FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards

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The Buffalo Soldiers Great Hall

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A P P E A R A N C E S

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A G E N D A

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Adjourn

P R O C E E D I N G S

MR. DE: All right. Good morning, everybody. We will start. I think it's 9:02 -- Monday morning, March 25, 2019.

So before we start, we -- oh, this meeting today is about Electronic Submission of Adverse Event Report to FDA FAERS System, which is FDA Adverse Event Reporting System, using the ICH E2B(R3) Standards. So we'll go over about three-half or four -- about four sessions to go over all the regional needs and regional requirements.

So before we start, just a few housekeeping items. One is a request to silence your cell phone during the meeting. As you see, the restroom is located on the far end on the right here. The Wi-Fi network is MC Guest. Of course we have lunch as your own and it's an hour long. But I have the fifth session. I have not got any request for presentation. So we may -- depending on the first part, we may make lunch hour to probably add 15-20 more minutes.

So this meeting is being webcast for outside participants, who are on the WebEx. And any questions

for them, they should send their comments to our dockets by April 25th. And then we have -- the information about submitting the docket are on the Federal Register notice and also instructions are available on the registration table on how to submit your comments to the docket for folks who are here.

Parking. You may have seen, I parked on the right side of the parking lot here. And that's about it. We're going to have two breaks: one in the morning, one in the afternoon. Of course there's some coffee and bagels kept here.

So E2B(R3). So this is a topic which FDA is now ready to start implementing. Today we'll go over some of the plans of what we're going to do with E2B(R3). It's a very important topic for us. FDA is one of the founding members of ICH, so it's mandated for us as part of -- as a member country to be implementing this.

And we are going to go over some of our plans of how -- what we are planning to do, some timelines. And then we will have Meredith, who's going to join us soon, to talk about electronic submission of IND safety

reporting. She's going to talk a little bit about the pilot which we are doing and which is in the R2 standard and then what is the transition path for getting into R3. She's going to talk a little more about the implementation plan, some use case examples.

And then we will have Ta-Jen Chen, who's going to talk more about the ICH R3 regional requirements for IND safety reporting and then some -- a little more about the plans on IDMP. And then he's going to go over a little bit on the model of the regional requirement with the HL7 RIM model.

And then, after lunch, we will actually then go over the electronic submission on R3 with post-market safety reporting, where I'll come back and talk about the regional requirements. We'll talk a little bit more about some of the forward compatibility. And then we get into talking about different electronic submission mechanism and you will hear about two submission paths: one for post-market and one for pre-market. And then the plans for what FDA has for you to validate your E2Bs before you do your submissions, the method of your validations. And then we'll get into

some summary and closing remarks and some of the next steps.

So ICH E2B(R3). I believe we are probably the third organization here after Japan and Europe to be implementing ICH E2B(R3).

So again, I am Suranjan De. I'm the deputy director with Regulatory Science Staff in Office of Surveillance and Epidemiology with CDER.

So going on into Session Number 1, I'm going to talk a little bit about FAERS II, because ICH E2B(R3) up versioning is part of FAERS II. FAERS II is a contract which is -- or is a project, is a program which is upgrading our existing FAER system, which includes all our case processing, data analytics, and up versioning of our standards.

So the objective of our FAERS II. FAERS, as we all -- FDA is a very mission-critical system for CDER and CBER and the idea of FAERS II is to provide a modernized system for surveillance of now pre-market, post-market and product quality reports.

So current FAERS today just does post-market safety reporting. New FAERS II will do pre-market,

post-market and product quality report, will be a database for that. This will be a one-stop shop for intake triage and case processing for all those three types of reports, and then it will allow for some enhanced and unified data analytics and signal management lifecycle.

One of the key important objective is to achieve compliance with data standards, which is ICH E2B(R3). And of course it helps us in decommissioning some old tools which are vulnerable to security risk. And as probably not everybody knows, but actually Health and Human Services have designated FAERS II as a modernization priority, and so we have to get this done.

A scope of FAERS II is implementing and maintenance of pharmacovigilance software for the submission of case processing for pre, post-market and product quality and then data analytics. And then of course the maintenance of that, which end of the day would decommission some of our legacy systems which are used in those three types of reports.

So the tools which we will be using in FAERS

II, our upgrade, for analytics and signal management, we have picked a tool from a company called RxLogix called PV Signal and PV Reports. And then for case processing, we have from ArisGlobal a tool called LifeSphere, and that's to do just case processing.

So this is I think the most important slides for everybody, okay, and I'll go over it very slow so that we all can understand where we are, what we are doing.

So if you look at -- our contract for FAERS II was awarded October -- sorry, September 30, 2018. Since then, we have installed our tool into our environment and installing tool into different environments is going on. Our tools has been in the GovCloud. So that's where our -- both our tools will be deployed on.

Now, a few important things. Now, if you look down, is update of FDA E2B(R3) core and regional data elements. This is -- what we have done is: in ICH if you have seen the implementation guide, you have seen all the data elements which are in that PDF document. We have extracted out and put it into more as Excel

spreadsheet. This spreadsheet is also available on the ICH website today.

So we have taken that -- because first thing at ICH we realized that anybody who is implementing this -- first thing probably a contractor would come and then extract all that and put it in a spreadsheet to manage that, right? So we took all that, took that from ICH, and then we added our regional elements to that. So now you will have one spreadsheet of all U.S. regional requirements.

A similar method has been done by PMDA, a similar has been done by EMA. So the idea would be that all the data points which are in that spreadsheet will look the same, okay? And so when an organization is implementing this, it should be very easy to merge all of them together. Because end of the day, for an organization who is submitting, would submit to different regions, so they would need to have one big data set of all the data elements, which includes the ICH core elements and the regional elements from different regions.

So this is one element -- one document which

is a spreadsheet. We are adding new data elements to that and we have started updating that data elements to that spreadsheet. And as we move through, we will next start updating like combo data points in R3 -- R2 has been already published -- but in R3. And then eventually whatever comments we hear from you all, we will then go ahead and incorporate that into that spreadsheet.

Now, when FDA publishes this, FDA is going to publish probably three documents: one will be what we call as the ICH E2B(R3) technical specification, which will have some details, some more words in there; the spreadsheet, which I'm going to show some sample of that how it's going to look like; and then some sample E2B(R3) files, data files with some use cases. So we'll have some use cases and we'll generate some sample data files for you to consume and test in your organization.

So as we move through adding data points as our regional requirements, we are also trying to harmonize that with already implemented VAERS data elements, which is the electronic vaccine reporting

system, because they were already implemented. So as we're going through some of the data elements which we need on the drugs and therapeutic biologic side, we're also looking at harmonizing that with eVAERS. So if VAERS has a particular data element which is to be used from the drug side, then we sit down and we are harmonizing that.

So this spreadsheet you will see that many of the data points will now have saying -- currently, the way we are doing this is we have the FAERS data elements, we have the eVAERS data elements, if we harmonize, that ends up in saying FDA data element. So there is just one data element which has been harmonized.

Another items which we have is we're going to have three public meetings. So today is the first public meeting. We were planned to -- it was initially scheduled on January 25. But because of the shutdown, that had to be changed. So we are here today. The second public meeting will be sometime in July. It's on the meeting page. And the third public meeting will be in February.

As we go through this public meeting, as we hear comments, as we get comments on the docket, we will start updating the technical specification for R3. Technical specification has details; it has a lot more words in there. And as we go through, there are some milestone points where we will be updating the document. And our plan is to have the document ready for clearance sometime in October.

As I just -- I think last week I understand that because this is a technical document, it has to go through a more abbreviated clearance process rather than a whole guidance, the way it goes through. Our idea was to -- I gave some few months just in case, as we know with the clearance process. We were planning to -- we plan to publish that in March, but if it is cleared earlier, we will publish that earlier.

During this next period, from May through December, we will be testing in our environment the R3 mechanism and the R3 standards as we create some sample files for different use case scenarios. And then our plan is, is March 2020 is when FDA will be ready with R3 standard. And as we are ready with the R3 standard,

FDA also will provide a public URL for ICSR validations for R3.

So I'll go over -- at the end of the day, I'll go over some methods we plan to incorporate for somebody from outside could come and test their submissions first before doing production submission.

Right after March is when sponsored testing could start. You will have the spreadsheet of all the core and regional data elements, you will have the updated technical specification, and you'll have the sample files. Based on which, if you started setting this up in your organization, after March 2020 you could start testing your files.

And finally, this is a little different than what we have in the top six, seven lines. As you all know that we're also doing a pilot of IND safety reporting. So FDA -- currently, as per regulations, sponsors have to submit IND safety report as MedWatch through the eCTD route. We're currently doing a pilot with a few companies so that they voluntary also are submitting the E2Bs in R2 format to our gateway, along with of course the regulation, where they submit their

PDFs.

So we had gone through a few phases. So phase -- and Meredith will talk more about -- when she's here, she will talk more about what were the phases and how did it go through. The idea would be to FDA be ready by first of October where companies voluntary could start submitting E2B -- sorry, IND safety reporting in E2B(R2) format to the FDA.

Of course this is voluntary in nature. We will have both the safety reporting portal and the E2B standard available both in R2 to be submitted to FDA.

They will -- the draft -- probably we'll be putting the -- publishing the draft specifications some time end of May for the R2. And then typically the idea is -- I mean, we understand that many of the organizations are already submitting to other agencies in R2 format for pre-market safety reports, so hopefully this implementation would be not as complex. And the best part about that is it basically eliminates the cover letter, it just eliminates all the 1572s, and companies can directly submit through their safety system to FAERS.

So with that, I'll go into some of the testing plan and methods. So before I go into testing plan and methods, with respect to time -- I'm just looking at it. I'm waiting for Meredith to come. I can take some questions if somebody -- if you all in the room have any questions on the roadmap. By the way, this -- sorry, go ahead. If you can come to the microphone, that will be -- yeah, so that everybody can hear.

UNIDENTIFIED SPEAKER: Just a couple of questions. Kathy (ph) from Oracle. You indicated that in terms of reporting, the plan should be ready by March 2020 for R3 reporting, that you'll publish a URL and that sponsors can commence testing. What are the plans for vendors?

MR. DE: What are the plans for vendors?

UNIDENTIFIED SPEAKER: Yes, for being able to test. Is it within the same timeframe or --

MR. DE: The same timeframe.

UNIDENTIFIED SPEAKER: -- it could be before that? The same timeframe?

MR. DE: Yes, it's the same timeframe. After March 2020, anybody can come and test --

UNIDENTIFIED SPEAKER: Okay.

MR. DE: -- you know, the sponsor and the -- because we do understand that all sponsors are dependent on the vendors. And so, yes, they could come after March 2020 and start testing.

UNIDENTIFIED SPEAKER: Okay. And then in terms of R2 reporting for IND safety reporting, at what point would the MedWatch actually no longer be required for sponsors to use? Because IND safety reporting is the last --

MR. DE: Correct.

UNIDENTIFIED SPEAKER: -- leg in terms of --

MR. DE: So I will just hold that question. Meredith is here. She's our next presenter, the next -- after me, she is going to be speaking all about the IND safety reporting.

UNIDENTIFIED SPEAKER: Okay.

MR. DE: And she will go over some of the plans they have for the IND safety reporting.

UNIDENTIFIED SPEAKER: Right. Thank you.

MR. DE: Okay.

UNIDENTIFIED SPEAKER: Hi. Francois Audibert

(ph), Vitrana (ph). Do you expect the harmonization with eVAERS to have an impact on the eVAERS side?

MR. DE: Yeah. Look -- sorry, can you repeat that question again? I'm --

UNIDENTIFIED SPEAKER: Do you expect the harmonization with eVAERS of the data element to have an impact on the eVAERS side, meaning that the eVAERS will change and go through a new standard?

MR. DE: I don't think we will have any impact on the eVAERS side, because what we are trying to do is we're basically trying to harmonize in such a way that many of the things which eVAERS has done -- for example, I'll give you -- the race and ethnicity question which they're asking, we're just taking as is what they have. The conformance rule which they have, we're just going with the same conformance rule. All right?

So most of the data element -- so far where we have reached -- because as we are -- because since we have three meetings -- today when we talk about -- we're not going to talk about every data element today. I've kept some for the next sessions too. But so far

most of the data elements we have gone through, we are -- the elements which eVAERS already has, okay, if we are -- for drugs, we're not using every data element.

One example, reporter's address, there are four lines. It's important for VAERS. But for drug reporting, maybe two. But ICH only has one. So we may use one of that and use the same exact specification and exact conformance rule. So that's how we are approaching this. So that we have taken into account that should have the least impact on the sponsors who are submitting the reports. Yeah.

UNIDENTIFIED SPEAKER: One last question in terms of eSubmitter and the timelines within which you'll update that system as well to accommodate all the changes.

MR. DE: So eSubmitter currently is only used in the vaccine reporting. It's not used in the drug reporting. So for drug reporting, we'll still continue using -- if anybody has to use that, they will start using the safety reporting portal which we have. For post-market it will be used -- for both post-market and pre-market and that will continue as is. So --

UNIDENTIFIED SPEAKER: And that will be updated in line with the requirement --

MR. DE: Right, in line with -- yeah, all the additional R3 elements. Because if you note, the safety reporting portal is based on MedWatch form, right? So that -- we will be updating that based on some of the data elements in R3. Because you know that every 3 years the MedWatch is reauthorized.

UNIDENTIFIED SPEAKER: Yeah.

MR. DE: So based on that --

UNIDENTIFIED SPEAKER: I have a question about that too.

MR. DE: -- that's going to happen --

UNIDENTIFIED SPEAKER: Yes.

MR. DE: --- that's going to happen. So when we are in March 2020, you'll expect that the safety reporting portal, which is used by organizations who don't submit through E2B, will be updated with those data elements which needs to be there based on the MedWatch reauthorization.

UNIDENTIFIED SPEAKER: And so by then do you expect the proposed rules for the MedWatch to have been

incorporated into --

MR. DE: Yes.

UNIDENTIFIED SPEAKER: -- the safety reporting portal?

MR. DE: Right. I think the reauthorization has gone for the clearance now. So some more -- you'll find some of the new data elements. Or the way the data elements are captured, you'll find in the MedWatch there are certain changes in the 3500A Form.

UNIDENTIFIED SPEAKER: Yes.

MR. DE: Because the B and the 3500 are used for consumers and healthcare professionals. So yeah.

UNIDENTIFIED SPEAKER: Thank you.

MR. DE: All right. Some of the testing plans and methods. So there is no compliance date that has been set for R3 submission, right? So there's no compliance date that has been set as of today.

As we said, sponsors can start testing any time after March 2020, which also includes vendors who can start testing after March 2020.

As I said, FDA will provide a validator to pretest senders' ICSR and these validators can be

accessed via the public URL. Once validated, sponsors then can submit in a pre-production environment and receive Ack.

Now, this is something which I've put here. The reason being that, yes, you go to the validator, you test it, right? And you have some errors. You fix it. You test, re-test it. Done. But now you have an Ack which is in R3. So you would want to test the entire cycle.

So the idea here is that once you have tested through the validator, you have a valid URL -- sorry, a valid XML. You can then submit that through the gateway in a pre-production environment, get the submission, get your acknowledgement, and then maybe able to update your system so that you have gone through the entire cycle.

So that's we thought was important and could be done. But the prerequisite for that would be that you have first gone through the validator and tested your actual XML.

Now, the validator will be in the regional requirement -- with the regional requirement. So it

has the core data elements, but will also have the regional data elements. It will test the regional data elements too.

Sponsors continue to submit ICSRs in R2 format until they're ready for R3. And so as I said, there has been no compliance date that has been set, so you continue to submit in R2. And then of course when you're ready with R3, you could start submitting in R3. We will be both backward and forward compatible as we have not decided on any compliance date yet.

Now, these are some of the things which you may want to -- as a sponsor may want to take into account. Testing both pre and post-market, which includes combo products, because that combo products has certain data elements which are more regional elements. And combo products will be talked about in the next meeting. We don't -- we are not talking about that in today's meeting. And in R3 format. So you need to -- we want to test both pre and post-market, including combo products.

And then during that time using both routing mechanisms. We'll explain that in later slides what

are the two routing mechanisms. Today we just have one mechanism of submitting post-market report. And you will see in the later slides what we have explained about having two separate paths for submitting pre-market and post-market.

