going on.

4 As I said, our framework for how to do
5 pharmacovigilance on the generic drug side is still
6 evolving at this point, because it's really only been
7 in the last few years that we have had people who have
8 a clinical background and assigned staff who can really
9 look at generic drug safety from a generic drug
10 sameness versus differences perspective as opposed to
11 just looking at the generic drug data from an active
12 pharmaceutical ingredient perspective.

13 So that's what we do now. What we're going to
14 be doing in the future? We'll hopefully get further
15 defined and shaped over the next couple of years as we
16 have access to better analytics and more data.

17 UNIDENTIFIED SPEAKER: Karen, I think you
18 brought up the topic of what we were discussing during
19 the break, perhaps to have a meeting in between now and
20 in February. I think it will be great if you could
21 bring, you know, folks who are doing the pilot or even
22 from what you are learning to present use cases and

1 have kind of a workshop really to how to approach these
2 different data elements.

3 MR. DE: Okay. So yeah. So one thing which
4 we definitely want to -- you know, to some kind of --
5 to publish out in our FDA's website is what came out of
6 the pilot, you know, what we learned from the pilot
7 from the IND safety reporting, which includes the
8 different use cases which -- that we identified during
9 the pilot.

10 So that is one part of the pilot what we
11 learned from it. I think that definitely will be --
12 and that should -- our pilot starts August 17th I think
13 and goes all the way to September 15th or so.

14 So during that period of time, you know, eight
15 or nine sponsors who will be submitting reports.
16 They'll pick a few INDs and they'll be submitting those
17 reports. And we'll see all the different kinds of
18 reports. So that will also give us some examples of
19 these reports along with some sample XML outputs, which
20 we could definitely, you know, redact them and then --
21 and then we can -- I mean, it's as good as saying we'll
22 create our own, you know, sample files and we can post

1 them. So that definitely could be done before end of
2 September. You know, as we learn through it, we can
3 definitely do that.

4 As we move through our implementation of March
5 2020, you know, sometime then in fall I think we can
6 give you the technical -- not the technical spec, the
7 spreadsheet of all the data elements which you have.
8 We'll probably have -- by then hopefully we'll have the
9 OIDs set up for them. And our target is also that we
10 will have to have all the data elements ready by that
11 time so that we can also do our development and start
12 updating our actual technical specification.

13 So as we go through -- you know, I think it
14 will be just key that sometime in fall have a look at
15 our meeting page or our electronic submission website.
16 We have a FAERS electronic submission website. So we
17 will start putting in some documents there. So you can
18 start looking at those elements.

19 Now, by no means those will be put as draft.
20 So if you have any questions, any concerns about
21 certain data elements, you definitely, you know, send
22 an e-mail to the e-prompt e-mail address and then we

1 will we address those.

2 If you need to -- and I don't know, we don't
3 have it right now, but I have to talk to our team in
4 FDA just to see if maybe just a Webex between July --
5 now and February would help once we have like kind of
6 published, we have looked at certain things. So that
7 way -- I mean, the idea is that if our technical
8 specification final document which comes out -- I mean,
9 I'm wishing to have pretty much zero comments on that,
10 right? So that that can be quickly finalized and then
11 made final and then we can -- and many other
12 organizations can then start implementing that.

13 But yeah, if there is a suggestion -- I mean,
14 a certain suggestion to e-prompt website that if you'd
15 like to have some kind of -- just not on-site, but we
16 can just have a WebEx and talk about those data
17 elements when they are put into our website and between
18 now and -- between September and February we can
19 definitely have something during that time.

20 So yes. So I have written down a few items
21 which I think we can publish. And as these slides all
22 will be put down right after this meeting will be

1 available on the meeting page. So many of the elements
2 which we are basically talking about, all those
3 elements are actually in the spreadsheet. And what I'm
4 talking about, they are all in the spreadsheet,
5 especially the combination products, the IND one we
6 talked about. The last time I talked about a few pre-
7 market. And so, yes, they will be there.

8 The technical specification what it does, it
9 just highlights those elements in sections, right? But
10 the spreadsheet actually will also highlight -- the way
11 the spreadsheet is set up you will see is any element
12 which is an ICH -- core ICH element, basically the row
13 is highlighted in gray; anything which is FDA's element
14 is a light yellow. So you will exactly know which ones
15 are there. And then tomorrow if you're going to take
16 that element and you want to filter out by only the
17 ones which says "source as FDA," you got all your FDA
18 elements. So, yeah, so that's the idea.

19 So -- and this spreadsheet is basically a
20 spreadsheet template. If you go to the ICH website and
21 go through all the documentations they have put down
22 for R3, this template is actually one of the templates

1 there. So the idea at that time was that -- and I
2 think that is being -- basically been done, that EMA
3 will take that same spreadsheet, put all the core ICH
4 elements and their elements. PMD will do the same.
5 You know, other regulators -- Health Canada will do the
6 same.

7 So if all the spreadsheets look the same, then
8 especially as a vendor you're able to consolidate all
9 that together into one, where you know these are all
10 the core elements and these are all the regional
11 elements from different countries. So -- yeah, if you
12 can -- oh, there.

13 UNIDENTIFIED SPEAKER: So one of the things
14 with E2B(R3) is the introduction of null flavors. So
15 in the scenario where we talked about for both pre-
16 market and post-market submission, there's an
17 interesting challenge about how do you populate null
18 flavors, because null flavors typically for EMA are for
19 responding (ph) and supporting. So if we get a post-
20 marketing report and we populate the null flavors, how
21 would that work for the pre-market report for ICSR?

22 MR. DE: So that consideration has also been

1 taken. So as we are defining certain elements, right -
2 - now, for example, the AE where -- you know, IND on
3 which the AE occurred, right, and that won't applicable
4 for post-market, right? So that element's null flavor
5 because -- first thing, it's a conditional mandatory
6 field, means it's only applicable when you have a study
7 report. So which means that certain data points like
8 report from study and all that data points have the
9 appropriate values, then this field is important.

10 Now, typically speaking, when we're looking at
11 -- I think at some point I had said our rules are --
12 pretty much rules which we have set are what ICH has
13 said, okay? We are really not done -- any additional
14 rules we have applied to the data elements which we
15 have.

16 Now, these are all core data elements. Now,
17 if you come to that regional specific data elements, we
18 have taken into account that when we are looking at the
19 null flavors, pretty much many of the data elements you
20 will find will say it's an optional data point, right,
21 except the one or two which I mentioned today are
22 mandatory.

1 And if it is mandatory, it is mandatory --
2 conditional mandatory. So the null flavors will
3 appropriately reflect to say that -- if you do not have
4 that value, then the null flavor would say that no
5 information is, yes, in that spreadsheet. So when you
6 actually see the spreadsheet, you will see that, you
7 know, many of the things have been taken care of.
8 Hopefully, there is no conflict.

9 UNIDENTIFIED SPEAKER: So in terms of IND pre-
10 market for -- so you're suggesting in a sense you're
11 okay if the pre-market ICSR may have -- it seems a
12 little bit odd that it may have information such as "no
13 information available." So from a data quality, are
14 you okay with that?

15 MR. DE: No. So when we say pre-market, there
16 will be a certain data point. For example, when I said
17 that IND on which the AE occurred, on that we are
18 expecting an IND in there, right? But when you have,
19 let's say, a data field, which was right below that,
20 which was the other INDs on which you had the same
21 product, okay -- if you didn't have, I mean that would
22 be submitted as NI, right? So the null flavor will say

1 NI. And I think my business rule actually also said
2 that NI.

3 Other than that, I think whatever reports are
4 submitted -- I mean, you had -- today everything is
5 coming at MedWatch. I mean, actually we're getting
6 more than what we get today, right? When we go through
7 electronic submission, we'll actually get more than
8 what we get today.

9 Certain data points, for example, in products
10 is mandatory, so they have to be there. But many of
11 the data points are either marked as optional -- and
12 when you look at the additional data points, what we're
13 asking -- IND basically has what? I think two or three
14 additional data fields, okay? Rest of the data fields
15 are all ICH data fields, okay? This is where we are
16 asking for the IND on which the AE occurred and all the
17 other INDs on which the same product has been used.
18 Basically, these are two fields we are asking for IND.
19 Rest all the fields are standard data fields.

20 Only when it comes to combination products,
21 you will see there are so many more additional data
22 fields that we have to capture. But again, many of the

1 data -- most of data fields are all optional. So if
2 you have it, submit it. If you don't have it, you
3 know, you don't have it, you know. But we're not
4 telling them that if you don't have it, saying "no
5 information," we have not basically put that criteria
6 in there because it's optional.

7 So yeah. So as I said, any questions which
8 you have now or after this meeting, we have the docket,
9 where you can submit all your questions. And after the
10 docket period time is over -- I think that is after --
11 yeah, we're going to talk in the last few slides. Time
12 is over, then you have the e-prompt, you know, e-mail
13 address, where you can submit. And that gets monitored
14 almost every day. So anything else? Any other
15 questions? And yeah.

16 UNIDENTIFIED SPEAKER: Sometimes products are
17 approved and you receive an FDA approval letter
18 requesting that certain targeted -- will say adverse
19 events of special interest are to be submitted to a
20 special division of the FDA in addition to what might
21 ordinarily qualify to the gateway submission. So this
22 could be like a PML (ph) to the Division of Neurology.

1 And so I was wondering with the adoption of FAERS II if
2 these will be integrated to a gateway-based submission
3 rather than a manual...

4 MR. DE: Right. So this is one question I
5 have to refer back, but I think my understanding was
6 that end of the day it's one report. And because now
7 it's electronic and we have a data analytics tool, so
8 the other office will be able to even view that report
9 as they are submitted. But I still need to -- let me
10 confirm that. And I can take that question and come
11 back to you.

12 MS. FEIBUS: Based on my understanding and
13 being in meeting with FAERS' reviewers from the Office
14 of New Drugs, it sounds like reviewers are going to
15 have the ability to actually set up routine searches
16 for certain kinds of outcomes for certain drugs --

17 MR. DE: Yeah.

18 MS. FEIBUS: -- where the search will actually
19 be run automatically in the background at certain
20 intervals. And so I don't know whether that particular
21 approach has been specifically addressed yet, but the
22 capability within the system should be there such that

1 reviewers can access that information as it's coming in
2 on their own time.

3 MR. DE: Coming in, yeah.

4 ROGER: Suranjan, I think the main question is
5 that we have clinical trials which we know -- the
6 sponsors know the patients, the sponsors know the drug,
7 they know more information, and they're a lot different
8 than post-marketing safety reporting. So now we're
9 bringing these all into one schema, but we're adding
10 IND stuff.

11 But I really expect that the sponsors and the
12 companies will provide the thorough information that
13 they know on a clinical trial, because we know those
14 are different than post-marketing. Post-marketing
15 sometimes you don't have all the information. And
16 that's when you'd use a null flavor. But I think with
17 clinical trials, even though you're going from a 3500A
18 now to the electronic, I would expect the same high
19 level standard of the E2B form coming in and I think
20 that's very important.

21 MR. DE: No, you're right, Roger (ph). I
22 mean, with the post-market side, in a spontaneous

1 report, you just get so much of information, right?
2 You do your due-diligence and then, you know, whatever
3 you get, that's what you get. But clinical trial is
4 more controlled environment, so hopefully the data
5 which comes in are a little more complete and more
6 accurate.

7 UNIDENTIFIED SPEAKER: Yes. If you could
8 during the meeting where there will be a Webex about
9 the pilot findings, if you could address the
10 improvement or potential improvements in data quality.
11 That will be very interesting.

12 MR. DE: Yes, yes, yes. Yeah, that is one
13 thing we are -- my team here works every day on looking
14 at data quality, you know, with -- especially, right
15 now where electronic submissions are with post-market
16 reports. But if you look at these -- some of the
17 reports, you will find -- like 40 percent of the
18 information for which there are structured data points
19 are all in a narrative, the structured data points are
20 all empty.

21 And you would find that -- like a simple
22 example is like age. You try to do a stratification by

1 age, you know, about 60 percent of the report shows up
2 as not reported. But when you start looking at those
3 reports and the reviewer starts looking at the report
4 and look at the narrative, you see this there's an age
5 available there.

6 And then the question comes: Why they're not
7 reporting on the structured fields? And I said, you
8 know, those -- one sponsor which we found like 300
9 reports. All 300 reports had age in the narrative
10 field. So that sponsor we just went and talked to
11 them, saying that, "Hey, can you resubmit them with the
12 age in the structured field?" So our -- in data
13 analytics when we do by age group and sex, then we are
14 able to get those in the right numbers.

15 So we are continuously, you know, working
16 towards this. I mean, unfortunately, we don't have
17 this kind of data checks. But again, it's always been
18 our request to sponsors to, you know, populate as much
19 as they can on the structured fields so that, you know,
20 appropriate data analysis can be done.

21 UNIDENTIFIED SPEAKER: I have a question about
22 standard terminology that's used within the ICSRs, and

1 you've talked about the fact that you plan to do
2 testing with other health authorities as well. But
3 there's a complexity in that all -- not all health
4 authorities operate in the same way.

5 So, for instance, for the -- in Europe, you
6 have the EMA that oversees medicinal products and then
7 you have the European Commission that oversees medical
8 device reporting. And so for the electronic reporting
9 within the U.S., you plan to use FDA codes, but you're
10 also looking at mapping them to the IMDRF codes. And
11 the website currently indicates that you're in the
12 process of completing that mapping exercise. And it
13 was really to find out -- are there any timelines by
14 when the FDA codes will be mapped to the IMDRF codes?

