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) StaNDA-rds

_____

MEETING

DATE: Wednesday, February 19, 2020

TIME: 9:17 a.m.

LOCATION: FDA White Oak Campus
10903 New Hampshire Avenue
Bldg. 31 Conference Center
the Great Room (Rm. 1503, Section A)
Silver Spring, MD, 20993

REPORTED BY: Eliza Spikes, Notary Public

JOB No.: 3662002

A P P E A R A N C E S

Suranjan De

Ta-Jen Chen

Rick Hester

Una Casey

P R O C E E D I N G S

SURGANJAN DE: All right. Good morning, everyone. My name is Suranjan De. I am the Deputy Director with Regulatory Science in the Office of Surveillance & Epidemiology in the Center for Drugs at the FDA.

So today we have the third meeting. We're going to be going through all that we have discussed at the first two meetings, plus we had a webinar. And we will be going over all the data elements that we have discussed earlier, and here we are talking about all the regional elements that we're talking about.

So we're going to have first morning session will be talking about all the different kind of regional data elements with pre-market combination products any other regional elements. Then we'll take a break. We will then have TJ, who's going to talk about some FDA specific OIDS because of these regional data elements. We also have the regional FDA specific OIDS.

We're go into lunch. We talked about -

- we'll talk about some regional forward compatibility from E2B R3. We'll talk about the submission mechanisms because now we're going to have pre-market/post-market, so the helping mechanism splits.

Then we're going to go into the afternoon into the demonstration of the E2B validator. So this is a validator with any sponsor can validate the regional R2 and convert that to a regional R3 or upload a regional R3 and validate that to see if the data is -- the valid -- the data is correct and they could submit -- before they could submit, they could do that check.

And then finally, I will have it as an open discussion and not make it too formal for any kind of questions we want to discuss, only specific things that we came across during the day. And we can sit together to come up with a solution, if you have questions or any suggestions that, you know, you all want to provide.

So with that, there's some housekeeping items I want to get aside: is one being, you know, please silence your cellphones; the restrooms are

located at the far end of the main hallway, the right of the room; wi-fi is available here, the wi-fi network is FDA public and the passcode is public access, all small letters.

So we'll save the questions for the end of each session. Lunch is 11:45 to 1:00, and you have seen the kiosks here where you could go and order your food.

As you will recall, this meeting has been requested, so there will be a link available on the FDA site once we have the recording, which will also have the transcripts, these slides that we present today, and eventually we will also post the regional data elements that I'm going to go over.

When we go over the regional data elements, you will also see that these elements are placed in a huge big Excel spreadsheet that constitutes off all the ICH elements and the regional elements with the variations being highlighted. And you will have 20 to 30 days from this meeting to post your comments in the docket. And how to do that is available at the registration table and our Docket No.

is FDA-2018-N-4002.

So with that, I will start with my updates on FAERS II. So we'll go over a little bit on the plans and the timelines, and then go swiftly or into the data elements.

So we have discussed -- we had talked about this at my first meeting last year, March. Just to revise what was our objectives for FAERS II as FAERS II is very mission critical system for CDER and CBER. And this is to provide a modernized system for pre-market, post-market, and product quality defect reports.

And we plan to enhance and unified data analytics and signal management. We have to achieve the data staNDA-rds for ICH E2B R3 and decommission our old tools, and this has been designated by HHS as a modernization priority.

So going into the scope. So scope was very straightforward: it's to implement the system, which has a case processing platform and data analytics by including the staNDA-rds of ICH. And then we go into the operation mode and maintain the

software tools that we have -- we are implementing, and the decommission of old tools.

The tools that we use are implementing is for the analytics, we have the Rx tool, and for case processing, we have the Aris Global LifeSphere tool.

So going into some of the timelines. So we had our first ePrompt meeting March 25th; our second one we had on March -- July 17th. Then we drafted our regional elements for public review, so that is what we're going to be presenting today. From March to now, we have been communicating the data elements through these ePrompt meetings. But today we're going to go over, like, a final draft, which then we will provide for your comments.

So today is our ePrompt meeting, and then we will go into -- we'll try to post this draft by end of this month so we can post this, all the data elements. So you will see a huge big basically a spreadsheet, actually two spreadsheets: one will have all the data elements; and the second spreadsheet will have the forward compatibility document, which shows

how you for the regional elements from an R2 to R3.

And then, hopefully, by end of this fiscal year, we will provide -- make the E2B validator available that we're going to demonstrate today and the technical specification. And then sometime by end of this year, we will have this ready for E2B R3 testing. So that's, so far, that's the tentative timelines that we have.

There has been some change. Initially, our plan was to have something by March, but there have been circumstances where for which we have to move this, and so here's the next tentative timelines that we have planned for.

So just to go over some of the testing plans and the methods that, once we have, you know, ready for it to be R3 testing, how will you do some kind of -- this kind of testing when you are ready with the R3 submission, the regional submissions.

So first thing first, we have no compliance date defined for R3 submissions, okay. Sponsors can start testing after September 2020, which means here's the date for September 2020 when we have

the validator available and the technical spec available. Since you already would have the regional data elements available to you and sponsors could start developing, there are three submission files using those data elements, and then start testing them through the validator, and then eventually also test them by submitting that to FDA in a non-production environment.

So as I said, FDA will to provide the validator to pretest sender's ICSR. This validator actually will be available publicly through a URL. We plan to put this validator actually on the electronic submission webpage that we have for FAERS, so you will have a link there and you could go there and use a validator to test your ICSRs.

One thing to you know, this validator does not give you an acknowledgement; it gives you the error message right on the screen. But when we got to the process where you actually submit the file to a non-production environment to test through the gateway, we would send acknowledgments back, so you could see those acknowledgements and test it out.

So you continue to submit in R2 format until you are ready for R3. And as I said in the first bullet point, there's no compliance date for R3 that has been defined.

So the idea would be to also test both pre-market or post-market, including combo products if you have in the R3 format with the regional data elements and developing mechanism. This is where I'm going to talk to you around 1:30 of the different routing mechanisms that you need to submit these when you are submitting to a non-production environment for the pre-market and the post-market. There's going to be two different routes and we just can send ours in the afternoon.

When you're doing your first production submission, it will be nice if you can just notify that to us when you're ready, and so that we are also prepared from our side to make sure that it's going through, it's passing through. And if you face any issues, then we are able to notify that immediately.

And then any questions during your testing, you can send it to this email address.

Anything even after the docket, you know, time period is over, you can also shoot an email to this email address with any questions you would have.

So as we go through the -- as you go through the data elements, as we go through the list of all the different data elements, the spreadsheet that we're going to post has the headers in this format. So what we have is the first column in this spreadsheet has something called the source. The source will define, there's two values; either the source of this data element is originally from ICH, or the source is FDA. If it says FDA, that means that it's a regional element. Okay?

Then you have the element header and the element -- data element number. Any data element number that has been prefixed by an FDA.c.1.1, anything that is prefixed by FDA, that's a regional data element, okay, that has been defined by FDA.

Then you have the data element name, you know, you have the max length, data type, and field values allowed. Now, let's say we had data element which was defined by ICH, so the source will

say ICH. You have the data element number; there'll be no prefix to those element number. You have the data element name, the max length that was defined by ICH, the data type defined by them. You have the allowed value, and then you have the ICH conformance and the ICH business rule.

Now, if you had a data element that was defined by FDA, then you will see -- you'll see the source saying FDA, the data element number will have a prefix of FDA, you will have a data element name, the data max length that was defined by FDA, the data type, the data values, but you won't have any information under ICH conformance and business rules. You will see something like this where you will have the post-market, the conformance, and its business rule; you have pre-market, the conformance and business rule.

If a specific data element was truly only used by pre-market, you will find that it will say under the conformance the pre-market business rule; in such case, the post-market conformance and the business rule for post-market will probably be

blank or just a hyphen listed there, so printed there.

And then for the ICH element or non- -- or regional element, it'll say the type of change, and the type of change will say, hey, this is FDA element -- FDA-defined element, or it'll say that this is -- it conforms to ICH rules. Any notes, and then you have the non-flavor applicable, the field OIDS, and the HL7 data types.

The same spreadsheet also has a second tab which lists all these data elements with the expanse, anything which is the non-expanse or anything which is the values that it has in expanse.

So as we go through the data elements after this, you will find that anywhere we have a change that only has been listed in the slides. It also lists down, you know -- basically, they give you the data element name and then lists down the specific sections where we have a change. And once you see the spreadsheet, they are also color-coded, and it highlights in the spreadsheet, you know, which ones are FDA with what other change.

Also, we will also find in the

spreadsheet that -- and also in the slides, there are some data elements where, you know, we had to make it, let's say, conditional-maNDA-tory based on a particular rule even though the ICH rule have may have said optional. But as far as FDA is concerned, it's conditional-maNDA-tory and it is very clearly highlighted in those, in the spreadsheet and the slides will also say that.

So with that, I will go on the second topic. But before I go on the second topic, any questions I can entertain? Yes, sir. Yeah, if you're going to use that, then others could. You can pull it up.

RICK HESTER: Hi, Rick Hester, GlaxoSmithKline. Suranjan, a couple of questions related to sort of testing and transition. So will there be a required set of test cases or test reports that will be required by industry to certify in advance with the FDA before transitioning?

SURGANJAN DE: So we didn't plan for any specific test cases. I mean, the idea here was since now we have a validator, the expectation would

be that sponsors could go to the validator, you know, test maybe different scenarios that they have as part of their submission. And once it's validated, then you would submit that through the gateway, through a non-production environment because we want to test two things here: once is the validity of the data that you have and the structure, and then passing it through the gateway to make sure that you get the acknowledgement.

So we're not going to have to typically not do what we done, which was say, hey, send us those 10 files in of this type. Here, we would request, if you're looking for a specific type of data files you want to submit, pre-market reports, post-market report, and combination product; that will basically cover all the different types of three general data elements.

RICK HESTER: Second question along the same lines. Do you know when you'll be ready to publish a date by which you'll be ready to accept submissions in E2B R3 format?

SURGANJAN DE: We, according to the

timeline, we would like to start our testing by November. So I think from FDA's perspective, we are targeting to be ready by November, but not enforcing that all sponsors have to be ready to November because we are accepting the data so we need to be ready in some way or form so that if somebody wants to test, they can test, or if somebody's ready, they can submit. So our target date is sometime end of this year to be ready.

RICK HESTER: And my last question is to do with your core and regional data element spreadsheet, and you mentioned how there will be clearly identified whether it's a source from ICH or FDA. And I was curious for ICH source data elements, will the FDA change the conformance of the business rules for any of the ICH elements?

SURGANJAN DE: So I think there are very few elements where typically what has changed is I think the conformance of the data elements, and the structure, data type, data length has the -- we'd never try, we don't want to even touch them. But there are some rules where if he said that this was,

you know, a pre-market data element used for, let's see, I don't know -- I'm just thinking of an example.

But if there was an element where FDA is in the post-market side, there's a rule that if this is this, then that should be that, but that data element was an optional data element. But just because, you know, FDA requires a data element, we have made it in such a way that if you don't have it, then you will have to use a non-flavor to kind of compensate with that data element. All right?

UNA CASEY: Good morning, Suranjan. Una Casey from Oracle. We just have a couple of questions, one of them being for software vendors. Will there be the opportunity to start testing before the November 2020 timeline?

SURGANJAN DE: I think we will be ready -- I mean, you can start once you have the validator available. This afternoon when you see the validator, you will see. I mean, it's as simple as somebody uploading an XML file, which you have, and you have to just click on a button called validate and it'll start showing you if the XML is validated or -- it's a valid

XML or what errors it has. It gives you a list of errors.

I think your first step probably would be to start using that to test that file is good. And then once you are done with that, the second stage would be to sending it to the gateway so that you want to also test the acknowledgement that will come along with. But, yeah, so based on this timeline, we are targeting that by September, we make this URL available for everyone to use it.

UNA CASEY: Okay. Then request as well for the software vendors, we can make our own cases, but it would be helpful to have some sample files of expectations to meet the minimum requirements that you have for the system as well.

SURGANJAN DE: Good. So, yeah, even if you look at most of our -- when you look at all the data elements that we -- I mean, this when it comes to a spreadsheet, you will find many of our data elements, especially with FDA. It's very lenient and many of them are optional; very few you will find that there is some conditional-maNDA-tory put in. But most

of them, especially all the ICH elements has been to skip as is. And when we added some regional data elements, many of the regional data elements are also kept very optional, you know.

So I think the concept here, the way they look at it at -- and I don't want to reject a report because our administration was wrong and it was a fatal report, all right, so you don't want a rejected a report because of that. So that's the reason why many of the data elements are all just skipped, very optional.

In pre-market site, there are a few rules, I would say. And also the reason being, we do also understand when you have pre-market report, you know, the data is much better than what you get in a spontaneous report; it is much more controlled. So, yeah, you will see all the different rules as we go through the different data elements.

UNA CASEY: Okay. And then as you are talking about E2B R3 data elements, there was a question about when will the SBL routes of administration and dose formulation code must be

harmonized for mapping with EDQM and then the ICH code lists. Is there any work in that area, and when will you publish your details?

SURGANJAN DE: So that will -- TJ will help me answer that question. TJ, you want to go to the microphone, please?

UNA CASEY: I asked that question simply because the EMA have now published their date for MoNDA-y, June 14 of R3, and they also speak about the use of some of the ISO referentials, so it's just having the harmonization in that area.

TAN-JEN CHEN: So the EDQM is a complicated case. At ICH, it could be we committed to use EDQM as a dosage form for submission. However, when we tried to map our regional dosage from to EDQM, we found that there's no one-to-one mapping. I mean, try to achieve one-to-one mapping is almost impossible.

I can give you a very quick example. For example, we got at vail liquid filled gel that is approved in U.S. as a capsule. Now, EDQM does not have capsule; they have capsule soft or capsule hard,

so there's no one-to-one mapping in that case.

However, in E2B, we also said you can use the basic dosage from use of rendering term, so that a capsule is available for that, so we need to do some transformation on our end. For U.S. domestic product, you can continue to use EDQM. You would select the one that is most resemble or most close to your product, and we need to do some transformation on our end. At ISO, we are trying to find out a solution so that we can generate this global PHP ID, but that's a separate topic.

TAN-JEN CHEN: Yes, it is.

UNA CASEY: Okay. So I just want to just have a follow-up question on that. So if a company is following the EMA spec, right, and they just happen to pick an EDQM term to then send the file to FDA, as an example, would you guys reject that file because that's not the code that you are looking for? Okay. Now, the company chooses a current SPL code, would you accept that and not reject the file?

TAN-JEN CHEN: I mean, I think from my -- and our last sentence was, I don't think we will

reject data element because the dosage form used EDQM value on an SPL value.

UNA CASEY: Okay.

TAN-JEN CHEN: You know, if I have a fatal report and I just reject a submission with dosage form being incorrect, I don't think -- I mean, I don't think you're going to hear I compliance folks also agree to that. But I think we will still accept it and we will figure out internally how to make and do the appropriate conversion.