When you do your production submission, when you're ready for R3, we are just requesting as to notify just that this is your first submission with R3 in the production environment. So that just we can keep a track on who is submitting in R3, and if we have any hiccups, we will be able to immediately contact the sponsor on their submission.

One thing which we want to -- we plan to do in the future -- we have not -- we don't have it in our plan yet -- is we plan to conduct a cross regional testing, just to make sure that if our FDA -- the XML file which is submitted to the FDA, if the same file was to be sent to Europe and Japan, what would happen then. Or if -- now that we will have our parcel and everything ready, if we got a file from Europe or Japan, how will it react with our parcel here.

We did a small testing, we did at part of our

ICH Committee, and most of the results were promising that it just ignores the regional element of another country. But that testing is something we want to do to make sure the sponsors who are submitting have -- don't have all those hiccups of the different elements they need to include. Hopefully, one day they're able to generate this one ICSR and be able to submit to all the regions.

And then if you have any questions during the testing, you want to send it to this e-mail address which we have called eprompt@fda.hhs.gov. And people are monitoring this mailbox. And as we go through the meetings today, you can -- first, we want you to submit all our comments into the docket, and maybe after 30 days if you still have any questions which you have, you can send it to this e-mail address.

So here is the spreadsheet. It's just a long, long spreadsheet. I've broken down into different fields. So if you look at the spreadsheet here, this source will tell you it's an ICH source or an FDA source, okay? So if it's an ICH source, it is a core data element of ICH. If the source is FDA, then it is

a harmonized data element of FDA. It gives you the header element. It's gives you the data element number, data element name, length, data type and allowed field.

Now, this part is the ICH business rule. So if you see a ICH core element, you will see all it's rules and conformance and so on. After this, this part comes, which is for post-market, which talks about the same data element, what is its conformance and the business rule behind that.

If the same data element is used for IND, then it will tell you the conformance and the IND business rule. And if it is used for combo products, it will tell you the conformance and the combo business rule.

We have not put VAERS today, but eventually we will have the VAERS columns added to that, because there are still elements we have not harmonized. And we will -- once we come through the harmonization, we'll do that.

Also future, future plan is eventually have all safety database as one database in FDA, which we don't have today. VAERS has its own database; FAERS

has its own database. The plan is eventually have all into one. And we are slowly getting into from post-market to pre-market to product quality, so eventually we will get to vaccine.

And then it talks about the null flavor, any field (ph) OIDs. And then this one is basically giving you the XPaths for the regional elements which we are defining.

So this is a spreadsheet which you will get and hopefully will be able to see everything in here, which is like a combination of the ICH IG and the regional technical spec. Everything taken together and put into this one spreadsheet for implementation.

So with that, I will request Meredith to come and talk about IND safety reporting. But prior to that, if anybody has any questions which I can answer before Meredith comes and speaks on IND safety reporting? All right, Meredith, the podium is all yours.

MS. CHUK: Good morning, everyone. I'm pleased to talk to you about and introduce the new edition -- newest edition to FAERS, which will be IND

safety reporting.

I think we have plenty of time and the group is small enough that if you have questions throughout, please feel free and I'm happy to address them. Because again, since this is a new concept, there maybe quite a few questions.

So what I want to do is just briefly outline a little bit of the background of the program, where we've been, where we're going, and then obviously describe the implementation plans. This is a new process both for industry and for FDA, so we'll talk a little bit about the changes on both sides.

We'll talk about a pilot and several phases of the pilot that we have been undergoing for the last several years. Most importantly, talk about some of the requirements and the timeline for implementation, which I'm sure everyone is very interested in. Give a little bit of information about the data flow, how data comes into FDA, how it gets to our reviewers, what kind of acknowledgements the sponsors will receive back.

And then discuss in a little bit of detail about the types of IND safety reports that we will have

sponsors submit to FAERS. And then talk about specifically some of data elements that are ICH data elements, but used a little bit differently in the pre-market space as there are different concepts such as IND that don't exist in the pre-market space and some of the other regulatory requirements for events that need criteria for submission are different in pre and post-market.

And then we'll go over a couple of case examples that we came up with through the course of our pilot and working with sponsors about particular questions that may come up in terms of preparing these IND safety reports in the E2B data standard.

So just to remind everybody. So IND safety reports. Any sponsor who conducts clinical trial under IND is required to submit certain events -- and we'll talk about them exactly what they are in a couple of slides -- in an expedited fashion. And again, when we talk about IND safety reports, we're talking about the expedited reports. These are the 7-day reports, the 15-day reports and all associated follow-ups that are required under 312.32. And it's really important.

So nothing about 312.32 is changing. This is simply a logistic change. It's a change in electronic format requirement. So the types of events -- serious, unexpected, suspected to be related to the drug -- are exactly the same. Again, this is just a change in format requirement.

How we get those data elements and put them into an E2B data standard, we'll talk about. But what you need to put in your report, what you are currently putting in MedWatch or a narrative report or something like that stays the same. Again, this is just a change in format requirements. So instead of these reports going into eCTD format, they'll then be going into FAERS.

So again, just to kind of review the current process, these are generally submitted at least for commercial INDs in eCTD format as a PDF. And for the tens of thousands of these that FDA receives every year, it's an extremely inefficient and labor-intensive process for our reviewers to review and there's no standard tracking mechanism. So this is really a big leap forward for us in terms of being able to view the

safety information as structured data elements.

So the new process again, as I mentioned, it is just a change in format. So instead of MedWatch forms as PDFs through eCTD, these will be sent as XML files to FAERS in the ICH E2B data format. And we are starting in R2. So these will be E2B(R2) data standards. And that will allow for more consistent data tracking of the safety signals, data visualization, and certainly just a more streamline process for submission and review.

Other good things about this process. Again, as we've heard about before, this obviously is consistent with what sponsors are doing in the post-market. Although the regulations for what types of events are different, the mechanism for submission is the same. And then it also complies with our existing Federal Regulations under 312.32, which allows us to specify electronic format for submission of these IND safety reports. But again, just format, not content.

Any questions about that? Again, please stop me if you have any questions. I'm happy to address. A little bit of background about the pilots. So a couple

of years ago, we started with these and this really rose out of a concern about the volume of reports that we were receiving and the ability to consistently track these and review them in an efficient manner.

So we worked with our colleagues in FAERS to essentially take a couple of MedWatch forms, see if we were able to take the information in the MedWatch form turn it into an XML file that needed to be format and submitted in a pre-production environment in FAERS. And as you would imagine, since MedWatch is sort of a subset of E2B, that worked out fairly well.

We worked with several commercial sponsors so that they were able to submit some legacy files that they had to FAERS in this pre-production environment so we are able to view that data recurrently. And then we moved on to a technical pilot, which is actually still ongoing.

We're working with several commercial sponsors who are doing a parallel submission. So they submit their MedWatch forms as PDFs in eCTD format for regulatory purposes, but then in parallel, they submit the same IND safety reports formatted in E2B to FAERS.

And then we're able to sort of look at the data elements to ensure that we're getting the same information in the same way that we want for the IND safety reports for our review divisions to review this data. And it also helped us to configure FAERS for some additional data values that were needed for some concepts that were not particular -- that were specific to the pre-market environment that were not used in post-market. So this helped us to revise and to finalize our technical specifications document to be able to do that.

And it was actually very helpful for us to do this because we are able to get a bunch of use cases -- which I'll talk to you about a little bit later -- in terms of I have a -- you know, some clinical trial information can be a little bit more complicated than some of the post-market reporting, the number of drugs, some of them are approved, some of them non-approved, and how do we fit that information into the E2B data standard. So that has been very helpful to us.

And we are also looking forward to an end-to-end pilot before implementation. So this is in the

August to September timeframe. And this is really, as the title implies, is an end-to-end testing of our systems. Once all of our regulatory systems and all of our systems that are needed for coding investigational drugs appropriately, all of the systems that we have in order for our reviewers to be able to review and document on these reports are connected, then we'll work with several commercial sponsors to, over a short period of time, ensure that we have and that we are ready for production and to have these reports to be submitted for regulatory purposes.

So here are the requirements and timelines. So this will be required change in format under 745A of the FD&C Act. So as you I'm sure know, so the FD&C -- or the 745A are electronic submission requirements. And currently INDs under 745A are required to be submitted to an eCTD format. So that's initial INDs and every subsequent submission.

Essentially, what this program will do is just carve out IND safety reports as a change in format. So instead of going in eCTD format, IND safety reports will now be submitted to FAERS.

And I'll say we have up here specified IND safety reports and I'll go into that in a little bit more detail it in a slide or two. But essentially, these are IND safety reports that contain individual patient data. So there are -- 312.32 has a number of different reports that are required for submission. But again, the ICH E2B data standard is really for ICSRs. So these are IND safety reports that fit that ICSR individual patient level data. And we'll talk about which of those and what goes where shortly. But just to let you know.

So sponsors will have two options. And again, because this is 745A, these will be for commercial INDs, although we encourage sponsors of non-commercial INDs to use one of these two methods if they are able as well because we would like to get all of the safety data into FAERS into the same format.

But sponsors will have two options. So either through the gateway. So if they have the database-to-database capabilities, they are able to submit directly their files formatted, it needs to be to FAERS. Or for sponsors who don't have that capability, the safety

reporting portal, which I believe was mentioned and is currently in use for the post-market, is being configured to accept IND safety reports. So sponsors will have the option of a web-based interface that will then generate an E2B file and be submitted to FAERS. So those are two options that sponsors will have.

The requirement -- because it's considered a major change in format for 745A, it will be 24 months after the final guidance is published. So it just gives you sort of a sense of where we are.

However, the goal at this point is to accept voluntary submissions and encourage voluntary submissions starting in October. So the guidance will be out prior to that. And I'll talk about the communication plan in a bit. And then we'll post on the FAERS' website 30 days prior when we'll be beginning to accept voluntary submissions for IND safety reports.

So this timing is a bit different than the R3 implementation. And again, remember we're starting in R2. And the reason for that is there's no compliance date set for R3 and we wanted to get going on this

program so sponsors can submit an R2 and continue to submit an R2 for pre and post-market. But again, the October timeframe is an R2 to for IND safety reports. Any questions about any of that?

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: No. So the goal is that regulatory set forth -- the purposes of regulatory submission in October, that's a good point, yes. So just one report. The goal is that that -- you know, the systems will be up and ready in time to get those reports from FAERS to our pre-market reviewers and the review divisions will be using the FAERS' reports for regulatory review. Yes.

So no -- the duplicate submission was really just part of the technical pilot to ensure that what we're used to seeing in a MedWatch form and that we're able to get all of the pre-market elements in the E2B format. So, yes, that's a great point.

So no parallel submission once we go live for regulatory submission -- for regulatory purposes. Okay. So the -- go ahead.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Yes, yes. So the same process for -- if you're just starting out submitting to FAERS in any way, to e-mail -- and I think it's -- it was certainly on Suranjan's slides and maybe on mine later on to -- to email the FAERS coordinator to make sure that you have all of the system requirements to begin submitting. And then to submit a number of test files just to make sure that you're receiving -- you know, that the test file is accepted.

And then there's a -- there will be an opportunity for submission in a pre-production environment as well too. And I believe Acks will be given in that pre-production environment. So you can also see and make sure that you receive the appropriate acknowledgments when you submit those forms.

And we actually strongly encourage sponsors to do that if you're submitting for the first time either pre or post-market, but certainly for IND safety reports given that there will be some data elements that will be required. And we want to make sure the sponsors are putting those in the appropriate places.

Okay. So in terms of communication plan,

obviously we have meetings such as this. We'll have draft guidance and technical specification document that is both -- so two of those that are both new for this program that will be published along with the updated existing technical specifications document that's in use for post-market and combination products, will be updated with data elements for IND safety reports.

There will also be an updated link on the FAERS' webpage, which has information and a link to a separate page, which has also -- it has all of those documents and also has frequently asked questions and some case examples and things like that that we'll keep current for IND safety reporting.

We're planning on a webinar that will address some of the comments to the docket on the draft guidance as well. And then there will be various other FDA communications so that nobody is caught by surprise that this is coming.

All right. So this is the data flow, just to give you a sense. And do I have a pointer here somewhere? Okay, that was not working. Anyway, so

we'll start here. And get me a pointer here. So the sponsor from their PV system will generate an IND safety report, an XML file in E2B(R2) standards. And again, 312.32 doesn't change. This is just a change in format. So our requirements in the pre-market for events that are serious, unexpected and suspected to be related to the investigational agent as per the sponsor's assessment still holds. So it's the same events that we want; it's just a different format.

They will be submitted to the FDA gateway. The sponsor will receive the appropriate acknowledgments once it's received in the gateway and then once it's successfully processed in FAERS. And then FAERS will have pre-market IND safety reports and also post-market reports. And then those reports will be available for reviewers for data analytics and tracking.

And again, the goal to begin accepting IND safety reports and E2B(R2) on a voluntary basis is October. And certainly, we'll post that on the FAERS' website 30 days ahead.

So we alluded to before and Suranjan mentioned

that there are two separate paths for the pre-market and the post-market, and this is important. So -- and FDA has defined new header attributes and routing IDs for sponsors who are using database-to-database transmission. And this allows separation. So there will essentially be two separate submission paths: one for IND safety reports and one for post-market reports.

And as you can see in the schematic down here, this is the sponsor and here's the ESG. So whether -- if the sponsor either is using AS2 headers or AS2 routing IDs, it's the AERS for the AS2 headers or the AERS_Attachments if there is an attachment. And again, this is post-market. And then if the sponsor is using routing IDs, it's the FDA_Errors or FDA_Errors_Attachments if there's an attachment.

For the pre-market, essentially all we did was add IND into that. So for a pre-market, if the sponsor is using AS2 headers, it will be AERS_IND and AERS_Attachments_IND if that is an attachment. And if the sponsor is using routing IDs, it will be FDA_AERS_IND and the same thing for attachments as well.

And this is really critical, because we've had a lot of questions about this. Obviously, the post-market data is posted on a quarterly basis and is available via the public dashboard. IND safety reports will not be made and will not be posted publicly. And sponsors have a lot of questions about that. And this is the main mechanism by which we are assuring that these are not public -- hosted publicly as well. So it really is incumbent upon the sponsor to send these to the appropriate location. Does anybody have any questions about that?

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Great idea. Two reports.

UNIDENTIFIED SPEAKER: There will two?

MS. CHUK: Yes. So --

UNIDENTIFIED SPEAKER: Okay.

MS. CHUK: Right.

UNIDENTIFIED SPEAKER: Because we know that (Off mic).

MS. CHUK: Right. However, there's IND information on the IND report. And they're not -- it's not a -- just because you're submitting an IND safety

report doesn't necessarily mean you're submitting a post-market report and vice versa, because the reporting requirements are different. So it shouldn't be a default "if I have one, I'm submitting the other." But you're right.

I mean, if you have an approved drug being studied under IND, you may meet both reporting requirements. But there will be two reports. And primarily for this reason: so that they are truly separated in the two systems.

UNIDENTIFIED SPEAKER: How about death (Off mic).

MS. CHUK: Death reports for pre or post for IND? I mean, that would be considered a 7-day report. So same -- you know, the -- again, what's under 312.32, so the content of the report and the timing for submission.

So a death report that is serious, unexpected and suspected would have a 7-day timeframe for submission from when the sponsor receives notice. So that timeframe remains the same. They're not going to be treated any differently.

And I have a slide coming up about the types of reports that are required under 312.32. It doesn't address timing per se. But again, this doesn't change timing. So something that would be a 15-day report is still going to be required within 15 days and follow-ups to those again. Any -- nothing, none of the -- you know, none of the mandates in 312.32 is going to change.

All right. Oh, and here it is. Okay, so this is the slide that talks about the different types of IND safety reports that are required under 312.32. These are a little bit of an arbitrary bucket. I mean, obviously the requirements are serious, unexpected -- so not listed in the IB -- suspected to be related, at least there's a reasonable possibility that the event was caused by the drug according to the sponsor assessment.

However, 312.32 does provide sort of these buckets in terms of what types of evidence you might use to assess whether or not an event would be required in an IND safety report.

So there are six buckets there. And then the

two columns are whether or not these submit to FAERS and whether or not they're continuing to be submitted in eCTD format.