15 At the moment what we know is that annexes A
16 to F are available and published on the IMDRF website.
17 Annex G, what we heard from the working group is that
18 they're hoping to have them published this month. And
19 it's really to just get an update on what's happening
20 with the FDA codes and that mapping?

21 MR. DE: Okay. TJ?

22 UNIDENTIFIED SPEAKER: The reason why I ask --

1 MR. DE: Yeah.

2 UNIDENTIFIED SPEAKER: -- is because the ICSRs
3 -- it's a single ICSR for a pharmaceutical company.
4 But in terms of how all the data gets entered, it
5 becomes more complex when you have to think about each
6 individual health authority.

7 And then additionally, for the testing, you
8 talked about making sure that an ICSR that gets
9 submitted to various regions, you want to test that in
10 advance and ensure that it works. And really just
11 finding out will you consult other health authorities
12 in advance and just in some ways agree the UCUM codes
13 that are being used.

14 What we're finding is the EMA are very
15 accommodating and they've said, "Oh, if you come across
16 a UCUM code that isn't on our list, let us know." But
17 that's quite difficult to handle across the board if
18 each health authority is saying, "Just let us know if
19 there's a UCUM code that isn't in our list. We'll add
20 it in to accommodate it." And whether or not there
21 could be some way of harmonizing the codes that you're
22 planning to use across the regions that you do talk to.

1 MR. DE: Yeah. TJ, can you comment? You are
2 our...

3 MR. CHEN: Right. So I did not hear all of
4 your question because kind of some missing. But if
5 you're referring to IDMP (ph)? No.

6 UNIDENTIFIED SPEAKER: IMDRF.

7 MR. CHEN: I -- the UCUM number?

8 UNIDENTIFIED SPEAKER: No, International
9 Medical Device Regulators Forum, adverse event
10 terminology code upgrade. Yeah.

11 UNIDENTIFIED SPEAKER: So just a off the
12 record input. When we have the afternoon session,
13 maybe Melissa can address that in more detail, because
14 we have had a number of meetings to discuss that
15 specific topic. So I don't want to take away from
16 that. All right. Thanks.

17 MR. CHEN: We all -- all the ICH region agree
18 to use UCUM code as a base for the unit of measurement.
19 Now, UCUM has what they call the base unit, like 'm'
20 for mass -- no, no -- wait a minute. Okay. 'M' for
21 length, 'g' for mass and all that and then they have
22 prefix and then they have a formula, so that you can

1 construct like milligram per milliliter per a hour
2 shift. So the combination is unlimited, okay?

3 EMA refer to a list published by LOINC. I
4 think they're about 200-300 combination. FDA is not
5 going to constrain any use. You can use any
6 combination. It's almost -- those are UCUM code, okay?
7 So you can construct milligram, per milligram, per
8 milligram, per milligram, which make no sense at all,
9 but you can do that. You have a bunch of so-called
10 unit, right, basic unit. And then they have prefix:
11 'k' for kilo, 'm' for million and then -- you know, you
12 have all kind of prefix and you can make them together.
13 So milliliter, milligram, microgram, microliter, you
14 can do all the combination. And then you can even bind
15 them together, milligram per milliliter and you can
16 even put per 8 hours, so you can do all kind of
17 combination.

18 UNIDENTIFIED SPEAKER: Yes, so the response
19 that you are giving -- it sounds -- it sounds as though
20 you may well be creating a lot of work for the other
21 health authorities. And that it is possible to add
22 any, you concurred within an X amount filed for the

1 FDA. However, it may possibly not be accepted for the
2 other health authorities that don't have that code on
3 their list.

4 MR. CHEN: Well I think for the dose strengths
5 this is going to be simple, right. The reason we don't
6 constrain is for the lab test results. Okay, that can
7 be very tricky. You can have whatever number of count
8 of -- and then you can do the annotation with curly
9 bracket and put, I think it's called RBC, red blood
10 cell count, right? So you can have all kind of
11 annotation to that unit and that is a -- that's a legit
12 UCUM unit. And it is kind of difficult to constrain
13 that because in that annotation, after the curly
14 bracket you can spell out a whole thing or you can just
15 do RBC.

16 There are some organizations trying to create
17 a constrain list that people can use. I think CDC has
18 one. Some unit in German that create something, also
19 allowing (ph) has one. We just don't feel like we need
20 to comply to one, because then we have to tell people
21 this will be the only one you can use. But if you -- I
22 mean, during the lab test it's complicated. I mean,

1 lab test can always come out with new units and we just
2 don't want to do that. Those trends I think you will
3 be finding.

4 UNIDENTIFIED SPEAKER: So I think the
5 practical problems I think our customers are facing, so
6 for example if you take PMDA versus EMA. So PMDA
7 follows a defined set from ICH and EMA has additional
8 UCUM codes that they have defined. And so what that
9 happens is, during case processing, and then you want
10 to export to two different -- send that report to two
11 different agencies, now there is manual process
12 involved.

13 MR. CHEN: Right. So PMDA use old E2B(R2)
14 list which was published when UCUM unit was not agreed
15 among ICH and agreement is we all move to the UCUM
16 unit. When will that happen for PMDA? We don't know.
17 But the idea is we all move to the UCUM unit. And then
18 we are not to validate. EMA decided to use just the
19 confined (ph) list.

20 UNIDENTIFIED SPEAKER: Right.

21 MR. CHEN: And PMDA still using the old
22 E2B(R2) list. When do they migrate? We don't know.

1 UNIDENTIFIED SPEAKER: So would yours be
2 similar as EMA -- same as EMA, not even similar --
3 same?

4 MR. CHEN: We would be -- yes.

5 UNIDENTIFIED SPEAKER: Same as EMA?

6 MR. CHEN: Yes.

7 UNIDENTIFIED SPEAKER: Okay.

8 MR. CHEN: Yes.

9 UNIDENTIFIED SPEAKER: That's great.

10 MR. CHEN: Well, basically if not as same, we
11 will not reject anyway.

12 MR. DE: Yes. And then as you know for the
13 code list for route and administration dosage form will
14 be the EDQM list, that's what ICH has decided and
15 that's what we are all going to be using. So that will
16 be the list and we will be using for ICSRs.

17 UNIDENTIFIED SPEAKER: So for the E2B(R3)
18 submission for March 2020, in terms of attachments. So
19 today we are submitting literature articles, OTC
20 monographs through a separate process. And also as
21 part of the premarket we have AOAC as well. So how do
22 you see that working as part of the March 2020? Do

1 they just go as PDF attachments, any thoughts on that?

2 MR. DE: I think now with (R3), I think it's a
3 much more different data -- sorry, file types. So if
4 you look at our current (R3) technical specification it
5 lists down all the different file types, which is --
6 and now in (R3) it's embedded. So the whole different
7 process will basically go away when we go to -- we will
8 move to (R3). So as I said, I mean, we will be
9 continuing with (R2) and (R3) parallelly, so if companies
10 were not still ready, they will be submitting through
11 the old method. And with the new method you will have
12 it embedded and the different type of file types
13 already -- I've mentioned there what all things we will
14 accept. I mean -- I think most of the time its --
15 becomes a PDF -- its -- sponsors are submitting. But
16 just in case, if there is image file or whatever that
17 is, it's embedded into the schema and submitted.

18 UNIDENTIFIED SPEAKER: Every time what you're
19 going to do with follow ups? Is it -- if you have an
20 attachment for the initial report and you attach a
21 literature report, now the follow-up comes are you
22 going to have to -- the attachments going to be there

1 for the follow-up too to make a complete report or do
2 you carry on the initial --

3 MR. DE: That carries on.

4 UNIDENTIFIED SPEAKER: It will carry on. So
5 with the follow-up, they don't have to have the
6 attachment again, built in within the (R3)?

7 MR. DE: Right. The data has to be
8 cumulative. Okay. I know that's why I was looking at
9 my watch.

10 UNIDENTIFIED SPEAKER: Last question.

11 MR. DE: Because this has been very
12 interactive, because since our first meeting, I am
13 enjoying it so.

14 UNIDENTIFIED SPEAKER: You're keeping it open,
15 so I thought bring up any question I can.

16 MR. DE: Yes, I mean --

17 UNIDENTIFIED SPEAKER: So I am hoping I am not
18 out of date that when you submit an IND safety report
19 to the FDA there is a requirement for an analysis of
20 similar events be included with that particular ICSR.
21 And I was just wondering is there any requirements for
22 that in relation to how that data should be submitted

1 in the XML file.

2 MR. DE: That was -- I think that is the one I
3 was talking about which is aggregate.

4 UNIDENTIFIED SPEAKER: Oh, that's the same
5 thing.

6 MR. DE: Yes.

7 UNIDENTIFIED SPEAKER: So you've just changed
8 the terminology.

9 MR. DE: Yes. I mean, we had to get -- yes.

10 UNIDENTIFIED SPEAKER: Is that what you are
11 talking about?

12 MR. DE: Yes I think that's the one I was
13 talking about. No?

14 UNIDENTIFIED SPEAKER: I think some sponsors,
15 I think, take their analysis the same way --

16 MR. DE: Similar.

17 UNIDENTIFIED SPEAKER: And you put it in their
18 narrative.

19 UNIDENTIFIED SPEAKER: Yes.

20 MR. DE: Yes.

21 UNIDENTIFIED SPEAKER: So when this comes
22 through in the narrative, I think some sponsors are

1 like --

2 UNIDENTIFIED SPEAKER: So --

3 UNIDENTIFIED SPEAKER: -- they put it in a
4 cover letter for the IND safety reports and --

5 MR. DE: Yes, but -- yes, so -- but when you
6 are talking about all the similar -- yes, tagged as --
7 exactly.

8 UNIDENTIFIED SPEAKER: So you are saying it's
9 the same thing.

10 UNIDENTIFIED SPEAKER: No, that's not the
11 aggregate.

12 MR. DE: No.

13 UNIDENTIFIED SPEAKER: It's not.

14 UNIDENTIFIED SPEAKER: Aggregate is different
15 process, made of series of cases.

16 MR. DE: Then you have series of cases right,
17 right, right.

18 UNIDENTIFIED SPEAKER: Okay. So for the
19 analysis of similar events you would search for your
20 database.

21 MR. DE: So the similar -- so I think that --

22 UNIDENTIFIED SPEAKER: -- you were searching

1 for relevant cases, come up with a summary of what
2 you've concluded. And how would you expect all the
3 related ICSRs to be captured? Would you just mention
4 those MCNs in the narrative and there wouldn't be any
5 refinement -- for linking or anything like that?

6 MR. DE: One is mentioning again the narrative
7 or you have a concept of a -- what is that a linked
8 report or linked case ID.

9 UNIDENTIFIED SPEAKER: Yes, there is a concept
10 of linking. But as far as I recall when I was involved
11 in that process, there was no requirement to link all
12 of those cases within your database. So just to find
13 out have you given any consideration to how you managed
14 analysis of similar events, because I know that that's
15 a process that involved sometimes your regulatory
16 department to just include that information in the
17 covering letter or perhaps you just agreed within your
18 company that you would just cut and past the relevant
19 text and add it into your narrative before the case was
20 submitted?

21 MR. DE: Let me check -- during the break let
22 me check with Meredith and find it out. All right,

1 okay, so if no more questions, we will have ample time
2 for other questions in the next sessions. So we can
3 take a break and let me look at the agenda. So we can
4 come back -- reconvene at 1:00 and start with the
5 session number 4.

6 LUNCH

7 MR. DE: Let's see. All right, so the
8 afternoon session today, we will start with Session
9 number 4 as per the agenda which -- where we are going
10 to be talking all about combination products. So this
11 will be -- the combination product is split into two
12 presentations. The first presentation will be given by
13 Melissa Burns she is a Senior Program Manager in Office
14 of Combination Products. And then we will have the
15 next part which will be then by me going over the
16 regional data elements. So Melissa welcome you to come
17 and present the first part of the presentation on
18 combination products. So this is back, this is front.

19 SESSION 4: E2B R3 REGIONAL REQUIREMENTS FOR COMBO

20 PRODUCT SAFETY REPORTING

21 MS. BURNS: Hi. Again, Melissa Burns, Office
22 of Combination Products. And I'm here primarily just

1 to give you some of the regulatory and policy
2 backgrounds here that will obviously inform your
3 technical discussions. Just for your information the
4 Office of Combination Products is not within any of the
5 centers, it's a crosscutting office, policy group. So
6 we obviously work with Suranjan and others within the
7 centers on all the details and so forth.

8 So I'm just going to highlight what the final
9 rule says as far Postmarket Safety Reporting and I'll
10 will focus my discussion on drug and biological led
11 combination products since the audience is -- what the
12 audience is today. I will also highlight some
13 information from the guidance -- draft guidance
14 document that we have published on this topic. And
15 then I will talk about some next steps and key dates
16 related to Postmarket Safety Reporting rule.

17 So just to set some framework here, the scope
18 of the requirements under the Combination Products
19 Postmarket Safety Reporting rule apply to two groups.
20 One, our combination product applicants and the other
21 is constituent part applicant.

22 So combination product applicants is fairly

1 easy to understand. They are the holders of NDAs, BLAs
2 and ANDAs for combination products. Constituent part
3 applicants is a different term which is related to
4 someone who's marketing only one constituent part of a
5 combination product. And I have a slide later to just
6 sort of explain what that is, because there has been
7 some confusion on that topic.

