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

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Silver Spring, MD 20993

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

INTRODUCTIONS

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

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

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

As you all probably know, the Adverse Event

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

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

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

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

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

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

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

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

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

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

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

MR. DE: Okay.

MR. DAL PAN: Thank you.

SESSION 1: SYNOPSYS FROM PREVIOUS MEETING

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

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

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

where FDAs plans is.

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

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

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

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

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

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

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

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

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

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

visit them and look at them and download them.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SESSION 2: E2B R3 REGIONAL REQUIREMENTS FOR IND SAFETY REPORTING

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

your safety databases.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

actually giving us a lot of information.

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

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

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

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

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

BREAK

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

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

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

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

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

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

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

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

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

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

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

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

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

our safety data review and concern.

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

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

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

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

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

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

Our data team on a regular monthly basis is

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

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

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

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

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

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

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

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

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

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

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

So this slide I actually borrowed from

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

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

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

And submitting these reports electronically

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

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

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

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

All of the pre-market adverse event reports

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

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

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

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

ultimately submitted.

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

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

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

bioequivalence study is probably a good way to do it.

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

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

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

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

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

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

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

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

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

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

distinguish these pre-ANDA cases through the MedWatch form.

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

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

substituted.

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

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

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

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

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

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

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

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

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

MS. FEIBUS: No.

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

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

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

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

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

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

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

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

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

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

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

MR. DE: Separating out.

MR. IYER: Yeah.

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

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

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

MR. DE: Oh.

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

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

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

MR. IYER: Yeah.

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

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

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

identify cases being expedited.

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

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

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

MR. DE: Oh.

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

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

MR. DE: Yeah.

MS. FEIBUS: -- incredible disconnect.

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

MS. FEIBUS: So I'm going to…

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

will we address those.

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

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

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

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

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

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

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

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

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

MR. DE: So that consideration has also been

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. DE: Yeah.

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

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

MR. DE: Coming in, yeah.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. DE: Okay. TJ?

UNIDENTIFIED SPEAKER: The reason why I ask --

MR. DE: Yeah.

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

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

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

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

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

UNIDENTIFIED SPEAKER: IMDRF.

MR. CHEN: I -- the UCUM number?

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

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

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

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

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

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Right.

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

UNIDENTIFIED SPEAKER: So would yours he similar as EMA -- same as EMA, not even similar -- same?

MR. CHEN: We would be -- yes.

UNIDENTIFIED SPEAKER: Same as EMA?

MR. CHEN: Yes.

UNIDENTIFIED SPEAKER: Okay.

MR. CHEN: Yes.

UNIDENTIFIED SPEAKER: That's great.

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

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

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

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

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

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

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

MR. DE: That carries on.

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

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

UNIDENTIFIED SPEAKER: Last question.

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

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

MR. DE: Yes, I mean --

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

in the XML file.

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

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

MR. DE: Yes.

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

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

UNIDENTIFIED SPEAKER: Is that what you are talking about?

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

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

MR. DE: Similar.

UNIDENTIFIED SPEAKER: And you put it in their narrative.

UNIDENTIFIED SPEAKER: Yes.

MR. DE: Yes.

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

like --

UNIDENTIFIED SPEAKER: So --

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

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

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

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

MR. DE: No.

UNIDENTIFIED SPEAKER: It's not.

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

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

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

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

UNIDENTIFIED SPEAKER: -- you were searching

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

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

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

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

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

LUNCH

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

SESSION 4: E2B R3 REGIONAL REQUIREMENTS FOR COMBO PRODUCT SAFETY REPORTING

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

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

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

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

So combination product applicants is fairly

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

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

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

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

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

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

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

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

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

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

necessary for both types of reports.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Okay.

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

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

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

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Okay.

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

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

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

that's the question.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS. BURNS: Uh-huh.

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

MS. BURNS: Uh-huh.

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

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

UNIDENTIFIED SPEAKER: -- there is a code?

MS. BURNS: -- standardized code for it.

UNIDENTIFIED SPEAKER: Okay. Great. Thank you.

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

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

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

UNIDENTIFIED SPEAKER: Okay.

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

UNIDENTIFIED SPEAKER: Not to both just one.

MS. BURNS: Not to both just to one.