And really the distinction is: is there individual patient data that would fulfill and would fit into that E2B data standard, or are these more narrative summaries that would not fit very well at all into that data standard? Those continue to be submitted to eCTD -- in the eCTD format as narrative summaries.

We would appreciate them not being on MedWatch forms. And that will be listed as well, because they are narrative summaries that they are something that can fit in MedWatch form. You should be submitting it to FAERS.

But just to talk a little bit about these events. So a single occurrence of -- oops. A single occurrence of an event that's uncommon and known to be strongly associated with drug and not much else -- so these are your Steven-Johnsons, your agranulocytosis, generally one event, one patient information from a clinical trial -- submit that FAERS.

One or more occurrences of events that are not real common in your population and maybe not so common with drugs, but there's a reasonable possibility your drug could have done that with one or more events, those go to FAERS.

The third bucket is an aggregate analysis or a report that's a result of an aggregate analysis. So these are events that are common in your population. Say, pancreatitis is common in your population, but you get a higher number of reports in the clinical trial than you would expect baseline, enough to be able to say, "You know what? My drug may actually cause pancreatitis."

So -- and we'll show you in a couple of slides how to do this. So you submit the pancreatitis as the index report and then you submit the X number of ICSRs that contribute to that assessment. So you'll have your summary of what that event is. And then all of your reports linked.

And this really is consistent with what we ask for in the 2012 IND safety reporting guidance that talks about "if you have a report that's a result of an

aggregate analysis, we also want you to submit all of the MedWatch forms that make up that analysis." So this is really just doing that within the context of FAERS.

So there will be a particular -- and I'll talk about this in a couple slides. Those reports will be designated as an aggregate. So they're only counted as each of those individual reports, but then they will all be able to link together for reviewers to see and people interrogating for the system to know that that was an index report with all of those cases that are linked. So it will give us a more appropriate account of all of those individual cases and keep all of that safety data together.

Now, if you have some change to your clinical development program, if there's a change in the IB or informed consent or something like that, that needs to have some separate action done on several INDs, that information is separate from the report. That still goes to eCTD format.

Any question about those individual -- so really these are cases that have individual patient

level data that you could very easily fill out a MedWatch form for any of these. They would go to FAERS.

The other ones are essentially narrative summaries of events, and this is described in 312.32 as well. So findings from other studies, whether it's a literature report or some other where you don't have patient level data on those trials or not other studies that were perhaps conducted, SUS (ph), where you don't have that patient level data. Findings from animal in vitro studies, the pharm-tox IND safety reports will still be continued to submit in eCTD format. And there's an eCTD section where those should appropriately continue to be submitted.

And then an increased rate over a known over expected event. So, you know, I thought pancreatitis occurred in X percent. Now, I see it in X plus Y percent. I think that's a clinically meaningful increase to pose an additional safety risk. So now I submit that as an IND safety report. But again, you're not likely going to have individual patient data on that increase in incidents. So that's an error of

summary; that continues to go to eCTD.

Questions about that? All right. So I'm going to talk -- I'll switch -- talk a little bit about some of the data elements that are specific and very important for IND safety reports that are not necessarily used in the post-market setting.

So again, as I mentioned, the tech -- the in use technical specifications document that's already published and in use for post-market and for combination products will be updated with these data elements for IND safety reporting.

And if you remember nothing else from this session, there are two things I want you to remember, is this: where to put the ID number and then also the separate routing. But the ID number is critical. So this will be a required data element. Essentially, we cannot process these reports if we don't know which IND -- under which IND the event occurred.

So just like in the same way we wouldn't be able to process them if they were submitted in eCTD format, if they're submitted to FAERS with an ID number that is not in the correct location or that it's not a

valid number, these will not be able to be processed.

So this is -- so A232 or the sponsor study number tag is where the IND -- where the clinical event happened, where that clinical trial is being conducted. So A232 and then A233, which is essentially going to talk about the type of report. And these will generally be report from study. I have it on the next slide.

So that's for the primary IND. Our 2012 IND safety reporting guidance also states that sponsors should send these reports to all other INDs under which they're evaluating that suspect product. We do not want more than one ICSR in FAERS, but we do need sponsors to list all of those other INDs.

So the way that we're doing that is that the first block will have the IND safety report -- and maybe this is a little bit easier to sort of see. So the first block, the sponsor study number tag, will have the IND safety report, under which the clinical trial or the event occurred. And your observed study type is likely going to be a clinical trial.

A2 is a repeatable block. So in that -- for

every -- if there are five other INDs where that suspect product is being investigated, repeat just A232 and A233 for those five INDs, that will have all of those other IND numbers in each of those separately in those blocks. And then data element, which is a new data element number five, which is cross -- oops -- which is cross-referenced INDs.

And so does that make sense? Any questions about that? So only one report, because we don't want these events to be counted more than once. But it is still critical for the review divisions who don't have that IND but are also evaluating that drug to get notification.

So it's A232 with a clinical trial, is the IND under which the event occurred. And then you repeat A232, A233 for every other IND under which that drug is being evaluated with the new data element of the cross-referenced safety -- cross-referenced IND. There's also a note here that -- so -- go ahead.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: So great question. And that's where I'm leading up to. So, right. No, that's a

great leading -- so if it is a result of an aggregate analysis. So again, pancreatitis I thought was X percent. It's X plus Y. I think this is a new signal. But my analysis expand five INDs. You submit it to what we call the parent IND. So that is the IND under which clinical trials were initiated in the U.S. It's generally the one with the lowest number. This would be the same concept.

So if you don't have -- I'm trying to think about this. So if it's an ex-U.S. trial and you don't have an IND, why would you be submitting us a report?

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: So you do have an open IND for that product. You're just not conducting the trial. Got you, got you, got you. Okay. Yes. So if it meets our reporting requirements, it would be submitted to the parent IND again. So that's -- sort of the default is: if you have something that meets 312.32 reporting requirements and either it -- but you have individual patient data that -- yes, so send it to the parent IND.

A lot of times those things will also have implications for clinical trial conduction. So you may

be also submitting things through eCTD to say "I changed this. I'm, you know, changing my eligibility criteria. I'm changing my monitoring," something like that. So that information about -- or, you know, here's a protocol amendment to talk about this or an updated informed consent document, that also goes in eCTD format. But the IND safety report itself will go to FAERS under the parent IND.

And this just tells you a little bit about how to put the numbers in the field. And again -- so these -- so the 8 -- so if -- so if you have an A232, you need an A233s. So those will be sort of conditionally required. We at least need to have one. And then if you have other INDs where you're evaluating that drug, those two tags will be repeated then in that block.

You don't need to repeat everything in the block. A2 is a big block. But we just need those repeated. You can. But we just need what's repeated for A232 and A233.

Let's see. So the clinical trial. Generally -- again, generally speaking, these will be clinical trials or a report from aggregate analysis as well.

Some of these other things were -- you can submit for individual patient, but they wouldn't be required. And then these are basically, if you have a report from an aggregate analysis, those are generally considered 15-day reports. So that's where this A19, that is -- that's where it's that fulfill expedited criteria, so that would be a 1 or a yes. And we'll get to that. I think that's the next one.

Right. Okay. So here are some other data elements that are specific and not necessarily unique to IND safety reporting, but perhaps more emphasize the type of report. Again, the default is going to be report from study, unless there's a good reason not to have that.

The expedited criteria. There is a new data element here. So that 7-day report is obviously not a post-market concept. That's unique to the pre-market. And this gets back to the timing requirements. So the timing requirements will not change. So if something is to be submitted in 7 days, you'll just use this -- the data element value of 7 -- or number 6, which is a 7 day. And then number 1 is -- 1 for 15-day expedited.

So for IND safety reporting, you'll either be using a 1 or a 6 to denote either a 15-day or a 7-day report. And then obviously your follow-ups to that will be either a follow up to whichever the initial report was.

The clinical trial identification. So for R2 we will be using in this field the eCTD study tag identification that allows us -- so basically, whatever that study identifier that you're using in the rest of the IND submission, when you're submitting an eCTD format, we're going to use -- we'll have you put that same study ID in there. And it just allows us to be able to identify the clinical trial as is being used and as is being identified for every other FDA submission.

And there's also a recommendation to concatenate that with the abbreviated trial name, similar to what's done for EMA, essentially the EudraCT number concatenating with the abbreviated trial name. So that's similar.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: For -- no. So these are all of the data elements for anything in FAERS. So I think 5 is a

quality product --

MR. DE: So when you have a -- when you have combination products, combination products actually has a 5-day, which is -- I don't remember the full -- but there's a 5-day and a 30-day for combination products. So that's why those values.

UNIDENTIFIED SPEAKER: (Off mic)

MR. DE: Yes.

UNIDENTIFIED SPEAKER: Remedial action?

MR. DE: Remedial action, correct.

MS. CHUK: Yes. So all of the element values are listed here. We just highlighted the ones that will be used for IND safety reporting. Would it -- do you think it would be clearer in that section -- we can think about sort of not having that in there. But we essentially were calling out what you would be using in the note section if there's something particular and specific about IND safety reporting and we've tried to put that in the note section.

UNIDENTIFIED SPEAKER: (Off mic) a 7-day report is fatal or life-threatening?

MS. CHUK: I'm sorry, can you come a little

closer?

UNIDENTIFIED SPEAKER: If it's a fatal report -- if it's a 7-day report, it's fatal or life-threatening.

MS. CHUK: Uh-huh.

UNIDENTIFIED SPEAKER: So then you would mark off 7-day as your expedited criteria?

MS. CHUK: Yes, yes.

UNIDENTIFIED SPEAKER: And then normally if you have additional information, you have another 8 days within which to submit the rest of the information.

MS. CHUK: And that would be a follow up --

UNIDENTIFIED SPEAKER: In that case, just go as one 7-day report to the FDA?

MS. CHUK: I mean, if you can meet this -- you know, if you have that additional information within that 7 days -- you know, say, you --

UNIDENTIFIED SPEAKER: It would all go --

MS. CHUK: -- find out about the event and find out follow-up sort of at the same time and you're generating an E2B report that meets that 7-day follow

up, that's fine -- you know, if that meets that 7-day requirement, that's fine. Generally, what happens is that we get sort of the initial 7-day, something happened, and then there's a follow up later that says "okay, these are the details." But if you happen to get all that information at the same time -- but remember your time clock starts from the sponsor's receipt of information --

UNIDENTIFIED SPEAKER: Yes.

MS. CHUK: -- of an event that would qualify for that 7-day reporting.

UNIDENTIFIED SPEAKER: Okay, great. Thank you.

MS. CHUK: So again, this is only format. This doesn't have any -- and follow-ups are similar to post-market. So anything that you would submit in an initial report, you should resubmit in the follow up and then just add, you know, new things. So it should be sort of an add-on to that report.

So those will be different case version numbers essentially. So you'll be assigned a case when you submit the initial report and then every follow up

will be a different case version in FAERS.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: It's in the notes section. And I think that it's currently what in use for post-market for the 15-day expedited. So, you know, do not create more confusion by creating some things totally separate for IND safety reports. We're just using the same -- yes, meaning that it's a 15-day expedited. I completely agree with you that what meets criteria is different, but the timing is the same. So --

MR. DE: So one point that -- actually, the technical specification for R2 which we have today, the regional, has explanation in the note section, which says 1 --

MS. CHUK: Yeah.

MR. DE: -- means this and 2 means that and 3 means this, just for the slide sake. And then when we go to R3, you will find this whole concept will be a little more different than the way -- here we were trying to fit in existing data elements so that it doesn't have impact, where just adding a codeless value helps to resolve this. Because everybody's trying to

eventually move to R3, so.

MS. CHUK: And in R3 we'll have a field that's IND number and that's cross-referenced IND number. So, you know, it will be a little bit clearer. Again, until we sort of get there, it's a little bit of repurposing what already exists just to -- as Suranjan said, to ease the impact.

But, yes, once R3 -- and TJ will talk a little bit more about the sort of -- what kind of maps from R2 to R3 for both pre and post-market as well. But you'll see those more dedicated data elements that are specific for U.S. reporting.

So the other kind of buckets of data elements are causality assessment. So again, critical in the pre-market to be able to -- so that at least one of these products should be a suspect product for each of those. There may be several products, but at least one of them should have a suspected causality as determined by the sponsor.

And again, for the drug assessment source, given our 312.32 regulations, that it is the responsibility of the sponsor to determine the criteria

that meets reporting. This should always be defaulted -- this drug assessment source tag field should always be defaulted to the sponsor.

There is a place for investigator assessment in the narrative and that can be done as well. But in this field there should be sponsor assessment and at least one of them should be suspected.

And again, down here. So this is actually an open -- open for whatever sponsors want to put in there. We have created -- so there are two new element values: 1 or 2, suspected or not suspected. We recommend that you pick one of those just for consistency of how the data is presented. So any questions about the -- uh-huh.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: So that is -- it's the element value underneath that particular field. So either a 1 or a -- it should be a 1 or a 2. I think it's still an alphanumeric field. I don't -- Suranjan, we haven't -- that hasn't been changed, right? So, I mean, it's not mandated to be that, but the recommendation is that it's 1 or 2. And that will then be coded within the

system to be suspected or not suspected.

You'll still be able to use that as an alphanumeric field, but the recommendation is that -- just because that can be dealer's choice for whatever people want to put in there. It's not a consistent response in there. We're just encouraging sponsors to be consistent with either suspected or not suspected.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Right, right. Okay. The narrative field. So again, critical obviously in pre and post-market. But there is likely to be more information in the pre-market setting. And given our 2 (sic) character limitations, you know, we anticipate that there may be some challenges. Although -- you know, I think the encouragement is that sponsors should construct an informative narrative that should be able to fit within that 20,000 character limitations, especially given the ability to structure some of the other data elements such as laboratory values and tests and things like that.

So, you know, our strong recommendation is that sponsors be able to use and put that narrative

within that field. Because again, for ease of reviewing for our reviewers, if that information comes within that field, it's certainly much easier to do so.

However, there is always the option to use attachments for things -- we're encouraging more for things like autopsy reports or biopsies or something that truly would not necessarily be within that narrative field.

However, you know, if there is a lengthy narrative that sponsors would like to convey to the review division, they can always put what doesn't fit within that narrative field into an attachment.

What we don't want, though, is for sponsors to not put anything in the field and just to attach a PDF with a narrative. So again, that's just something to keep in mind about -- once we get to R3, those limitations will be less of an issue with 100,000 characters. But in R2, you know, we'll just have to see how much of an issue it is.

But we really are encouraging people to think about their narratives and be thoughtful about how they construct them so that they do fit within the fields.

And they tend to be a little bit more informative when they're -- not data dumps as well too.

And so the other thing is to be able to separate some things out. Sponsors can use B52 or the sender comment to talk a little bit about their causality assessment and the reason for assessment as well too. So we encourage them to sort of use the appropriate narrative -- or fields to convey that information to not have to use attachments. But the option is there. Questions about that at all? No? Okay.

For the investigational product -- or any product identification becomes a little bit more challenging when they're investigational products. We're not looking at SPL. So, you know, the two fields that we'll be looking at are the medicinal product field and the active substance.

Obviously, drugs in the investigational stage are not necessarily going to have a proprietary medicinal name. But if there is an INN or a USAN name, we encourage that information in there. And then to use a company code if that information is not

available.

Or for particularly the biologic products, if the character length is exceeded by the full name of the product or, you know, the components of the product, just to use the company code as well. And then to put the active substance in the other field, as would normally be done. Questions? Okay.

And this is going back to the reports from the aggregate analysis that I talked about before. So this is a -- you know, here's an event that is now I think a signal based upon these X number of individual reports. So the A112 data element or the linked report number tag is where all of those individual cases should be listed in that sort of index report.

You don't need to resubmit something that's already been submitted in the system. If there are new reports you want to add to that index case, you can do that, but you don't need to resubmit. As long as all of those safety report ID numbers, MCN numbers that you used in those previous cases are within this field, the system can then link those in there.

This is this -- the A232 should be -- we

talked about before the parent IND, so again that's -- if this came from a number of INDs, that should be the IND generally with the lowest number, the one that investigations in the U.S. were begun.

One thing I didn't mention before is that because -- let me just go back here for a second. For investigational product information the -- there is the -- there is another B.4 field that talks about drug authorization number tag. I don't have it up here, but I think that's the tag.