8 But essentially the rule lays out a structure
9 which is similar to a lot of that we ways we manage
10 combination product regulation at FDA, which is that
11 you use the requirements that apply to the underlying
12 regs for the product, so those application-based
13 requirements that apply to NDAs continue to apply if
14 it's a combination product. But we layer on top of
15 that constituent part based reporting requirements that
16 arise from the other constituent parts. So the most
17 common situation, obviously, is you reporting under an
18 NDA would already require you to report adverse events.
19 But we're adding in those report types associated with
20 the device that we think are essential for us to get a
21 full picture of the postmarket safety information for
22 the product. And the reporting duties as with other

1 products only apply to that applicant's products, so
2 you are not necessarily -- you don't need to report
3 another information.

4 The constituent part applicants, and again
5 I'll spend a little on time what that means in a
6 moment. But there's also duties under the rule for
7 them to share information. So they are already
8 reporting per the type of product that they have. What
9 the role added for those entities is a requirement that
10 they are sharing information with the person who holds
11 the other constituent part application for the product.
12 The goal here was that you may be two separate
13 entities. Your product is being used together. So in
14 order for you to understand what's going on with the
15 products in the fields you will need to get some
16 information from that other constituent part applicant
17 about safety reports that they receive.

18 This is a pretty baseline requirement. All
19 they are required to do is share information with the
20 other applicant within 5 days. They don't have to do
21 analysis of it. They don't have to keep sharing as
22 they further investigate the requirement is. I know

1 about -- something about this product. I am going to
2 share it with the other entity who is marketing other
3 part of this combination product.

4 I will focus on the left and the center. So
5 for the purposes of this audience again, we are going
6 to look at the top two rows. Because what's really new
7 under Postmarket Safety Reporting rule for NDA, ANDA
8 and BLAs is the requirement to file 5-day reports which
9 is an requirement that comes from the underlying 803
10 reporting regulations for devices and malfunction
11 reports, another underlying requirement from devices.
12 Both of those now bubble up to the combination product
13 and under the rule you are required to report.

14 We laid out -- I, obviously, not going to try
15 to read this to you. But we did try to lay out some
16 assistance within the guidance about the thought
17 process of walking through. I have received
18 information on an event what are the sort of things I
19 need to be asking myself in order to know what sort of
20 report I need to be filing with FDA, and what report or
21 reports I need to be filing with FDA for that
22 particular event.

1 So as far as the goals and what else it says
2 besides just what new reporting obligations you may
3 have as a combination products applicant. First we
4 made it clear that there is streamlining available, so
5 there were a lot of questions and confusion prior to
6 the rule about needing to report to, for example, both
7 cedar and CDRH, because you had a device event. Did
8 you need to report that to the eMDR system versus drug
9 event, to FAERS, or how those work together?

10 So we talk about streamlining in the rule
11 saying, you can report -- you should -- you report all
12 of that through your lead center. So you report all of
13 that to FAERS, which is why we are here today. Because
14 FAERS that made -- that forced their requirements that
15 the FAERS system can accommodate that type of
16 information. But we made it clear that you don't need
17 to keep making separate report. So if you have an
18 event that triggers two different reporting obligations
19 you can make that in a single report, identified as
20 such. So a malfunction with a 15 day report for
21 example, as long as that's submitted in the shortest
22 timeframe, and as long as it has the information

1 necessary for both types of reports.

2 Again, you follow the procedure requirements
3 of your lead center, so if you're an NDA holder, you
4 are reporting to FAERS, all the events associated with
5 the -- ICSR associated with the combination product, I
6 will spend a lot of time. But there's also reporting
7 for non-individual case safety reports, other safety
8 reports, Recall and FARS and BPDRs and so forth.
9 Because they have a separate reporting process and
10 places that they go, those reporting requirements
11 follow the regulations. We have posted technical
12 information.

13 There's also some records keeping requirements
14 to make sure it was clear how long you needed to hold
15 onto these records given that the different size,
16 what's required by 803 for devices and what's required
17 by 314s for drugs, for example, may differ in with the
18 record-keeping requirements are. So we tried to
19 clarify that as well.

20 So as far as the constituent part applicant
21 definition, to be clear a constituent part applicant is
22 only for a product that's being where the constituent

1 part of a combination product is being marketed under a
2 given application. So the most common scenario where
3 there is lot of confusion about this was. I'm the NDA
4 holder. I buy my syringe from someone who manufactures
5 devices. They may even hold a clearance or an approval
6 for that device. I'm buying that device from them. I
7 am incorporating it into NDA product. I am
8 distributing that NDA product.

9 That -- if all they're doing is providing you
10 a syringe, they're not marketing that syringe to be
11 used with your drug product, for example, they're not
12 marketing that syringe for specific use in the
13 combination product. They just happen to be providing
14 you with that syringe that, that entity is not a
15 constitute part applicant. In order to be a
16 constituent part applicant, you need to be marketing
17 that device or that drug or that biological product as
18 part of a combination product.

19 If there's any confusion on this, because this
20 can be a tricky topic, you're welcome to check on with
21 your lead center or with Office of Combination Products
22 to help with clarity there. But, again, the goal of

1 the constituent part was really so that both sides of
2 the combination product are getting relevant safety
3 information to consider.

4 I won't speak anymore -- I think I already hit
5 streamlining. But, again, we did let organizations
6 know they can report in a single report. That we like
7 or we would preferred that information comes in follow-
8 up reports related to those events. I think the real
9 goal, if I'm speaking from an FDA perspective, is it
10 helps us to have a comprehensive picture of the event
11 no matter what information you have about it. If you
12 know about a device related -- something associated
13 with the device, something associated with the drug.
14 If those come in in a single report and follow-ups to
15 that report, then obviously that gives the agency and
16 it may be helpful for you as well a more comprehensive
17 picture of what happened in that event as opposed to
18 filing, for example, a 15 day report and then later
19 filing a separate malfunction report. It's just
20 helpful.

21 And we also discussed that the rule requires
22 that malfunctions and 5-day reports be included in

1 periodic reports. So there was comment on this so you
2 should maybe expect to see a little bit more detail
3 when the guidance is finalized. But you will be
4 required to submit malfunction and 5-day information in
5 your periodic reports.

6 What we also tried to do in the guidance was
7 sort of highlight those pieces of information that we
8 felt were fairly critical in order for us to understand
9 the event and to understand the product implicated in
10 the event. And so we highlighted sort of some minimum
11 required elements in combination product reports. If
12 they're not already required to be included these
13 pieces of information should be included.

14 The first is the combination production
15 identifiers. So first telling us that what you are
16 reporting on is a combination product. And we have
17 gotten questions about this saying, well, the
18 application is for a combination products, so why do I
19 have to tell you it is for a combination product. We
20 are on the FDA side, you have to understand, we are
21 trying to manage thousands and thousands and thousands
22 of reports. We have some situations where, for

1 example, a single NDA has different configurations,
2 some of which are combination products, some of which
3 aren't. And so in order for us to be able to work
4 through the information, and which things are really
5 relevant for the combination product configurations, we
6 need to know that it is for the combination product
7 configuration.

8 Likewise, I will focus on the suspect medical
9 device. I hear there was a question related to
10 managing device information within FAERS reports. So
11 again what we said in the guidance was that the device
12 information and the drug information or biological
13 product information should be routinely submitted,
14 regardless of what you think quote unquote "Cause of
15 the event". Again, the reason for this is, we think of
16 combination products as a product. We don't think of
17 it as just a device and just a drug and they are
18 separate things. When you put them together, they are
19 a combination product. They've been approved that way.
20 And so, again, what we are looking for is information
21 on the suspect combination product and that includes a
22 device constituent part of that product.

1 We also spoke about adverse event coding. So
2 on this space we shouldn't get a lot of questions here,
3 because that still the MedDRA coding you've always
4 used. Where I know there was a question raised already
5 in this forum and an elsewhere was related to the
6 device problem codes. So CDRH has a fairly robust and
7 harmonized device problem code structure. And again,
8 we are trying to look at information that we are
9 getting from multiple places, which means we may be
10 getting some information on a delivery device coming
11 through FAERS, but we may also be getting information
12 on that same product or similar products so that coming
13 in through the device side. And so we need
14 standardized way of managing what actually happened
15 with the product.

16 And I'm aware that MedDRA has some codes for
17 device problem codes. I think the topic came up before
18 the break. I think we are open to thinking about how
19 we could harmonize those. But what we needed and what
20 we've asked for is for you to use the standardized
21 device codes that already exist and have been
22 harmonized on the device side.

1 The guidance goes through some hopefully
2 helpful examples on what goes where, how to report the
3 information through the FAERS system and also some
4 situations where you might have multiple entities in
5 the combination product. So the device came from one
6 place, the combination product manufacturer is someone
7 different. How you might capture that within the
8 report. We are certainly open to, as we go forward, if
9 there's places where you feel like we are not clear on
10 exactly how you report information, of course, we are
11 open to feedback on how -- what else we can do to help
12 make it clear.

13 The tech specs have been updated, so we are
14 obviously here and you know a lot about FAERS. The
15 eMDR system was also updated. It was actually updated
16 first to allow the capturing of combination product
17 information. And the VAERS, there's been proposed
18 updates posted related to VAERS. So FAERS and eMDR
19 actually can accept these reports now. And Suranjan
20 and you can certainly -- Suranjan's group has already
21 worked with companies who are trying to make sure their
22 systems are working.

1 As far as some of the themes that recurred in
2 the comments we got to the guidance that I thought
3 might be of interest to this group. There was requests
4 for additional clarity on what information needs to go
5 into ICSRs and to the periodic reports. We also got,
6 as I've already spent some time on, what device
7 constituent part information should be included in the
8 reports. And again the guidance, I hope was fairly
9 clear, that it was routinely anticipated that you would
10 provide it regardless of whether you thought the device
11 was implicated in the report.

12 And then there was a section related to
13 foreign reporting, so there's a concept of same or
14 similar devices on the MDR and device side, related to
15 reporting for a product on a foreign event that has a
16 device that's the same or similar to the product that
17 you market in the U.S. So folks asked for a lot more -
18 - or as much more clarity as we could provide around
19 what we really thought that meant for combination
20 products and for your reporting under combination
21 products. So you should hopefully -- you should
22 anticipate that you will see more in the final guidance

1 on these topics. And when you see it, let us know how
2 we did.

3 So as far as key dates, we have pushed out the
4 compliance date now twice for this rule. The original
5 compliance date was back in 2018. We initially pushed
6 it back because the guidance document. You wanted more
7 clarity through the guidance. We provided that clarity
8 and then we received what we thought was pretty
9 compelling feedback from industry, from IT and vendors
10 and so forth. That you really just needed more time in
11 order to make sure we were getting the information we
12 wanted, which was for information to come in a
13 structured way where you are trying to avoid all the
14 way through this process was things just being dumped
15 into narratives and so forth, that's really hard for us
16 to analyze and manage. And that we had created -- we
17 had done all this work to try to create structured
18 locations for information to reside.

19 And so, we received feedback that if we really
20 wanted that, we needed to give a little bit more time
21 to make sure the companies, both from an IT point of
22 view and also from a process point of view, were

1 prepared to submit the information that we had
2 requested. So we pushed it out again until basically a
3 year from now for FAERS and eMDR. FAERS was given more
4 time because their technical specs were lagging for
5 reasons that we can't always control. So we've now
6 given until 2020 for FAERS, and eMDR to 2021, January
7 for VAERS. We are very close on the guidance. I know
8 we've -- if you have been in other forums where we
9 spoke and we've been saying that for a while.

10 But we really are close for that guidance to
11 come out in final that gives the clarity that you have
12 been -- and hopefully gives more clarity around the
13 topics you've been asking for since the eight draft
14 published.

15 But even in absence of the guidance, we have
16 been working with companies and trying to be as
17 responsive as we can be to enquiries about this is my
18 scenario, this is what I think I need to do. Or this
19 is the devices I have. This is how I think I need to
20 provide that device information for you. We have tried
21 to be as responsive as we can be. And we have gotten a
22 lot of enquiries from companies about, I want to make

1 sure I'm doing the right things or am I on the right
2 track.

3 It helps us if those enquiries are sent to us
4 in a sort of a specific fact pattern. When you ask
5 broad questions we can usually only give broad answers.
6 If you ask more specific questions where we can really
7 focus on what issue or scenario, that helps us in
8 providing hopefully more helpful response. We are open
9 to request for additional clarity, resources, things
10 that we can do to give you the tools you need to make
11 decisions on implementing the Postmarket Safety
12 Reporting rule. And we are very collaborative. OCP --
13 we are not the -- we are not the technical or product
14 experts. We are sort of a policy group and so anything
15 you send in -- and there is frequently lot of
16 collaboration on how we will respond and how we will
17 make sure we are providing the information that you're
18 requesting.

19 We do have a centralized webpage. You should
20 be watching that webpage for updates related to
21 Postmarket Safety Reporting. So these are just general
22 links for you. I don't know Suranjan is the normal

1 format that they are allowed to ask questions now or
2 how do you. So if there are questions, again, so I
3 can't speak to the detailed technical part, that's for
4 Suranjan after me. But if you have more policy or why
5 are we are where we are questions, I'm happy to take
6 them now. Okay. Thank you.

7 UNIDENTIFIED SPEAKER: Sorry. Have you done
8 an analysis of the benefit of sharing information on
9 one-time event with the constitute part. What
10 information, what benefit they will get from that
11 communication that they don't get today?

12 MS. BURNS: So I think the challenge is that
13 we don't know how that will work, how that's working,
14 because it's a new requirement. So I think that we did
15 have information at the time that we wrote the rules
16 and so forth. They suggested to us that the
17 information sharing wasn't very robust. And in fact
18 the original proposed rule specified a much more
19 rigorous amount of sharing between companies and we got
20 feedback saying, that's burdensome that we don't
21 necessarily see the value and that level of information
22 sharing between these constituent part applicants. And

1 so we actually relaxed that requirements to what we
2 thought got our -- got to the goal of companies need to
3 be sharing information without doing that in an overly
4 burdensome way.