UNA CASEY: Okay. So that's like an example of what you were trying to describe as that's an optional field, meaning -- well, actually, let me ask the question actually. Is it considered a maNDA-tory field; meaning, you're just going to check to see if anything's populated there, but you wouldn't necessarily again reject the file if the term or the code was not correct. So that's -- you understand what I'm saying? It's like different levels of conformance, right, or validation.

TAN-JEN CHEN: Exactly.

UNA CASEY: So that's what I was asking

about.

SURGANJAN DE: All right. Any other questions before I move to the next topic?

TAN-JEN CHEN: Actually, let me also jump in here. The dosage form in the E2B actually has three data elements. So you can pick a term, then you provide a version, or you can do free text. So we're not going to reject because one of the element is not mapping to what we need.

SURGANJAN DE: All right. So here, we're going to -- so the next session, we're going to go over the R3 regional requirements. I have, even though I said in the sublet pre-market, combination, and other regional elements, I just went over -- I didn't divide that into pre-market and post-market. I just went over the data elements sequentially by the numbers.

So as you go through that, I will just say which ones are specifically for pre-market and which ones are for post-market. But within post-market, you know, combination products are also considered within post-market. So when I go over the

data elements which is specific to combination products, just assume that they are post-market, they're used for post-market.

Okay. So you have these, do have the technical specification that was posted, of course, in 2016. We are working on updating the technical spec. So the idea would be something like this: that end of the day, there will be a package, like, how I see it has an implementation type package.

So we'll have the FDA regional requirements package, which will have a Word doc, a pdf document which will be the technical specification document, which will -- that will, you know, define some of the data elements of the regional data elements, which will then point to the spreadsheet, which is basically listing of all the data elements in the spreadsheet, and then also it'll point to the hardware compatibility document, right.

And then the last thing which we're going to have that I think we're going to put it into the technical specification, the pdf document, are snippets of the regional element as to how will that

look with an example XML, right. So if we had a field called, you know, local criteria for reporting, which is, you know, 15-day, 30-day, 5-day, 7-day which FDA has, then how will that look in that snippet of the XML, so that we'll put in the technical spec.

So to it could be a package of four or five -- for three or four documents packaged together, and they will be posted on the FDA's FAERS website. But, again, prior to that posting of all the package, we will definitely be sending out by, hopefully, by end of this month the spreadsheet which I've been talking about, so that will come to you by end of this month. We will post that on the meeting page where we post all of today's meeting where you will have those documents available.

So going to into the regional requirements, we have, you know, the regional controlled terminology; especially we encourage companies to submit the product names which -- that they have been submitted as part of the SPL. Because just to let you know that when the product gets approved, you know, the final step, you're submitting

the as-structured product label wherever that goes to.

That, we get the data on a daily basis and update our FAERS product dictionary, and that is then -- those names are used to code the product name that is in the ICS site. Of course, if it's a foreign product, then we'll go through the older dictionary and so forth and we'll do our research. But for all the domestic products, we look at SPL.

So these are the different types of reporting that you would probably do as part of your submission where of course, also includes pre-market reports.

So as I said, we had posted this on June 23rd. Now, this technical regional implementation specification does not include vaccine reporting. They are a separate deck spec. But when you see this Excel spreadsheet, there's one thing you will notice: there will be many data elements.

Now, I need to also tell you this: the way you see here post-market, pre-market, which has its own conformance and business rule, there is a column called FAERS and it has its own conformance and

business rule, and the reason being that, you know, they implemented first. We have tried to harmonize many, many data elements so that we use the same observation code, we use the same data point, data element name, data type, data length, and so on and so forth.

But there are still some data elements in FAERS where we are working with them to harmonize, especially -- I think the key thing that is left to harmonize is the code list values. Just because -- because FAERS implemented first the E2B R3, many of the code list values were values that points to the EVS enterprise -- NCI EVS values, which are the sequels.

But now that we have come with the concept of FDA OIDS, and in the beginning, he talks about all the OIDS and dots and dots and dots and dots and where it point to, I think now there is an opportunity that we can manage our own OIDS and be able to migrate all those code list into these OIDS so that it can be totally harmonized.

But pretty much, most of the things

that are left overs are these code list values. And as a result, what is happening is -- and you will see in the spreadsheet -- is if there was a specific data element, the unfortunate part is some places we have FAERS needs this data element and we had tried to make it as a one numeric because we have one for so-and-so, two for so-and-so, three for so-and-so. But when you start using sequels, you have to have that whole field as an alphanumeric of probably six or eight.

I think that's the difference, and we are still trying to harmonize that to get all into making -- using FDA, all right, so we have control over to add new values. All right?

So we do support all the ICH E2B R3 FAERS. We support all the R3 element, their conformances. There may be very few variances, but these variances we will see and they will be all documented in the technical specification and the spreadsheet of data elements, and then we will go over some of the exceptions that we have in the next few slides.

So first let's start with terminology.

So when we talk about terminology, we support MedDRA, right. So you can submit -- we encourage to submit the code because then it's easy; we exactly know what the code list operating than the term. So we use the lowest level term, so that's what we use, so MedDRA numeric code rather than the LLT term, so that's one suggestion. And we basically follow what ICH IG is saying all about MedDRA, so there's not -- don't have any variation in that.

So we support the UCUM codes, and for terminology for the NCI EVS, we just talked about. So if you send it, it's not going to be rejected. We're just saying that we support this. We're not saying that if you don't send it, we're going to rejected. No, we don't say that. And for substance names, it's just easier for us to call them if the name is used which is registered in the global substance registration system.

And, again, as we say, EDQM dosage form and route of administration. We support that from a perspective that, you know, if you send it and we're not going to do any kind of rejection because you

didn't send me EVS, but you send me EDQM. No, we're not going to do any kind of rejection.

All right. I need my glasses here. All right. So the way, as I said, it does not really -- when you see all the data elements as we go through, they follow a pattern of the way the numbering is, and that's how it follows a pattern.

And then I have defined that in such a way that -- so here, it would say that you have a -- if this applicable to both pre- and post-market or if you have something like this, then it is applicable to pre-market or post-market. And then when you say only business rule, that means the only change was a business rule. But you may see some places where it may say -- it may say something to do with data type and business rules. So what your region has, areas that has been updated, you will see that on the slide.

So for the first one, batch sender identification, you know, sender should use the DUNS number; that just makes it easier. We know exactly what it is for the object identified, you know, the right number it is. Yeah, so that's basically for

pre-market and post-market, the batch and the identifier.

The batch receiver identified, that's where we're looking for, you know, we use ZZFDA for production, ZZFDATST will come to me with that. And for pre-market, we will have ZZFD_PREMKT and ZZFDATST_PREMKT. Then we send the same thing as part of the acknowledgement, so we exactly know where it comes from and what ICSR in your system you need to update, the close the loop.

All right, message sender identifier. Again, here, we're talking about the DUNS number for both post-market and pre-market.

Then you have the message receiver identifier. So here, we are talking about the message receiver identifier to use for post-market CDER and for pre-market, you have CDER pre-market and CBER pre-market. I think what will happen is this actually helps us. This is something we can, you know, debate on if it's really required.

But the idea here is that when these reports come in to FDA, especially from the pre-market

site, you may have a CBER IND and a CDER IND. So this information can help us route the report to the appropriate centers literally submission systems. So today, as you are submitting this IND safety reports in a pdf format through ECTD, for CDER, when you submit that, that goes into a system in FDA called dots, and the same system in CBER is called (inaudible). That's where regulatory submissions are stored.

Since these are -- these will come into FAERS first. But to keep a record, to close the loop for the entire IND, which will have so many other documentations of which one is the ICSR. This helps us to actually close the loop where we can send this information of this submission record to those regulatory systems and show them that, hey, we received it and FAERS has it. So that was the purpose of having this particular message identifier to be used.

So safety report unique identifier, try to use the same MCN number of the previously submitted paper reports, and this is required for our processing

of cases. There is one part which we came out with and I think I want to discuss that with you all, is you have the very unique number now, right? So there are only two numbers. Initially, in R3 -- R2 there were a company, I think a worldwide and a safety report ID, there were three numbers there. Now, there are two in R3.

And the idea here is that as we are implementing our core tool, the more and more what we are seeing is I think we have to probably move towards a norm. And the norm that we are looking at is the worldwide unique number, that number does not change. The safety report ID could change because, you know, one company buys another company and there is a marketing partnership between two companies and so on and so forth.

So how do we make sure that the initials and follow-ups are appropriately done. And if we know that the worldwide unique number is not going to change, then in that case, how about using the worldwide unique number to do that check. But currently in FAERS with R2, we are doing the check

with the manufacturer control number, which is the safety report ID. All right?

And so, the thought process is that how do we move. So the way to move is we will continue doing that check, but as we see that the worldwide unique number gets filled up in our database and as we start the worldwide unique number, then we start checking the worldwide unique number where worldwide unique number is available because, yeah, we want to be on the same page with everybody else and just not be different or unique. So something to think about if you -- you know, when you have your comment period, just think about and see if this idea, you know, works.

For the type of report we are seeing for pre-market report and are used to report from study. And then documents included both CDER and CBER have harmonized on that, the data type is to be B64. So we don't use compression for U.S. reporting and encoding is limited to B64.

So then we have the C.1.7: Does this case fulfill local criteria for an expedited report.

For both pre- and post-market, we're not supporting the use of NullFlavor here, so which means if you said true, that means it's expedited; if you say false, it's not expedited because this has now become Boolean field.

Now here is a new data element. So if you see a prefix saying FDA, so we have FDA C.1.7.1, we call it local criteria report type for use for both post-market and pre-market. Max length is 1. Data type is numeric. Values allowed: 1 is 15 day, 2 is periodic, 4-5 day, 30 day, and 7 day.

This is the same values as we have in R2 with the same fulfill expedited criteria because in R2 that was a numeric field and not Boolean, so we were able to use that field in R2 for these additional values. So in R3, it's a Boolean field, so we have added a new data element. And this conformance is maNDA-tory, and the business rules for post-market is you use day for 15 day -- 1 for 15 day, 2 for periodic or non-expedited. The value 4 for remedial action, 5 for malfunctions; and for pre-market, you would use 1 for 15-day expedited and 6 for 7-day expedited.

And that has a code system, which is this OID, and TJ will talk to you about all the different OIDS after the break.

Next element, so case identified is it's more warning than a rejection and acknowledgement to say that if C.1.9.1 is true, then C.1.9.1 -- sorry. If C.1.9.1 is true and C.1.9.1.r.1 is not provided, so that's the source of the case identifier.

And then C.1.9.1.r.2., the case identifiers is the rule there is again similar to the previous rule; and for pre-market -- yeah, this needs to go off. I think this was a typo or a copy/paste. Yeah, when you do a -- you should not create slides at midnight, then it doesn't work. So just ignore the pre-market part.

FDA C.2.r.2.8, this is reporter's email, which is pre- or post-market, max length 10, alphanumeric, and optional.

Okay. When it comes to a study name in pre-market, we're requesting for concatenate study ID with the abbreviated trial name, so that the study ID should be the same value used in the study tagging

file format in the eCTD submission.

All right. Next data element is a regional element. If you have a study where reaction events were absurd. Now, the reason why this was done is that there's a concept called aggregate report. And, you know, we have heard many times from FDA, especially from merit that what the aggregate reporting is, it's one kind of reporting. And initial thought was, hey, if this value can it be not added to this other study type. The other study type I think today has three or four values. And if we try to add this there and then the OID doesn't match because that has its own OID, right, and that OID has been defined and is part of ICH and it has got four values in there, right. Which would probably say clinical trial and, I forgot, the four values there, I know.

So if you're trying to add aggregate, then we are violating the ICH rule. So in that case, the only option that was discussed was to have a specific data type, dictate a field which will have aggregated in the future that it has its own OID, so if you have any other allowed values, FDA has any type

of allowed values for other study type. I know we will utilize this data element and not use the study type where reaction event were observed; that is an ICH data element.

So many of the data, some places you would find these data elements. We had initially thought of using the ICH data element just because that ICH data elements has the code list values and it is own OID and the OID goes with the data element, it resulted in having FDA specific element in order to accommodate these type of situations.

Now these two are very important data fields. These are -- okay, the previous one is to be used in the pre-market side. These two are also in the pre-market side.

IND number where the adverse event occurred. So basically, this is like the primary idea where the adverse event occurred and not the cross-reported INDs, all right, so you would have a separate data element for the cross-reported INDs.

So this is a data element with max length of 10. It's numeric, so you'll input in the

IND number only, the number part; it's conditional-maNDA-tory. And it's based on I think C.1.3.e -- yeah, C.1.3 is going to report from study; the format must be just a number. And this field is very important because this actually routes the report to the approved FDA medical officer and who is the primary reviewer of the IND.

So the next field is we call it a pre-ender where adverse event occurred, so now we have a BA/BE trial. I think in the first or the second session, we had talked about -- I think Karen had comments. She had talked about the BA/BE trial on the -- you know, try to end the application.

In this situation, we have a separate field where you will submit only the number part, and this will then route the report to the appropriate reviewer in our Office of Generic Drug.

So the next field is IND number for the cross-report IND, so this is repeatable, so now I don't have to submit my (inaudible) reports on cross-reporting. You have just one report. You just mention the IND numbers of the cross-reported INDs.

So in this case, it's -- we have made this -- yeah, in this, the last bullet would say is Null Flavor applicable, NA; that is incorrect. I mean, that has to be and the slash would not be there. But the rule is that if you don't have any cross-reporting, they just use a NullFlavor not applicable.

So this will be maNDA-tory if you have filled in especially the pre-market side. If not, then you could have pre- and there will not be a cross-reporting IND, so that will be sent in as NA, non-applicable.

All right, so next one is patient initial name are initials D.1. So in this case, what we are looking for is especially on the pre-market side for aggregate reports, if you would enter the patient identifier as aggregate. Now, of course, to have an identifiable patient, you know, either age or date or birth or sex or any of those data elements must be available to have an identifiable patient.

But it just helps us to also segregate this report where we see that the foreign aggregate report on the pre-market side, if you have the --

because there is no patient, in this case, it was an aggregate of a case series, maybe all related events. So when you send ICSR for an aggregate, then here the decision is to make the B1 use the word aggregate there.

For post-market, we have combination products. And with combination products, we could have where just a malfunction occurred and that malfunction occurred prior to reaching the patient, so in that case there's no patient. But if you have to do a check that, you know, you need to have at least identifiable patient, the best way is to put the value of none in the patient name or the patient name or initial, so that will pass through.

And then there's a concept of summary report in combination product. So in that case, somebody is a -- somebody of, let's say there were 50 malfunction occurred on a particular batch of device, then in that case, there's no patient involved, so in that case you would submit that. You don't submit 50 reports. You submit one report mentioning about the 50 malfunctions that had not reached the patient; and

in that case, the patient initial becomes somebody.

Date of birth. If outcome attributed to adverse event is death, then date is required for pre-market only.