No need to fill that in for IND because obviously you're not going to have -- there's not going be an NDA or a BLA number for an investigational substance. So we don't want the IND number there.

So really for B4 drug authorization number tag, we don't need any information at all for INDs, because again there isn't an NDA or a BLA number. And that's just basically what that means here, is this B.4.k drug authorization tag. Yeah?

UNIDENTIFIED SPEAKER: Is FDA using the self registration (Off mic)

MS. CHUK: Yes.

UNIDENTIFIED SPEAKER: -- (Off mic) --

MS. CHUK: Not the number, but the --

UNIDENTIFIED SPEAKER: (cross talk)

MS. CHUK: -- the preferred name.

UNIDENTIFIED SPEAKER: Okay.

MS. CHUK: Yes, absolutely. If you know what that is for the SRS, absolutely. And that's basically what we're using internally.

UNIDENTIFIED SPEAKER: Okay. But for the (Off mic) active ingredient name --

MS. CHUK: The active ingredient name, right.

UNIDENTIFIED SPEAKER: -- (Off mic).

MS. CHUK: Correct, correct, correct. Yes, yes. Let's see. And then observed study type. This is for the reports from aggregate analysis. That would be a data element value of number 4, report from aggregate analysis for that index case. And then, again, since there is no patient identifier specific for that one report that's your index case, the element value should just be aggregate. So that lets our system know that it's an aggregate report and it also doesn't count that as one of the individual numbers

when calculating number of reports or reports of a particular event.

MR. DE: Meredith, I want to add something. So -- because we have those four elements that make a case, which is -- and one of them is patient, so in the aggregate -- the only way for us to get this -- patient being mandatory is to put in the patient identifier the word aggregate. So that when the system checks, yeah, there is a patient, but even though it's an aggregate, it's accepted.

MS. CHUK: Questions about those reports? Okay. So based upon -- so clearly we've talked about the benefits to FDA. We also think that there are benefits for industry. And talking with our industry partners in the context of our pilot, they really focused on the efficiency gains that are likely to happen from these reports being sent from their PV database and not necessarily having to go through regulatory affairs, because there's no 1571, there's no cover letter with these reports, so that you have the ability to automate within the system itself.

And we've actually heard that some sponsors

say it could save them up to 24 to 48 hours, and on a 7 day report, that's a lot of time. So certainly we think from a -- it requires a change in process, but from what we've heard, that change in process really can be time saving from an efficiency standpoint as well.

And then it also eliminates the need for duplicate reports for -- if you have 15 INDs evaluating that product, you only have to send 1 report. We still need the other 14 INDs listed in that report, but you only have to send 1 report.

It's more comprehensive and more structured, more data elements, more opportunity for some more granular unstructured data than the MedWatch form. And then also it's consistent with ex-U.S. reporting as well. So hopefully -- again, although not -- we're not harmonizing the requirements for what criteria or what events meet submission, but we're trying -- we're harmonizing the technical solution for how to submit the reports.

I'm going to pause there. Are there any questions before I'll talk a little bit on the case

scenarios? Okay. Uh-huh.

UNIDENTIFIED SPEAKER: I just have one question about (Off mic)

MS. CHUK: So for commercial sponsors, the reporting to FAERS is 24 months after the final guidance. So whenever -- so draft guidance in the next couple of months before the -- before voluntary submission. So whenever the final guidance is published, it will be -- now the MedWatch form isn't going to go away. Obviously, it will still be available. Noncommercial -- sponsors of noncommercial INDs will be able to use them. But for commercial sponsors, IND safety reports should not be submitted on a MedWatch form once the 745A change in format requirement is in effect, and again, 24 months after the final guidance.

UNIDENTIFIED SPEAKER: Okay.

MS. CHUK: Sure. All right. So this is -- in case you haven't heard this enough, this is just a demonstration on where to put the IND numbers, how to put them, and exactly, you know, in which fields they are to be used.

So again, A232, that's the IND for the clinical event, where the clinical event occurred is the primary. And then that will likely be in A233 for a clinical trial. And then you repeat block A232 and A233 with any subsequent sort of cross referenced IND.

So that's for any IND safety report where the suspect product is being evaluated in more than one IND. So the onus is still on the sponsor to identify those particular INDs, but we only want one report submitted.

Case scenario two. So if you have an investigational drug A compared to approved drugs B and C, what do you do? So if your suspect drug is drug A only, in your medicinal product field you would use the company code. If there's not an established name or if there is either a proprietary, another established name, you can put that in that one. And then medicinal product field and any active substance will be there.

If it's -- B or C is your suspect product and it meets IND safety reporting requirements -- again, not a default, but if it meets requirements for 312.32, that product field should have B or C in there with

active substance as well.

And then if it's B and C, you would just repeat the medicinal product and the active substance field twice with all of these A232 being the IND where the clinical event occurred.

So, you know, A232 is higher up at the case level and that's really what's going to drive the routing for reporting to the appropriate review division.

And this is just talking a little bit -- so you have an investigational drug A plus B and C which are approved compared to B and C -- those are really all just sort of variations on the same theme, meaning that you need -- for each product that's a suspect product it needs -- it needs a separate identification and a separate field. And you can repeat it twice if needed. And then just the reminder that these are not always default IND safety reports if they meet post market requirements. And we do need two reports, one with the IND number and one with the NDA, BLA number.

So that is really the only time where you would still need to put in (ph) reports. Although we

would argue that they're not necessarily a duplicate report. It's just to meet -- it is one event that meets both pre and post-market reporting requirements. And again, for any of these, it would be the IND number where the clinical trial is conducted.

And similarly, if you have an approved product that's being studied under an IND, say, for a new indication and your suspect product is drug A, then that drug even though it's an approved product, reporting requirements strictly meet 312.32 versus the other ones that you would have to meet post-market plus -- at least for IND reporting you would have to do both then as well. And again, the same thing IND where the clinical trial was conducted. Questions?

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Uh-huh.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Yeah, the attachment has to be sent after an R2, yes. So you have to --

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Right. Approximately, yes. But it's the -- it will be considered the same case,

essentially that -- and then when you -- and it's a good point to bring up. So when you have a follow-up report although we say we want everything from the initial sort of with everything else added, if it's a literature case or autopsy report, you don't need to resubmit those attachments with every version with every follow-up that you have. So if it's an attachment that specific to the whole case, that will stay with the case.

UNIDENTIFIED SPEAKER: (Off mic)

MS. CHUK: Okay. Uh-huh.

UNIDENTIFIED SPEAKER: Any special considerations for (Off mic)

MS. CHUK: I'm sorry. Would you mind coming to the -- I'm having trouble hearing you -- to the mic please.

UNIDENTIFIED SPEAKER: Any special considerations for cases that were previously submitted on paper and are now on R2?

MS. CHUK: Right. So, no, we're not retroactively putting any cases into FAERS. It's essentially whenever you start. So if you start

submitting in eCTD and you're ready to go and are -- you know, any follow up, presumably that would then be into FAERS. So we're not asking you to resubmit things that were in PDF.

So there's going to be a transition period. Presumably that follow up should have all of the information that you had from the initial case. So someone looking at this in FAERS will be able to know that that's a follow up and should be able to reconstruct sort of what that case is. But that initial report, if that's submitted in PDF and eCTD, we're not asking you to resubmit those. It all stays.

So, you know, we just -- that's the -- it's what's going to happen when you have a transition, so. And then, again, sort of overall we're not acting -- we're not asking for any retrospective submission into FAERS for things that have already been submitted.

So whatever you've submitted previously for regulatory purposes, whenever that line is, then you can -- what we don't want you to do is go back and forth, okay? So once you sort of start submitting to FAERS, we don't want you to go back then to eCTD.

And there will be a -- you know, for -- any -- barring any technical complications or things like that, there will be waiver process that is similar to eCTD as well too for this process. But again, we expect that to be temporary and sort of under the same criteria for that as well too.

And it's also a good point because that's the same thing about the submitting through the gateway and through SRP. We don't want people to go back and forth, because there are different case numbers that are assigned once you submit to FAERS versus submitting through SRP. So don't start SRP, then go to the gateway versus the other way -- you know, how those -- although that way is probably okay. But we don't -- ideally, we just don't want people to go back and forth, because SRP creates a separate case ID than the gateway does.

MR. DE: One most important thing is that the MCN number at the top right corner (Off mic)

MS. CHUK: Right.

MR. DE: (Off mic)

MS. CHUK: Right. And that's our internal

tracking as well. So the same -- you know, even if you submit it in PDF on a MedWatch form, your MCN number, yes. So make sure that's the same. And that will allow reviewers to -- if they need to go back and find that report in the eCTD format, they're able to do that and search it by the MCN number. Okay. All right. Thank you very much. I think -- do we want to go for a break?

MR. DE: Yes. So we'll -- excuse me -- introduce Ta-Jen and go for a break.

MS. CHUK: Okay.

MR. DE: So the next will be Mr. TJ Chen. He's going to be talking more about the technicalities and -- of the data elements, going into the RIM model and so on. So before we -- he starts, we will take a 15 minute break. But just because we have some time, we can extend that to about 20 minutes. Thank you.

(Break)

MR. DE: All right. So we're back. So we have session number two now, where we will -- where TJ Chen is going to talk about up versioning to ICH E2B R3 and the regional requirements. So he'll go over some

of the data elements, which -- and some of the R3 -- or regional data elements for R3, and then go over the model to show you where that comes from and what typically would be the XPaths for those data elements. So, TJ, all yours.

UP VERSIONING TO ICH E2B R3 – REGIONAL REQUIREMENTS

MR. CHEN: All right. Thank you. So as Suranjan mentioned, for this section I'm going to talk about the FDA regional data elements. Because we're using HL7 V3 message, so I would briefly touch some of the object data type. And also because V3 use OID, object ID, a lot, so I would also mention a little bit about OID. And also because ICSR Release 3 also support the IDMP, which is an important concept, so I would go through that also.

So -- now, first thing first, right? When you come to up version, the first thing you want to do is go the ICH website to download this IP (ph) package. Within the package, once you unzip it, Appendix 1.B is a folder that includes a spreadsheet that has the mapping of all of the data elements between R2 and R3. And then there's also a specification or a

recommendation on how do you migrate from R2 to R3.

Appendix I.H has schema files. Those are created by EMA mainly for converting between E2B(R2) and (R3) the message. That is not a version maintained by ICH. That is not a version that we use in FDA. But it's a good tool if you want to use it, all right.

So, first, the regional data element. As Meredith mentioned earlier this morning -- actually, I'm not going to go through the element as what you need to support, how you support it. I'll just go through how you populate into the R3. Okay.

So the A19, those -- we're mixing the concept here, right, because we repurpose this data element, we try to minimize the impact. I know people are moving from -- moving away from R2, so we don't want to introduce new data element in R2. So we repurpose the data element, adding number 4 for 5 days; number 5, 30 days; and of course number 6 for the 7 days.

In R3, this actually split. The C17 is a Boolean data type, so you can only say yes/no to it. And we're adding C171 for FDA report type. And here you have the 15 days periodic report, 5 days, 30 days

and 7 days. So that's a new data element.

And then the others -- oh, the CU -- the A110.2, actually that one is interesting. We are mapping that one to -- the A110.1 and A110.2 are now combined into C181, OI (ph) unique number. And then 1.8.2 determine whether that initial report is sent by a regulator or others. So if the company is a first one to send the report, then you're C11 (ph) or you go to C181. And only different when you forward report from other, say, partner or from the regulators. Okay?

So this is the HL7 V3 message or what I call the refined message information model. We're going to reuse this section. It's called -- can't see -- oh, investigation characteristic. We're going to use this class to document C171. This is how it looks. Okay.

This investigation characteristic is HL7 observation class. In the observation class, you have certain attributes. Actually, there are more attributes than this. This was added out during the modeling, but here we use the code and the value. The code determines what the observation is and the value has a data type called NE, okay. So it depends on what

kind of observation you can use different kind of value.

In this case, we're going to use CE coded with equivalent, okay. Coded with equivalent is HL7 data type, is a complex data type. You have attributes or components of the data type. The one that I highlighted are the one that we will use. Those gray out are not used in this particular instance, okay. And the most important are those two used: one is a code, one is a code system.

So how does it work? If you give me a number, 78 -- I think it's 784.0. If you give me this, what it is I don't know, right? It's a code. But then you tell me this is ICD9, the code system. Once you give me the code system, then I know, oh, this is headache, okay. So the code and code system always go as a pair, okay. And the code system is a UID. You can use object ID for that. So I'm going to talk about ID later, okay. So I hope that we get clear as we go further down.

So in this case, the C171, we reuse this investigation now -- investigation characteristic. We

use the code system. And this is the OID that we get from ICH. This will be the root of FDA OID. And if you think about OID, it's like a tree, okay. You come from a root, you come from a trunk, and then you branch out, okay. So FDA now get a major trunk or a major branch, and from that branch, we're going to start creating more object, more branch to it, okay. And I will touch upon that later, okay.

So for this one, we're going to create -- we're going use a FDA OID with a code for the observation. So this code will say this is a FDA report type. So now this observation -- what kind of an observation is this? This is a FDA report type. And the value will be a coded equivalent, so you need to use another code, okay, 1, 2, 4, 5, 6.

Now, what is 1 and what is 4? Well, you need to tell me the code system. Okay, this code system will be a branch under FDA OID. Okay? Does that make sense to you? So this is how the XPath is going to look like. Don't worry about it, because we have not set on how we're going to structure FDA branch yet, so this number is still not set in stone yet.

Now, the next one is a combination product FAQ (ph). We're not talking about combination product here today, but I kind of want to touch this because, again, this is how we use this investigation characteristic, okay. We -- the code system here for the code now has a different number. By looking at this number, now you know this observation is for combination product, okay. And the value -- because value can be any data type. Now, this time we're not using coded equivalent. This time we use Boolean. So as true or false.

So this is the way that HL7 object -- you can instantiate the object more than once. And every time when you instantiate the object, you want to tell people what it is. Observation is a tricky object because it's almost like catch all, okay. We use observation for patient's body weight, we use observation for patient's height, and we use observation for the cases seriousness. Okay. So I'm going to touch a little bit on the body weight and height because we also will use that for other purpose. Okay.

Now, the next one. I'm not going to go

through the A14, but for the A233. Again, this morning Meredith mentioned about how you reuse the A232 and A233 to record the primary IND where the AE (ph) happened and the cross reference. In R3, we have the luxury to create two more data elements and to make it more clear. So we're going to create this C1 -- C55 and the C5R6. It's R because it's repeatable. This is a cross reference, okay.

So you can -- I mean, like if you have 15 INDs, you have one being the primary, the other 14 would be repeat in C5R6. And C5R6 is going to be mandatory, okay. And we did it on purpose. If you don't have a cross reference IND, then you use HL7 null flavor, put NI, no information. So we want to make you conscious on what you're sending. If you don't have a cross reference, just put NI, okay?

And this is where we're going to populate this data element. This is the same object class that you use for the starting number. And since they fall into the same concept area, we're going to use this for the IND number.

This is the HL7-8 class. It has data. It has

attributes. And again, it -- there are other attributes that are added out. We're going to use this ID. The ID is a instant identifier, is a II data type. Okay. II data type has fours attributes. Again, we only use these two: the extension -- sorry, I need -- we only use extension and the root. And extension is a string and the root is again a UID, so it's OID. So the OID will point to -- the OID will point to the FDA site and then extension will be the IND. And the M1 -- the branch of M1 would indicate this is a primary IND and the M2 would indicate this is a cross reference IND.

So this is how the reports are going to come in. With this XPath, if we see this as M2, then we know this one is a cross reference. And this extension is the IND that you put in, okay?

And another thing we mentioned this morning is about street number. In the VAERS, you can have up to four street lines. In FAERS, we think two might be enough. And since this is the HL7 postal address data type AD, this is easy to do. AD is a list of address part. And the address part, ADXP is address part. So

in a part, you have street number, you have CT, you have state, you have even country, postal code, anything. So we just repeat the street number twice, and that's it. So this is easy.

FDA also requires reporter e-mail. That is not a ICH data element. But you -- because this is a HL7 data type telecom, you can use the same construct as a C348 sender's e-mail address. It's the same construct, the XPath will be a little different, but same construct.