5 But as far as do I have evidence and numbers,
6 I mean that's challenging first of all, because that's
7 company-to-company interaction. They are reporting to
8 us in some cases about their specific constituent part.
9 But the company to company interaction piece of it, we
10 won't routinely see exactly when and how that happened.
11 Does it make sense or is that somewhat responsive to
12 question?

13 UNIDENTIFIED SPEAKER: Hi, Melissa. I know
14 through different (cross talk) through different forums
15 we had submitted a few questions for answers and I know
16 you're trying to incorporate in the final guidance.
17 But is it also possible for you to publish as a Q&A
18 perhaps, so that will help us to give clarity to move
19 forward while we are waiting for the final guidance.

20 MS. BURNS: So -- by the time I got a Q&A out,
21 the guidance will be out.

22 UNIDENTIFIED SPEAKER: Okay.

1 MS. BURNS: I mean, I really am fairly
2 confident that you will see it in a matter of days or
3 weeks not in a matter of more months, okay. So we --
4 but to your question, once you see it, as is always the
5 case, there'll be some areas where you felt like we
6 still left gray. And so those are the ones where, I'm
7 certain -- you know, we are certainly welcome to either
8 answer questions specifically on a product or if you
9 feel like there's topics we need to hit harder,
10 especially once we all got little more experience with
11 how this works. I think we're very open to hearing
12 where those voids still are once you see that.

13 UNIDENTIFIED SPEAKER: Okay. And one of the
14 questions that's been -- we have been trying to figure
15 out is about the reportable and malfunction. Should it
16 be for only the constituent parts that are reported and
17 malfunction that we need to submit or should we list
18 every constituent part in the combination -- in the
19 combination application?

20 MS. BURNS: So, again, you need to check the
21 final guidance. But I will say that what was -- what
22 was the intent of the message we gave and the draft was

1 we want to know what's in the product. No matter
2 what's suspect or non-suspect. Because it becomes very
3 -- we thought that was actually a reason -- a more
4 reasonable approach than try to parse. Because what we
5 find with combinations products is that sometimes it is
6 really hard to say it was specifically this or
7 specifically that. You know the product event
8 happened. There are various interactions that may have
9 happened. And so instead of requesting parsing out of
10 individual suspect constituent parts, that if you told
11 us what the product configuration was and then you told
12 us what happened in the event. That then we would have
13 a picture of what happened with the product. So that
14 was -- that was sort of the goal and we actually
15 perceived that as reasonable even though what we heard
16 was we were very confused or we feel like that might be
17 burdensome in some cases. But that was sort of the
18 goal of that ask from the Agency side.

19 UNIDENTIFIED SPEAKER: Okay. I think the
20 burdensome comes from the amount of case processing
21 that might need to -- the processes that might need to
22 be instituted if you we have to include everything.

1 And also there was -- there were questions around the
2 assessment, the casualty assessment of, should it be
3 considered as a whole or for each constituent part and
4 what was your take on that?

5 MS. BURNS: Right. So I mean I think -- I
6 think just in combination -- just to back it all the
7 way up to combination product perspective in general is
8 that. We try to think about it as -- we have the
9 vantage in the United States of it actually being a
10 regulatory entity in and of its own comprised of other
11 regularly constituent parts. And so because of that,
12 and maybe -- hopefully in some cases, it's a benefit
13 where we try to think of it as a product. And so if
14 you're telling us about the event and what you know
15 about how the product contributed, how the constituent
16 parts contributed, than that's sort of how we were
17 thinking of it as opposed to trying to always slice and
18 dice information.

19 UNIDENTIFIED SPEAKER: Okay, that's great.
20 And there was another area of ambiguity about periodic
21 reporting. How we would want the data to be presented
22 and if there is any format that we were going to

1 suggest. Is that something we can expect in the final
2 guidance?

3 MS. BURNS: It will be -- there should be more
4 robust information in the final.

5 UNIDENTIFIED SPEAKER: Okay.

6 MS. BURNS: Whether it's to the level that
7 you're asking for, you'll have to let us know. I think
8 one of the challenges there -- and maybe Suranjan can
9 follow up when he is at the mic, is that, the formats
10 now -- there's some flexibility in the format even now
11 for periodic reports. And so for us to give a very
12 specific recommendation for combinations products,
13 given that there's already some allowable flexibility
14 within the current reporting, is challenging. And so,
15 we obviously want to give you a frameworks so that you
16 feel comfortable that what you're reporting is what we
17 are asking for. But trying to get too granular becomes
18 challenging for us.

19 UNIDENTIFIED SPEAKER: Okay. And I suspect
20 this is going to be a tricky question to answer. But
21 I'm sure some of this has been --

22 MS. BURNS: The answers, it depends and -- if

1 that's the question.

2 UNIDENTIFIED SPEAKER: So this is (R2) and we
3 are here talking about (R3) that influence combination
4 product, and they are very close to each other almost.
5 Right? So you have March 2020 and then you have this
6 coming up in July. So do you expect companies to do
7 these twice or would you have -- MAH do this once as
8 (R3).

9 MS. BURNS: So I am going to -- I am also
10 going to point part of this to Suranjan. But I think,
11 our understanding -- so first of all, we've already
12 given a significant amount of leeway here and the
13 amount of time to report so that the systems could be
14 brought online. And my understanding also is that the
15 transition to (R3) is not an instantaneous thing that
16 happens. And so we want the combinations product
17 information to start coming in in a reasonable
18 timeframe and if we are sort of tied to that, it may
19 delay things for companies that aren't even ready to go
20 to (R3). But then we are not getting the combination
21 product information that we had asked for couple of
22 years ago. So as far as how it -- or how the

1 implementation works and so forth, I think I'll let
2 Suranjan answer that. It is a little bit tricky.

3 MR. DE: Yes, I think -- I think, Melissa,
4 it's that we don't have a compliance date for (R3),
5 right. So companies could just -- if we say we go
6 everything to (R3), you don't have a compliance date.
7 So we would never get combinations product reports
8 electronically. Right? So I think from a perspective
9 of that we have already changed our timeline twice with
10 the (R2) submission of combination product. I think we
11 should continue with that timeline which she just
12 showed on the slides and then while companies are
13 working towards (R3), because it doesn't have a
14 compliance date. So with that perspective I think we
15 will still stay with the July 31, 2020 date for
16 submitting combination product in (R2).

17 MS. BURNS: Yes. I mean, I guess, all we can
18 say is that you should be planning for that date. I
19 mean that's our published date at this point, so.

20 MR. ROMMING: I mean, my question -- Hans-Jorg
21 Romming, Merck KGaA, Darmstadt, Germany. So my
22 question goes into the same direction. What we learned

1 this morning is that the guidance for the (R3)
2 limitation will be ready by March and then the deadline
3 for the combination -- or including the guidance also
4 for the combination products. But then the timeline
5 for the combination products is already July. So these
6 3 months will of course definitely not be sufficient to
7 do an implementation of the guidance. And, of course,
8 yes, industry want avoid to do double implementation
9 first in (R2) and then in (R3) also.

10 MR. DE: Yes I think combination product has
11 such that -- because we had got request from industry
12 to expand the timeline, the combination product would
13 have got implemented last year, right. So we had -- so
14 we had an extension which had to be given. We had
15 given an extension twice. So I think if we go with the
16 March 2020 -- I mean in March 2020 we cannot mandate it
17 that you have to submit by March 2020. And the
18 combination product, we have given extended by -- to
19 July 31st.

20 It is a same situation where -- because there
21 is no compliance date for (R3) we would never get -- I
22 mean a company -- if we say go with (R3), then we don't

1 know when the first combination product report
2 electronically will come. It will come in 2023 or
3 2022, which is just throws away all the timelines.

4 So I think the idea would be that -- I mean,
5 yes, we do have -- we do see this timing issue is
6 creating -- it's kind of falling in such a -- the
7 timing is falling in such a place that that (R3) is
8 coming while you are doing (R2). I think we have also
9 gone through that. It's just the timing of the
10 reports. I mean just no guarantee when the first
11 combination product report will come, because we don't
12 have an (R3) deadline. So I think that's what's where
13 the thinking is that we have to get those reports. Now
14 the guidance is out and the rule is out, we have to get
15 those reports -- start getting those reports in now.

16 Of course, when (R3) happens, (R3) you still
17 have to work through the INDs part of (R3). You have
18 to -- of course, through combination product and a few
19 postmarketing part of (R3). So the way we are doing it
20 is, okay, we did (R2). But all the (R3) are clubbed
21 together. Now in this case you are not separating out
22 combination products or you are not separating up IND,

1 you are not separating out all other postmarket. For
2 (R3) combining -- we're trying to combine everything
3 together as one and trying to report that. So, yes,
4 again it is just the timing factor. It has become such
5 that because of these two extensions and it is coming
6 closer to when we will be ready.

7 But again as I said, we -- FDA will be ready
8 with the draft guidance, draft technical specification
9 and their system. But like how other agencies gave 2
10 years, 3 years to implement (R3), it probably will be
11 that. I mean, we'll have to get a vibe from sponsors
12 to find out how long will it take to eventually get
13 (R3) from the time the technical specification is out
14 or his final. From that point onwards will get a vibe.
15 But right now we don't know that. Our hope is that
16 since companies are already doing for other agencies,
17 hopefully, it may be little quicker, but still we don't
18 know that. So we didn't want to put any kind of fixed
19 date as to when sponsors have to be ready for (R3).

20 UNIDENTIFIED SPEAKER: Hi Melissa. Just a
21 question on Slide 44, the last bullet point.

22 MS. BURNS: Uh-huh.

1 UNIDENTIFIED SPEAKER: Where you talk about
2 device problem codes, and if no device problem, and to
3 know known device problem.

4 MS. BURNS: Uh-huh.

5 UNIDENTIFIED SPEAKER: Is there a code for
6 that or is it feature --

7 MS. BURNS: There is. There is a --

8 UNIDENTIFIED SPEAKER: -- there is a code?

9 MS. BURNS: -- standardized code for it.

10 UNIDENTIFIED SPEAKER: Okay. Great. Thank
11 you.

12 UNIDENTIFIED SPEAKER: Maybe it's a
13 clarification for me. So you talked about FAERS an
14 eMDR can accept combination products submissions now.
15 But I think you also mentioned that we should submit to
16 FAERS and not to eMDR, if that makes sense.

17 MS. BURNS: You should submit to your lead
18 center. So I'm assuming that this audience is
19 primarily drug and biological product lead combo. So
20 if that's -- if that's the case, then you will submit
21 to FAERS. If you were a PMA company or 510(k) or if
22 you had a device application type, and that's your lead

1 center, then you would submit via eMDR. So the goal
2 was, you're only going to one place, no matter what
3 type of problem you're reporting --

4 UNIDENTIFIED SPEAKER: Okay.

5 MS. BURNS: -- was the intent. Does that --

6 UNIDENTIFIED SPEAKER: Not to both just one.

7 MS. BURNS: Not to both just to one.

8 UNIDENTIFIED SPEAKER: I've got a question.
9 Suranjan is going to introduce new report types, and
10 one of them is a 30 day report.

11 MS. BURNS: Uh-huh.

12 UNIDENTIFIED SPEAKER: Which device it has?
13 Can you give me a scenario where a 30 day report would
14 come into FAERS?

15 MS. BURNS: Absolutely. If all you know about
16 is a device malfunction with no patient, no negative
17 patient outcomes, so the device failed or malfunctioned
18 in some way, but the patient wasn't impacted. Those
19 reports are required to be reported, because they are
20 malfunction events. Because this standard for
21 malfunction is could cause or contribute to a serious
22 adverse event or death, not dead. And so in that case,

1 you may be reporting to FAERS about your delivery
2 device, there was no patient negative outcome. But it
3 meets the definition of malfunction, in that case,
4 you're filing just a 30 day malfunction report.

5 UNIDENTIFIED SPEAKER: Even though with your
6 NDA that you are going to report with it, is not a
7 suspect product -- it's not an issue.

8 MS. BURNS: But you will -- but again, so what
9 we're asking for in the report is the -- everything
10 about the suspect product. So the device and drug
11 constituent part information. So you will be providing
12 both whether you're just filing for example, a 15 day
13 alert about something you thought was related to the
14 drug or you're filing a malfunction report, which is
15 just about the device. You're recording on a suspect
16 product --

17 UNIDENTIFIED SPEAKER: So that that would go
18 for devices or would it? If it's of device -- device
19 is the center that's approved it, right?

20 MR. DE: But it's part of the entire product,
21 which was approved as an NDA.

22 MS. BURNS: It was approved under your NDA.

1 UNIDENTIFIED SPEAKER: Okay. So, it was
2 approved under the NDA, and somehow the syringe broke
3 or something like?

4 MS. BURNS: Exactly. But it didn't injure the
5 patient. So all you're saying is my -- my syringe
6 broke -- it -- if it happens again, it could injure my
7 patient. It just didn't in this case.

8 UNIDENTIFIED SPEAKER: Okay. Thanks.

9 MS. BURNS: And so you're reporting that
10 malfunction event.

11 UNIDENTIFIED SPEAKER: Okay.

12 UNIDENTIFIED SPEAKER: Okay. Well, real
13 quickly. In the scenario you just described where
14 there's no patient, but there's a malfunction to be
15 reported in 30 days. Is that considered to be in the
16 PADER as well in that scenario -- those cases?