Next we have a regional element called the patient race code. In this, we are basically harmonized with the way CBER has done it, and that's where they have used the C-codes and we have said that's what we're going to go with. It's max line 10, alphanumeric, and then you have those C-codes.

Okay. So in this one, the business rule is incorrect, so just ignore that part. And the next one also business rule is incorrect; please ignore that part and cut it off, check it off.

We have the next data element, which is the patient ethnicity code. It has two values. This has been harmonized with the VAER system they used; we use the same C-codes. And it's maNDA-tory, and because they made it maNDA-tory, we also kept it maNDA-tory, and you can use a NullFlavor. Please ignore the business rule on this.

This is another field for required

intervention. In this case, this was a data element which we have an element watch form also, and it is maNDA-tory. And it acts same way as we have that hospitalization, you know, those fields, life threatening and the allowed flavors, NullFlavor. If you don't have any information, then NA. And typically used in device reporting on medication and are reporting.

All right. Next one is characterization of drug role, which is an existing R2 -- sorry, existing ICH data element. And in the pre-market side, we're just saying that you would use 1 is suspect, 2 concomitant, and 3 interacting. There is one 4, drug not administered. So in the pre-market side, only these three values are applicable.

All right. Now, in same situation where we had the characterization of drug role where if you have read the combination product, there's a concept called similar device. And in there, the concept is that you have an ingredient which was used -- which was in a combination with, let's say, a syringe. Now you could have another ingredient using

the similar syringe, so in this case, they're considered a similar device.

So if you had an adverse event on the first group, the first product, then you have to also report about the similar product. Now how do you identify that it's a similar product, right? It's not suspect because the adverse event or malfunction did not occur on that, right -- yeah, sorry -- did not occur on that. But then how do you identify that? Now if we had used a concept like the drug rule and used it here, okay, the problem is this has its own OID, right. Now, if I try to add it in this, then I violate, I see its rule, right? So I have -- the only way to do it is have something like this so that I can have my own OID and the rules.

And in the future, if we have any other kind, like similar device or something, which came up very recently with the combination product rule. If tomorrow there is something else that FDA comes up with, then this data element gets used and then we don't have to create any new elements or worry about being non-compliant with a specific ICH element.

So with this, we call this data element as every other characterization of drug rule, which has, again, right now it has similar device, has only one value. And then use 5, similar, when reporting for similar combination product. It says each ICH must contain at least one suspect interacting or drug not administered. For a similar device, you could G.k.1, drug not administered, and then if 5 is reported, the malfunction must be true.

So here's the problem: that if you submit an ICSR, you have to submit this with at least one suspect or interacting or drug not administered, right. So you cannot have just this tag and not have this tag, so you have to have both of the tags.

So in order to have both the tags, what do you do with the first tag, right? You're talking about a similar product, right. But the similar products are the only way we thought about it, that similar product was not truly administered. So in such case, if you look at that tag, then you will have the drug characterization of the drug rule as drug not administered, but the FDA regional characterization of

the drug rule is 1, which is similar device. So that was the way -- that is what this is depicting and saying that you use drug not administered for that similar renewed reporting for that similar; that's the only way this could be.

Now, again, when I'm mentioning all this, in all the slides a little bit later, you guys have time to think about it and send your comments to us. And at the end, you know, I'm also open to having maybe a WebEx even after we have finished the third ePrompt meeting, so you guys can think about, you know...

So in this, we have the medicinal product I just talked about that I said this to use, we're committed to use the SPL name, so the name which is in the SPL file. And when you have the merits of the products not provided, but active substance is known, then provide active substance as it appears in the global substance registration system. And if it's a foreign product, then provide a foreign product trade name used free text element, and then here we will figure how to code that to -- we typically use an

old drug to look into that foreign product and code that product. And then we have, you know, upload the substance name. If it is registered NDA-, we're going to use that substance name.

All right, authorization and application number, especially in the post-market side, you will have, you know, an NDA- or an ANDA-. And how do you report that? This is how you would report that because ICH doesn't have an application type, so it has an authorization application number. So the only way the FDA can identify is to prefix that with an NDA-/ANDA-, and this is all on the post-market side, all with the BLA. If it is no Rx, no application, that six zeros; no Rx, no application, six 9s, and for compounding, we use the comp99. This still stays the same as we have in R2 today.

All right. Next is these are specific elements for pre-market. So you have the source of assessment, method of assessment, and result of assessment.

In the source of assessment, you have, you know, it's conditional-maNDA-tory if you have

report from study. And the recommeNDA-tion here is defer to sponsor and include investigative assessment in H1, and in R2, it's B.5.1. There is no rules set here where there's a code list value, because this is a free X field. I think it's 60 alphanumeric, I think, or 30 alphanumeric, so are distinct to recommending to put sponsors for sponsors this maNDA-te.

And then for method of assessment, what we noticed with our pilot program that we did was there were various method of assessment. European has their own, French has their own and all that. So here, the method of assessment, we're saying FDA because we are most interested in that. This helps us to only pull information, even though the ICS could have this as when (inaudible) has been sent to different other agencies, but we will just, for review purposes, we are most interested in the ones which are -- whose method of assessment would be FDA, so we're asking to default that one FDA.

And then finally, you have the result of assessment. This, we are saying to use the value

suspected or not suspected, because you have so many different variations that's related possible probable. So our rule is CDS unexpected and suspected, right, for the (inaudible). So is it suspected or not suspected?

Okay. So now this is another field, it's an optional field, called FDA specialized product category. We just harmonized this with our VAERS system. So in VAERS, we have this data point and allowed values if you see it mostly with combination products. Again, this conformance is optional. If you have this information, then you could use it; if not, these are optional, so there's no rejections here.

And this is a new data element, which will be either be (inaudible) or for pre-ANDA-. Now this is the pre-ANDA- drug rule. This was something that our Office of Generic Drug wants to know about the product, and this is a 1 numeric value, so identified as a test drug instead of reference or placebo or a vehicle. And this is conformance is optional, and that's the OID that you have here.

Next is malfunction flag, so here is where we are going into combination products now. From here onwards, I think most of the fields you'll see to the end are combination product. So in this, the combination product data field is malfunction. We have harmonized this with VAERS. And it's an observation code you see here, true or false, conditional-maNDA-tory, and this field must be set to true for at least one suspect product per ICSR if the FDA C.1.7.1, it goes to 5. So C.1.7.1 would probably 3 data point I think, which is a malfunction.

This reminds me there is one data field I think I missed, and the Excel spreadsheet will probably tell you that. There's a combination product flag. So I don't know the exact field number; it'll still start with an FDA. But maybe during the break I can find that out. It's called a combination product flag, which says that it's a combination product report.

All right. So next data element is a follow-up, what type of follow-up. This was an element which we have been using in R2. This is

repeatable. So now within the device block, now you have this, so you have the entire product; within the product, you could have multiple devices. And then this is -- you could have one or more values where it was a collection and additional information provided of any -- one or more values could be used in the allowed values.

Then you have the device problem code, same C-codes. This is what has been harmonized with CBER on vaccine combination products, so we're using the FDA device problem code list. Yeah, many questions have come, have we harmonized it with MedDRA because MedDRA also does have the whole list of problem codes. And, I mean, there are activities which are going on and eventually making this harmonized, but as of today, we are using the FDA device problem codes.

Then we have the device brand name, common device name and the device product code. So these are three elements which identifies the device. So you have a device brand name, which is the free text field. And what we are seeing here is, I mean,

if you give us a brand name, then great. But then you have the common device name and then you have the device product code; at least one of them should be there when asked to identify what the constituent part of the device part is furthering that product.

So in such case, we have the device brand name, which is at ATL for numeric, free text, conditional-maNDA-tory, and conditional-maNDA-tory just because it's a combination product, flag is checked, then you have to mention about the constituent part. Then you have the device, common device name, which is again a free text, again conditional-maNDA-tory. For the first and the second rule, please ignore that. I don't know it's getting messed up, but please ignore the business rule. The business rule in the first and the second is if it's a combination product.

Then the third one is device product code. Device product code is a device product code, it's allowed when using FDA device component codes, which is available on FDA.gov so that they have a code there. Alphanumeric 10 and conditional-maNDA-tory,

and the business rule in this case is that it should be a combination product report.

And the next is the device is the device manufacturer name; it's an optional field. It's a free text alphanumeric. And device manufacturer also will have address, city, that should be state and this is country. So they are all optional and free text fields. Of course, this is not free text, but they're all optional.

Device usage.

One thing to remind before I post this, I will have corrected the slides and posted.

The device usage. This is another combination product datapoint. Data type, numeric 1, and the values are initial use, device reuse, and unknown. So, again, conformance is optional.

Next is device lot number, again, conformance is optional. Operator of the device, again, conformance is optional. All right.

Remedial action initiated. In this, the conformance is conditional-maNDA-tory. And if malfunction is true, you see C.1.7 is yes, local for

report criteria is 5. This is where the remedial action type of report, which is to be submitted in five days. Then these are the values that needs to be -- these are allowed values for remedial action, and you could have one or more values.

All right. So before we take a break, this is the last slide here, and we are probably early; we can have questions.

Linking initial and follow-up. This is where I was talking about using the worldwide unique identifier. So if the initial was submitted on paper, but it's follow-up will be submitted electronically include the safety report unique identifier from the initial report in this and worldwide unique identifier in a follow-up electronic submissions.

Always use the same identifier for C.1.8 that was assigned to the initial ICSR when submitting the follow-up report. So the second word is very important because that will be used to designate the follow-up reports because we're expecting that that will stay the same and will not change.

Now in the first case, the way we are planning to set this up is we have many cases where we just have the safety report ID, we don't have to worry about any kind of device in our database because we have been checking always with the safety report ID for the initial and follow-up. We'll continue to do that until we find that this worldwide unique identifier now has got populated from your submissions.

So let's say you had a follow-up report. When you submit the follow-up report, the report comes in. It has got safety report unique identifier and it has got the worldwide. Now, our database, let's say, doesn't have the worldwide; we will still check it with the safety report unique identifier. We'll say, yeah, it's a follow-up. When we update our database, we'll update the database with now the worldwide unique identifier. Now the worldwide unique identifier is available.

Next follow-up that you have, then the check will happen saying that, yes, worldwide unique identifier is available, let me check with that, find

out if it's a follow-up, yes, it's a follow-up, and set it up as a follow-up report. So that way, you know, probably in a few years, all of our reports will have the worldwide unique identifier and we are checking everything with the worldwide unique identifier.

So with that, these were/are basically the data elements, regional elements that we propose for FDA. And with that, you know, if you have any questions now you want to ask, just go ahead. If you have anything you will think about later, then you have the docket or send it to the ePrompt email address.

MAN 1: Hi, Suranjan. I just have a couple of questions. Go back to your --

SURGANJAN DE: You can't have questions.

MAN 1: I have questions. Go back to your last slide. I just want to make sure that the vendors know that their names should not be in there; it should be the sponsors.

SURGANJAN DE: Yes, yes.

MAN 1: Because we're getting some questions about resubmissions, resubmitting and things like that, so it should all be the sponsor.

SURGANJAN DE: It's always the sponsor. And especially what we have also seen is the sender organization names, especially when you have a Seattle working, okay; the name in the sender comes with Seattle's name. Now when we go into compliance, you'll say, hey, how many reports submitted in 15 days, how many reports were late, how many reports were this.

They all run based on their sender organization. And when we look at that, we said, hey, it's Seattle's name; we can't go behind the Seattle, we have to go to the sponsor, right. So it's very important that, especially when any Seattle is setting up their systems to make sure that the sender organization information is about their client or their sponsor and not theirs.

MAN 1: The other question, can you go back to the slides on drug roll. I was confused with this. For the initial drug roll, you have three

things: you have suspect, concomitant, and drug interaction. Go to the next slide.

SURGANJAN DE: This?

MAN 1: That one right there. Shouldn't no. 4 be not administered?

SURGANJAN DE: This is only for --

MAN 1: Is this R3 or R2?

SURGANJAN DE: This is R3, it's only for pre-market.

MAN 1: This is only pre-market, okay. Maybe that's where I was confused.

SURGANJAN DE: When you have pre-market, then this. So when you have post-market, then you have this for -- I mean, in this case, there is no --

MAN 1: There is no 5, right?

SURGANJAN DE: No.

MAN 1: There should be a 1, right?

SURGANJAN DE: So 1 is suspect, I think.

MAN 1: No, 1 in this slide should be just similar device.

SURGANJAN DE: Because this is a new field.

MAN 1: It is a new field.

SURGANJAN DE: Right? So when this is a new field, when you set up your tags, your first tag in the drug will be this tag. The second tag will be this tag.

MAN 1: Exactly.

SURGANJAN DE: 1.

MAN 1: Yeah. So the first one, even though it's pre-marketing, post-marketing would use it too.

SURGANJAN DE: Yeah, yeah, yeah.

MAN 1: And then you'd come or you need to report similar device. This is where you'd only use this field.

SURGANJAN DE: Correct. So what I'm saying here is that if when you use this tag to say similar device, you need to make sure that this tag should have one of these, at least this.

MAN 1: Exactly, and I would think the first tag would have to have drug not administered,

which would be no. 4.

SURGANJAN DE: Which is no. 4.

MAN 1: Which is back in the old field.

SURGANJAN DE: Exactly, okay. In this old field, if I would have given another bullet saying post-market and would have said a business rule that only use this for, which is staNDA-rd, which is an ICH staNDA-rd.

MAN 1: Right.

SURGANJAN DE: So that's why this is, there was no variation, in this slide, I did not put another bullet to mention about post-market.

MAN 1: And there is no 5.

SURGANJAN DE: And there's 5. And initially, when we had planned -- remember that we had --

MAN 1: That should be a 1, so use a 1 in there.

SURGANJAN DE: Oh, yeah, yeah, yeah. Yeah, it is 1, sorry.

MAN 1: There is no 5, okay, it's a 1. And go back to the other one, it should have 4.

SURGANJAN DE: Now, yes. And so, in this case, yeah, you will use 1 as similar device. It's a 1, sorry. Yeah, it's a 1.

MAN 1: When you go over the slides, it would be helpful to clarify the business rule.

SURGANJAN DE: Oh, yeah. No, I think I need to explain this a little more, maybe with an example, I'd probably make it clearer.

MAN 1: So Suranjan, for pre-market for G.k.1, there's no expectation of used drug not administration because the FDA doesn't want screening cases like the ICH requires. That's the key.

SURGANJAN DE: That's the key, yeah.

MAN 1: That's the message you get across, even though it's the same field.

WOMAN 1: I have a follow-up question for the aggregate reports. Are those aggregate reports from a compliance perspective should have a relationship with, like, the summarized data sets that will come in in SDTM, because they have, like, an AE domain and they summarize all of that.

SURGANJAN DE: Right.

WOMAN 1: So I was just curious about that in terms of the relationship.

SURGANJAN DE: I think the way I understood from Office of New Drug. So they have this concept where you have, you know, like similar events and you have -- you may have submitted individual ICSRs.

WOMAN 1: Right.

SURGANJAN DE: Right?

WOMAN 1: So if it's an IND safety report, you'd follow the ICSR rules for that.