And the next one is patient race. Now, here is the person class, this is HL7 class. We're going to use this one to capture the race information. And luckily, the race is a attribute of this class. So all we need to do is point -- and again, this is CE coded with equivalence and is a set. That means it's repeatable. Okay, within this data element, you can have more than one race. And it's coded with equivalence. So all we need to do is OID and then code.

We've taken this from eVAERS, okay, and we're using the NCI Thesaurus as the code, because eVAERS

already registered this with NCI. And these are the code that are maintained by the Census Bureau. So since this is external, we are thinking not to create the FDA branch to maintain the code. We may change our mind. But, I mean, for now we're thinking it makes sense to point to NCI.

And ethnicity. Now, this one unfortunately it was -- well, it is a attribute in HL7 person class. However, during the ISO ballot for this human pharmaceutical model, the attribute was added out. So it's not in the person anymore. We can add it back. Because if we put it back to this person class, then it will fail schema validation, because in the ISO schema it will not have that attribute. And it would also cause cross region conflict because -- I mean, of course you don't send that to Japan or EMEA. But in case if you do that, it will fail the validation.

So to do the workaround is, from a patient play -- I mean, the person play a role as a patient and it has some observation here, okay. So we again use the observation. Now, this observation class has more attribute than the other one, okay. And this is where

actually your patient body weight and the patient height come. So this is going to be the same XPath, but with different observation code.

Now, you know this type -- so we're going to step into this observation at least three times, right? The first time it comes in is the body weight. The second time is the height. And the third time would be the ethnicity. How do you tell the difference? The code, right? I mean, like we mentioned earlier. So to do that, we need to give it a code system, a code value. Again, this is going to be for now for ethnicity same as race. We may use the NCI code, which is the Census Bureau code, okay. So the OID point to NCI Thesaurus and then the value is a C value. Okay? That makes sense?

The receiver information. In R3 -- you know, the HL7 has a patch wrapper, and then within the patch wrapper, you have individual message wrapper. And then in that wrapper, then you have the message. So there is a good mapping between -- at patch level and for the individual message level. All of the A32 element now reduced to 1. It's M2R3.

We may do -- I mean, earlier Suranjan and Meredith mentioned about the FDA -- the head session you have the IND and non-IND thing. We are thinking to use that in this area and we can even separate CDER or CBER report. Now, I'm just tossing that out because we have not, you know, set that yet. But if you have any, you know, thinking, you can always share with us, right?

So object ID. Object ID is a sequence of numbers that separate with that. Like I mentioned earlier, it's like a tree, right? It starts with trunk. So what is a trunk? The trunk has -- you can only start with one of the three numbers: 0, 1 or 2. 0 means you initiate this -- everything started from the International Telecommunication Union. If you start with 1, then you know that everything -- the whole -- so you have three trees basically, okay. You have either the ITU tree or the ISO tree or the joint tree. And then from the tree, you start to develop branch. So -- and it's hierarchical.

So I'm -- so here's the example, okay. 2.16.840.1.113883.3.989.5.1.2, what does that mean?

Well, it means, again, start with this trunk, okay. This is a joint-iso-itu tree. It has a country. Okay, 16 means country. 840 means U.S. And then 1 is organization. 113883 is HL7. So what is this up to here? It says HL7 is a organization in U.S. under that joint tree, okay.

And HL7 branch then give -- further branch out. So it go to this external -- okay, it go to external use root number 3 and assign 989 to ICH. Okay. And the ICH also then maintain that -- number 5 would the regional specialized branch. And in that branch, you have number 1 as a sub region. And dot 2 will be FDA. Dot 1 actually is EMEA and dot 5 is Swissmedic.

So all the ICH member country can -- or organization can always come into ICH under 989 to get OID assigned, okay. So we are now appending this OID, that will be our root almost, right? And we need to figure out the structure how we branch out.

So I just put simply dot N1 earlier for the type of report. It's not as simple. I mean, we're going to have to figure it out whether we want to do a

dot 1 for CBER, dot 2 for CDER. And then under dot 1, we have whatever -- I don't know -- I mean, we need to have an internal discussion because this has a long term impact to that, okay. But this is how OID work. Any question before I go to IDMP? Okay.

IDMP. Oh, I have more than half an hour. Okay, let's do IDMP a little longer. Okay. Now, what is IDMP? IDMP stands for identification for medicinal product. So this is a suite of five ISO standards, okay. Within this five standards -- well, maybe let's go through what it does, right? It defines the data element and structure to uniquely and unambiguously identify medicinal product, pharmaceutical product and substance.

So within the standard -- within this IDMP project, there are five standards. ISO 11615 defines those element and structure for the medicinal product. 616 for pharmaceutical product and then 11238 for substance. And the standard also create common vocabulary for improved people communication and also machine communication. Because if you have a list of value -- I think the question Jim (ph) had this morning

about that whether we use 1 or 2 for the IND data type. Code is easier for computing because it's unambiguous. If you type the character string upper case and lower case, you know, it sometime gets more difficult for a query. If you send a code, it's always easier, right?

So the common vocabulary is not just for human, it's also for machine. 11240 -- actually, 11239, pharmaceutical dosage form, unit of presentation and route of administration try to achieve that. We try to have a common definition on tablet, a common definition on injection, right?

And then also the ISO standard not -- not based on -- well, based on this five standards, there are techno specification on how do you create message to exchange. So you create this common messaging standard to provide IT system communication.

So we -- I just touched upon those five standards, expect this 11240. 11240, units of measurement. It's -- well, when we refer to strengths, we all want to use the same unit of measurement. U.S. is the only country -- well, not the only. I mean, there are two other countries that don't use the

international standard. You all know that. I mean, we use the U.S. convention. And it's always trouble for you to convert back and forth, right? So a standardized unit of measurement is kind of important in many aspects, right? Okay.

Medicinal product, maybe I don't need to go through that. Okay. Medicinal product 11615, okay. It establishes the definition and concept and also the detailed description on how do you uniquely identify medicinal product. Within that, there are like four types of ID. The first one is medicinal product ID. The ISO standard says you want to precede with a country code, followed by the marketing authorization holder information, and then followed by the country code.

And beneath the medicinal product ID, you can even go down to the package level, okay? It's called PCID. And all you need to do is under the MPID you just get the package description code. And then you can also go down to the batch level for each of the product.

Now, BAID 1 is for the outer package and BAID

2 is for the inner package. In most case it would be the same, okay. If you have a Tylenol 50 milligram -- I mean, 500 milligram 50 tablets in a bottle put in a box, most likely BAID 1 equal to BAID 2. But when you come to the kids' product, okay, if you have multiple components in this product, each component would have its own BAID 2. And the outer box would have BAID 1, likely would be the first one to expire -- likely, right? Okay.

Now, when you look at this MPID, if you kind of take away the country code -- and for most people that have been -- deal with FDA, you know, this is very similar to NDC code, right? So NDC code has the, you know, marketing authorization holder number, product code and then package code.

So since MPID at ISO description is going to be implemented regionally due to, you know, the regulations and all that, it's difficult to get a international MPID. But because you prefix with country code, it will be unique, right? So in U.S., we're going to use NDC code. The first two segment of -- the first two segment would be the MPID level. And

if you give the whole NDC code, then that would be the PCID.

And the next one is pharmaceutical product ID. And this is -- this one is very important to link product together, because earlier I mentioned that MPID is going to be implemented regionally. So how do you know that one product in EU equal to a product in FDA? Well, it all depends on this PHPID.

PHPID is a derived ID based on three components: the substance, strengths and the dosage form. So it depends on the availability of those three elements. It defines four levels. Okay, level 1 is just substance. Level 2 substance and strengths. Level 3 substance and dosage form. And level 4 will be everything.

So each level gives you a different precision to map product. So how does it work? Well, you got a Tylenol Extra Strength tablet. This is a medicinal product, right? It's marketed in U.S. It has -- as a pharmaceutical product it has acetaminophen, 500 milligram dosage form tablet. It generates a PHPID, and with the same PHPID, you can link to the generic

version of Tylenol in U.S., right?

Now, if internationally or at least cross region we agree to adopt the same dosage form and we use the same substance ID, and again, we'll use the same dosage strength, unit, then we can identify product cross region, right? So with 11238, we know that acetaminophen actually equal to Paracetamol. And the tablet equal to -- all that, well, it's not very clear but its foreign language, okay? So with that we know that we can map to, yeah, Panadol. I don't even know what it is but now I know, okay. So if Panadol is causing a problem itself, I think this is kind of Asian product I believe in Vietnam (ph) or somewhere, I don't know. I mean if there's any pharmacist here who would know.

But anyway, so if Panadol is causing any severe adverse event in some way, we know that Tylenol would do the same. We know this Japanese version Tylenol will do the same, right? And so this is very useful for pharmacovigilance. It also is useful to address products shortage, right? If you travel to, again to Japan, well Japan is Tylenol, it is easy. If

you go to China or Taiwan, in Iran also Tylenol, what do you do? Well, you know you can do this, right. And again, we also mentioned that PhPID has more than -- has three level or four levels, right? So some time in the pharmacovigilance the dosage form may not be very, very -- well it is important, I'm in the release character is important. But sometimes it's not the first thing you look at. If a tablet kill -- capsule will kill, unless you choke on a tablet -- not choke on the capsule, right? But anyway, so the dosage form may not be that critical. Also when you run out of -- when you have product shortage you may not really care about that dosage form. Again, take out the release characteristics because that one is different, right?

So if you don't do that, you revert to PhPID Level Two what it's going to be look like. Well, you can now map to product, Tylenol to all other form of similar product. And I use similar because instead of saying pharmaceutical equivalent we might be able to say that for chemical. But for biological product you would have some substance based on the ISO standard, the substance, from different manufacturer that I not

consider equivalent, they are biosimilar. So I don't want to say you link in bioequivalent or pharmaceutical equivalent. But I say linking like product, okay. So this is how PhPID can do. Now before I go to next session because I have a lot of time to kill, I can share with you the status, okay? Now the -- you will see this benefit, if we can all agreed to the same substance ID, use the same unit for restraints and use the same dosage form, then we will be living in this happy where everybody will be happy, right. But this take a lot of agreement, cross region. FDA had been working -- and also to start with this whole MPID or IDMP concept started as a ICH project to support E2B, okay? And because the scope get expanded it went to ISO. Now under ISO you don't have to send binding like in ICH, and you don't have the opportunity for the regulators and the industry to sit down to agree the term to use, right.

So with that understanding we kind of agree to use EDQM to sustain the provider for dosage from route administration, and E2B actually is using EDQM for administration. E2B(R3) is using EDQM term for dosage

form and route administration. When we try to implement that within FDA and we're doing this mapping we found out this is not that easy, okay. You have same definition, different term, easy, that's synonym, okay. We all use extended release in U.S. I think it's called modified release in EDQM.

Now if the concept is the same, easy synonym, we map that. Now we have definition data not exactly same, like chewable tablet. In the EDQM definition it says, whatever, whatever and called it whatever, whatever, right? When we look at that in U.S., we don't have uncoated. A chewable can be sugar coated, can have flavor. So what do we do? I mean are they the same?

At one point we think they are not the same. And when we take a step back and we say, well, pharmaceutically it would not affect anything, right? I mean -- and if you look at the product shortage and the pharmacovigilance, sugar coated, flavor coated versus not sugar coated, not favor coated might be okay. So we might be able to map that, okay. But then also in EDQM, well, the way EDQM define terms, they

have certain characteristic. They have statometer (ph), they have release calculator, they have site, they have intended site, they have route. So the dosage form can be very detailed like, powder for injection, for whatever. Always a site and route.

We may not have the same thing in FDA site. And the most interesting one is capsule. We have a lot of the products that are in the capsule dosage form. EDQM only use hard capsule or soft capsule, and we cannot map. I mean this is fairly simple one but we cannot map.

They do have capsule at so-called patient-friendly term. So in EDQM they have different domains, okay. That one is not in the pharmaceutical dosage form, sub-area. So what do we do? We still struggle. We still work -- and we still try to figure out how do we move forward but we spend a lot of time with help from NCI, try to map our term. And in the end we were like, we're not going anywhere, we need to go back EDQM and discuss further. So that's -- I don't know, 11239.

Now because we cannot agree to the same dosage form then that put the PhPID in jeopardy. And without

PhPID you cannot link product together, right? So we also talked with WHO. WHO want to be the standard provider for PhPID. Again, PhPID is algorithm generated. Not every region or every regulators or even the sponsors has a capacity to generate PhPID on the fly. So we are thinking that if someone generate that PhPID and then other can download. That might be easiest way to do. And also when you have product with multiple active ingredient, that will make that generate PhPID become kind of interesting, because which one go first, okay. I think ISL kind of addressed that. Hopefully the algorithm is mine after it would generate same result.

And also do you normalize the strengths. So you have 5 milligram per 10 milliliter. And you have 25 milligram per 50 milliliter. Do you normalize that, right? So those are -- well, the tech spec tell you how to do it, but to generate that it take another step. So we were thinking that if that WHO can generate that and share with everybody else, that will be a good idea.

So WHO agree to that. Actually it was last

year they kick-off -- they invited EMA, FDA, Health Canada to a meeting to see if we together can work with WHO to do a pilot to generate PhPID. So that is still, you know, in progress, okay. So once WHO generate PhPID, and at that time we need to resolve the problem with dosage form, because capsule is not just in U.S. Capsule is also used in Health Canada and I believe even in EMA, Europe, they got to be capsule. I don't know -- I mean I don't think everything can be hard or soft yet, okay. So WHO may need to figure out how to do it. Maybe they take a step back, right, they do level two map and put a product together. And then with human intervention to determine whether they can do a more precise, maybe no, not. So that's next step.

So that's international side. On FDA side, well, as we say the PhPID -- MPID, we're going to use NDC code. We look at the reg, I don't remember the number, I think it's 270, that's 35? Anybody? I don't know if anybody know that. So if you don't then don't worry about the number. But basically the FDA, NDC, there's -- regulatory requirement says when the active ingredient name change, when manufacture name change,

when the package size change, the scoping (ph) change, when you switch between prescription and LTC or when you switch between human drug and animal drug, then new NDC need to assigned. Okay, so those are the data element that are required to uniquely identify a medicinal product.

The ISO 11615 also has certain data element, also says the same thing when the name change, when strands change, when the active ingredient change, also when the indication change, then you need to assign a new MPID.

Now compare this to -- pretty much they are the same. The only thing different is on the FDA side its switching between human and animal. The MPID, the ISO standard concern only in human pharmaceutical, so they don't have that language there, that's fine, right. The 615 also say when an indication challenge, you can -- not you must, you can assign a new MPID. FDA does not have that language. And as you now that aspirin was a pain killer and got a new indication as blood thinner, they never changed the NDC, right?

So in general, we look at that, we know, okay,

MPID align with FDA requirements for NDC, we're going to use NDC code for FDA regional use. Most of you are familiar with SPL, we already use an SPL to exchange medicinal product information. SPL actually is a technical spec at ISO to specify how you exchange medicinal product information, so we can do that already, so we're in compliance. PhPID, we're not doing that. Substance, we have a system called substance registration system that had been in place for a long time. It did not go to the same granularity as ISO 11238. So we have since then upgraded our system to go again -- to go along with the ISO 11238.

And there was a question, actually it was released this morning about IND. For the safety report do you send UNI which is a unique ID for the substance or to using the company code? We have the system in place. And but the process there's no regulation at this moment to require pre-registration. So there would be no UNI assigned in IND. We assign the UNI only on the when the PQCMC (ph) information sent in. And that's a time we can identify the substance and we would assign a UNI.

So the timing is not relevant. We're thinking about pre-registration, and also we need to think about how do we then send the unit back to sponsor so that you can use. But because most of you use that company code, and it does not change throughout the study phase, so we think that's okay, we think that's okay to use that. But anyway back to the substance. So as I mentioned earlier, FDA have been working with EMA closely. So EMA is taking the same -- so -- well, let me take another step back, I'm all over the place, FDA upgraded that SRS into GSRS, Global System Registration System. This is the system that we co-developed with NCI or NIH and KET. They use the open source code to create a system so anybody can take a version of that and stand up in your organization, okay. That will be the same system. That EMA is going to take.

And actually, its -- I'm -- it's going to be installed in Germany, where I think the project management will be under Dutch for EMA. We have already stand up the same version in FDA and customize to integrate with our internal systems. So we're going to figure out how can we exchange information without -

- or at least we need to protect our, you know, trade secret and all that.