17 MS. BURNS: That's the Periodic Report, you
18 mean?

19 UNIDENTIFIED SPEAKER: Yes.

20 MS. BURNS: Yes. So that says 5 days and
21 malfunction. It doesn't say only malfunctions
22 associated with 15 day reports, for example.

1 UNIDENTIFIED SPEAKER: Yes. So those -- those
2 --

3 MS. BURNS: And either case, yes.

4 UNIDENTIFIED SPEAKER: -- those types of
5 malfunctions are considered reportable malfunctions.
6 And in that regard it should be in the PADER.

7 MS. BURNS: Right. I think their language is
8 pretty broad, as an you need to report about 5 days and
9 malfunctions. It doesn't tie that to -- that that is
10 just you made a report.

11 UNIDENTIFIED SPEAKER: Right.

12 MS. BURNS: That -- because you made that type
13 of report that should also be summarized in your
14 Periodic Report.

15 UNIDENTIFIED SPEAKER: Okay. Thank you.
16 Second part of this question, it goes back to the
17 technical specifications of (R3) Plus (ph). Are the
18 updated or clarified guidelines that are going to come
19 out? I think you said in maybe in a few weeks. But I
20 also heard October as well. So I don't know. But are
21 those going to impact the (R2) specifications, or is
22 that's --

1 MR. DE: No.

2 UNIDENTIFIED SPEAKER: -- purely
3 clarifications?

4 MR. DE: That's only clarification. That's
5 not impacting the (R2). There was one item, I think
6 there is a feel, length change, probably. But other
7 than that, the data per data -- data elements and their
8 properties have no updates.

9 UNIDENTIFIED SPEAKER: Okay. Thank you.

10 UNIDENTIFIED SPEAKER: I just wanted to ask if
11 you can repeat or clarify for the different types of
12 reports that it will be reported towards a combination
13 product. What is the suspect product information? Is
14 it the same for all or does it change depending on the
15 report, that is a CDER or CBER lead combination
16 products sent to FAERS?

17 MS. BURNS: So what we said in the guidance,
18 which I apparently wasn't as clear as we hoped, so read
19 again the final, was you reporting on the parts of the
20 combination -- all parts of the combination product
21 regardless of the type of report, because it had
22 language about, regardless of whether you think this is

1 implicated in the event or something like that. I
2 can't remember the exact words. So that was what we
3 had said in the guidance. And again, part of that was
4 we -- we perceive that as being maybe a little bit more
5 repeatable and relevant than always trying to slice and
6 dice, because that can become really hard in some --
7 for some events.

8 UNIDENTIFIED SPEAKER: So we've heard that the
9 FAERS system is up and running and ready for
10 combination product reporting, and there are possibly
11 companies out there that are doing testing with you,
12 and possibly companies who've already started
13 submitting combination product reports to you. Are you
14 able to give any feedback on how that's going, what
15 sort of problems have been encountered so far, and are
16 there any learnings from that experience so far based
17 on the draft guidance that that's out?

18 MR. DE: So right now most of the combination
19 products, I can say, which has come are come through
20 our actually our portal, because pretty much everybody
21 uses commercial off the shelf tools today. So they all
22 have to be ready with their commercial vendors to

1 submit it to E2Bs. The reports which have come so far,
2 because we have the safety reporting portal site, which
3 is a UI based frontend tool. So the companies who have
4 that they have -- they have gone through that process
5 to submit that, because they already have an account to
6 submit, which kind of goes in very smoothly for us,
7 because this is internal to us. So far, what we have
8 learned is, companies have actually sent us some test
9 files to test. And the issues which we have seen
10 mostly are that using the new DDD, which was 2.2. And
11 most of the errors are with the headers they have not
12 set up correctly in their system. Because they
13 probably are using the DDD2.1. Now when they're
14 generating DDD2.2, if you on the headers, which says
15 ICH, ICSR or whatever there, so they have not set it up
16 correctly. And unfortunately, that we also have,
17 because our parcel is older, we are still using UTF, I
18 think, eight or -- I think eight or yes. So that has
19 to be set appropriately in for -- so this is more of
20 the structural part of generating an XML then that
21 actual data in there. Whenever we have got the actual
22 data, the data actually has got -- once they have fixed

1 that and we have loaded those sample files, they've
2 actually got positive acknowledgments.

3 UNIDENTIFIED SPEAKER: Uh-huh.

4 MR. DE: So yes, that's so far -- that's far,
5 how far we have reached. And we have already -- we've
6 also said that if anybody wants to do a testing with
7 us, please feel free to submit to the FAERS Esub, and
8 at fda.hhs.gov and we can help you out in testing your
9 files.

10 UNIDENTIFIED SPEAKER: We did -- just a follow
11 up to that. We did here there were some issues with
12 acknowledgement, like I know, we -- that there were
13 positive acknowledgement received. But then I think it
14 had not the right version number and so that was
15 causing issues.

16 MR. DE: Yes, so that's -- that was fixed.

17 UNIDENTIFIED SPEAKER: That was fixed already.

18 MR. DE: Yes, that was fixed. Yes.

19 UNIDENTIFIED SPEAKER: Okay.

20 MR. DE: I mean, it had to have the same DDD
21 version number. Yes.

22 UNIDENTIFIED SPEAKER: Okay.

1 MR. DE: So that was fixed. That was actually
2 fixed in production. So --

3 UNIDENTIFIED SPEAKER: Okay.

4 MR. DE: So, because -- I mean, we would have
5 got -- identified that because, we have not received
6 anything directly to production from the gateway. It
7 has only come through the safety reporting portal.
8 That's why, I guess, we did not identify that. But
9 yes, now we have got that fixed. So it's there.

10 UNIDENTIFIED SPEAKER: Referring back to the
11 July 20th compliance date for next year -- the July
12 2020 compliance date next year for the combination
13 products. Will you accept the information if it's in
14 the narrative -- provided in the narrative in (R2) at
15 that time, or will you not?

16 MS. BURNS: I mean, I think the answer to that
17 is, we have to get the information. I don't know that
18 we can mandate how it comes into us. But I think one
19 of the major goals of this effort was for us to allow
20 for structured information to come into us. And so
21 certainly, my strong encouragement is that we -- that
22 the fields that we've made available are the fields

1 that are used to report specific information, narrative
2 just -- it's -- and I'm assuming it's the same on your
3 side. Narrative is just challenging to make a lot of
4 sense, lot of -- especially in trending and so forth,
5 what's happening in postmarket.

6 MR. DE: Also that some of these data elements
7 which have become structured had that -- had like the
8 device name. Now, this reports are going to be shared
9 with the other centers. So when they have to run their
10 queries, it's just not possible to run from narratives.
11 So there are some structured data points, which
12 indicates what the device constituent part is.

13 UNIDENTIFIED SPEAKER: Well, I'm proposing
14 this only as an interim solution until and so we --

15 MS. BURNS: Right. And that was -- so sort of
16 one of the reasons we gave the extension of time is
17 because we heard a lot of companies were going to use -
18 - that was potentially going to be the impact of
19 holding to our original date was that. And that we
20 just didn't think that was -- that was a good outcome.
21 Along with the fact that internally, they were still
22 struggling with what the process was going to be,

1 because they didn't have the final guidance in front of
2 them. So between the guidance not being final, and
3 there being potential for you to not use the fields and
4 tools that we have opened up. That's what sort of led
5 us to extend the date.

6 UNIDENTIFIED SPEAKER: Thank you.

7 MR. DE: All right. So, I think with expected
8 time I have -- yes, I have about seven, eight slides to
9 go over, which has to do with combination products.
10 And there are many data points now in there. So I will
11 start -- we'll go over that. And thank you, Melissa,
12 for presenting the guidance and the regulation.

13 UP VERSIONING TO ICH E2B R3 -

14 REGIONAL REQUIREMENTS

15 MR. DE: So let me go back. All right. I
16 think now it's really more fun. We'll have more
17 questions. All right. Okay. So we come to all the
18 (R3) data elements. I think it would be easy, if I
19 just say these are all (R2), and we're taking it (R3),
20 right? We can finish the session. But -- All right.
21 So let's go over to some of the data elements we have.

22 So the first data element is identifying with

1 the combination product flag. So this is a new data
2 element, which kind of flags that this is a combination
3 product case. So as you see, it's a Boolean -- true
4 false, null, flavor is no information. Conformance is
5 mandatory. Yes, indicates that the report is
6 combination product, if not, then use the null flavor.

7 All right. Okay, first question is, can you
8 all see the font size and is this clear. Okay. Okay.
9 All right. So going into the drug identification.

10 Now, the previous element was under the case
11 identification. So now we'll have drug identification.
12 I think most of the elements now will fall on the drug
13 identification, which we'd go over. So this -- and you
14 will see most of this data elements are the same data
15 elements, which we have, which were in (R2). They have
16 been just transferred over to (R3) and now I have to
17 have this right schema and the right OID (ph) and --
18 and XPATHs (ph). So the Excel spreadsheet will
19 publish, will have the OID number and the XPATHs. So I
20 didn't put that XPATHs here, but you will see that.

21 So this first element is the expiration date,
22 which we already had for in (R2). Then we have the

1 product available for evaluation. Again, if you see
2 many of these fields are all optional, okay. So
3 whatever information you have, I think, Office of
4 Combination Product has said that many times, whatever
5 information you have, you give us this information. If
6 you don't have them, you don't have them. And we have
7 kept all these fields as optional data points.

8 Product available for evaluation, then you
9 have a 1, 2 and 3. It's a numeric value. Now this we
10 are requested for an OID for this. So when we the --
11 the technical specification, the Excel spreadsheet
12 comes out, you will see the OID. Product return date,
13 that's again, same field which was in (R2). Now, also
14 if you notice that these data points all have a prefix
15 of FDA.

16 Then you have a brand name, common device name
17 and product code, at least one of the three must be
18 there. And so these are alphanumeric, and the product
19 code has a link which is the three alphanumeric product
20 code. Now with that third, the last one product code,
21 I think -- correct -- on the product code, we talked
22 about using the UDI product code, right? So there was

1 a -- there is a less stuff, all the product codes which
2 -- how many is that? Alphanumeric code, okay, yes. So
3 that's -- that's the link we could.

4 Then we have the model number, the catalog
5 number, the serial number. Again, you see all our
6 optional fields. This I have to change. This as a
7 typo. This is I think 150, I think CTRH changed that
8 UDI -- unique identifier number to 150 characters. So
9 we just want to keep it the same.

10 Single use device, Boolean, true or false. We
11 have device manufacturer date. So that is the same
12 field as we had before. Then we have the manufacturer
13 who as we said the device manufacturer name, the device
14 manufacturer address, city, state, country. All right,
15 so here is another type of field now. Here is a little
16 -- I'm sorry.

17 UNIDENTIFIED SPEAKER: Yes, on the country,
18 why did you stick with the two position and not the
19 three position?

20 MR. DE: Why did we have two position?

21 UNIDENTIFIED SPEAKER: The ISO (ph) code.

22 MR. DE: That maybe -- that maybe -- that's

1 probably is -- it should act as same as how we're doing
2 the other -- all other countries in (R3), that's three.
3 That maybe -- yes Ta Jen.

4 MR. CHEN: So ISO -- has two digit and three
5 digit. The reason we've used two digit is, in ICSR
6 report, EU is a reserve word for the two digit, there's
7 no equivalent of three digit, for Europe. So we pick
8 two digit for ICSR report and we just take that
9 convention here.

10 MR. DE: Thanks, Ta Jen. Okay. So, here we
11 have this is -- this is interesting now. Remedial
12 action. So if you look at (R2) specs, (R2) specs
13 actually had -- each of these items the values are
14 allowed, they are -- they were individual data fields.
15 So each of them will -- would have said, whatever, if
16 they had a number called GK223 (ph), 1A, 1B, 1C, 1D,
17 1E, F, G. So, so this would have -- in (R2) this were
18 like nine separate fields, data points, if you look at
19 the specification. So in (R3), then -- because you
20 could have one or more values. So in (R3) we plan to
21 make it as repeating tag, so you can have one or more
22 values. Okay. So this will have its own OID numbers,

1 and then it's XPATH. Okay. And then if you had the
2 other -- than you have for that other what is the other
3 -- if the other was selected, then you just mentioned
4 what the other value is, which is R -- sorry, GK223,
5 (R2). All right. So next is -- I'm sorry.

6 UNIDENTIFIED SPEAKER: I think we just looking
7 at the -- the VAERS specification that they're given
8 out for the updated one. So they also have similar
9 data points, but the identification is different. So
10 right now here, you have remedial action under GK223
11 (R1). It's different on the VAERS one. Are you
12 looking to harmonize?

13 MR. DE: Yes, we will -- we are looking to
14 harmonize because they had to get their specifications
15 out before us. So we have to -- yes. That's what we
16 are doing, we're trying to harmonize that. Yes, the
17 number we may have to get. The concept is still the
18 same, the way they're doing it. We'll just have to fix
19 the number.

20 UNIDENTIFIED SPEAKER: I think even the values
21 allowed is different, I think they have C codes. And
22 here we have 1, 2, 3, 4, 5, 6, 7, 8, 9. That's just

1 something --

2 MR. DE: Yes, that's the next harmonization.
3 There are many places where -- because we are trying to
4 go with OIDs. And -- at that time when they were
5 writing the specification that that whole OID concept
6 was very new. So the C codes were used. Ta Jen you
7 have some to say?