SURGANJAN DE: Right. I'll make the connection.

WOMAN 1: Right. And then, and I was just trying to make the association between the individual reports, the aggregate reports, and then how that maps ultimately to the summarized data sets that come in SDTM. And, again, it may not necessarily be for this group, but that's what I was thinking about and trying to make notes about.

SURGANJAN DE: Yeah. Let's put this as a question.

TAN-JEN CHEN: Why it mapped, yeah.

WOMAN 1: Okay.

TAN-JEN CHEN: Come back to the safety SDTM AE domain, yes.

WOMAN 1: Okay. Because I was thinking more for a compliance when you're kind of explaining that to a client that uses a CRO. So like Roger was saying, when they're submitting those reports, again, for ICSR, you can't use the CROs sender ID.

SURGANJAN DE: Yeah, exactly.

WOMAN 1: You have to map it back to the sponsor.

SURGANJAN DE: To the sponsor, yeah. And also with the aggregated report, another thing is you may have something unusual ICSRs. But now when you do the aggregate, you look for, you know, some similar events which you have identified and have written a summary, an aggregate summary about that case series that you have. That aggregate results to a single ICSR, but then under the link reports --

WOMAN 1: Oh, yeah, that's where you put those.

SURGANJAN DE: -- you use those individual reports that you have already sent.

WOMAN 1: Yes, got it, okay.

SURGANJAN DE: And so that way, we can make the relationship saying that, hey, this was aggregated based on these five reports that you already submitted, right?

WOMAN 1: Yeah, got it, okay.

SURGANJAN DE: And then you can still have a follow-up, right, for the aggregate where you say, hey, I had filed three more reports. Now, those three reports, also you have sent individually. And now when you send the follow-up on the aggregate, it will be easier to manage to say, hey, yup, the worldwide unique number is the same, it's a follow-up. And under the link report now, you don't have these five, but you have this eight now, and that makes the relationship and the connections. And it also makes the relationship and the connections such a way that when I go and click on that link report, it now opens me.

WOMAN 1: Right.

SURGANJAN DE: It's the individual ICS up on that link, of course.

WOMAN 1: Okay. And then the other question I had was related to the device data elements. Assuming that is harmonized with EMDR or is it the MedWatch form? I mean, I know they have the same elements.

SURGANJAN DE: MedWatch, but I think EMDR, their version is based on MedWatch because when they started. But all of the elements that we had have here are basically the elements which come from MedWatch.

WOMAN 1: Oh, okay.

SURGANJAN DE: So these same elements are in R2 and these are the elements we just (crosstalk).

WOMAN 1: Okay. And the reason I was asking was, again, because just trying to pay attention to, like, any field length differences between, you know, again, a company who is doing EMDR reporting, which is separate from ICSR. But if they want to try to again harmonize to --

SURGANJAN DE: If you find any fee length differences, please let us know.

WOMAN 1: Okay.

SURGANJAN DE: Because we still have the opportunity now here to, you know, update the length.

WOMAN 2: I have a few more questions. So the first one was about the business rule sheet that you spoke about, and you said the second tab will have the ex-path details listed there. And it was really to find out where they also include the ex-paths for eVAERS as well?

SURGANJAN DE: Yes, everything into one. I think what will happen is afternoon, I'm going to have my laptop set up to show the E2B validator. At that point, I can open up the spreadsheet and show that to you. I'll do that because, unfortunately, this is connected to the rooms computer. But afternoon when I do that, you know, please remind me, I can show -- open up this whole spreadsheet for you.

WOMAN 2: Okay, and then another question to find out if the validator. Will it also

work for vaccine reports, eVAERS, especially for the combination products?

SURGANJAN DE: Currently not. Combination products, it will work for the combination products. But if it's vaccine specific, no, but that is not included in that validator. Now, of course, there are future plans to put vaccine into here, but no, not presently.

WOMAN 2: Then for the aggregate analysis reports. Is it possible to have a sample file snippet in Excel or something for the aggregate analysis reports?

SURGANJAN DE: So for the aggregate report that we're talking about here.

WOMAN 2: Yes.

SURGANJAN DE: This is an ICSR.

WOMAN 2: Yes.

SURGANJAN DE: It is considered at an ICSR, right?

WOMAN 2: Exactly.

SURGANJAN DE: So it will be in ICSR where the type is aggregate; basically, that's where

we have an FDA other study type that we have introduced where it would -- your type of report is to a report from study, and then every other report type would say one, which is aggregate, and then your narratives will define -- I'm sorry, will explain the aggregation and some of the similar events and all that kind of explanation. And your linked reports will then point the ICSR numbers, the manufacturer control number and the safety report ID of all those individual ICSRs.

So this will be considered as its own entity as an ICSR, and then that's what you would be submitting to.

WOMAN 2: Yes.

SURGANJAN DE: And that would also be checked.

WOMAN 2: We understand that and we can put one together based on the business rules sheet, but it would be helpful to have a sample file.

SURGANJAN DE: Oh, sample file, okay.

WOMAN 2: Customers, some of our customers don't have a lot of experience with the

aggregate in these reports either. So just having a sample to see what it looks like.

SURGANJAN DE: Sample file, okay. Yeah, let's document this so we can have -- I mean, I think based on Ray's question, I think what is expected, I think that is something which we can provide as a sample and then during testing, test the aggregate report.

WOMAN 2: So I have got quite a few questions, so I'm only trying to pick the ones that link to something that you mentioned during the session that's just taken place. So you did touch on the BA/BE studies. Again, can you provide sample files for those types?

SURGANJAN DE: A sample file for those. Yes, we can do that. Yes, we can do that.

WOMAN 2: And can you remind us of the timelines for the BA/BE studies; where do they fall in terms of when customers will need to start using that format for reporting.

SURGANJAN DE: So for BA/BE studies, I think -- yeah, when the guidance. I think we

currently still have a draft guidance, right? So when the draft guidance finally becomes final, then from that point, we are --

WOMAN 2: (Off mic).

SURGANJAN DE: Yes. Because now there's a conformance document and then there is the technical spec documents and then the 745 is the binding thing. So they are all in the draft stage, which has been published. So once they are made final, then from that point, two years.

WOMAN 2: Okay. Then for the data element, C.1.7 for expedited reporting, you talked about the 7-day option. And it's really just to find out if the MedWatch form will be harmonized as the MedWatch describes the use of 7-day for blood ICSRs involving blood supply products. The instructions don't list it as being specifically for fatal and life-threatening ICSRs, and it's just to find out if there'll be harmonization between those two.

SURGANJAN DE: Okay, yeah. Let's produced down question because that needs to go to a whole different group to check and see if that...

WOMAN 2: Okay. So you talked about the business rule sheet being published at the end of this month. Currently, it's draft, then you're going to receive our comments. Do you have a timeline for when that business rule sheet will become final?

SURGANJAN DE: So my target is to get that business rule pretty much final by end of summer. If we're going to get it final by end of summer, then after your comments, because if some comments come that has a change to our system, then, you know, we'll have to accommodate that. But, hopefully, by end of summer, we plan to have that, the business rule document finalized, so that we have received all your comments.

WOMAN 2: (Off mic).

SURGANJAN DE: End of August, yeah. Towards September, if you want, if you want to give this, the validator out, I would probably see that getting it final by August.

MAN 1: Suranjan, can we go back to the causality block. You have some default values that you're expecting in the source method and result tags.

So here in the first one, the source you mention include the investigator assessment in H1, the narrative block. Is that telling me that you don't want the investigator assessment in the structured causality block or you'll accept it if it's in this metric block?

SURGANJAN DE: We'll accept it, yeah. If it's submitted, we'll accept it. In this, we are not rejecting anything here; we'll accept it. If you say investigator and FDA and suspected, yeah, we will still accept it.

MAN 1: And are you also conditionally maNDA-ting that at least one of the drug event assessment is what the value sponsor it's suspected?

SURGANJAN DE: Yes, that's the -- yeah, that rule, which is -- which we are expecting that you at least have one suspected sponsors' assessment.

MAN 1: Okay, thank you.

MAN 3: Hi. Real quick question about the NullFlavors and the approach that FDA is taking to those because those can be kind of tricky. At Astellas, we implemented both the PMDA and the EMA R3,

and we found that during those implementations, their use of NullFlavors differed in terms of some things that they would accept and not accept. So those differences made for some tricky mapping and conventions, if you will, about how we're going to use that.

So I'm just curious if the FDA has put some thought on which values are going to be accepted, if they're just going to use staNDA-rd ICH across the values?

SURGANJAN DE: Yeah. We have -- I don't think we have any value we have used, which is not in ICH, it's NullFlavor values. Right, TJ?

TAN-JEN CHEN: We may have different rules. We need to go back and check.

MAN 3: My question is more than that, not focused on if you're going to be introduced non-ICH values, but rather if you're going to just simply exclude or not accept certain ICH values as PMDA did because there are certain ones that they just don't accept, even though they're ICH values. And so -- and EMA does, so we found that we had kind of a conflict

in the way we had to enter those and map those.

SURGANJAN DE: Yeah. I think from our side, I do not see we will be rejecting anything where you have, like, different -- six steps of let's say NullFlavors. And I don't think we have any rules which says, yeah, don't use this and don't use that. There may be some data fields where we may -- I think one or two data fields where we may have said that the NullFlavor wasn't -- I think there's one or two data ponts where I do remember that the NullFlavor only could do this, this and that, all right, because it just made sense for that particular data point.

I don't know where one of the fields I remember we have said that, to use unknown or not applicable or no information. Like, for example, required intervention. So that was one field where we said to use only NI, no information. And that's how I think if you take this field acts very similar to the data field like that life-threatening, hospitalization whose values allowed a true all the NullFlavor NI, so it just stays the same. So we didn't want to make any exceptions there and keep it the same way.

If you find something once you see this slide, you find something, please let us know because as much as possible we want to make this as staNDA-rd as possible and not get into too many exceptions.

All right, any other questions? If not, I think we are right on the time for break, so we come back at 11:20.

(Off the Record.)

SURGANJAN DE: All right, so let’s start with the next item on the ageNDA-. So until now, we heard about the FAERS 2 updates and we went over the E2B(R3) regional data elements. And thank you for all your question that you’ve had for the first two sessions.

So the third session now after the break is the review of FDA-specific object identifiers and you did see that some of the FDA regional data elements have these OIDs mentioned and T.J. will talk about -- to we have T.J. Chen who is a project manager from Office of Strategic Program in CDER and he’s going to be talking about these FDA-specific OIDs, what was the concept behind it, how these OIDs were

instituted, and then assigned to the appropriate data elements. So with that, T.J., all yours for...

TAN-JEN CHEN: And the controller is... All right, thank you, Suranjan, and thank you everyone. I think I have spoke about object ID before, but anyway, we're going to do it again. So I'm going the wrong direction. Right. Very good. It's before lunch, you know. Okay. So object ID or object identifier, OID is a sequence -- normally is a sequence of number and separated by dot. Okay, and it's used in the computer world to uniquely identify an object.

It's a tree structure, okay, so you can -- you have a trunk and then you have branch. The branch can have more branch, just keep going on, and in the end it reach to the end point will be the leaf. And at any point of the branch, there will be a ID that is corresponding to that particular object. The OID started by the ITU, the International Telecommunications Union, as the staNDA-rd for the telecommunication use.

And then ISO get involved and so it

created this three -- you can call it three trees, okay. It start -- it always start with either zero -- it means this is all assigned by ITU -- or start from one. That is ISO. I think we mentioned about ISO country called the (inaudible). I know that if you look at their OID, it will be, like, 1.0.3166. Okay, so by looking at the number 1, you know it's coming from ISO.

Zero means it's a staNDA-rd and then the 3166 is a country code. If you see anything start from 2, those are the trunk or the branch starting from the joint ISO-ITU and you're going to see most of those coming from 2 nowadays. So then the object can be represented as a sequence of number, like -- okay, like here you see the 2.16.840.1.113883.6.163. Every number along that sequence represents something. Again, we start with number 2 is a joint ISO-ITU tree and then the first branch out of that tree is number 16, which is country.

And then the 840 is U.S. And then within U.S., you have .1 is a organization and then 113883 is HL7. And then after the HL7, they assign

external system number 6 and that system is 163, that's major. So any organization along the tree can register themselves as a registrar, okay. HL7 decided to become a registrar, so if we need a OID, we can go to HL7 and get a OID assigned from that particular branch. Once you get it, you can register yourself as a registrar if you like and then you can start to assign OID to other organization.

And if you register as a registrar, you can search the OID and that, I think it's called OID repository. If you go there, enter the sequence, you will find out who -- you can find out a whole branch until the point that the recipient not register. So next one I can -- well, okay. Before that, okay. So why we talk about OID. OID is particularly important with HL7 model V3.

In the V3, as you can see, there's a diagram there. There are two classes that I'm -- kind of highlighted. I'm going to kind of blow it out in the next slide. In the HL7, there are data type like CE, CD, those data are even II. Those data type -- again, HL7 data type is complex data type. A lot of

data types are complex data type. There are attributes within the date type. So give you one that we use a lot, address. HL7 has a data type called address, okay, that is for you to do modeling.

But when you go to address, it break down into street, city, state, even have -- I mean, you can repeat street many times. Okay, so HL7 data type is complete -- complex. And this CE data type allow you to transmit a code. But in order for you to understand what a code means, you to provide a code system. And the code system is an object that you need to be able to identify in a computer world.

So the code system normally is -- we use OID for the code system. So this -- and also, besides the data type, the HL7 class itself can also use code. This one, we are looking at is observation class, okay. Observation class has certain attribute, as you see here. One of the attribute is called code. So you assign a code to the observation class to let people know what kind of observation that you are performing, okay.

So if you make a code as a body weight,

then you're observing a person's body weight. If you make a code as height, then you observe -- you are observing a person's height. And in the -- in certain event, for example, if you make a code of seriousness, then you are observing how serious is the event. So the observation class code will keep changing and in order for you to know what code it is, you need to refer to a object ID. Here, we have this HO& -- well, ICHC13 type of report. As you can see, the code could be 1, 2, or 3.

Actually -- yeah. And you need to provide a code system so that you know this is a ICH report type. Okay. Like, Suranjan mentioned earlier, we also created FDA regional data element and to do that, we reused the -- we need to fit into HL7 model. So we reused this object class and then use a different OID to show that if you pick that OID and provide a code, then we noticed this will fit FDA regional or local criteria report type.

Same thing here. This is about II. Again, II, an instant identifier, has a root and then the extension. The root can be a OID also, so you

know what ID you are assigning to. So again, let me go back to that OID tree. At ICH, we went to HL7 and acquired an ID so HL7, if you see that 113AA3, that is HL7. So HL7 assigned that 3 which is a external root and 989 to ICH. And ICH received that note or the branch, then we start to assign further branch out, so we assign number 5 for regional regulator.

And then that one for subregion, that 2 then is FDA. I think that 1 is -- I think it's EMA or PMDA. So every regulator gets a branch out of this ICH. And once we received that it's like you have -- like, when you go to a company and company give you a shared drive on the network. So what do you do first? You create subfolders, right? You're not going to put everything in the same folder.