And even though ISO at one point tried to use SPL or more precisely the common product model to exchange that information, but because HL7 is moving away from V3, now getting to FHIR, EMA is more interest to create a FHIR resource for the substance information. And even for the medicinal product information, so FDA is working closely with EMA, and HL7 FHIR resource to exchange substance information and medicinal product information. That does not mean we're going to change SPL. You're going to continue to use SPL. Once the FHIR resource mature, it could be a alternative. if you don't want to do SPL you can do FHIR. Okay, but that's long way -- that's not in the next 3 years, that's way down the road. But that's what we're thinking.

So did I -- do I need to keep going? I think that's about it. I mean unless you have any other questions. All right. So if there's no questions, Suranjan?

MR. DE: All right. Thank you, TJ. That was

a lot of technical sides on how we are planning to setup these regional elements, where we are picking it up from in R3. And so eventually when you see the expats (ph), you will know where it's all coming from, okay? So with that if anybody has any questions which they did not ask in the morning from the presentations which I gave or the presentation that Meredith gave, we have some time to -- in the room to -- for folks to ask questions. So if not then it's 11:45, so I guess we can stop here for lunch. And we can come back around -- only we can do about 1.00, 1:15, because after that the next few presentations -- we can actually afford to start at 1:15. So we'll have little time to peacefully have lunch. All right. Thank you so much and I'll see you at 1:15. Thank you.

(Lunch)

MR. DE: Again, I'm Suranjan De with CDER. And our Session 3, we'll talk now about electronic submission post market safety reporting. And we'll go over all the regional requirements for R-3. Now as I said, we are not going to talk about combination product which will be the next session in July. So you

will not see any data elements related to combination products.

So our FDA regional requirement, so the FDA's technical approach, this is the FDA's technical approach for submitting ICSRs and incorporating regionally controlled terminology, regional data elements which are not addressed in the R3 implementation guide. And it's for post-market, premarket, prescription products, nonprescription biologic products.

Okay, so this region requirement as you all know that in June 2016 a regional technical specification was published. So the idea here is to take that and update the regional technical specification. Of course eventually when we harmonize fully with vaccines we would be able to remove this. But currently it is what it is. So -- and this is a document which will get updated based on the timeline what you saw.

We followed the core ICH E2B(R3) and we have a few regional requirements. So we start with a few regional requirements and, and as I said we'll go over

the carbonation product next -- the next session. So the first regional requirement is batch sender identifier N.1.3. So in here the sender should use the DUNS number for N.1.3 using the D&B and the object identifier which is listed here. The DUNS number for business entity identifier is used to validate the business entities in various FDA information system, so pretty much most of the places we use the DUNS number. All right.

So next is message receiver identifier which is N.2.r.3. TJ talked about a little bit on this before the lunch session. And so FDA used two different message identifiers for test and production submissions. And these identifiers today are this. For post-market in the test -- currently this is what we use today, which is ZZFDATST, is used for post-market, and for production we use ZZFDA.

Now when we go into pre-market, we're talking about using ZZFDATST_IND and ZZFDA_IND. So that differentiates between post-market and pre-market. Now there is some considerations here, is this is what we want to ask you all here as audience that for pre-

market, now you have pre-market trial for CBER products and CDER.

So our -- one of our considerations here is for the pre-market instead of using ZZFDA_IND what if you use ZZFDA CDER IND and CBER IND. So that way it differentiates which are CBER premarket safety reports and which are CDER pre-market safety reports. So that especially when it comes to FDA, there is some routing which needs to be done to retake the report and send it to the appropriate reviewer. Because you have just one system, FAERS, to be used by both CDER and CBER, this will very clearly identify which one goes to which center.

Now this is for consideration. This is something we would like you all to provide your comments when you provide your -- when you put the docket. So something to consider this. I don't know if I said this, but all these slides will be posted on the FDA meeting page, by -- within -- the slide and the video which is being taken will be posted on the meeting page. So you will have access to that -- it'll be available for a year.

So this is something for consideration. So please, you know, provide your comments and then we -- we'll accordingly look into and update this. So with regional requirement there are some conformance which we -- which FDA supports, so FDA supports the ICH R3 data element conformance categories. We -- FDA data elements conformance may vary due to regional regulatory specification which is not addressed in the ICH E2B(R3) so which will be addressed in that spreadsheet which I was talking about in the morning and the technical specification for R3. And now some exceptions which we -- which are -- which FDA has which now becomes regional requirements, in the next few slides you're going to see.

Some of the terminologies that FDA uses, so FDA supports MedDRA for coding. And FDA recommends that when possible use the LLT term to record. I mean, in fact if we use the numeric code then it's very specific, so we can code that too, and you can submit that too. And basically a sponsor should refer to all the data elements that specify using MedDRA. So the data points that R3 core elements uses MedDR are the

elements which FDA supports fully.

Some other terminology. We use/support UCUM code for coding unit of measures. And this is one exception -- regional requirement which we have, is it uses some of the NCI codes which is the C-code (ph). And you saw with race and ethnicity we had the C-codes which we used. And this morning we also talked about the global substance registration system, the GSRS where the substance name is used from there.

Finally, FDA supports the use of EDQM dosage form and route of administration for post-market reporting. All right, before I go to the specific data elements, any questions?

UNIDENTIFIED SPEAKER: Well, you mentioned sender ID should use (off mic) or is --

MR. DE: This one?

UNIDENTIFIED SPEAKER: Both. Yeah, it's this, yeah, this one. If we are already submitting (off mic) already.

MR. DE: So the question here is that the batch sender identifier, is it mandatory to use the DUNS number. This is recommended to use the DUNS

number because in exactly -- because many other systems in FDA use DUNS number, for example, when product quality report comes in the DUNS number is provided. So it just makes it easier to then connect all of them together.

UNIDENTIFIED SPEAKER: But if you already (off mic).

MR. DE: Yeah, exactly. If you're using that you can continue to use that.

All right. So we'll go into some of the regional requirements. And the first regional requirement is Section C, identification of case safety report. So this is where there is a little difference between the ICH conformance ruled and the FDA's conformance rule.

ICH's conformance rule -- FDA's conformance rule does not support nullFlavor, okay? So if case says fulfill expected criteria, yes or no, true or false. There is a rule conformance in the Core E2B which also supports nullFlavor. And FDA says that we will not -- we will reject any nullFlavor. So this C.1.7 needs to be true or false. So that's the first

exception which we have, regional requirement which we have.

The second regional requirement is linking initial and follow-up reports. I talked about it a little bit in the morning. It's very, very, very important that the safety report unique identifier for the initial and follow-up needs to be the same, all right.

And the reason why I say this, I pretty much say this in most of my presentation, the check which we do FAERS is all based on that number to identify initial and follow-up. If there's slight difference in that number it creates initial report again. So it matches against that number to make sure that we understand it's initial or follow-up, right? Every report which comes in with that same number, we just make them as follow-ups.

So we just increment our versions, okay. Like some organizations have a concept of, you know, a minor -- follow a minor change versus a major change and then so whatever you change send us even if you had the age change from 45 to 46 and you submit that, it just

creates another follow-up. And the reviewers pretty much are looking at the latest and greatest information. So it's very important that that number stays the same so that the initials and follow-ups are appropriately created in our system.

UNIDENTIFIED SPEAKER: I have a question. For c1811 (off mic) what happened if the (off mic) holder (off mic) for example (off mic) name the change according to (off mic) so then --

MR. DE: So what we have done traditionally is we have asked to keep the safety report number the same for the life of the case.

UNIDENTIFIED SPEAKER: But you transferred (off mic).

MR. DE: Yeah.

UNIDENTIFIED SPEAKER: (off mic) member ID?

MR. DE: There is a company ID, I think.

UNIDENTIFIED SPEAKER: Company number always the same.

MR. DE: Same.

UNIDENTIFIED SPEAKER: Yes, IC (ph).

UNIDENTIFIED SPEAKER: Yes.

UNIDENTIFIED SPEAKER: But normally according to IC (ph) guideline when you issue the company name then the CPI (ph) I think will reflect a new company.

MR. DE: Right. Yeah. At least today we actually -- we keep the same safety report ID -- suggest to keep the same safety report ID through the life of the case. If the situation happens like that where what we have recommended if you look at the technical specification, you will probably find that -- it would probably say that you need to connect with FDA if this truly need to be a change in the safety report ID where the number needs to be updated from our end so that when you submit the next report. But we -- what we do is we always recommend to -- try to keep the same number through the life of the case.

UNIDENTIFIED SPEAKER: So Suranjan, do you expect the DUNS number be in there? So what you're getting at is USA company name which you're now saying you want the DUNS number.

MR. DE: No that's --

UNIDENTIFIED SPEAKER: You want that in t he header?

MR. DE: That's in the header.

UNIDENTIFIED SPEAKER: Okay, so --

MR. DE: So the DUNS -- so yeah.

UNIDENTIFIED SPEAKER: You're happy with the company's name right now?

MR. DE: So the question here was that do we expect DUNS number in the safety report unique identifier because it's got three sections. So the answer is the DUNS number is only required -- is in the header which is a batch sender identifier and not in the case safety report unique identifier. I mean our key is that as long as you have the number and you continue with that number because end of the day inside FDA we create our own case ID. All our reviewers point to that review to that case ID.

UNIDENTIFIED SPEAKER: So the DUNS number you have to translate it. So within that you have to translate (off mic) number.

MR. DE: Right. So I think for the safety report ID, the unique identifier you don't have to have the DUNS number. I mean we really don't -- are not going to translate this. We're going to take it as is

and that's going to be our manufacturer control number, right? So when the reviewers look at this report, they will look at FAERS case ID and the manufacturer control number so and so. So that's what it's going to be.

And if you submit the same manufacturer control number again, it creates a follow-up in the system.

UNIDENTIFIED SPEAKER: Also I think the DUNS number is really just primarily for the gateway.

MR. DE: Yeah, it's for the gateway.

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: Yeah, for the gateway, but for the program it's stripped down.

MR. DE: Yeah, DUNS number typically we are looking at the gateway and --

UNIDENTIFIED SPEAKER: (Off mic) because I've seen people use the DUNS number within the company name. And we don't want that.

MR. DE: Yeah. All right. So here it is the question which you had. Correcting an incorrect safety report identifier. So if you have a situation like that in the event that an incorrect safety ID has been

used in a follow-up report, you need to contact them so that, you know, mutually we can work it out to get that fixed.

Okay. Safety report type. TJ talked little bit about safety report type but this is how that Excel spreadsheet is going to look like. So in there the column will talk about the FDA report type. And if you noticed that anything which is regional has been prefixed the number -- element ID has been prefixed by FDA. So that very clearly identifies which are ICH elements and which are regional FDA elements.

Now this element as we said is the FDA report type, is one numeric, conformance is mandatory and allowed values are here. So if you look at this for post-market you typically use 1 and 2, for IND you would use 1 and 6, and then for combo product -- no, combo product, I don't think you have periodic, that's 1, 4, and 5.

UNIDENTIFIED SPEAKER: Say that again, please.

MR. DE: What's that?

UNIDENTIFIED SPEAKER: Could you say that again, please?

MR. DE: So for post-market you have 1 and 2, for IND you have 1 and 6, which is 15-day, 7-day and for combo product you have 1, 4, and 5. I don't we'll have a periodic consult (ph), it's a typo here. So they have 1, 4, and 5. So for this we have to have a new ID which will make sure those values 1, 2, 4, 5 and 6 are there.

Now you may have a question what happened to 3. So the way we use 3 is we use it internally because we have a concept of direct reports which are voluntary reports coming to FDA, that comes to our triage system where we triage those reports because when voluntary reports are sent to FDA it's just not for drugs or biologics, it could be tobacco, it could device, it could be food, so the triage -- when it comes to FDA the triager is triaging that and sending it to the appropriate center. Anything which is supposed to be -- supposed to reside in FAERS comes from the Triage system as 3.

So where they call it as 3 is we call it as direct reports. So we know these are -- because direct reports are very important for our reviewers because

it's the first time information our reviewers are getting. For these all other type of reports at least the sponsor has looked at it. But direct reports are very important because it's the first time somebody is looking at it, so.

All right. Next regional requirement is reporter e-mail. So we talked about -- TJ little -- talked little bit, went over the where it comes from. But again this field is something which ICH does not have and we are introducing this.

Now this has -- actually this field, and I think the previous one, this one has been harmonized with the eVAERS vaccine, okay? And they have -- same numbers have been taken from vaccine and it's C2R28, reporters' e-mail, and this has 100 alphanumeric, free text and conformance is optional. So this field was originated when VAERS was being done. So it did not come from FAERS. So we just took the same properties of that data field.

Patient characteristics. We have race code and ethnicity. TJ did talk about this field, where it comes from. But as far as implementation is concerned,

this has a length and type of 10 alphanumeric. We just took exactly how we have in VAERS and eVAERS, the same allowed values. The conformance is the same and the business rule also is the same. There's no change in that.

If you look at ethnicity, again the data type, data length is the same with 10 alphanumeric, the same allowed values, conformance is mandatory and uses the same nullFlavor. And this is where the (inaudible) when we first started with in drug in CDER, these were optional fields. Then we looked at VAERS. We found that these fields are mandatory but uses a nullFlavor. So we said, okay. We just use it as it because sponsors may have already done their work in that way so we will just continue to do it in the same way.

Another one is patient information. So this is Section D. In here the one which I highlighted and that's the only difference we have between E2B(R3) core elements and FDA's regional requirement. So basically it's no information. Because eventually sometimes you may have like medication errors, you may not have any patient because the -- because there's no information.

There may not be a patient involved in a medication error or you were unable to get any of these data fields like age, date of birth, sex, they're all unknown. So you could use asked but unknown but then you have -- you may not have -- also have and ever have any information so you could use the NI.

Also another thing is you can use MSK because there are some foreign reports where you may have regional privacy restrictions, so that's when you use the MSK identifiers for -- identifies the race of the patient and the patient can have more -- of course the patient can have more than one race but you could use MSK in that case.

All right. So seriousness criteria. So seriousness criteria, we have 5 seriousness criteria but there's another one which we actually have called required intervention which is -- if you look at the Medwatch form you will see that. It's not there in R3. So the properties of this still is like the other seriousness criteria and the properties are it's a Boolean, allowed nullFlavor which is NI, no information if it's true. And then you have -- it's mandatory for

post-market only, it's not used anywhere else. So this is a new -- it's not a new but it's a regional requirement.

All right. Next. Before I go there, anybody -- any questions on any elements which we just went through? Yeah, just ask me as we go through. Yeah, I think we have enough time.

G.k. drug information. So this is another section where we're talking about medicinal product name as reported by the primary source. So we validate that name against the SPL for post-market. And so when the product has an SPL file using the naming convention in ICSRS the name appears in the SPL file, so because we check against that. And then for the substance, again we check against the global substance registration system so which you can submit the name in G.k.2.3.r.1 for substance name because we get more than one substance.

And if the name is on a foreign product trade name and need to provide the -- you should provide the active substance name as it appears in the FDA's, you know, GSRS as G.k.2.3.r.1 because that will help us to

then match up to know the exact product. Of course if we had IDMP at that time -- I mean IDMP then of course you should be -- we should be able to do that. But as we know that we're not already with IDMP so this is how we will try to match up.

Okay. Drug authorization application number. So we have to have a prefix. And because in R2 as well as in R3 there is no concept of a type, right? So I mean ideal would have been a type and a number. But since we don't have a type so the only way to identify if the number is an ANDA number or a NDA number or a BLA number is to provide the prefix. So the prefix would say ANDA and the number or NDA and a number. If you're a BLA then biologic application you have BLA and a number. For prescription product drugs marketed without an approved application, Rx with no application say 000000 which we also do today in R2. For non-Rx no application then we put as 999999, which we do today. And then compounding product we say COMP99. If we had a compounding product then it would submit that way. So this basically is what we do today and we continue to stay.

UNIDENTIFIED SPEAKER: Suranjan, do you see a problem with INDs, if you can have a space in a number?

MR. DE: In INDs, IND because you have the field at the case level we talked about, yeah, so that -- yeah, the space has to go away.

UNIDENTIFIED SPEAKER: We want the space.