8 MR. CHEN: Yes, so VAERS use the concept
9 called register under NCI EVS. We considered those
10 codes and because of this NCI EVS, every time we need
11 to change the code, we need to go to NCI EVS, because
12 those codes are more FDA internal. So we are thinking
13 to maintain that as code list within FDA. So if we do
14 that then OID will change. That list -- the ID would
15 change too. But we're going to harmonize with VAERS.
16 We going to -- I mean, we look for the minimum impact
17 when possible.

18 MR. DE: Yes, these are synchronized with the
19 eMDR values. Yes. These things we really didn't do
20 any upgrades too. So, actually the MedWatch Form says
21 this and they are all based on the MedWatch Form. We
22 just took these values as they were in the MidWatch old

1 form. Because many of the times you will find once his
2 values come in, even though the report has come into
3 CEDER, those values come in, they will be most
4 interested to see what is there in this particular data
5 point.

6 All right. Next we have device usage. So
7 again, that has three values. So that will have its
8 own OID. And then you have device lot number. Is it a
9 malfunction? True or false. Okay. And then you have
10 same follow-up type and -- which is again you have
11 three values there -- or four values there, which will
12 have its own OIDs. And then we did device problem and
13 evaluation code, so this is the concept where the
14 evaluation type and evaluation values are there. So
15 evaluation type is for device problem then what do you
16 use -- what values do you use and that value comes
17 under the under the value. If you have a method which
18 was, then what is the method. Then that comes under
19 value and these are repeatable tasks. So it repeats.
20 And this is exactly how we have in (R2) also.

21 And the last two fields were its operator of
22 the device and then other operator of the device. If

1 it is 1, 2 or 3 is other, then how this is to be done.
2 So you have 1, 2, if you have value of 3 then you put
3 "other" here. Now when it comes to actually the XPATH,
4 in the XPATH you will find there is -- the HSL model
5 actually, I think TJ can explain that better, as to how
6 -- to represent here what's in the slides were
7 difficult, but I think that TJ, if you can just touch
8 upon --

9 MR. CHEN: Okay. Okay. So, the HL7 Data Type
10 for this particular data element is CE, Coded
11 Equivalent. And the CE Data Type has many attribute to
12 it. It has the code itself, the code system, original
13 text, the code system name, the code name. So,
14 ideally, if you have a data element that's CE, you can
15 put in the code number.

16 So let me give you an example here. You can
17 put in code equal to 1, and then the text or the name
18 for the code, you can put in health professional. And
19 then the code system will be the FDA OE list. And
20 then, the code system name you can spell it out and the
21 original text, you can even put in something else,
22 right? So when you come to the number 3, "others."

1 Okay, so the code is number 3, the original text, you
2 can put in whatever reason, and that is a reason that
3 you pick number 3. So the original text is the text
4 that make you select a code.

5 So if for number 1, for example, if you do
6 number 1 original text, you can you can put in
7 physician, because a physician is a health professional
8 or you can put in nurse. We now require that. But for
9 3, when you pick three, we want to know what is "other"
10 so you populate with the original text. And that's one
11 data element.

12 UNIDENTIFIED SPEAKER: -- this element has a
13 bunch of codes, NCI codes that are listed for operator
14 of device. I'm just looking at it as like attorney,
15 biomedical engineer, et cetera, et cetera.

16 MR. DE: The operator of device?

17 UNIDENTIFIED SPEAKER: Yes.

18 MR. DE: That maybe the new --

19 UNIDENTIFIED SPEAKER: T5 operator of device.

20 MR. DE: Then that may be the new MedWatch
21 Form, I guess. We'll have to look at that. We will
22 have to harmonize that, because the original had 1, 2

1 and 3. I think the new reauthorized MedWatch Form
2 probably may have got these new ones.

3 UNIDENTIFIED SPEAKER: Okay.

4 MR. DE: But that probably is occupation of
5 the reporter.

6 UNIDENTIFIED SPEAKER: That is also, but it's
7 also applicable for D5, from what I'm seeing.

8 MR. DE: Operator of device?

9 UNIDENTIFIED SPEAKER: Yes.

10 MR. DE: Because I know occupation of the
11 reporter has so many biomedical engineer and this and
12 that and that.

13 UNIDENTIFIED SPEAKER: Yes. It says the list
14 of allowed values are the same as operator -- same as
15 the occupation of reporter.

16 MR. DE: Occupation -- okay, so operator of
17 device and occupation actually you're saying has the
18 similar list?

19 UNIDENTIFIED SPEAKER: Yes.

20 MR. DE: Okay.

21 UNIDENTIFIED SPEAKER: I'll double-check.

22 MR. DE: Can you note that? We'll look at

1 that, because I know those kind of fields values were
2 there in occupation. I didn't know they added that to
3 the operator.

4 UNIDENTIFIED SPEAKER: I'll double-check too
5 to make sure.

6 MR. DE: Okay. Yes, we'll check from our side
7 too. So these are basically the fields for combination
8 products. So there is -- and these are the same fields
9 as we had in R2. There is no change and there is no
10 additional fields or no fields that has been removed.
11 So they are the same fields that we will be collecting
12 when an R3 message is submitted. So with that --

13 UNIDENTIFIED SPEAKER: Have you guys decided
14 if any of these are going to have no flavors associated
15 with them?

16 MR. DE: If they're optional, they're
17 optional, right. So --

18 UNIDENTIFIED SPEAKER: So if it has no value -
19 -

20 MR. DE: nullFlavors would be required if you
21 had mandatory data point, right?

22 UNIDENTIFIED SPEAKER: Yes. Well, okay. Yes.

1 UNIDENTIFIED SPEAKER: So you said might come
2 to it this afternoon. In Melissa's presentation, she
3 did say that for now, we need to use the FDA codes.
4 But I had asked the question this morning about plans
5 for mapping IMDRF to the FDA codes and what are the
6 timelines for that?

7 MR. DE: So I think -- Sonya, did we any --
8 Yes, Sonya is --

9 MS. SONYA: So all I can say is that that we
10 are aware of the request to make that mapping between
11 the most frequently used device problem codes in
12 combination products mapped to the international
13 medical devices, regulatory forum terminology for
14 medical device problem codes, right? So the patient
15 problem codes have already been mapped, there is a one-
16 to-one crosswalk for those. The device problem codes
17 are very different. So we've taken a look at the
18 landscape and we've initiated communication with the
19 MSSO, the MedDRA maintenance organization and CDRH to
20 represent the Medical Devices Regulatory Forum, to try
21 and harmonize as much as possible. But there are no
22 timelines. There is no -- nothing that more -- that

1 can be said to that other than we are aware and doing
2 our best to address it.

3 MR. DE: All right.

4 UNIDENTIFIED SPEAKER: The question regularly
5 comes up, because our customers will say, what are you
6 guys doing because IMDRF have published Annex A to F?
7 So what are you doing? And we always have to point
8 them to the FDA website in terms of what the FDA is
9 doing in that area. So it was just to find out if
10 they're on a timeline, so thank you for that answer.

11 MR. DE: All right. Okay, so I have one.
12 Wait. Okay. I think these slides needs to be --
13 should have been eliminated. So, so we are at 2
14 o'clock and we are at our break time, and we'll be
15 reconvening at 2:15. And that's when we will have
16 Craig Zinderman, who is going to be presenting an
17 update on electronic safety reporting for vaccine. So
18 we will see you all at 2:15. Okay, thank you.

19 BREAK

20 SESSION 5: CBER'S UPDATE ON ELECTRONIC SAFETY

21 REPORTING FOR VACCINE

22 MR. ZINDERMAN: -- using any submitter tool.

1 At that time, in 2015, we published a technical
2 specification and a business rules document. And all
3 of those or both of those are available at the -- on
4 the CBER's vaccine ICSR implementation page, which
5 looks like that.

6 So here you can find both the tech spec,
7 there's a guidance for vaccine reporting, for
8 submitting electronic submissions of adverse event
9 reports for vaccines. There's the tech spec and then
10 there's the business rules, which is an Excel
11 spreadsheet that is an appendix to the tech spec.

12 So like FAERS, VAERS or eVAERS is built on the
13 ICH E2B(R3) implementation guide, combined with some
14 FDA regional extensions, to the ICH data elements. And
15 all of that, especially the regional extensions, are
16 explained in the tech spec and the associated business
17 rules.

18 VAERS receives about 50,000 to 60,000 reports
19 annually, so it's much, much smaller than FAERS, or at
20 least the volume of report submissions. That's a good
21 thing. Vaccines are fairly safe. About 40% to 50% of
22 the database comes from manufacturers -- at least in

1 the last few years. These data are from 2015 to 2018,
2 that's somewhat higher than it has been in the past.
3 So it's different than FAERS. And that a much smaller
4 portion of the database comes from manufacturers. We
5 get a lot more reports from parents, providers,
6 vaccinees themselves.

7 Over time, since the 2015 launch,
8 manufacturers have gradually transitioned from paper
9 reporting. At the beginning, most manufacturers
10 received waivers to continue to report on paper as the
11 E2B(R3) spec was very new then. A lot of vendors
12 hadn't released any software that was available to
13 report in (R3) at that time. So we've gone from
14 initially, every vaccine manufacturer being on waivers,
15 to report on paper, to now today all of them are
16 reporting electronically.

17 So what updates are we making now? There's
18 three reasons that we're making updates. One is to
19 enable the reporting that's required by the combination
20 products, postmarket safety rule, which we've discussed
21 at length last couple of hours. For vaccines, a lot of
22 people might think how's that a combination product? A

1 lot of vaccines are supplied as a prefilled syringe.
2 And as you probably know, something supplied as a
3 prefilled syringe, that's considered a combination
4 product by FDA. The syringe is the device constituent
5 part of the vaccine.

6 So the new reporting -- the new requirements
7 are malfunction reports and 5-day reports, as Melissa
8 explained. Another change that we're making is to
9 present the business rules in the ICH's prescribed
10 format. This is -- this format of the business rule
11 spreadsheet that Suranjan presented at the last meeting
12 and was also just going over now. So you'll see that
13 new format in a minute.

14 And we're also incorporating various updates
15 and clarifications to the business rules that we've
16 learned, were necessary and would help explain the
17 rules to people from feedback that we've received over
18 the years since the 2015 launch. There haven't been
19 any significant updates or changes to the original
20 rules.

21 We posted the new technical specification and
22 business rules, I think third or fourth week of May, so

1 it's been available for a few weeks now. That link is
2 the website where you can go see them. The website
3 that I just showed you that was the CBER vaccine ICSR
4 implementation page. The link is on there to get to
5 where the new proposed updates are. There is a docket
6 for submitting comments on the tech spec in the
7 business rules. And that same website has the docket
8 number and information for reaching the docket. So if
9 you have any comments or questions, feel free to submit
10 comments. I don't believe we've received any comments,
11 at least as of last week.

12 Now these changes aren't implemented yet, the
13 tech spec and business rules that we released, those
14 are just proposed at this point. They're not allowed -
15 - they tell us we're not allowed to call them draft.
16 So they're just proposed. So they're -- but they're
17 out there for you to look at. We haven't made any
18 actual programming changes. So you're still submitting
19 the way you have been for the past 3, 4 or 5 years. No
20 changes to current submissions. And as Melissa
21 explained, the compliance policy for combination
22 product reporting is in January 2021.

1 We are in the process of beginning to
2 implement programming changes in order to incorporate
3 the proposed updates and proposed new rules and we hope
4 to get to production for those new updates by the end
5 of -- or early 2020, possibly by the end of this year.
6 We anticipate that after that point, you'll still be
7 able to report the way that you do now. The compliance
8 with combination products won't be for another year
9 from then until early 2021. So you'll still be able to
10 report as you do now. And that's what we mean by dual
11 reporting options.

12 For companies that are ready to report using
13 the new tech spec and the new business rules, we hope
14 to have or we anticipate having the programming done,
15 so they're able to do that and they can just let us
16 know when they're ready to switch over. And then
17 they'll switch from the old way to the new way. But
18 both reporting options will be available for some
19 length of time.

20 All right, so what's new? I previously said
21 we were moving to the new ICH prescribed or
22 standardized format. So this is the new format.

1 There's a column where we described the source of the
2 data elements. So if it's an ICH data element, it's
3 standard from implementation guide. If it's an FDA
4 data element, then it's a regional data element. There
5 is -- we added the numbering system that Suranjan
6 explained for the FDA data elements.

7 There's a column for conformance that says
8 whether something's required or it's conditional,
9 mandatory or it's optional. There's a column that
10 explains the IG business rule, if we need to say
11 something special or notable from the IG business rule.
12 And there's a column that has the FDA business rules.
13 So wherever we differ from the rules in the IG, then we
14 explain what's different, what's the specific regional
15 requirement. And then there's another column for type
16 of change and that indicates what the difference is.
17 So it's an FDA regional requirement, and it just says
18 new FDA regional data element.

19 So the second change, of course, was that we
20 added all of the new information that we need for
21 devices in order to accommodate or enable combination
22 product safety reporting. So the first one is the

1 combination products report flag or indicator.
2 Suranjan presented this one as well. It's basically
3 just "Yes" or "No", if you're reporting about a
4 combination product, combination vaccine or not. Then
5 there's local criteria report type, which has
6 additional values. We have 15-day adverse event and
7 non-expedited adverse event, which are values that
8 we've already had. But now we're adding a 5-day and
9 the malfunction flag or the malfunction type of event,
10 if you don't have an adverse event, but you only have a
11 malfunction.

12 There's also a field in the product section --
13 in the GK section for malfunction. So for that
14 vaccine, which experienced a malfunction, you would put
15 true if that vaccine had a malfunction. Then there's a
16 series of additional device data elements. Many of the
17 -- or all of these you've already seen from Suranjan's
18 list. Device problem code, identifying the device, the
19 device brand name, common device name or device pro
20 code, information about the manufacturer, and the
21 remedial action indicated field that we talked about
22 previously.