So this is what we do, okay. we create a subfolder, .1, after the FDA branch for FAERS and then dot -- as you can read this, I mean, this again, started from the joint ITU number 2, country, and all the way down and then you see FAERS highlighted and that 2 is for eCTD. So in the future, when eCTD start to assign regional information, they will start with

.2, okay, and when FAERS receive .2 from FDA, again, FAERS is going to create subfolders, right.

So we use .1 -- well, we have this .1 then we'll create .1.1 for the co-list and .2 for the name space and .3 is the HL7 observation class with a class code that are not provided by HL7. Okay, so if you see the number 2 and number 3, any number assigned to that is the end point, is a leaf. Okay, they cannot further branch out. So in a .1, then we create certain co-list.

Okay, you may already see that in Suranjan's regional data element. The .1.1.1, the green one, is a local criteria or a local -- local criteria reporting type, okay, and you should see the value. I'm sorry, I kind of mess up -- mixed up with the animations. You should see the green ones with one for 15, two for (inaudible) periodic, right. And then the .6 would be the operator for the device. Okay. And one step up for the 2.

Again, we -- it's a name space. So there will be no list of value. So if you see the -- well, I'm going to read it. If you see

2.16.840.1.113883.3.989.5.1.2.1.2.1, then it's a primary IND. So when you give us a report with a number, we need to know what number it is and whether it is a primary IND or is a primary pre-ender. So by giving us the code, we know what it is. And again, observation code, same here. Suranjan mentioned about a combination (inaudible).

It's again, it's observation of the report type and when the observation equal to combination product (inaudible), the value tell you yes or no. Okay. Same thing a single-use device. So that's pretty much about OID and during the break, Lee's going to ask me about why we use some of the NCIC code and why we use some of the FDA regional code.

The thought behind that is when -- well, first, to begin with, EVAERS implemented before FAERS and at that time, a lot of code system like IDMP for the dosage from the medicinal product ID, those are not available. So EVAERS use SPL dosage (inaudible). And those point to NCI EVS. And so when we try to harmonize with EVAERS, we take that into

consideration, race code being 1. Okay race code point to NCI EVS, so we were like, okay, do we create our own OID and a list of value? Then we think about it first.

That is not something controlled by FDA. It's actually a OMB controlled list. So we're not in the business of taking a copy of that and create our own regional copy, right, and also EVAERS 01:49:27 share data with CDC. So by using a NCI code, that will make sense. So the thought behind it, behind the whole creation of regional code is if the code is available internationally and used by multiple partners, like ISO country code, we're not going to mess with it. Okay.

If that's a code used regionally by multiple agencies or even within FDA by multiple centers, we are not going to mess with it. Okay. then if those code really pertaining to FAERS reporting like FDA local report criteria, I mean, who else care? I mean, that's not even provide to CDC. This does not apply to Japan, right, so that is something we truly own.

And if for some reason that is a new report that coming up in the future, we don't want to go to NCI and plead them to add a code for us that nobody else would use, only us, right. So when we create regional code list based on the thought. During the implementation, we have discussion with some of the vendor and we heard that some people implemented in a different way. I don't know it's true or not, but I was told that some regulator took ICH OID and make a extension to it as a subversion and create that list behind it.

I need to verify that, but this is not a good approach, okay. You only manage the branch you own. You don't manage the branch that you don't own. Okay. Other than that, I don't think there's not much to go on with OIDs. I mean, this is a technical thing, but welcome any question if you have.

SURANJAN DE: Yeah, I think this session I asked you to do this to get in just for you all to see a view of, you know, when these elements that I described in the previous sessions and you saw OID number, where did this OID number come from? I

think that's what's important for you all to know, that this came from here, because when you go into the ICH IG document, you will not see that OID anywhere.

So that's -- was the whole intention of this presentation for T.J. to show where these OIDs are coming from, how we are using it, where did we think to use OID, where did we decide to not use OID, and what was the best method of using OIDs, as you heard from T.J. that, you know, some regions just made a subversion of this, added their criteria, added their code list value into it, and said, hey, this is what we're going to be using.

But then you're not managing your own OID, but you're managing somebody else's OID. Also sometimes, we've also heard that, you know, you take that OID which ends up in ICH and then to that OID -- of course, to that OID you have created a subversion and added your additional new code list value to it, so tomorrow, what happens to the main OID where let's say, ICH decides in the future, hey, that new code list value, new value next to come in, that doesn't match with this and if you had values of 1 through 4

and now you have already added five with some value, but now I see it says five means this, what happens to those things.

So I don't -- those kind of discrepancies come into picture so, yeah. Thanks, T.J., for explaining this whole OID thing because it's important that our audience and our sponsors understand what are -- what is going in our thought process of introducing OIDs for some of the regional data elements.

TAN-JEN CHEN: Yeah, actually talking about regional data element, I also like to share some of the thought that we had. A good example is a similar device the similar device. So for the -- since we're using the same HL7 model, right, we are using the same -- I don't know if that's this guy. Let me take a look. No, not. Okay, anyway. So if you're familiar with HL7 model, you are taking from the investigation or event and go traverse the classes and go to the node, right.

So the drug role for the similar product would actually use the same data element of

the drug role. So if you look at that as the same X path, okay, on the model, you go to the same location. So at one point, we were thinking, okay, let's just reuse this data element and instead of code it out as a separated item, you use the same data element and then use a different OID and different value. And that's why you see number 5.

Okay, so we try to maintain the same data element in HL7 and then you will see as -- you go to the same place but when you want to report similar product, all you need to do is swap out a OID and then pluck in value 5. Okay, so in that case, you will still be able to report similar product. And then we discover, well, after discuss with, you know, some technical people, and they feel like it make the validation a little difficult because X path now need to swap back and forth with the OID.

So the recommeNDA-tion is to yank it out. Code it out as a separated item. But because we code it out as a separated item and the original data element is maNDA-tory, so now you have two data element. If you don't code it out as a same data

element, it's maNDA-tory, you just say number 5, similar device, you're done. But since you code it out, now you have two data element and the first one's still maNDA-tory.

So what do you do when you report similar? And that's why, you know, the suggestion is, then you use -- do not administer. So that -- those are some of the thought process we had when we created the regional data element and how we assign regional OID. Hope that helped.

SURANJAN DE: Also with some vendors, we were talking to some of the technical folks, they said hey, now you're saying one field but two OIDs. So you're telling that during submission, you have to swap that and figure out how to swap that, at what instance you will swap, and what instance you will not.

So that was something else, yeah, that is not going to be an easy thing to and also storing that, where typically most of the tools you would kind of store in a way, saying that this is a field, this is the X path for that, right. And now, you have to

go into the X path and remove that OID and put this other OID in there because the condition is this. I said, no, that is not going to be a easy method, so that got to us, saying that hey, I think we need to split it now and have its own OID.

TAN-JEN CHEN: And also, the recommeNDA-tion is cleaner because if, when you report to other region, you know this is FDA regional data item and you just totally ignore this one. You don't worry about X paths. You don't worry about a OID. Nothing. I mean, this is only for FDA.

SURANJAN DE: Any question? Anyone? Maybe everybody's hungry. It is -- because we're almost at lunchtime, so. All right. If no questions, we can go for lunch. We'll start at 1 again and T.J. and me, we are here, so any questions you want, we can discuss. No problem. So, all right. So we'll adjourn for lunch and then come back here at 1 where we start with the forward compatibility. We'll talk about, based on regional elements.

(Off the Record.)

SURANJAN DE: Welcome back. So, after

lunch now we have three more topics that we need to go over. And the first topic, which we'll start right now, is that you saw all the data elements for R3 -- now, the question is how do we do a forward comparability between the R2 regional elements to the R3 regional elements?

We all know what the forward comparability with the ICH elements -- they have the forward and backward comparability. And here the -- here, we did not do a backward comparability, and the reason being that, you know, at the end of the day we need to move forward, we need to move from R2 to R3 and, of course, there are certain data elements. Sorry.

So, we need to move -- from R2 to R3 and then again, there are certain data elements which are new in R3 which you will have a data loss when you move from R3 too back to R2. So, with that, we will go over the different data elements. There is one element we identified where we need to...okay.

So, let's go over each and every data element. So, if you look at this here, at the first

data element, the first data element you have the element called A.1.9, which in R2 used to be called does this case fulfill the local criteria for an expert report? As we said, this data has now become ebullient in R3, so we have the regional data element called Local Criteria Report Type, which has the same values. Now, under the comment, we realized -- which we very recently -- we actually -- I uploaded on Tuesday, this was the values will just go straight. There is no null flavor in there. That was a mistake. And when we move from R2 to R3, A.1.9 moves to FDAC171 with the same values. Okay?

Then we have the combination product flag. So, in R2 it was called A1.FDA.15; in R3 it is -- sorry -- so, in R2 it's called A1.FDA.15; in R3 it's FDA.C.1.12. This was a combination product flag which I was talking about, which I think I missed in the previous slides. And the mapping -- yes, true and no, false. If not set in R2, use is null in R3.

Then we have A233, which is a study type where the reaction event observed. So, in this case, in R3 we have this field C54 where, if you look

at R2 you have some additional values, which is 4 and 5. And when you go R3, C54 will just have those three values, clinical trial, individual patient and 3 as other studies.

For 4, if the value of 4 occurs, then you would move that to set your patient identified aggregate and then you will have the new data element which is other FDA study type where adverse reaction occurred. That's where this needs to be moved.

And then for 5, which is clause supported IND, if the value is 5, then you would take the numbers, the IND numbers from the sponsor study numbers, which is where the IND numbers are, and populate those -- that regional data element called cross-reported IND. So, which is FDAC.5.R.6.

So, again, going back to A2.3.2, for 1, 2, 3 it's a straightforward mapping. If you have a 4, then you would have the new field called Other FDA Study -- FDA Other Study Type Where Reaction Event was Observed, which is nothing but this field here. I think I need to go to the field. This is field where you put aggregate.

And then if you had 5, then you would use the FDAC5R6 where you would put the cross-reported IND numbers in that field. And if you have more than one cross-reported IND number, you know, if you have seen a technical specification that was posted last year, in there for the IND section, this particular Section A.2.3.2 -- 3.3 repeats for each cross-reported IND, and you would take -- where there's a value of 5, you would take the cross-supported IND number which will be stored in this field, and place it in FDAC5R6.

Now, going to A.2.3.2, the sponsor study number, if you have the value of a 1, 2 and 3... Yeah, if all you have is the value of 1, 2, 3, 4 and not 5, then for that IND number which is stored in sponsor study number, is moved to FDAC55A, which is the IND number where the A occurred. And you would only store the number part because FDAC55A is a numeric ten. And for cross-reporting IND I just talked about, if the value of A233 is 5, then you would take the IND number and put it into FDAC5R6.

Then there are some other fields where we have that malfunction. If it is yes -- a

malfunction as in R2, we have a regional data element called Malfunction. And when we go to R3, there's a regional data element malfunction, if R2 is the value of yes/no, and if it is not set in R3 we're making it true and false as ebullient. So mapping, yes is true, no is false. If not set to R3, then set the values to false in R3.

Same with -- oh, so now then you have these fields which are correction additional information response to FDA request. Now, these fields are -- and devise evaluation -- these were four separate data elements in R2. And in R3, that has been combined into one data element -- the element name is a follow-up of what type. So, what type of follow-up has a value 1, 2, 3, 4, and the logic there is if the correction was yes, then the value is set to 1. If it is additional information, the value is set to 2, and so on.

Since this is a repeating entity, there could be multiple values, so there could be correction and additionally information. So, you need to set that to 1 and 2. The R2 tag value is set up as a

repeatable -- yes, that's a repeatable value in R3. And then we're saying if the value of R2 field is no or not set, then don't include them. So, if this value is no, then -- or not set, then you don't need to include them because you're just mapping it to one data element, and we need to know what those values are.

So, similarly, we have a data field Remedial Action Initiated. Each codeless value of remedial action in R2 are separate data elements. They all merge into now one data element in R3, just the remedial action. And the same pretty much rule applies as we talked about in this follow-up type. So, anything which is yes is a 1, and that 1 is -- and that is set up when you do a follow-up compatibility.

All right, so the next one is -- if you had -- there was a value called Other. And then in that case, if the value is present in R2, then include 9 as Other. So, the way in R2 we had it set up, you had all this and then you had a data field called Other, which was a free text. And since in R3 there is a special field called Other, then if there is any

value in that field, then -- if there is any value in this field, then you migrate it to this and set it to 9 as Other.

Then you have the evaluation value, which is a devise problem code, so that goes where -- you copy the evaluation value to the devise problem code where the R2 tag evaluation type is equal to devise problem. So, there is a tag in R2 called BK420FDA191A, which is the type of evaluation. I think it could have two or three types of values -- devise problem, patient problem and something else.

Plan name, common device name and product code, you just copy from the R2 value to the R3 value. Manufacturer name, manufacturer address, city -- this, you copy the value from R2 to R3 as is. Then we have the devise usage. This could be set at 1, 2, 3. So, you will basically copy the value as is.

Then we have the device lot number. It's a free text and so you copy the value from R2 to R3 as is. Operator of the device. So, the operator of the device is currently a free text and an operator of the device we have health professional, lay user,

patient and other. Now, even though we say a free text, there is some suggestions in the technical specification to use health professional or lay user, patient. And what we're saying here is map the R2 value of health professional if you have health professional to 1 in R3. Lay user to 2 in R3. If R2 value is not health professional or lay user, then set that to other, which is the value of 3.

Patient race code. Actually, we don't have any patient race code in R2, and we don't have patient ethnicity or required intervention in R2. So, it's a whole new data element in R3. So, in such case, ethnicity and race are manually treated elements, so you would use a non-flavor of unknown. And requiring an intervention will be NA.

Next is characterization of drug role. So, here there is a fix in the -- yeah, R2 is 1, 2, 3 and 4. These are the four values. When it comes to R3, we have the FDA other characterization of drug role, which is one similar device. So, we discussed that new regional element.

But when you move that, what will you

set for the characterization of drug role? Because you have to have that value also. So, in that case, we set the value to Drug Not Administered because we're talking about a similar device and not the suspect.

All right, so those are some of the rules that we have documented based on some of the regional elements that we have where some rules apply. Not every element we have a rule that applies because many places they are optional. So, before I get into the routing mechanisms, you know, any questions? Any thoughts? Any ideas?

PUBLIC COMMENT: (inaudible) ...to FDA IND are 2 reporting in that the technical specification is specifically for R2 and in this graph. At what point in time would that technical specification be republished and also include the R3 data elements? It feels like there's a bit of catch-up between the documentation.

So, you've got the forward compatibility document that speaks about IND R2 data elements and it gives the R3 equivalent. And I think

the same possibly with the Business Rules spreadsheet, that there'll be IND data elements which also display the R3 details. But the actual FDA IND technical specification only speaks about R2 currently.