MR. DE: No, no, we're going to move the space away.

UNIDENTIFIED SPEAKER: She mentioned the space.

MR. DE: She mentioned the space, yeah, we have to --

UNIDENTIFIED SPEAKER: -- space numbers.

MR. DE: No, we'll have to talk about it to clarify that and when we publish it we'll -- so I think the idea would be to remove the space because that creates a problem. But then again, remember for IND reports it's at the case level. This is at the drug level.

Okay. Now there is another field which we have regional requirements which is G.k. and drug information which is G.k.10.r, additional information

on the drug. So FDA regionally control -- here is the -- FDA's regionally controlled terminology for FDA specialized product category, it's used to provide characteristics associated with the product information. So if you had combination product then you could see it's a Type 1, Type 2 to up to Type 7, Type 9. And so these are the different types which we mentioned in the additional information on the drug. And if you have compounding products then those are the C codes which you would use in the drug G.k.10.r. So this course comprised of both combination product and compounding product.

Okay. All right. Now let's go to the acknowledgment message. We're going to go back because we talked about this when we -- when we were submitting the report. Now you get an acknowledgment back. So in the acknowledgment back we're talking about this because when Meredith mentioned about the pilot which we are doing, we had request from some sponsors saying that, you know, acknowledgment, can you send this back to us so that we exactly know that this was going through the IND route or the -- the pre-market route or

the post-market route.

So then accordingly then we can update our database to know where it is -- what we send and what is coming back. Now you also have the routing IDs, right? But this message is what we -- to this again the consideration is if we had under IND saying ZZFDA_CDER_IND and ZZFDA_CBER_IND, if we get comment and we all decide to go with that then this will also come back, the acknowledgment will come back with the same thing.

UNIDENTIFIED SPEAKER: You're still going to have to develop those (off mic).

MR. DE: Yeah, so we're going to still have two acknowledgments. We're not going to have three. The first one will be the gateway, the MDN (ph) coming up. And next one FAERS accepts it, it's going to send an acknowledgment out.

Thanks for this. So the question was will we have two acknowledgments and the answer is yes. We'll continue with two acknowledgments.

Okay. All right. So any questions on the regional requirements on the data elements?

UNIDENTIFIED SPEAKER: I just have one questions. With your outcomes, are you expecting a null value for everything that's not populated?

MR. DE: No, no information, NI.

UNIDENTIFIED SPEAKER: NI, so you want something populated for everyone (off mic) intervention is also device.

MR. DE: Yeah, but sometimes they use in the medication error side also.

UNIDENTIFIED SPEAKER: We just need to change that (off mic) it definitely says (off mic).

MR. DE: Yeah, but again we have no combination products.

UNIDENTIFIED SPEAKER: That's true.

MR. DE: So --

UNIDENTIFIED SPEAKER: When can we expect the time to be published so that we can --

MR. DE: What's --

UNIDENTIFIED SPEAKER: When can we expect all those times --

MR. DE: To be published? So I will just go back and -- so we will have all that published sometime

between this timeframe.

UNIDENTIFIED SPEAKER: (Off mic) federal register (off mic).

MR. DE: It'll have to go through federal registrar. So but between this -- this is the timeframe when you will -- we will have this published. Now our publish date is this. But as I said in the morning that -- because this is a technical document the clearance process is more like an ANDA process. I'll give an example, like abbreviated clearance.

So this could happen earlier. Could happen earlier. And if it happens earlier we'll publish it. As I said, two documents gets -- three things get published. One is the spreadsheet, okay? Which is something like this. One is a technical specification which is published today, that will be updated with all these new elements. And the third item will be, there will be sample examples of using some case scenarios saying that if you have this type of report and that, this is how your XML is going to look like.

If you have this scenario and that, okay, in this scenario these are the elements, so your XML is

going to look like that. So that's what we're going to put down for -- some of the examples which Meredith gave in the morning, the case scenarios, we can -- we'll include them also in that example. So those will be 3 documents which will be published during this timeframe.

UNIDENTIFIED SPEAKER: So if you (off mic) specification (off mic) details about (off mic) proposed rule (off mic).

MR. DE: Right. So yes, so the Medwatch data elements which will be there they will be included in there. And the Medwatch rules data points which are there, I have not included all of -- not all of them, not included them at this time because it's still not published, so probably by July when we have the next meeting you will probably see a few more data elements in addition to combination products because hopefully by then they all will be available and then we will discuss them there.

And they all will be included in the spreadsheet with its conformance and number and IDs and everything. They will also be provided in the

technical specification. And then of course in the sample examples which we produced, those will be included in there.

All right. Okay. It's almost 2:00. So I think based on the number of slides I have now left probably we'll be done by 2:30. We won't -- probably won't go to 4:00. But after that I have a suggestion, if any questions come up we can answer those questions. But if anybody has any experiences with implementing R3 with other agencies, I would like somebody to speak about some considerations that FDA could take or the challenges they may have faced and how they resolved it. I think it will be a good learning for us to know that so that we don't go that path and able to eliminate those kind of challenges.

All right. So yeah, so the last section was all the data elements. So we go into now the routing mechanisms. Because of IND safety reporting we now have a new routing mechanism which we have introduced. This is what happens today. So we have the trading partners, we have the safety reporting portal, we have the web trader. They all go through the electronic

gateway and then goes into a model -- currently we have the FAERS system which we have the electronic submission module which looks up the data, parses and all, puts it into our system which currently we have Oracle AERS which -- and then eventually we have FLARe which we called it first look at report which are those the triaging which I was talking about. And they goes as XML R2+ and goes into triage system, CTU and which is eventually going into our safety database. So this is the current flow our routing mechanism. So everything comes through this one path and gets into our electronic submission module.

In this the problem which we see is if we submit both IND and NDA products pre and post-market, we wanted to remove the confusion of -- maybe in other words to make it foolproof and safe that these pre-market safety reports are not published publicly. That's the key here. That's the objective here. So in order to do that whatever methods we could take so that they are kind of identified separately in the FAERS database.

So Meredith talked about these 2 methods

today, the trading partner changes, right? I won't go over this but then let me go over the two methods which we have today at FDA. So the two separate routes for submission for safety reports, so Method 1 is AS2 header attributes or the AS2 routing IDs. And so we submit pre-market and post-market safety report using the appropriate attributes and E2B data element IND were event occurred now will be designated specifically for pre-market to route reports.

So this field is required to route reports, so that's why this becomes now a mandatory data field. And when it goes into R3, the data field which TJ talked about, that will become a mandatory data field. Okay.

So in AS2 headers, so the current state is we had CDER, CBER, the destination. We'll have CDER in this case. We have post-market, so CDER, we have attribute values AERS and -- for XMLs and AERS attachment for PDF. When we move to IND it will become A_IND (sic) and AERSATTACHMENT_IND (sic). Now, this is R2 and these attribute values are only applicable to R2 and R3. They are all embedded. So this whole

attachment concept will go away when we move to R3. But this will still continue to be there.

AS2 routing IDs. In AS2 routing IDs we have FDA AERS and FDA AERS attachment. For IND it will become FDA AERS IND and FDA AERS IND attachment IND. And of course it again applies for R2. In R3 the attachments are going to go away. Now this system is right now ready in our preproduction environment, okay? Some of this pilot which Meredith had displayed on the screen actually are submitting in that route and appropriately we are seeing how these reports are getting separated out in our FAERS database. Okay. Now how do we truly segregate in our database? So what we do is our safety reports are submitted by different routes and are stored in different folders. When we pick from that folder if it's picked from the folder where all the pre-market reports are kept, we actually append a -IND to the safety report ID and store it.

But when the acknowledgment goes out, it goes out with the original number. Whatever you sent in the safety report unique identifier. So that also is a

second method of basically making sure that we have very clearly identified which ones are pre-market reports which ones are post-market reports, okay? So this check safeguards the pre-market reports. And all reports as IND postfix will be treated different from the post-market which is without the dash IND. So that's -- now, this we are doing now, we may also -- there was some talk about maybe introducing a internal field where we can mark them as pre-market versus post-market.

So here it is, which we have here. You have the sponsor submission. So the top is pre-market. So the data comes in. It gets into the database and then goes in here, appends the -IND and that's how it is stored. And if you look at the AS2 header and AS2 routing, the underscore IND has been appended.

If you look at the bottom part which is the post-market submission, you have the header as AERS and routing ID as FDA AERS. I think they should be FDA AERS IND, no. Oh, this is a post-market so it stays as the same whatever we had here without the IND.

And then you have the safety report ID which

goes as the same safety report ID. Now the reason why we are doing this because we just don't know what the sponsor is going to submit because remember we had a question of a post-market -- a marketed product being studied, okay, under the IND. So in that case we said to submit two reports.

We don't know how the sponsor stores and report our number, right? So if we had the same number follow-up. You don't want that to happen. So if you keep it separately then that's how -- that's the reason why this is being -- this is being done, to append the -IND so that we can very clearly separate them out. But I think also it will probably future help us to kind of know which report is related to each other. So you have whatever the report number is without the IND if I take this part out and try to match with this I will be able to probably say that.

So this is how we envision the future approach of the triaging of ICSRs electronically would happen. You will have two routing places to be sent to, one for pre-market, one for post-market. So it will be very important where what report goes. Of course since we

are checking for this particular field here, so if accidentally if you try to send this here it will try to check for this field and probably send you a rejection, right? And if you try to send this here, in this case -- in this case we still have to figure out what will happen. I have not even thought -- I've not thought about it.

But I guess when you -- if you send -- try to send this here, this will probably still process and that might -- that might end up in the post-market side. So that needs to be very -- I mean the sponsor needs to be aware of where they are sending the pre-market versus post-market using the appropriate AS2 headers and the routing IDs. Okay.

The setup of IND route AS2 headers and routing IDs are available and here at the two links which you have where you can see very clearly every information about that. And that site has still not been updated with the new IDs because we're still in preproduction. As we go into production you will find the sites when you go to click on this, you will go -- you will eventually see they have been updated with pre-market

and post-market. They have still not been updated. But when you get the slides you will be able to click on this and I think it opens up. Yeah, that's where it goes and it shows you where what is. Okay.

So we talked about the two routing mechanism, how the routing should happen and what would be the setup and how they need to be submitted. So what will be the changes which the trading partners have to do because of this? So basically you have to take into account the attribute values for post-market and the attribute values for pre-market when you're doing R2 because morning you heard about the IND safety reports. Of course when you go into R3 you don't have to worry about this part. You just have to take care of this part. And same thing with the routing IDs for trading partners where you have again for XML and the PDFs. Go to R3, we don't have to worry about this part and we just have to worry about these two.

So with that any questions on the whole routing mechanism for submitting pre-market and post-market safety reports?

Okay. All right. So with that I'll go into

now -- this morning when I was talking about the validator, what does this validator kind of look like. We don't have it ready yet but just to give you some glimpse on how this validator will look like and what all things you can do about this -- through this validator. So I am going to the mechanisms to validate the E2B.

So as you know today, if a company has to come in, a sponsor has to come in and submit E2Bs, still have to go to the -- first you have to go to the gateway, okay? Typically the companies first submit 10 files to the FAERS e-sub (ph) e-mail address, okay? And you get acknowledgment back through the e-mail saying that okay, here's your acknowledgment files. Then you start setting up your gateway ESG in a preproduction site. And once that is done then you would submit and make sure that the whole cycle is going right, right? You got submit the file, you got the acknowledgment, you get both acknowledgments.

And then eventually once you have proven that you have tested that in a preproduction side then ESG will give you a production account. Of course you have

to exchange your certificate and so on and then finally you start your submission. Okay.

So the later two part, probably most of the companies already have that. You have a preproduction environment and a production environment, so you don't have to go through that again, okay? It's the part where you submit those 10 files, so we want to eliminate that process because then you're dependant on FDA to process them and submit them. And what will happen in R3 implementation. So everybody's trying to go to R3. So there will be a whole rush of files which will be coming to us and we have to process them, get the acknowledgment and e-mail it back to you. So rather than doing all that the thought process was why don't we have a public URL where you can either copy or XML and paste it there or you can browse your XML and pick the file and say, "Hey, can I validate this?"

So that's the whole concept of how do we want to do it. So the idea is to provide a mechanism to validate the regional R2 and R3 data element files and of course to convert an R2 to an R3. So if you upload an R2 how will it show up in an R3, right? And then a

mechanism used before production submission. This mechanism case is available through a public URL. One important thing, the uploaded files are never stored, okay? And this whole information will be also available on the FAERS electronic submission webpage.

Now, the documents which we said, the three documents which will be publish all will be all mentioned about in the FAERS electronic submission webpage. That's a webpage where eventually everybody will go to. And that page will be updated information about whatever we have for R2 and plus now with R3. So this mechanism will run something like this where you have the source XML -- oh god, it doesn't show up right. So -- I have to explain this. So this area, there are basically two windows here, this is one window and this is the second window. And what this window is doing is this window says source XML and this window says converted XML.

So you can actually copy and paste your entire XML here or this is -- this is upload button so you can click on this and pick a file which will automatically then show up, the XML will show up here. Once it shows

up here this is the window button called validate. Unfortunately it's showing up here, it doesn't show up very clearly there.

It's a button called validate and a button called convert and a button called download. So if you click on validate, then it's going to then validate against the regional specification. And so this will be validated and -- this part will validated. And down below here it will show you all the messages of what the issues are.

If everything is good then it will say, you know, the validation is -- it's all validated and everything is good. After uploading, this kind of shows you the list of all the error messages so validation messages are displayed after validating against R2 or R3 regional specification. And the list of elements whatever there are issues will list down here.

Then you have something as XML viewer there where now you can see there are certain areas here which are in different colors. This red in color actually is the error within that XML file. And then

you will -- you can actually go and fix those errors here. And if you try -- if you fix those errors here you can actually revalidate again. And once you have revalidated you can actually then download with a download button, you can download that same file and say let me import that into my local database and see how that works out.

So some of these back and forth things which we have to do can be all done by the sponsor before doing the next step of getting the submission done through preproduction to get the acknowledgment back and then eventually to production.

An E2B conversion. So this is where you can take -- convert taking a regional R2 element on this side, clicking on this convert here button, it converts to an R3 based on the forward compatibility where some of the elements that TJ was showing from R2 how it is move to R3, okay? Which you can do yourself and vice versa.

So this is the converter which we kind of -- it's some mock up design now. But the idea is to have something like this available to the sponsors to be

able to test their XML files. So any specific questions, any thoughts about validation and maybe some feature which you may be interested in to just make your life easy. Yes?

UNIDENTIFIED SPEAKER: Suranjan, one of these (off mic) you talked (off mic). So when we are using this validation tool (off mic)?

MR. DE: No. So it's -- basically what it is doing is whatever the schema dictates. So the question is if we place the file here things like product name will it go into SPL and check and validate the name of the product or will it go into the product dictionary? No, it's not going to go into those dictionaries to check. It validates the schema to make sure that the rules that are dictated by the schema is correct or not.

UNIDENTIFIED SPEAKER: So it's not verifying the (off mic) verifying the structure --

MR. DE: Yes, and I'm sure we all know that. Currently today you hardly get rejections from FDA because we just check for data elements to make sure it's a case, most of them. I mean FDA's rules are not

as strict as other regulators. So -- and it'll probably continue for some time -- probably continue, I mean. But, you know, the hope is that one day, you know, as companies are submitting to other regulators, you know, they already have done their checks and data checks and all that on their end. So hopefully the files which are coming to FDA are also in that, you know, post-checked fashion.

So this is actually not checking the data element but yes, I would -- I could say that if you're looking under the FDA type of report which is an OID, which is an FDA-defined OID of 1, 2, 4, 5, 6. Now if you didn't have that right, of course it will get -- because the Schema will dictate that, so it will get, you know, it will give you the error here. It will show the error here.

But yeah, if you -- if you have a product name which you have put in there, that data probably you would want to check to tell you that this product does not -- because again you're testing here, right? You can just put some fictitious product name and try to test this out to make sure that structurally you're

correct. And that structurally you have taken care of all your regional data element, right? So that's the idea here. So with that I think -- yeah?

UNIDENTIFIED SPEAKER: Okay. I just want to make sure I'm following correctly. So your validator is checking all the E2B required, right? And then if there is anything that FDA has now or will in the future as far as a mandatory data element, they will also check for the presence of that but not necessarily the OID and code from -- I'm thinking like patient race categories as an example. So you're just going to say are the elements there that (off mic) are you going to require they have to use that same vocabulary.