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

MS. BURNS: Uh-huh.

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

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

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

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

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

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

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

MS. BURNS: It was approved under your NDA.

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

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

UNIDENTIFIED SPEAKER: Okay. Thanks.

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

UNIDENTIFIED SPEAKER: Okay.

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

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

UNIDENTIFIED SPEAKER: Yes.

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

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

MS. BURNS: And either case, yes.

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

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

UNIDENTIFIED SPEAKER: Right.

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

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

MR. DE: No.

UNIDENTIFIED SPEAKER: -- purely clarifications?

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

UNIDENTIFIED SPEAKER: Okay. Thank you.

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Uh-huh.

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

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

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

UNIDENTIFIED SPEAKER: That was fixed already.

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

UNIDENTIFIED SPEAKER: Okay.

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

UNIDENTIFIED SPEAKER: Okay.

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

UNIDENTIFIED SPEAKER: Okay.

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

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

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: Thank you.

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

UP VERSIONING TO ICH E2B R3 –

REGIONAL REQUIREMENTS

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

So the first data element is identifying with

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

All right. Okay, first question is, can you all see the font size and is this clear. Okay. Okay. All right. So going into the drug identification. Now, the previous element was under the case identification. So now we'll have drug identification. I think most of the elements now will fall on the drug identification, which we'd go over. So this -- and you will see most of this data elements are the same data elements, which we have, which were in (R2). They have been just transferred over to (R3) and now I have to have this right schema and the right OID (ph) and -- and XPATHs (ph). So the Excel spreadsheet will publish, will have the OID number and the XPATHs. So I didn't put that XPATHs here, but you will see that.

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

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

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

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

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

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

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

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

MR. DE: Why did we have two position?

UNIDENTIFIED SPEAKER: The ISO (ph) code.

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

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

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

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

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

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

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

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

something --

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

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

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

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

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

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

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

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

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

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

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

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

MR. DE: The operator of device?

UNIDENTIFIED SPEAKER: Yes.

MR. DE: That maybe the new --

UNIDENTIFIED SPEAKER: T5 operator of device.

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

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

UNIDENTIFIED SPEAKER: Okay.

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

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

MR. DE: Operator of device?

UNIDENTIFIED SPEAKER: Yes.

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

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

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

UNIDENTIFIED SPEAKER: Yes.

MR. DE: Okay.

UNIDENTIFIED SPEAKER: I'll double-check.

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: So if it has no value --

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

UNIDENTIFIED SPEAKER: Yes. Well, okay. Yes.

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

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

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

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

MR. DE: All right.

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

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

BREAK

SESSION 5: CBER'S UPDATE ON ELECTRONIC SAFETY REPORTING FOR VACCINE

MR. ZINDERMAN: -- using any submitter tool.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. ZINDERMAN: Yes, you did. Thanks.

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

the next session.

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

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

SESSION 6: E2B R3 IMPLEMENTATION – INDUSTRY EXPERIENCE WITH REGULATORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

working on them with the implementation.

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

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

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

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

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

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

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

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

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

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

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

MR. CHEN: Okay.

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

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

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

MR. CHEN: Okay. Thank you.

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

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

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

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

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

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

MR. DE: Yes.

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

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

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

MR. ROMMING: Sorry, which list?

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

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

UNIDENTIFIED SPEAKER: Yes. Okay.

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

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

UNIDENTIFIED SPEAKER: Yes. Yes, yes. Okay.

MR. ROMMING: Yes. Exactly. Yes.

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

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

MR. DE: All right. Any more questions for

Hans?

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

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

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

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

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

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

UNIDENTIFIED SPEAKER: The Bible, yes.

MR. ROMMING: Yes. Thank you.

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

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

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

UNIDENTIFIED SPEAKER: Thank you.

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

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

SUMMARY AND CLOSING REMARKS

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

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

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

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

So with that, I would again thank everybody for attending this meeting. We have -- this meeting will be posted hopefully within a week, 2 weeks, because this whole recording -- there' a video recording going on. So that will be posted, and the slides will also be posted along with it. The transcripts will be posted along with it. So you will have all this available on the meeting page. Typically, it takes about 2 weeks to set all this up.

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

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

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

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

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

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

(Applause)

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