SURANJAN DE: Correct. So, the R2 specification that was published that had -- I think it has combination products and IND -- that specification, there's a change, a minor change that we had to do to include the similar device concept. So, that has gone into revision. I understand that last week we just got a clearance on that document. So, the R2 document. So, that document will have -- the document will specify two changes: One is how to use this in R2, which is a similar device. And then the second thing is that when we talked about the causality assessment, it just mentions that you suspected or not suspected or you investigated our sponsor. That's only to use... So, that will get posted now.

Now, if you fast-forward now, you will have the spreadsheet which has all the R3 data elements with the forward comparability, with the

expats. That we will post it by end of this month. So, my hope is that since the R2 document's already cleared, that should hopefully get posted this week. Because I know it got cleared through our office. Because the technical document doesn't have to go through Regulatory Affairs clearance or Regulatory Policy clearance.

So, that, hopefully, we are waiting -- I think on the web team to post it on the FDA.gov end of this month. Now you have the R3, so you already have the final R2, you have the R3 the spreadsheet. The document -- the technical spec of R3, right? So, that we are working on to get it, hopefully, by September. The reason being that that needs a lot of change based on all the different regional elements.

But that document mostly will not go into the detail of what is the data of an element, what does the data lend, and so on, and so forth, because that's already in the Excel Spreadsheet. It'll just point to that spreadsheet, all right? But it will at least give you what this element is about, maybe a snippet of the example as to how it's going to

look like. And all the attributes of that element still will be maintained in that spreadsheet. And that technical specification will come in September.

So, if you look at the timeline, we hopefully get our R2 specification out this week. We have by the end of this month, we have the business rule document that has all the elements with the rules, and the expats, and the forward comparability posted by the end of this month. And then the big PDF document of other technical spec come out in September.

PUBLIC COMMENT: So, then my second question is are there any -- or is there any information in terms of the date when voluntary IND R2 reporting starts? And is there any likelihood that marketing authorization holders or applicants could just go straight to R3 reporting for IND safety records?

SURANJAN DE: Right. So, right now, the guidance is still in draft. So, once you have the guidance which is final, after which you have two years to submit. Now, it so happened by that time you

have -- you're ready with probably R3. Right? So, you must really jump into R3 at that time because you still have two years from the time the guidance and the rule becomes final for submitting IND electronically. Right?

So, you may decide that, hey, I have two years, I can get R3 -- R3 specifications out, and I may just straight go into submitting R3. Of course, until that time, you still have to involve your regulatory affairs to submit those reports through them, through ECTD, right? But if you decide that, hey, you know what? I think I can do R2, R2 -- I'm ready with R2, it's not too much of a hassle to do R2, then you may start doing R2. That means you don't have to now submit anymore the cover letters and all that -- all that administrative, you know, documentation that you have to submit with an ICSR. And while you are working on R3, and then when you're ready with R3, then you move over to R3. Does it make sense?

PUBLIC COMMENT: I'm trying to get at whether or not there are applicants that

(inaudible)...to stick with what they're doing right now (inaudible)...

SURANJAN DE: Right.

PUBLIC COMMENT: (inaudible)

SURANJAN DE: Right. And that's true. Some companies -- some sponsor that we understand -- I mean, who have been also talking to us and asking us questions on the IND safety reporting. They have been saying, you know, when can FDA ask us to even start voluntarily for us to submit? Because if we can start voluntarily, then we don't have to submit to ECTD. That means it saves all the time where you have to stake that report to the Regulatory Affairs, create the cover letter, and all that -- generating those PDFs, and then submitting it to ECTD.

It goes actually through -- probably sponsors have their safety system. That takes care of all the electronic submissions automatically. And then they don't have to worry about the next few steps that they have to do. So, that's why they are very eager to start this process.

So, as I said, we are still working on

getting our data analytics up and running for post-premarket. And the reason being is, as you can understand, that all this time, the reviewers at the medical offices have been looking at PDF documents in ECTD. Now you give them this whole app system where alerts are coming, they go in the alerts, they see the line listing of INDs, 15-day, 7-day report that has come. They click on that and right there, they take their assessment and do things. Which is very different than going through and printing a PDF and reading through it.

So, there's a change management process which we are working through and that's not very easy when you have a medical officer who is looking at -- probably got one report in three months, and now you have to train him to feel -- have a feel of the new tool.

So, as far as -- we have that setup. I think the website and the FAERS website will say that -- right now it says we don't -- we are not accepting voluntarily. That would then change to say, yes, we have started accepting voluntarily. And if you're

ready, yes, you can submit. But, again, as I said, it's voluntary -- on a voluntary basis. Only when the rule is finalized, then from that -- two years from that point, then it becomes maNDA-tory. But many companies want to do it voluntarily because to get rid of that next set of process they have to follow. It's actually -- their Regulatory Affairs are saying, hey, can you just -- when can you start? So...

So, it all depends on how the sponsor wants to, you know, work through this process and when.

PUBLIC COMMENT: (inaudible)

SURANJAN DE: Sure, I mean -- so, there will be a period of time where you can do R2 and R3, right? So, there's no stopping that. And for R3, we don't have a set date that by this date you have to be compliant with R3. So, that's what I talked during the slides in the morning on testing. There's no compliance date for when you have to be R3. So...

But definitely -- let's say we don't have a compliance date and let's say middle of this year we have the IND premarket, the final guidance

comes out -- becomes final, right? So, now you have two years, right? So, you have 2021, ’22. By that time, you have to be compliant with submitting electronically the IND Safety Report. Now, at 2022, do you want us to use still R2 or do you want to jump over to R3 because FDA is ready in 2020 -- ready to accept R3? All right.

SHAWN GREEN: Hi. Shawn Green with AVI. I want to revisit the -- or clarify something related to the FDA characterization of drug role. If I understand it correctly, the whole purpose of GK1A is when you have NICSR with two devices that are similar but only one of them is suspect or concomitant. I understand the second one --

SURANJAN DE: No.

SHAWN GREEN: No.

SURANJAN DE: So, in the concept of a similar device, is -- you have a -- so, you have -- let’s say, let’s take it by application number. So, NDA-1, NDA-2. Right? So, NDA-1 has an Active Ingredient 1, which has a Device A. NDA-2 has Active Ingredient 2, but Device A. That’s a similar device.

SHAWN GREEN: Okay.

SURANJAN DE: So, in that -- in this situation, what we're talking about is if you had a malfunction that happened on NDA-1, you have to also report NDA-2 as a similar device.

SHAWN GREEN: Okay.

SHAWN GREEN: Okay. So that being said, NDA-2, which doesn't have the malfunction, you list G.k.1a as similar device and that field is taken care of. That field is still available for Device 1 though, correct? But there's only one value there. What's the guidance for that data point for the first device?

SURANJAN DE: So in that case -- so your -- you would repeat the drug block, right? The--

SHAWN GREEN: Right.

SURANJAN DE: -- product block. So the first product block you would probably NDA -- you would say NDA-1, that drug characterization is suspect.

SHAWN GREEN: Right.

SURANJAN DE: And then other drug

characterization row will be empty.

SHAWN GREEN: It's empty, so it's null.

SURANJAN DE: Yeah. Because that's not a similar --

SHAWN GREEN: There's no (inaudible).

SURANJAN DE: Right.

SHAWN GREEN: Okay. (inaudible)

SURANJAN DE: And then you have the second block --

SHAWN GREEN: Right.

SURANJAN DE: -- which gets repeated in which your drug characterization would say, Drug Not Administered because that's the value we can use. But this FDA.G.k.1a would then say 1, which is similar.

SHAWN GREEN: Right.

SURANJAN DE: So that way we would know that that was a suspect, there was a -- and now another thing which I think I understand from the similar concept is if this has to be reported to Europe, they don't care about the similar part.

And the question which I think came to us saying that, what if you have to report this whole

similar -- we'd report to you but we don't have to report to other agencies. But in that case, if it was similar, you probably will exclude that repeat, next repeated block and say you don't want to repeat that -- you want to report that.

Another instance which happens is -- the question came to us is, let's say you have a product which was outside U.S., right? Now, the device component is still the same because there is a similar NDA in the U.S. which uses the same device, right? So maybe the company had -- the same company, their one application was outside U.S., and there's an application within U.S., but the ingredients are different, right? But using the same device component.

So in that case, how would you report? Now, some of our reviewers are saying -- says -- they say, I don't care about the foreign product. I'm most interested in the U.S. similar product, right? So in that case, you know, what would be the matter of reporting? Currently in R2, the way it is, you have to report that foreign product as well as the similar

product, right?

But when it comes to R3, because the way this is set up, you could only have one block where characterization is Drug Not Administered, and then the other characterization of drug is similar. And then only one can be submitted.

I don't think we -- we're not going to reject the report because if you have reported the foreign product and the U.S. similar product, I mean, maximum what our (inaudible) team is going to do is try to code that foreign product to maybe the (inaudible). Because we code all suspect and -- yeah, all suspect product we code, so we'll probably code it and not reject it. So that's the concept behind the similar...

SHAWN GREEN: Okay. And just one more note. I think in the R2 column there, 4 should be Drug Not Administered, right?

SURANJAN DE: So in the R2 -- no, (inaudible) R2 doesn't have a value called Drug Not Administered. (inaudible) R2 only has in the (inaudible), only these three are there today. In --

SHAWN GREEN: Right, but I'm assuming you listed in there for the R3 (inaudible).

SURANJAN DE: No, no. So this column is R2, right? So there is a field in R2 called B.k.4.1 -- B.4.k.1, which is Characterization of drug role, which only has these three values. We are introducing a fourth one as a regional need for R2, which when you migrate to R3 you will be migrating to FDA.G.k.1a, right? And in this case, 1, 2, 3 is straightforward, right?

So that's nothing. But when you have this 4, this 4 now moves to a whole different field in R3, okay? And that becomes 1=Equal to Similar Device, but when you make this to Similar Device, there is already a field called FDA.G.k.1, which is called Characterization of the drug role, that needs to have some value, and that value will be set to 4=Drug not administered.

SHAWN GREEN: Right. Okay. Thank you. Yeah.

WOMAN 1: Is there any possibility that you could -- yeah. Is there any possibility that you

could revise that row just to make it clearer and still just include more details about G.k.1? To split it?

SURANJAN DE: Yeah.

WOMAN 1: To make it make more sense? So that G.k.1 would map to points one to three.

SURANJAN DE: Yeah, we can do that. I'll just put another row where we say one, two, three just goes to one, two, three, and the remaining four goes this way. Okay. Yeah. All right. One, 13. All right. So if no other questions, we can start with the next topic.

This is a topic where the whole idea is to make sure that the pre-market and the post-market reports are set and put in two different locations, and they are managed appropriately, because we all know that post-market -- redacted post-market reports gets posted publicly, and this is very, very, very important. More so that many of the data elements, especially the current data elements, we don't have too many checks, we do, because we don't want to reject reports.

That makes things challenging especially we had had incidents where even though we have not started electronic submission of pre-market safety reports electronically, we have had situations where IND safety report was submitted to our post-market gateway, and that showed up on the (inaudible) public dashboard. Okay?

Of course, we found out that as for the checks we can put, we have put those checks, but in this case it just went through and this was something that was -- the company had not directly submitted, but they walked through a (inaudible), and we found out that it came -- (inaudible) had submitted that to us. So yeah.

It was a huge big deal, you know. The same company stock price went down like 40 percent in one day. So yeah. So it’s very important that we make sure -- and I would also suggest to you all that if you all even can think about some criteria to help us to say hey, after we go through this, what I show here, that hey, you know, maybe you should think about this -- these criteria to clearly identify that this

is a pre-market report versus this is a post-market report.

Because then there are confusion that comes in, what happens if it's a post-market study report? Right? Then you have two reports to be submitted. One for the IND and one for the NDA, right? So then in that case, how do you basically manage this? Because in these reports, the NDA is redacted and posted publicly.

The IND will not get posted. It will be only available here. So -- and the whole two sets of reviewers are there, one from Office of New Drug, who is looking at the IND, and then Office of Surveillance and Epidemiology, who are looking at the post-market.

All right. So here's the proposal. And I think some sponsors from here have already probably tried this as part of the pilot program that we had done, last year summer. But two separate routes for submission, right? So we have two methods, first thing. We have the AS2 Header Attributes and the AS2 Routing IDs.

And what we are suggesting here is within each of those methods, we split it. So you have AS2 Header Attributes, one for pre-market side, one for post-market. Or if you use AS2 Routing IDs then you have a routing ID for pre-market and one for post-market. So that way, you know...

So if we submit the pre-market and post-market safety reports using the appropriate attributes or the routing IDs for R2 and R3... So and then of course we said IND where the adverse event occurred will be -- is a mandatory data element, and will be available -- has to be filled in, so when we see that a pre-market ICSR in R2 or R3 has come through the pre-market route, we'll check for the IND number to make sure the IND number is available. If not -- then without that IND we really can't do anything because the report will go nowhere.

So that report will probably get rejected because the IND number is not available. It just will not go anywhere. It will just stay in a black box somewhere because it's all routed based on the IND number and a reviewer. That's how the

assignment is set up. So to show how the AS2 Header Attributes could look like -- so what is our current state?

So our current state is we have the destination CDER, we have the attribute value AERS, and then we have for the XML and AERS_ATTACHMENT for the PDF, right? Now, if you -- for the proposed future state, this -- the proposed future state, that works very well when you have an R2 submission, but when you go to R3, the whole attachment is embedded, so that basically goes over here, right?

So we have the attribute values saying AERS_PREMKT for pre-market. So now the attribute values for the XMLs for post-market stays as AERS, as we do today, and for pre-market it's AERS and just go pre-market, PREMKT. And for attachments, it's appended by _PREMKT. So that way now we know that, okay, this is for post-market and this is for pre-market. Right?

So when it comes to E2B R2 of course PDFs are -- is applicable, but when it comes to R3 then they're omitted, so there's still no attachment,

because attachments are sent later, right? So with that attribute value. If you go to the routing ID mechanism -- I think that's mostly what many of them use -- the current state is the routing ID is FDA_AERS and the attachments is FDAAERS_ATTACHMENT.

And the proposed state for IND or pre-market. In this case I would say pre-market because we have also B2B trials. The routing ID stay the FDA_AERS_PREMARKET, and then for the attachment it's FDA_AERS_ATTACHMENTS_PREMARKET. Okay?

Okay. So safety reports are submitted to FDA via different routes, are stored in different folders, because they'll eventually automatically go to different folders. The XMLs will go there -- to different folders. Acknowledgement will be sent with the original Safety Report Unique Identification.

Now, why do I say this? Number two, the bullet point? I don't know how sponsors will store their ICSR on a post-market study report, okay? If it is stored with the same ICSR number or the safety report or the manufacture control number. If you had a post-market study report, and let's say you

had serious and unexpected, not suspected yet, you will probably submit that report to the post-market site because that's the rule, right? For the -- on the NDA.

But if you have serious unexpected and suspected, right? So that goes to the post -- pre-market also. So when this data comes into FAERS, right, I will have one safety report ID. But when I start to get the pre-market, I do not want that safety report ID to basically clash with the safety report ID of the post-market safety report ID.