1 So some of the other changes that we've made
2 to clarify or simplify things. Regarding combination
3 products, we've modified some rules in order to
4 accommodate malfunction events. Malfunction events, as
5 we've said previously, may or may not involve a
6 patient. So if it doesn't involve a patient, then
7 there's no way to provide those patient identifiers
8 that are required in the various system, patient name
9 and other such identifiers. So there's a business --
10 the business rule explains that you enter none, as you
11 do for FAERS, you enter none if there's no patient name
12 for instance.

13 We added a field for pregnancy, whether the
14 patient was pregnant at time of vaccination, simply
15 "Yes", "No". And that's to be consistent with the
16 VAERS Form 2.0. So CDC released a new updated version
17 of the VAERS form maybe 2 years ago -- 1 or 2 years ago
18 and they've added this question. So in order to
19 maintain consistency with that, we've added this
20 question as an FDA regional data element.

21 We deleted a few fields that we felt were
22 unnecessary. Parent identifier fields that asked for

1 the name -- the title, the name, the race and ethnicity
2 of the parent, this is just information that we don't
3 need to have and doesn't impact safety evaluation.

4 Body weight unit, it always had to be
5 kilograms. That's all that was allowed. So there's no
6 reason to have that data element. When you report the
7 body weight, it has to be in kilograms.

8 For qualification, we removed one of the no
9 flavors that we had allowed, which was just confusing
10 and unclear, it was "other." You are still allowed to
11 report "unknown", which pretty much accomplishes the
12 same thing.

13 We are making another change for message
14 sender identifier N2R2 (ph). We receive some feedback
15 from CDC and the VAERS program contractor that many
16 establishments were using different sender identifier
17 names at different times for the same product. So it's
18 difficult to identify, which manufacturers are
19 reporting, which manufacturer reporting for which
20 product because there can be, you know, 10, 20, 30
21 different sender IDs that a particular manufacturer is
22 using.

1 So in order to maintain some consistency when
2 we implement these new changes, we're going to ask that
3 all the manufacturers identify what their sender ID is,
4 and then consistently use that same sender ID so that
5 once we have agreement with you, or with the company
6 what the sender ID is, then we'll expect that sender ID
7 not change. And if we received a new ID, that's not
8 what we agreed upon, then that report would get
9 rejected.

10 So going forward, the updated documents are
11 available, as I said. So please go ahead and look at
12 them. You can make tech specs -- you can make comments
13 to the docket that's provided. We will review the
14 comments. We expect to look at them in mass in August.
15 And -- but we will continue to check in periodically
16 and continue to look at them. But as we have to
17 proceed towards having a finalized version of our tech
18 spec and business rules, the earlier that you submit
19 them, the more likely that we're able to address them
20 in the updated rules. We hope to get an updated tech
21 spec and business rules finalized what we've already
22 proposed by the end of 2019.

1 And as I said, we've already started to make
2 the programming changes. So anticipate that in early
3 2020, we'll be able to release the new version in
4 production. And as we said a number of times now,
5 compliance is required by January 2021 for -- at least
6 for combination product reporting. Any questions?
7 We've already answered everything. Good. Yes?

8 UNIDENTIFIED SPEAKER: -- in one of your
9 slides, I think where it's just the table where you
10 have a comparison of the IG versus the FDA rule. When
11 you say "IG business rule" -- yes, 75 -- Slide 75.
12 Where you see say "IG business rule", do you mean ICH?

13 MR. ZINDERMAN: Yes, yes. Sorry. IG is
14 implementation guide. There might be a little cut off,
15 it might say ICH IG in the actual spreadsheet, I'm not
16 sure. But yes, we mean IC, ICH it's the same thing.
17 Other questions? Okay. Suranjan?

18 MR. DE: All right. I think I answered most
19 of your questions in the morning for --

20 MR. ZINDERMAN: Yes, you did. Thanks.

21 MR. DE: All right. Thank you, Craig. So,
22 looks like we are ahead of time. So we will go with

1 the next session.

2 All right. So we'll go with the next session,
3 Session 6. This topic is on E2B(R3) Implementation
4 Industry Experience with Regulators. And we have Dr.
5 Hans Romming. He is the Senior Director, Head of GPS
6 PV Operations at Merck KGaA in Darmstadt, Germany. So
7 he's here with us to give us his -- their experiences
8 with implementing (R3) with other regulators.

9 Just to give you the whole purpose of --
10 again, this is also for us to learn as to what
11 experiences others had. So that's -- we'll be very
12 thankful to Dr. Hans to come and present at the FDA.
13 Thank you. Hans, all yours.

14 SESSION 6: E2B R3 IMPLEMENTATION -
15 INDUSTRY EXPERIENCE WITH REGULATORS

16 MR. ROMMING: Thank you very much, Suranjan.
17 And thanks a lot for providing the opportunity to talk
18 here about our experiences with E2B(R3) Reporting. So,
19 we at Merck KGaA in Darmstadt, Germany, we have started
20 the electronic reporting in (R3) to EMA and to PMDA in
21 February this year. And since then, we have submitted
22 around about 10,000 cases, to those both health

1 authorities. And I would just like to show you how we
2 have managed this project, what our challenges have
3 been and how we know envision the next steps,
4 especially also, with regards to (R3) reporting to the
5 FDA.

6 Just to let you know, Merck KGaA is an
7 independent company not related to Merck & Co. in the
8 U.S. In the U.S., we operate under the name EMD
9 Serono. So that's the content that I would like to
10 present. First a short background where we were with
11 our systems implementation before we started the
12 project, then the actual project implementation, the
13 strategy that we followed to address these two
14 authorities. The status quo right now after the
15 project has been implemented, and then the challenges
16 that we have seen during the implementation internally,
17 especially in the HyperCare phase.

18 Then I will have a look out into requirements
19 that are upcoming and then in particular the
20 requirements from the FDA and looking into the three
21 areas that we've also discussed today. So the
22 postmarketing reporting, the combination products, and

1 the IND reporting, followed then by a summary and
2 proposed next steps.

3 So at Merck, we are running our an integrated
4 safety system, which means that from a single safety
5 database, report to all health authorities worldwide,
6 including, of course, EMA, FDA, PMDA and also other
7 health authorities. In the picture on the right-hand
8 side you see, we started in 2005 as EMA, and then 2010
9 started reporting to the FDA, followed by Japan 2011
10 and then most recently, Switzerland and Canada.

11 Also -- and it's the lower part of the graph,
12 you report from the same database, obviously CIOMS and
13 MedWatch and also to some authorities in E2B5, which is
14 just attached to an to an e-mail and all other
15 possibilities of reporting. You know that in November
16 2017, EMA has upgraded to the (R3) standard. And since
17 then, there was the requirement already to import the
18 (R3) messages. So that's what we've done. So since
19 November 28, 2017, we were importing (R3). But the
20 export -- so the reporting, actually in (R3) -- it is
21 something that still had to be configured, tested and
22 the project was initiated in 2018.

1 The main driver for us was the deadline from
2 the PMDA, which required the reporting in E2B(R3) since
3 1st of April this year. And since we have this
4 integrated database, we needed to comply with this
5 deadline.

6 So due to the timelines that we had to adjust
7 to, namely the 1st of April this year for Japan, and
8 the situation in which we were with our current system,
9 and then the next system which should have been fully
10 compliant available, this didn't fit together. So we
11 had to find some way of co-development with our
12 software vendor, in this case, ArisGlobal to identify a
13 way to adjust our current system to make this reporting
14 possible. And this was also just to avoid any risks on
15 the project timeline since this deadline from Japan, --
16 from the PMDA was very fixed.

17 We decided to run this project for both health
18 authorities in parallel EMA and PMDA in order to avoid
19 two projects and to streamline the resources. We had
20 to consider that, besides now switching those two
21 health authorities to the E2B(R3), still we need to
22 maintain the possibility to report in the E2B(R2) for

1 the FDA, but also for other business partners with whom
2 we exchange cases. Then it was, of course, also our
3 aim to avoid as much as possible, any double data
4 entry, so that we would have to enter (R2) fields and
5 then again (R3) fields through a manual process. So we
6 had in mind that those pieces of information will be
7 copied over automatically within the system without
8 involving a double data entry.

9 We had -- we started the project in Q2 2018.
10 So we had around about 10 months for the project.
11 Nevertheless, due to the experience that you have made
12 with the initial implementation at the PMDA back in
13 2011, we knew that this is rather complex. So we said
14 we need to have a certain buffer time, minimum 1,
15 better 2 months, to be able to react in case we find
16 any issues -- severe issues during the HyperCare Phase.
17 So -- therefore, we wanted to be ready actually by
18 February this year.

19 What we've implemented are roundabout 70 new
20 data validations. Data validations for us are the edit
21 checks that we do in the database before -- or during
22 the case processing actually to avoid that any data are

1 entered which finally do not match the business rules
2 of the health authorities.

3 We have implemented around about 35 E2B
4 mappings, so specific mappings, a couple of other
5 configurations and then not to forget the automatic
6 rollover, so the conversion between (R2) and (R3) in
7 the system during processing itself to make sure that
8 we can report in both formats.

9 So what is the status? After our completion, in fact,
10 we could go live in February 2019 as planned. And
11 again on the right-hand side, on the picture you see
12 the status right now. We are still reporting in (R2)
13 to U.S., Canada and Switzerland, whereas in (R3) to EMA
14 and PMDA. And yes, we could do this without any major
15 impact on the compliance. So the system has been
16 running rather smoothly from day 1 onwards without any
17 interruption of our productive processes.

18 And what we found out is that it was critical
19 to make sure that we have really strict data
20 validations during the processing to make sure that
21 anything that could go wrong during the processing is
22 captured already during the data entry, and not only

1 that we first send the wrong report for which then we
2 have to do a lot of investigation to identify what
3 actually went wrong and then fix and correct afterwards
4 and have then the risk also of a late case when we send
5 the follow up.

6 So, yes, the error handling is in fact
7 something that proved to be very, very complex. Not
8 only due to the fact that we have the two health
9 authorities with different sets of business rules, but
10 also the sheer number of the business rules applied are
11 quite large.

12 Yes. Then what we see is -- it always was
13 difficult when we had conflicting requirements from the
14 different health authorities, so some following the ICH
15 standards and the other one having a specific rule, but
16 I'll come later to this.

17 Yes, some of the challenges that we've seen.
18 So both health authorities do have their regional
19 concepts, like we've seen also today, also for the FDA.
20 But in addition, they also deviate partly from the
21 standard. And here I've listed some examples which are
22 of course not exhaustive. For the EMA on the left-hand

1 side, they are using nullFlavors, not always like ICH
2 has specified them. For example, a nullFlavor is
3 allowed for the batch number, whereas in ICH, it would
4 be an optional field. Then on the other hand, for the
5 required qualification, EMA does not allow the
6 nullFlavor, but it has to be there.

7 Then there are some individual code lists or
8 individually adapted code lists, so we talked about the
9 UCUM just before. Similarly, for the
10 codeSystemVersion, for the Route of Administration, EMA
11 is deviating. And then as mentioned there, the
12 regional concepts, so for EMA particularly about the --
13 or the -- we mentioned particularly here the causality
14 for the SUSAR reporting.

15 Then on the right-hand side for the PMDA, also
16 here they are using individual code lists, for example,
17 for the pharmaceutical dose form, the 3-letter code.
18 Then in certain fields it is required that it is -- the
19 timestamp has entered into -- in Japanese time zone,
20 although there would be the possibility to follow the
21 time zone component. But here it is required that the
22 time zone is entered in Japanese time.

1 Reporter details are not to be submitted. And
2 similar is for the Japanese time. Also the Japanese
3 local language has to be used in some fields, but ICH
4 specifies that English can be used. And then not to
5 forget, the "J" items which would also cause blocking
6 business validations. There are 32 "J" items itself.

7 So here just a few more examples, going a bit
8 more in detail, comparing on a field level what does
9 ICH specify, and then what does EMA want to see and
10 what does PMDA specify in their implementation
11 guidelines. And you see highlighted with the pink
12 background where one of the two authorities is
13 deviating from the standard. So just as mentioned,
14 PMDA is requesting the Japanese time for some fields.
15 The reporter -- some reporter fields are not allowed
16 for the PMDA. nullFlavors -- yes, the EMA does not
17 allow the nullFlavor for the reporter qualification.
18 The UCUM codes have to be used on the restricted
19 fashion by EMA -- for reporting to the EMA. And yes,
20 batch number I mentioned before that it is mandatory
21 for the EMA to be -- it is mandatory, but if we can't
22 provide it, then we have to provide the nullFlavor and

1 other things alike. So that's basically repeating what
2 I was saying before on the other slide.

3 So what is upcoming? Besides the EMA and the
4 PMDA, there are many more health authorities worldwide
5 who have already announced that they would want to go
6 live as we sooner or later. Besides the FDA, there are
7 quite a few others. And some of them have already
8 announced that they would also make use of the regional
9 concepts. We discussed it today what U.S. FDA is
10 expecting, but also China and Korea have published
11 their guidance documents and especially Korea with a
12 very short timeline also.

13 What's important is that all these
14 implementations have to be looked in very detail for
15 the individual countries, so what they are putting into
16 their guidance documents. And depending on the
17 variation from the standard, these may -- significant
18 efforts that we have to put into the implementation in
19 terms of efforts and costs.