MR. DE: Right. I think some of them are dictated by the schema, the way it is defined where you have the --

UNIDENTIFIED SPEAKER: I was thinking like nullFlavors are things that you can select, right, so just a presence of a nullFlavor (off mic).

MR. DE: No, not for a specific one. I mean when you say nullFlavor --

UNIDENTIFIED SPEAKER: -- I'm thinking like,

okay, I'm thinking like (off mic) assessment, right, so you're saying (off mic) earlier part you want each -- you want an assessment for each (off mic), you can't just leave it blank. So there is no assessment, but you have to include NI, right, as the nullFlavor. So would the validator be checking for that at this stage or this is --

MR. DE: No, the validator would check for that, yeah.

UNIDENTIFIED SPEAKER: Okay.

MR. DE: But if you have a data field where you have a name of a medicinal product name.

UNIDENTIFIED SPEAKER: Yeah, but free text -- yeah, yeah --

MR. DE: Yeah, yeah, free text, yeah, that part one.

UNIDENTIFIED SPEAKER: -- free text. But I was just thinking about like in the things that are hard (off mic) but then you also have to use it, correct?

MR. DE: Correct. So if you have --

UNIDENTIFIED SPEAKER: What value or (off mic)

or OID, whatever, well, the scheme of that will be embedded already in the value.

MR. DE: So the conformance rules which you have, right.

UNIDENTIFIED SPEAKER: Yeah, that (off mic) the conformance rules.

MR. DE: Right -- exactly.

UNIDENTIFIED SPEAKER: Okay, so you're going to have those embedded.

MR. DE: Exactly. Because again then you don't -- if I can't do that here then there is no point because once I submit the file there will be a rejection and you don't want that happen, right? So if you can get all of that caught here and they can fix it here then there is -- then when you submit into production then, you know, it's going to move through.

UNIDENTIFIED SPEAKER: Okay. All right. That's (off mic). Thank you.

UNIDENTIFIED SPEAKER: So will the same thing be true (off mic) choices, they're going to actually check the choices.

MR. DE: Right.

UNIDENTIFIED SPEAKER: So your (off mic) to check the (off mic).

MR. DE: And any free text, right, because sometimes, you know, some free text are such that it goes and checks against some dictionary in the back end. That probably -- that won't happen. But anything which is defined in that schema with the conform is what we just talked about. Those conformance will be there.

So if you looked at like race, ethnicity, right, it has a conformance that you have to use these values. That's the conformance, right? So it will check that.

UNIDENTIFIED SPEAKER: Of course. Just as a clarification, so basically it's validation of rules that will eventually accept parsing of the data (off mic) down the road before data is stolen (off mic) underlying database. So you can make all these changes (off mic) so after filing due process it will be accepted by the FDA (off mic).

MR. DE: Correct. So yes, you're right. So what -- the idea is that if I didn't -- we didn't have

that and sponsor submitted that then every time we have to go back and forth, I mean we'll probably find, okay, these are list of all the issues and now you fix it. You fixed it but then you miss something. Then again you go back and forth. Before that you do this back and forth, you would have checked all these and then submitted against that, right?

Now yes, if you had submitted a product name and the product name was not in our dictionary, right? Yes, what we will do, that report will typically stop for someone to take some manual intervention. And we have a whole dictionary team who works on that to make sure that is taken care of because as you know that for post-marketing all suspect products are coded to some name in our dictionary. So that part will probably still go and continue the same way. But we want to make sure that ones which are very well-defined data which has very well-defined conformance rules, they're all pre-checked before the actual submission is done.

UNIDENTIFIED SPEAKER: I have a question. I would integrate for the nation for the same province as well because right now (off mic) system in place isn't

going to be one-stop-shop for the nation for all the products we just submitted to FDA including --

MR. DE: So right now we have -- since we have not harmonized all the data element with vaccine. So this probably is not going to have -- the schema itself may not have the vaccine elements available now. As we are moving through data elements which is required by FAERS, okay, and these regional elements, we're trying to find out does vaccine already have that. If it has, let's take that element. But we will probably reach a point where we'll say, you know, FAERS doesn't need any more data elements. Okay, FAERS is ready.

Next is let's work on the vaccine element as to what is that delta we need to get in. Now when this goes to production we may not have the vaccine in there. It will at least have regional elements which probably is just required by FAERS -- required by both FAERS and vaccines and the core data elements. That it'll have.

And as we decide -- because just getting vaccine is not straightforward because vaccine has a whole database in CBER. The whole database has to

gotten -- has to be gotten, then you have the whole e-submitter process. They all have to be looked at how it's going to flow. And you have reports coming directly to be -- you have e-submitter and then you have CDC where you have the voluntary direct reports which are coming in.

So they all have to be looked at before we can say we can transfer that all over into FAERS. So -- but the path to move forward is as we look at new regional elements make sure that it is there in AERS (ph) or not. And if it is there, can we get that? Exactly. Yeah?

UNIDENTIFIED SPEAKER: (off mic).

MR. DE: So as I said -- so the question is, are we going to check validations like, you know, one date is greater than the other date or one date is less than the other date, so on? So currently as I said that our rules which we have does not have these kind of rules which we don't do it in R2 today, so it will probably not happen in R3.

The only rules we will comply -- not comply -- only rules we will check moving to R3 are the rules

which are based on the conformance rule which will be in their spreadsheet, okay?

It's -- I mean, and for -- I don't know if you have looked at the regulation, it's -- regulation very clearly says the four data elements makes a case, those four data elements needs to be there, right? And that's what we do in R2 today, okay?

I think another field which we do check is the narrative. The narrative, it is empty, I think today we give rejections for that. But otherwise valid patient, reporter, product and event is the four elements we check and we'll continue to do that. And anything which the schema now dictates is going to be available. Any other -- yes?

UNIDENTIFIED SPEAKER: Yeah, the previous process was formal in the sense that it was (off mic) this is kind of more informal. But I guess (off mic).

MR. DE: So -- but you have to realize, when I talked about the testing plan you have seen there is one bullet point which I said that in pre-production environment you will do a submission to submit file and get the acknowledgement back. So that will give you

the entire path. This is just before you're doing the submission. Rather than going back and forth, back and forth -- because I'll tell you what will happen during that time. Every company is trying to test. Every company will be submitting saying that, "Hey, can you test my files? Okay, I'll give you my files." And it will become a backlog for FDA for testing all of them. So the idea would be if you could go here, check it out, test it out, everything is fine, then do the pre-production, that keeps a record that you have done your testing through a process where you have submitted a file, FDA has processed it and you have got an acknowledgement back.

UNIDENTIFIED SPEAKER: This is like file till the program (off mic). So let me ask you this then, if I were to (off mic) and then I do (off mic) R3, it's going to create a file (off mic) where is that? That's when (off mic) environment then?

MR. DE: Yeah, I think it drops it and then you can -- if it converts it then you have a concept of downloading it. So once you have downloaded it then -- once you download it then the file is removed.

UNIDENTIFIED SPEAKER: Okay. This is test data only?

MR. DE: This is test data only.

UNIDENTIFIED SPEAKER: And you can put banners all over that --

MR. DE: Yeah. I mean as I just said, this whole thing is more like a mock-up which we have kind of done and then once it becomes real of course it will all have the disclaimers and all that.

UNIDENTIFIED SPEAKER: And will this work for both the IND products and --

MR. DE: Because the scheme is one, DTD is one, right? So one schema, you have one DTD, so it will -- has to work on that, you cannot have separate. So I mean that's the whole idea, is to try to harmonize all of them together. And believe it or not, every Friday we have a meeting with CBER where we are actually harmonizing -- trying to harmonize all that elements as much as possible so that we can get into that one -- end of the day the goal is to have just that one big spreadsheet where it will only have items saying ICH or FDA, that's it. So that's the goal.

Yeah?

UNIDENTIFIED SPEAKER: So Suranjan, (off mic) earlier that you will publish (off mic) test (off mic).

MR. DE: Yes, yes. Yeah, so the question is that are we -- FDA is going to post some sample XML files? And the answer is yes.

UNIDENTIFIED SPEAKER: I think one of the things that we found that was helpful (off mic) is that they make (off mic) uses cases that (off mic) specific to your company that might not (off mic).

MR. DE: We would really appreciate that. And believe it or not, those use cases which you saw that Meredith had put, they all came from sponsors actually. There were one or two which we thought about, but then the sponsors said, oh, you know we have a situation like this or we have a situation like that. And I e said, OH, yeah, makes sense. Okay, we will test that situation, let's test that situation or let's test that use case.

And we would -- we would definitely -- definitely would want sponsors to provide us with some of those use cases because they know better those use

cases and they have exceptions. And so we would really, truly appreciate if they can provide us with those use cases.

UNIDENTIFIED SPEAKER: And so then my question is how could other companies or software then become aware of the feedback that might come --

MR. DE: So in addition to these three documents which will be posted we will add in a Q&A link. As we are going through this whole process we're getting -- we're going to get new questions. And just to add that when combination product came out, with combination product we had so many questions which had come out.

Many organizations gave lots of questions. We were just responding back to that organization. And recently -- right now I'm actually working on updating that Q&A to make it little more generic so that this could be now shared with everybody and they can see this typical questions which are asked. So same concept will work for that because what will happen is you will typically start working as we -- when it comes to the March 2020.

Or if the specifications are published prior to that, you may start asking questions to us. But typical testing as you saw on the timeline that when we are ready with this available and we are ready to accept you will probably start testing.

And as you go through questionnaires, as you go through questions, we will document that and start posting that on to the FAERS electronic submission fda.gov webpage where you can then look at these questions and answers.

UNIDENTIFIED SPEAKER: So right now this is more (off mic).

MR. DE: This is -- we want to get this ready by December. So if you look at this timeline -- let me go back to the timeline, I think it's -- so this work will probably -- we'll finish it by, normally by this time, right, because we have to --

UNIDENTIFIED SPEAKER: (Off mic).

MR. DE: Right, because you're testing -- by the time we put it into production we will be here. So when I say production means -- production means we are ready to accept today R3, okay? And that this public

URL is available.

Now, the idea of having these three meetings here is to hear from you so that when we put something here, okay, hopefully we really don't have to do a 180 degree turn. So that's the idea here.

So with these three public meetings we are at a state where we can say, hey, we have heard from sponsors, we have heard from vendors and now we are at a point I think we are probably quite steady with the specifications. So should not be too much of an exception when we reach March 2020. That's the idea.

UNIDENTIFIED SPEAKER: I just have a comment. ICH did that spreadsheet, right, all those (off mic) cases, right (off mic) go ahead and use now, is that (off mic). And then for FDA on e-ver (ph) site you have some test files (off mic) still available, like for example (off mic) elements for example. That's already out there where you see where it shows that for the XML file. And then obviously you have (off mic) any XML editor they can (off mic) for example where you can take your own XML file blow (ph) it against the schema file that are also available.

MR. DE: Available.

UNIDENTIFIED SPEAKER: And you can kind of do some sort of framework now. And then when this validator is ready --

MR. DE: Yes.

UNIDENTIFIED SPEAKER: -- have a file that you can kind of look around (off mic) 3 or 4 months but then can kind of log in and then just plug in the rest of the stuff that's missing (off mic) by that time in terms of the additional data elements because lot of the stuff that you already, you know, like the batch ID, DUNS --

MR. DE: Right.

UNIDENTIFIED SPEAKER: -- things like that, that's already published, correct.

MR. DE: Yeah, that's already published, yeah.

UNIDENTIFIED SPEAKER: -- try to do to help yourself along.

MR. DE: True, true, true. I mean, some of the data points which I explained there, they're already there. It's like the type -- FDA report type, that is something which is new. But when I talked

about the DUNS number, and then I talked about, you know, race, ethnicity, they're all currently published and they're already there.

UNIDENTIFIED SPEAKER: All that stuff is already out there (off mic).

MR. DE: Yeah. Exactly, exactly. So again, as I said, this timeline is available. The slides will be posted so you can always share this timeline with your organization and your colleagues. So finally going back into this. All right. Any questions on the area of the validation? Any suggestions you have on validation, if we can do it, anything better, please do comment through the docket. I will really appreciate that. Maybe something we may not have thought about that right now or you are -- you have not thought about it right now. Now you can go back and talk to your colleagues and think about it, so please do comment on that in the docket, I'll really appreciate that.

So with that I'm just doing some summary and some closing comments. We basically planned -- have wanted planned for a fifth session which was somebody to come and basically present to us from the sponsor's

side as their experience with R3 implementation. Unfortunately because of this whole meeting which got cancelled in January and got -- we did in March, things got messed up there.

But for July if anybody is interested to come and present, we can give them 60 minutes. Come and present about their experience in implementing R3 with other regulators. We would really appreciate that. And you could send an e-mail to eprompt@fda.hss.gov to let us know. And then we can definitely accommodate that on the next meeting.

So today with Session 1 we went into talking about some of the plans. You saw the timelines. And then we -- our production date will be March 2020. Currently very -- we want to be very clear, currently no compliance timelines have been set for it to be R3 by FDA.

And we talked little bit about -- discussed about the testing plan and the methods. And one of them is all this validation we are talking about. Session 2 today we talked about the electronic submission of IND safety reports. We did the

introduction of IND safety reports to FAERS and then to the FDA. We also provided information on the implementation plan which Meredith. Regional requirements in R2. And then TJ talked about R3. Meredith did talk about some use case examples. And then we talked about the R2 to R3 transformation and then IDMP, okay?

So we talked a lot about IDMP. And hopefully the talk which TJ gave, the idea was kind of give a general understanding of where this data elements from the model we're picking up. And so how the expats will eventually look like. So that was the idea behind that presentation.

Session 3 I talked about on the post-marketing side all the regional data elements for R3 and what are their properties, what are the conformance rules which we have. As you saw that not too many data elements which we're adding here. I mean most of them are already -- have been published.

And then finally the Session 4 we talked about the routing mechanism for pre-market and post-market. And then we got into the mechanism for industry to or

sponsors to validate the E2B R3 regional files based on this regional schema which we will publish soon.

Now, what do we do next? So what do we do next is today's presentation we'll post it on the FDA meeting page and the recording which is happening here will be posted on the FDA meeting page. We invite comments on today's meeting to the docket and by April 25th, okay.

So it's 30 days from the meeting date.

We will start updating the schema with the regional elements if we -- when we hear things -- when we see things on the docket we will -- we want -- we will go ahead and update that. Along with that we start updating the FDA regional implementation specification, incorporate the comments we receive via the docket.

Our next meeting is the 17th where we discuss combination product plus any new elements that got added to the Medwatch as part of the reauthorization.

We start preparing some regional sample E2B R3 file, the schema file and so on based on whatever use cases we have now. And then after the docket timeframe if you have any questions please again submit to eprompt@fda.hss.gov. And so there are folks who are

monitoring this mailbox, and so we will respond back as we get these questions.

And so -- and any suggestions if you have for today's meeting, anything you want us to do differently, anything where, you know, you want to present, please shoot an e-mail to the eprompt and we will make sure we look at those suggestions and then work on, improve on in the next meeting.

After July, the last -- after July, the last meeting will be in February of 2020 before we go production because at that time we want to just make sure that we will summarize all these what we have talked about in the two meeting and go over in that third meeting and just make sure we are all on the same path, we all are thinking the same way. And the idea is that we have -- we are not turning 180 degrees after the third meeting.

So it's very important that we are all on the same page, and that's the whole purpose of having these e-prompt meetings. As we go through these meetings we will -- next meeting we will also update the timeline as to where we are, how far have we reached, so we'll

get an idea of where FDA is.

And so with that, if anybody has any questions we have -- I've tried to pull it by 2:45 p.m. Not bad. Any questions, please? And if not then we can adjourn the meeting for today.

UNIDENTIFIED SPEAKER: Suranjan, thank you so much for the discussion (off mic). Thank you.

MR. DE: No, welcome. Everybody welcome. And -- all right, thank you so much for attending. Really appreciate everybody's time to come here. And we will continue the dialog and successfully implement R3 at the FDA. Thank you so much.

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, 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 o

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Notary Public in and for the

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I, ANOSH KURANE, 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.

ANOSH KURANE

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