So internally what we are doing is when a report comes through the pre-market route, we take the safety report ID and we try to append that with a -IND. That also makes it very clear that these reports do not -- should not be published outside, right?

Secondly with that, it's very clear that if just in case, if a post-market safety reviewer looks at the report and say, hey, yeah, this is an IND report. I know that. This is not a post-market site report. Because within FDA, you know, the reviewers

can review the entire (inaudible) of these.

So when I say that will we send with the original, because we have appended, when the acknowledgement comes out, you will get your original safety report ID, what you had submitted. So that's why the statement -- this is just taking extra precautions of these reports to not get out from where it -- where we store them.

FAERS checks the E2B pre-market data elements to safeguard the pre-market reports are identified properly. We also are safeguarding it in such a way that if you had submitted a pre-market report through the pre-market route or the routing ID, okay, or using the appropriate ES2 header, we also mark that report saying that do not publish. All right?

So then when it comes for publishing, these reports are never picked up. Basically, there are three levels of checks we try to look into. One is, you know, we appended _IND to the number. We set it up to say, hey, you came through that route, which means these are IND reports and should not be

published.

And then also look into some of the data elements in those reports to say hey, is it a report from study? Yeah, but report from study could be also report from study for the post-market study report, right? What else can we check, right? Does it have an IND number, that field? Yeah, it has an IND number in the IND where adverse event occurred.

And, you know, some of these data elements verify to make sure that these reports are set to a flag saying that do not publish. And they do not get outside the agency. So that's the all pre-market reports will be treated differently from the post-market reports. These are the things why we have to treat it differently.

So it is very important, I mean, as much as checks you apply, you know, we try our best to make sure that they do not slip through the crack. But it's very important that also on the sponsor side, it becomes very important that they must submit the pre and post-market ICSRs via the appropriate route so that, you know, they come through that.

The biggest challenge which we have is when somebody is submitting a pre-market report and accidentally submits to the post-market route, right? Now, that could be a study report on an NDA, right? We're hoping that the IND on which the adverse event occurred, that also may be filled up, and in that case we might say hey, I see that field filled up, so I am not going to accept this report to the post-market route.

But let's say accidentally that field was not filled up. Then I'm not going to check that field to say that if it's empty or not empty, because all of the post-market report, that field could be empty, right? So it becomes very challenging sometimes, and that's where when I said that, you know, I truly encourage you all to think about that, what data elements really can -- I mean, after looking at all the data elements that you have, and once I provide you the list and this business (inaudible) document, if anybody has any suggestions, we are more than happy to, you know, talk about this as to how we can truly segregate this even after it has come

through two different routes like this.

All right? So then again, here the idea is you see that it's -- you have two different on the pre-market route and the post-market. It comes through and then gets basically routed through two different locations. And even though it's in the same FAERS database, but through appropriate channels and appropriate permissions and data permissions. They are segregated between pre-market and post-market.

All right? And also important to see here is, you know, in the pre-market side you have this. Now, this I have only showed for R2 applies to R3 when you have the new field, the G.k field. And for the NDA, you know, this particular will not have that. But if it's a post-market study report, even submitting through this route we'll probably be expected the NDA number on this tag. So...

And when I talked about sending the acknowledgement back with the original safety report ID, this is where we were thinking of -- the planning of doing. You will know this have no impact on you, but for us to make sure we have proper checks. Of

course, when we do try to, you know, post the data publicly, there's a whole QC check, but we are posting about close to 300,000 reports per quarter, three, 400,000 reports.

Because our last year report count was 2.18 million reports. And so that goes... Luckily, the year before that was 2.15, so the jump has not been that high, but, you know, submitting -- getting all those reports publicly is also a challenge. All right. So routing mechanism. Set up the routing controls. There's two ways to set up the routing controls dictating where the document is sent.

So one is add a custom header attribute. So that's attached to the headers. And the second one is the routing IDs. So when you see the slide, these are the locations where, you know, it points out to where on the FDA website the information about those headers are, and the routing IDs are.

One of the trading partner changes, you have the AS2 header. You have to make sure that, you know, this change is set when pre-market reports are submitted. And if you're using routing IDs, then

these changes are set when you're submitting a pre-market safety report.

All right. So with that, if you all have any questions you want to ask, we have like three minutes, four minutes before we take a break and then come with the E2B validator. Okay? Now, this whole routing mechanism is applicable to -- for both R2 and R3, so there's no separation here.

MAN 1: Okay, so Suranjan, if they do send it by mistake, do they nullify the report then, quickly? Call the agency, nullify?

SURANJAN DE: That's what we have done. As of today, we have -- believe it or not, I think you probably know the number better than I -- we probably have close to four, 5,000 reports in our FAERS database, which are all IND reports. And these reports are all set with -- we basically logically deleted those reports in our database.

I mean, even before we ask companies to go and nullify it, which of course the company will take time to set up this and send it. As soon as we are -- we know about it, we make sure we set those up

to logically delete those cases, and let the company also know about it, that they have accidentally sent it here.

We also let the appropriate sender know that a report has come here so that there may be a IND report with deals with a CBER product that has come to FAERS, okay? And sometimes some sponsors, they think that, you know, if they have submitted the -- at least at the current state, the where we are, where it's not mandated and we have not said that you can submit electronically.

And some sponsors will have submitted that electronically to FAERS thinking, hey, we got the acknowledge. Great, we're done. No, you have the -- currently the rule is that you submit that eCTD, right? We have still not started getting data voluntarily. We have not said yes. We just recently had one case where a sponsor submitted it and we've said, let's check eCTD to just make sure that this is also there, because then only the reviewer will get the report.

And what we find that, yeah, they

submitted to FAERS, they got an acknowledgement, we identified that report, we stopped that report, we nullified it, but it is not in eCTD. So that means that report has not gone to any reviewer. So we found out it was a CBER product. We let CBER know, and then from CBER the sponsor was notified and I think later they submitted the eCTD. So...

So all right. So with this, if you don't have any other questions, I'll -- I think we'll come back at two because the reason is I have to set up my laptop for showing the E2B validator. Right now I think everything comes from this conference room laptop -- computer. So just give me some time, and then I will also go over the spreadsheet, because on that I should be able to open that through my computer. So...

WOMAN 2: (inaudible)

MAN 2: So around two o'clock?

SURANJAN DE: Two.

WOMAN 2: It's two now.

MAN 2: It's two now.

SURANJAN DE: It's two now? Really?

MAN: We're about --

WOMAN: (inaudible)

SURANJAN DE: Oh. 2:20. My mistake. Sorry.

WOMAN 2: It's okay.

SURANJAN DE: Two, 2:20. All right. All right.

(Off the Record.)

SURANJAN DE: So, welcome back after the break. So, with this we're going to start the next topic item, which is to go over the E2 validator. All right, I've thought about this validator the morning, so I think it's time I can show some -- how this validator would function and how you would be able to use this validator. We're still testing through different kinds of files for this, but here to go -- so, the mechanism to validate E2B provides this mechanism to industrious sponsor to validate the E2B R2 and regional E2B R2 data files and you can convert it regionally to be R2 to a regional E2B R3. So, that's what this validator can do. It can validate and also convert. This -- you can use this as a

mechanism before your production submission. This validator can very easily access through public URL. The uploaded files are not stored anywhere and once you're done with it, you close it, the files are gone. And then -- and the updated phase of (inaudible) page will have this link some time in September, but you can straight go and click on that to start validating your E2Bs.

Just to give you a little bit of view on how it looks like. So, you basically have your source XML file. You can upload this -- you can upload this file here and the XML shows up here. In this case, I think I uploaded an R2. I hit on validate and the message shows up here, the XML is valid. This is where I converted an R2 to an R3, so the same file which I took here, it shows me here and then I click, hit on convert and this converts to an R3 Regional Element. If needed, I can download this file, and which downloads this R3 file.

Now once I had downloaded the R3 file, I wanted to check that this will validate, and the conversion has happened correctly. So, it would

validate and should validate and say the XML is valid. So, that's what I did. I saved it as a different name, R3 name, and then I browsed, uploaded it and then hit on validate and it gave me this.

This is where I had an exception data, so if any kind of errors come up, it will show up here and gives you a message. The element type, so and so. It's (inaudible) and so, if there's no (inaudible). These are some of the data elements where it then tells you when you did this, what kind of E2B tag would this issue came, the original XML value and it gives you a validation detailed message as to what the issue is. And somebody can then go and fix it.

So, with that -- so, we will have a link something like this and where this will typically be -- let me see, I think we will be posting this somewhere here. This is my easiest way to get to that page. This is the page, right, that pretty much everybody reviews. And so here we will have a section where you can have a validator or somewhere in the middle here where --

MAN: Who built the tool?

SURANJAN DE: Huh?

MAN: (inaudible)

SURANJAN DE: Yeah, it was a late night --

(Laughter)

SURANJAN DE: No, this was all vendors.

MAN: Okay.

SURANJAN DE: The vendors. A lot of back and forth with them, mitigate elements. Now that we get (inaudible) go back and make sure that it complies to the entire Excel business tool which I'm going to show next. All right. So, here is a method. I have some folders, some files available in -- so this is basically taking an R2, opening it, validating it, the XML is (inaudible) not valid and if I want to take this R2 and then convert it to a regional -- sorry, a regional R2 converted to a general R3 using some of those rules that we went through, it then converts that. So, it uses both the ICH forward compatibility and the regional forward compatibility rule 2 and converts this into an R3. And then from there, I could take this, and I can download this.

So, you may want to say, "Hey, let me try in my organization to get an R2, convert to an R3 and take that R3 and try to load it because I have a combination product R2. I may have an IMB R2 and I may want to convert to an R3 and then take that R3 and try to load it into my system to see how my safety database reacts to that same R3. Believe it or not, that's exactly how we are also trying to test this. So, take different kinds of ICSRs, combination product being (inaudible) pre-market, post-market and it's different kinds and then convert this and then take those XMLs and then create some gold-standard files to see every time we can test this if any changes comes in.

So, once we have downloaded this, I can take this -- all right and 34B, okay. So, now that same R3 I can clear, browse -- oh, I kept it in documents. Okay. So, this is the R3 file, open and revalidate. Good? So, now the same file I can take it and load it into my safety data base, right?

Let's go through a situation where we take a file where we may have an error in the file and

if you start to validate, then it kind of gives you the messages at the bottom to say which tag, what value and what the message for that tag value is. Let me also take another file where -- (inaudible) -- okay, so, let's take a field syntax error. So, this was again an R2 file. I'm trying to see if I have any R3 -- okay. All right, so most of the files which I have here, they are -- you saw that this is how the check can be done. So, you can use any of these and as soon as you clear, this is all gone, nothing is stored in our data base. So, this E2 validator, as I said, will be available through URL. You can browse, select and it, kind of, recognizes between -- also between the different DTDs that we have today.

So, because you could also have an R2, we're still using the DTD2.1 and 2.2. 2.2 is the one where you have combination products. So, if some organization or some sponsor does not have combination products, they can still continue with the DTD2.1, so it knows which one it is and then it does its appropriate conversion to R3. Now, we're not converting DTD2.1 to 2.2, that's not there, but

anything from R2 to R3, this conversion would happen. It's a simple web page. I think (inaudible), how you're going to do things and (inaudible) just provides you all the -- so, the intention behind doing this is that as sponsors get to move to R3, there will be a lot of questions which will come, right? But when we did R2, sponsors need to submit a standard to test it out, get acknowledgment and say, "Hey, yeah. Okay. We're ready to submit." So, now there are so many sponsors we're going to be doing this for R3, so this basically, probably helps both the sponsors and us to be able to go there and do the first round of testing before doing the actual -- not actual submission, I won't say -- before doing their, like a pre-submission, pre-production submission to get acknowledgements and be able to view the acknowledgment.

There is one more thing which -- it just came to my mind right now -- is, maybe we can also provide that if it is valid, what the acknowledgement is, and they can download acknowledgments from here. Which then could be taken

and put into -- and then say, "Hey, yeah. The acknowledgment exactly gives me that because it's valid." Or if there was an error, what will the acknowledgment show, right? So, that way, we basically have the food cycle probably done once and next time you may want to just test it through the gateway. All right?

So, let me see if I have another file which has -- I thought there was -- Oh, and also, if you have an XML file, you can actually copy and paste directly here. So, there is no restriction on that. I basically --

MAN: (inaudible) libraries, right?

SURANJAN DE: What's that?

MAN: There's no libraries?

SURANJAN DE: No libraries.

MAN: Just checking to see if it's the right controlled vocabularies.

SURANJAN DE: No. No.

MAN: Okay and how about --

SURANJAN DE: I mean it all depends on how the (inaudible), right?

MAN: And the business rules are there too?

SURANJAN DE: Business rules are there too.

MAN: Okay, great.

SURANJAN DE: Yeah. Yeah because we cannot check through the library because our check through the library is (inaudible) because we consider product name, event, they're all basically -- even though we say it's (inaudible) and all that, we still do our checking to make sure that we -- it matches with our controlled vocabulary and the dictionaries.

MAN: So, for combo products, it's the -- for R2, it's the DT2.

SURANJAN DE: Yeah.

MAN: Does this also accommodate 2.2 and 2.1?

SURANJAN DE: Yes.

MAN: Okay. Thanks.

SURANJAN DE: So --

MAN2: Does it accommodate all formats? So, EMDR from CDRH (inaudible) or just the FAERS?

SURANJAN DE: Just the FAERS.

MAN2: Just the FAERS.

SURANJAN DE: Yes. Just the FAERS. I mean, this whole purpose of this tool was more to check your R3, but then when we saw this and we said, "Hey, there's a conversion feature also. Yeah, why not just give it" because there may be organizations who are doing R2 today, but if they don't have that experience in R3, this may be a method for the R2 for them to, kind of, convert them just with a click of a button and be able to then play it on with that R3 message to see how it got created and how it looked. Right? So -- I mean, initially (inaudible) said, "Okay, you will just upload, and you just have a validate button. That's it." But yeah, now we've got to convert it and download.

So -- so, again, this validation takes care of all the rules that we talked about -- sorry, the conversion takes care of all the rules that we talked about in one of the sessions and takes care of all the rules that ICH has defined for transformation from R2 to R3. So, it is a combination, but if you

are expecting to just convert pure ICH core data elements from an R2 to an R3, this is not going to work.

WOMAN: Can you use the safety reporting for -- to create files? Oh, I'm sorry. Does the safety reporting portal support R3?

WOMAN2: No, it's just still R2. Okay.

SURANJAN DE: Yeah, R2.

WOMAN: I was thinking about a way to cheat and try --

SURANJAN DE: I know.

WOMAN: And create a file -- okay, well.

SURANJAN DE: Yeah, that is still going to be R2. It's basically just the complexity. Right? You know, the safety reporting portal is a front-end tool, so who really cares what happens at the back end, right? So, as far as a sponsor is concerned, go to the safety reporting tool, they submit their information, done. They don't care behind what happens. It's an R2, not R3.