20 So we concluded that -- yes, for each country
21 basically it's an independent decision. It's advised
22 to implement it also from the global database, is it

1 more -- whereas to look for a local vendor to transform
2 the files for a reporting. So this will be an
3 individual decision based on how much the different
4 countries will deviate from the standards. And this is
5 definitely a space that we need to monitor carefully.

6 So now looking more into the requirements from
7 the FDA. So this refers back to the meeting in March.
8 So far, it has been communicated that there would be no
9 deviations from the ICH standard, which is of course is
10 highly appreciated as it would make our implementation
11 much easier. Nevertheless, the use of regional fields
12 is expected. And this of course will have a
13 significant impact in terms of timelines and costs for
14 the implementation.

15 Usually these kind of updates go along with
16 the change in the database, so the vendors are
17 involved. And -- that means for the industry that we
18 can only implement these changes once we have also the
19 green light from the vendor that they are ready to
20 implement these changes. Therefore, as a consequence,
21 it would be important that the final documents would be
22 available as soon as possible so that vendors can start

1 working on them with the implementation.

2 So with regards to the combination products, I
3 mean, we've discussed it at length today. The draft
4 guidance for the E2B(R2) Standard specifies additional
5 fields which are outside the ICH standard. And FDA
6 describes these specifications for the combination
7 products as dedicated regional fields (R3) also, so
8 that's also what we discussed today. And, yes, the
9 timelines were still -- at least to us, not clear, what
10 is expected then by July 2020. And do we have to
11 report in structured fields or would it also be
12 acceptable as an interim solution to report the
13 additional data fields which we -- which are expected
14 in the narrative.

15 So actually that is what we would like to
16 propose that as long as the (R3) implementation is
17 ongoing that we would report in (R2) in the narrative,
18 nevertheless of course, working on the (R3)
19 implementation to make sure that we would provide this
20 information in structured fields as soon as it's
21 possible. And, of course, we want to avoid a double
22 implementations that we first implement in the (R2)

1 Standard and then later on do a similar effort again in
2 implementing in (R3).

3 Then the IND Reporting. Yes, it was announced
4 that by Q4, the testing can start, also on the E2B(R2).
5 But also here there are some extended use of ICH fields
6 specified with additional -- where fields should have
7 additional values, which are not part of the ICH
8 standard. This would cause additional efforts also on
9 the -- on our side, so the proposal would be to go
10 directly to an (R3) implementation rather than through
11 E2B(R2). And -- yes, I think that's also what was
12 discussed this morning which should be in principle
13 possible would be then just an half year later
14 basically.

15 Yes. Summary and recommendations. These
16 slides obviously were prepared before the meeting
17 today. So we wanted to achieve clarity, whether it's
18 required to -- yes, what is actually required with
19 regards to the combination products reporting. What is
20 required in 2020 and how does it fit for the (R3)
21 roadmap and similarly for the IND reporting.

22 Yes, of course, it's very much in our interest

1 that the ICH standards are used as specified by ICH
2 without additional changes, just using the regional
3 concepts obviously. The controlled vocabularies should
4 be standardized further so to avoid deviations that
5 you've seen with EMA and with the PMDA also. And, yes,
6 in order to make best use of the resources, the
7 preferred approach that we would propose is to address
8 the E2B(R3) requirements for PM reporting, also
9 combination products, and the IND reporting as one
10 project, as soon as the testing with E2B(R3) can start
11 to avoid several implementations and repeating
12 implementations for the same topics.

13 Given the experience that we've had with the
14 EMA and with the PMDA, we expect a duration of
15 approximately 20 months. So after the final
16 implementation, guidance would be published. Meaning,
17 about -- that's what is in the graph below. Roundabout
18 12 months for the software vendor to adjust their
19 solutions and then the time for the company internal
20 project to implement the solution in all system.

21 Thank you, and if there's any questions please
22 let me know.

1 MR. CHEN: Got a question about a reporter's
2 title and name and all that. PMDA not allow. Is that
3 -- so if you provide that information, would they
4 reject your report or they just up to ignore?

5 MR. ROMMING: I need to check this how it's
6 actually handled. But this is how we've implemented it
7 so far.

8 MR. CHEN: Okay.

9 MR. ROMMING: Whether they rejected, that's
10 something that I need to check.

11 MR. CHEN: Okay. Yes, because I think at ICH
12 we did discuss that there might be data element that a
13 region may not care, we would up to ignore instead of
14 reject the report. So I'm just curious about how Japan
15 implement that, because it's ICH data element.

16 MR. ROMMING: Yes, I can follow up what is our
17 experience there.

18 MR. CHEN: Okay. Thank you.

19 UNIDENTIFIED SPEAKER: Thank you for your
20 presentation. I just have a curiosity question in
21 relation to Slide 96, where you talk about other
22 regions. So for South Korea, you said that the

1 timelines are very short and it was just to find out
2 what timelines are you aware of?

3 MR. ROMMING: So just by chance, I had an
4 information from our local colleagues the day before.
5 And I think they said that the -- they expect the new
6 law to be finalized very soon. So -- and I think it's
7 question of months. And that then a grace period of 1
8 year would be provided. And I think there is around 14
9 regional fields that they are discussing.

10 UNIDENTIFIED SPEAKER: Yes. That's right.
11 Thank you.

12 MR. DE: So that's -- I mean to add to TJ's
13 point, I think that's what the whole idea of doing a
14 cross regional testing, we want to do, so that when you
15 have all this different data elements, that at least we
16 should know what to ignore, so that those reports are
17 not rejected just because some other country has some
18 certain rule.

19 MR. ROMMING: You mean regarding the cross
20 regional testing. Yes, okay.

21 MR. DE: Yes.

22 MR. ROMMING: Yes, I can follow up with you.

1 MR. DE: That's the whole purpose of doing
2 that cross regional testing. And -- I mean, at this
3 ICH, we actually -- I actually talk to some of the
4 regions saying that as soon as we are ready to some --
5 accept some (R3)s, we will start the cross regional
6 testing with them.

7 UNIDENTIFIED SPEAKER: Regarding UCUM, imagine
8 you implemented the restricted UCUM list for EMA is
9 that the LOINC list that they have put out there, is
10 that --

11 MR. ROMMING: Sorry, which list?

12 UNIDENTIFIED SPEAKER: It's the list of UCUM
13 codes from LOINC. It's a -- yes -- yes, that's the
14 list. Okay, okay. It's like a separate group that
15 kind of -- I don't know filtered down the UCUM codes to
16 a more like a acceptable set for a --

17 MR. ROMMING: It is a filtered set, yes.

18 UNIDENTIFIED SPEAKER: Yes. Okay.

19 MR. ROMMING: What filter is applied here,
20 that's also something I would need to follow up.

21 MR. DE: I think it applies to the test -- lab
22 test, right?

1 UNIDENTIFIED SPEAKER: Yes. Yes, yes. Okay.

2 MR. ROMMING: Yes. Exactly. Yes.

3 UNIDENTIFIED SPEAKER: Okay. Just confirming
4 that, yes. And I think that came up, yes, I could see
5 that with the FDA mentioning that they would be
6 providing -- it would accept a entire set of UCUM, that
7 could be kind of a -- it could be some codes that could
8 cause some conflicts, I guess. Yes. Okay.

9 MR. CHEN: It would not cause conflict. So
10 UCUM is a system that allow you to generate unlimited
11 combination, right. So that LOINC is empowered (ph)
12 list. It's can say that a subset of what you can
13 generate. Okay. So there should be no conflict.
14 That's potential that there might be a lab test result
15 in U.S. that is not on that list. That need to be
16 resolved. But -- yes -- because we allow -- yes, any
17 new kind of test, generate new kind of result that may
18 not be on that list. But hopefully, most of that lab
19 test use UCUM and use LOINC. So LOINC hopefully would
20 update their list at some point. That's the idea.
21 Yes. Yes.

22 MR. DE: All right. Any more questions for

1 Hans?

2 UNIDENTIFIED SPEAKER: So in Japan, they don't
3 let you actually test anything. So, you know when you
4 were submitting into Japan, my understanding is they
5 won't let you test first. You have to go live. Is
6 that still correct?

7 MR. ROMMING: It's correct. What you have to
8 do is just an infrastructure test, so that you
9 successfully send a message to and that you can
10 receives the acknowledgement back. That's the all
11 testing that we do --

12 UNIDENTIFIED SPEAKER: -- copy of their big
13 book. What is it, the white book or --

14 MR. ROMMING: No. The green book. Yes.

15 UNIDENTIFIED SPEAKER: Copy of the big green
16 book, right?

17 MR. ROMMING: The green book is the guidance.
18 Yes.

19 UNIDENTIFIED SPEAKER: The Bible, yes.

20 MR. ROMMING: Yes. Thank you.

21 UNIDENTIFIED SPEAKER: So (R3), you were
22 supposed to improve the data quality and streamline the

1 operations. We are far from it. As a member of the
2 industry, do you think, there is hope that we can still
3 get there or should we start thinking about (R4)?

4 MR. ROMMING: I mean, it reminds me quite a
5 bit of the situation that we've had in Europe in the
6 early 2000s years, when new reporting had just started.
7 And each of the countries had their own specificities
8 that they wanted to see implemented. For example,
9 Spain versus Spanish narrative, France versus French
10 imputability. U.K. only wanted to receive the medical
11 confirmed cases, so -- and I think nowadays -- I mean,
12 since 2017 we only report just to EMA and it works. So
13 I think there is still hope that in the similar fashion
14 now worldwide, we will see that, yes, there are
15 specificities, but over time, I think that this will be
16 reduced hopefully. So, I think that's hope for (R3)
17 without looking at R4 yet.

18 UNIDENTIFIED SPEAKER: Thank you.

19 MR. DE: So now I know what the problem is.
20 Sorry. The slide got -- so okay. Thank you, Hans.
21 And so we are almost at the closing. I think we are
22 little early. So yes, if anybody interested to see

1 D.C. in the heat, they still have some time.

2 SUMMARY AND CLOSING REMARKS

3 MR. DE: So in closing, I want to thank
4 everybody for attending this meeting and the presenters
5 who presented here. I think this second meeting has
6 generated a lot of questions. We talked about many,
7 many topics. And I think I really appreciate
8 everyone's participation and asking the questions. So
9 with that, I would like to just summarize and do some
10 closing comments.

11 So we -- just to summarize today's sessions,
12 we had six sessions. And we started with some synopsis
13 from session -- from Meeting 1. We went into talking
14 about some regional data elements on IND. I think I
15 messed it up.

16 So the second session was on IND. The third
17 session was on the BA/BE trials that Karen talked
18 about. Then we had into combination products, where
19 you heard lot about the background, the rule and
20 talking about the technical specs or regional
21 requirements. And then we had Craig who came and
22 talked about the CBER's update on safety reporting for

1 vaccines. And then finally, Dr. Hans who talked about
2 E2B(R3) implementation, their experiences with
3 regulators.

4 So with that, I would again thank everybody
5 for attending this meeting. We have -- this meeting
6 will be posted hopefully within a week, 2 weeks,
7 because this whole recording -- there' a video
8 recording going on. So that will be posted, and the
9 slides will also be posted along with it. The
10 transcripts will be posted along with it. So you will
11 have all this available on the meeting page.

12 Typically, it takes about 2 weeks to set all this up.

13 And then as I said, the docket will be open,
14 so anything you have to submit, please submit to the
15 docket. The docket time will be up to August 16th.
16 And then after that, you can still contact at that e-
17 mail address shown below. So based on all that
18 comments which we got today, the comments which we will
19 get on the docket or from the e-prompt, we will take
20 all those into account. We start preparing for the
21 February 19th meeting, but we also heard that it'll be
22 nice to have something in between now and that time

1 period, where if we can sooner than later, post the
2 spreadsheet of those specifications. I think will give
3 a good idea especially for vendors, who can then take
4 that to work through that.

5 And also between now and the February
6 timeframe we'll start preparing some sample files, so
7 that that can be shared with you all, especially in
8 (R3). And while we are doing this, we are also -- we
9 will be working actually we just -- we were talking
10 during the break. I think we will get this sooner than
11 later the Excel spreadsheet where we would have
12 harmonized many of the data elements between VAERS and
13 FAERS. So it could end up in one data element and they
14 are all harmonized.

15 So after -- there was another thing which we -
16 - just came to my mind that maybe after the February
17 meeting, we could still continue with more like maybe a
18 quarterly WebEx -- just a WebEx, not in person, but a
19 WebEx to kind of see how companies are doing with their
20 implementation, any kind of questions they have,
21 because by March 2020 we would have done our
22 implementation. And now it will be time for the

1 sponsors to start implementing, so we can probably do a
2 quarterly kind of catch up on how things are happening,
3 maybe address some of the questions which would have
4 come through our e-prompt mailbox. And probably we can
5 continue something like that for some period of time
6 before most of the companies kind of come and
7 implemented (R3).

8 ADJOURN

9 MR. DE: So with that, thank you all. And if
10 anybody has any closing comments, please. If -- no.
11 No. No. No problem. I mean, yes, we'll continue
12 doing this. I think this is helping us and helping you
13 all. I think as a collaborative team if we work this
14 out, I think we will be successful in our (R3)
15 implementation. So -- yes, and you heard Dr. Dal Pan
16 saying -- I mean, unfortunately, the last hour
17 regulatory ICH, regulators who are going doing (R3), so
18 we have to get this done. So thank you all, and you
19 have a wonderful evening, and we will catch up soon.

20 (Applause)

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7 ability; that I am neither counsel for, related to, nor
8 employed by any of the parties to the action in which
9 this was taken; and, further, that I am not a relative
10 or employee of any counsel or attorney employed by the
11 parties hereto, nor financially or otherwise interested
12 in the outcome of this action.

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