WOMAN: Well, I was just thinking so

they could at least create a file if they make it -- you know, like -- I'm sorry. Like, create a file, then cut and paste here and then do the conversion and then -- that's what my thinking was. Especially for the -- again, the IND. I think you had a question about that. Like, the people, if they start out doing R2, prior to safety reports because the volume's low. That's what I'm thinking.

SURANJAN DE: Yeah.

WOMAN: You know, so that might be a way to, kind of, start fooling around with some files, but never mind.

SURANJAN DE: Yeah, the safety reporting portal and even though we generate (inaudible), our safety reporting portal and then we import that into FAERS, we then don't have any plans to go to R3 yet. And as part of the whole FAERS 2 program, there are many organizations within FDA who ask for FAERS data. Okay, within FDA. They would ask for it. Like, recently I got a call from -- for tech products, which is also used in human, right? So, then for certain type of specific events, reporting

specific events. Now, how do I share it? So, moving forward in FAERS 2, the idea is to get everyone into the same standard of using probably E2B. That means we all talk the same language. So, if you have a safety system in CVM, if you have a safety system in CTP (Center for Tobacco Products), Center for Food, if we can all talk the same data element with the same definition, with the same language, then it's very easy for me to move -- send you the data.

Like, classic example is today, Center for Food actually gets -- so, when we get safety reports voluntarily from consumer healthcare professionals, they get triaged at some point, right? And the triage says, "Okay, because it's a drug and biologic -- teleported biologic, it needs to (inaudible). That (inaudible) needs to go to FAERS. If there is a report which deals with devices, it needs to go to CDRH to their safety system, the (inaudible) system. If it is (inaudible), then it needs to go to their safety system data base called Cares. Now, how do we send it to Cares? Through our triage tool, actually generates an E2B R2 and then

they import that into their -- what used to happen before that, we used to send them an attachment or send them that source document just as an attachment to the email to a mailbox and then from there, they would do their data entry and all that. Right now, the report comes in, gets OCRd, whatever gets actionable gets actionable, E2B gets generated and sent to (inaudible).

So, the whole idea here is that how much of standard can I get -- we can get into the organization where different Centers are talking to each other through this, basically, one standard.

WOMAN3: That's interesting because that's what the whole Med Watch Plus project was about and that's why (inaudible), so you have the Part 1, Part 2 and the Part 2 was just to confirm its profile just for ICH, right? Because they didn't want to carry the extra structure that the other Centers needed like the device class, the animal subject class, things like that. So, that's interesting --

SURANJAN DE: And the -- you said it right because there's the Med Watch Plus program,

that's when I had -- I was working here and according to the Med Watch Plus and FAERS program, in 2007, '06, yeah, right -- and it was ambitious that to get all five Centers trying to harmonize to get to this. But I guess what now -- the way I see it is, okay, here you have -- let's take CDC first, because they all always work together. They're slowly starting to get into the next Center to show them, "Hey, this is what we have done in CDC. This is the same model you can utilize in your Center." And I think more and more what happens is, now when you have such, kind of, big implementation done once, you have infrastructure, and everything set up already. Okay, for them, now they see it, "Hey, it's just a matter of now just getting the implementation done in the software because all of our infrastructure and everything is ready." So, I think some of those things have played and now, slowly, slowly things are coming to be making it more the whole idea of one safety data base for the agency, right?

So, I mean, some good ideas, which, you know, I've not shown this to any other Centers yet.

But that may be another thing to show other Centers to show and say, "Hey, we have a validator like this. Maybe you want to use the same validator for your device report and (inaudible) reporting." So, people can then go and do this. Or, working with CBER to say, "Hey, your vaccine reports which are there. You can use (inaudible) validator and we have created this validator to make just one validator for all these different kinds of reports."

We have another challenge which, there is no standard today, is reporting of product quality reports (inaudible). Which is currently used in the (inaudible) report (inaudible). We don't have a standard, but the companies still have to submit those reports. So, but I think that's a great idea that -- but that's a great idea where something like this validator can be now taken to all other types of reporting to validate. So, as a sponsor, "Hey, I have a (inaudible) file, I want to validate it." It validates. "Hey, I have (inaudible) E2B." It validates, so -- so yeah, so this basically -- I think we're on time. Basically, ends my presentation on the

E2B validator. So, any questions, any thoughts, any ideas? Please ask your questions. If not, I would then get into --

So, the next thing I have is -- we have -- I mean, I'm going to go over some of the summary and closing comments. But we still have time if anybody wants to put in some thoughts and ideas about all the things I talked about, discussed. I'm going to be here until next -- another hour, so we can talk -- anything specific you want to talk or if you want to discuss this within the group, please feel free to get to the microphone and talk about. Or if you have any -- (inaudible) saying, "Hey, you're thinking this way. Have you thought about this thing and that way?" So, please.

So, with that, the summary and the closing comments is -- we looked at -- I did discuss -- I talked about the FAERS updates. We showed some timelines as to when we want to do some -- set up some -- when we want to publish certain things. We did -- we went over the E2B R3 regional requirements. We go under the post-market, the pre-market regional

requirements. Again, for that, I know there are some slides that I need to fix some things. I'm going to fix that before I post it. TJ talked about all the specific OIDs. Hopefully, I hope that helped everybody to understand the concept of OIDs. How do we use OIDs? Why are we using OIDs and why are we using OIDs in that way? Giving you some use cases as to why these OIDs have to be set up in this way and what are the OIDs. We went over the regional for -- and of the forward compatibility. We went over the rules. That document will be posted by end of the month, along with the (inaudible) after this slide. So, summation (inaudible) for pre-market and post-market ICSRs and then finally, demonstration of the E2B validator.

So, with that, I think I can -- I don't think I can open it from here -- okay. So, folks who are part of ICH, they are very familiar with this spreadsheet. It looks very colorful and so -- so you will realize that what we had -- and this was something I think we talked about at the ICH where, let's have the spreadsheet with every region put

there. So, this spreadsheet actually comes then with all the whole data (inaudible) of ICH and then, as we go through, we start adding the regional elements into this (inaudible). Because as I -- I think one of the ideas was, when you see the IG and the PDF document that tables each element. I mean, the first thing anybody would do is (inaudible) to put into one. So, it's already put into one now, right? And as far as the sponsor is concerned, they would want to see all that into one where if the spreadsheets are very similar, then it's easy to read and understand.

So, this is the spreadsheet that we have. To the source where it says, which are the ICH elements and ICH element (inaudible) element (inaudible) for ICH, for post-market, pre-market, FAERS and then it goes into (inaudible).

Let's look at an element which is an FDA element. So, this is the element we have been talking about today, right? FDA C1, this local criteria 1 alphanumeric 1, 2, 4, 5, 6. So there is no conformance rule under the ICH because it's not an ICH rule, but under post and pre-market because that's

where we'll be using this, right? So, this was a combination indicator. I think I'm going to update the slide with this. I did miss this. So, this is a boolean value and it tells you that it's a combination product or not, right? This includes data elements for FAERS also, right? So, there's many places where, for example, this -- (inaudible) line 2.

FAERS is looking for this, but when it comes to post-market and pre-market, we don’t care about that. So, many of the data elements in this spreadsheet you will find are all FAERS related. Here is this other one where we talked about FDIC 54A, which is FDA other study report type (inaudible). Initially, this one was a 4 here, so that's where we had to save because of the OID concept, we had to make this and then this is an OID for that, right? And it says that -- where it says, "Conforms with ICH business rules versus FDA regional data element." Because I think, end of the day I will have to remove the colors because (inaudible) compliance and I have to make it such that it's clear that it's FDA. Many of these are FAERS elements.

Now, you have a history file. This is the XPATS, so each of those data elements now -- let's take that data element we just looked at, which is the local criteria type report. So, here is the XPAT that has been defined. And please, again, if you find any -- I'm not very expert in this, so I have folks who are expert in finding this XPAT, but if you find any kind of discrepancy in this XPAT, please let us know and we will look into it.

WOMAN4: (inaudible)

SURANJAN DE: I think -- yeah, I think one is for the (inaudible) and one is the value. Acknowledgment and raw data elements we are not using. Now when you say patient/parent ethnicity, I think the number is different. I believe this field is -- okay, we have to find this -- why this is there. But this is basically the entire ICSR with all the data elements. So, this is what I'm posting by end of this month. This whole spreadsheet. Now, along with this spreadsheet, I would also post this spreadsheet. Okay? It says the R2-R3 data elements and then it goes into each of the domain areas, the ICSR, case

safety report, the study, the drug, the patient, the reaction and then each of them has a rule and then there is a rule. Try to make it the same way how ICH has defined it, right? So, and then it goes with each of the rule IDs and then it points out to this to that, this to that. And retired E2B 11s and this is (inaudible).

WOMAN5: Full aggregate reports. Do you have any special instructions or additional information in terms of what detail should be included for the event assessment?

SURANJAN DE: What information would be included in the event --

WOMAN5: -- assessment.

SURANJAN DE: Right. So, I think what I understand from our clinical team is that these are the more -- what do you call -- and based on that assessment, the similar events are events with -- I think that is a rule. I think what -- I mean, the cluster or the pattern or the -- or the similar events that you see in the assessments you have done investigation product with all the similar events that

you see based on the five ICSRs you have. You will write an aggregate based on that. So, in this case, your events would be the events you are doing an assessment on.

WOMAN5: (inaudible) Well, the event assessment, like, for instance, the seriousness, onset date, all of those fields. What's your expectation in terms of what should be populated?

SURANJAN DE: Okay. Can we write this down and --

WOMAN5: (inaudible)

SURANJAN DE: When you come to the aggregate, an aggregate report, I think many of the data points will not be populated just because you're right about the aggregation is in your clinical narrative, right? Because you're taking five ICSRs where you have the details, right? Which now, you're making one aggregate report and you are filling in that report. So, many of the points in that report would -- most (inaudible) part of your clinical narrative. But I think the key information, what, at a minimum, needs to be there, that's something I

definitely would want to talk to our pre-market folks to make sure that what I'm saying is correct.

MAN3: So, I have one basic question. So, there is (inaudible) R3 to FDA (inaudible) if included any other region so they are (inaudible). For example, in (inaudible). So, is it included any other (inaudible)? Can you accept over FDA?

SURANJAN DE: Okay, so basically I think what I'm seeing is going through that thought process where you could want to generate one E2 -- one file so that if that file has got regional elements of other regions and that is submitted to FDA, would you accept that report or not, right? No impact, right? So, that is basically a concept that we had done a little bit in ICH, I think in the cross-regional testing. We have not done that yet. That is something we definitely do plan to work with our vendors to plan that and try that. If it is bad, can it just ignore those data elements? We have not tried that yet, but definitely we would -- we plan to do that as part of our implementation. I have definitely talked to my vendors about this, so hopefully we are

able to provide some information after we have done some level of testing.

WOMAN5: Just one last question because we have to keep up to date with various other business rule sheets for other health authorities, but also within the FDA. For instance, with EMDR and CDRH implementation packages, do you have any process set up for how applicants and so forth, vendors, will be updated or notified of any changes to the business rule sheets? We find that it can be quite haphazard that you go to the site and see that there's a new sheet uploaded and often, not very well version controlled with very comprehensive changes for your revision history.

SURANJAN DE: Okay. Yeah, I think -- I think that is -- I believe that when you register with the FDA's site and become a subscriber, any changes on this gets notified. If not, I think the idea first would be that based on all level electronic submission -- submitters, we actually have a list of, which we maintain to notify sometimes if they don't get notified. The way we have tried to approach everybody

on these (inaudible) meetings, I think that would be one mechanism of notifying. The second mechanism of notifying is that whenever we have any kind of changes, we probably set up some webinars to communicate this change. So, say that, "Hey, there is a change, and this is what the change is." This is how we plan to implement it so that we notify well in advance that this is coming, right? They may have a whole different compliance date, but at least if we're ahead, we can tell you because that may have an impact of something else you are already building, right? So, that is another way because now we know that this is a whole new standard that we are implementing and needs more attention than basically the R2, which at stock, needed a lot of attention, but then people became expert and things are pretty much moving in a more (inaudible). We do plan that -- to have a few more webinars to communicate this. Any kind of change that we identify, we would want to communicate that through webinar because as we are implementing, as we are testing, we will find something which may have an impact on this spreadsheet or may have an impact on

this spreadsheet. So, we definitely want to communicate this.

Another thing which we have done is this (inaudible) meeting actually had over close to 591 attendees registered. So, I have the email addresses of all of them that would basically help us in also communicating with, like, a blast email on if any changes are caught or implemented or plan to be implemented. So -- but definitely we have some ideas on how do we want to communicate this because this is something new. So -- and as we also start posting this site also will get updated, so, I believe that there is someplace where you can get feeds when the sites get -- I need to also check with that office of communication because they also have things like if anything gets (inaudible). If you have -- it's posted through (inaudible), Facebook and all that and sometimes updates can go through that FDA has those accounts. So, that is another mechanism that's some thoughts to use those if you always -- you would automatically get updates that happen and the FDA's Facebook page or FDA's (inaudible) can communicate

that update.

All right. All right, so with that, anything else you guys want to discuss, want to talk? I'm open for that. I'm here and -- but respective of the (inaudible) meeting, I hope I was able to provide some valuable information to you all on how -- what FDA is thinking about, what kind of regional requirements FDA is thinking about, how FDA wants to help in validating your submissions, how FDA wants to help in testing your submissions and some of the thought process that has -- that FDA has had in setting up these requirements for the regional R3. So, if any comments, any thoughts, anything which you would see in the future or you would like to see in the future, please write to us. You have the docket for 30 days and after the docket period, you have the e-prompt email address. We do (inaudible) that. And with that, we will do the following, which is today's presentation, as you see I have a few updates I need to do on this presentation and then post it. Which, again, including the regional requirements spreadsheet and the forward compatibility spreadsheet. I think

this is May 20th, May 18th, for the docket. And any update, any comments based on any update any specification based on the comments we receive and then we will start updating the FDA regional implementation specification document, which was last posted in 2016.

The second to last, third bullet, sorry -- excuse that. And now we are preparing -- we will prepare some sample regional R3 data files, as requested. So, if it's some of the examples that we have, maybe combination product, maybe pre-market (inaudible) post-standard, post-market product and then you can contact this email address after the docket time frame.

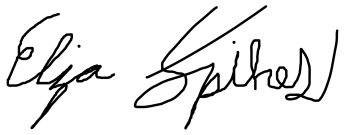
So, with that, I thank you all for being here and attending on the (inaudible). Thank you so much. This kind of collaboration really helps us in getting this successful and making sure that (cough) -- excuse me -- just making sure that the sender and the receiver of electronic submissions both are on the same page, are in synch and can end up in being successful. So, thank you again and hope you

all enjoyed the session.

(Whereupon, at 3:12 p.m., the proceeding was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, ELIZA SPIKES, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



ELIZA SPIKES

Notary Public in and for the

STATE OF MARYLAND

CERTIFICATE OF TRANSCRIBER

I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

SONYA LEDANSKI HYDE