FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

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

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Moderated by Suranjan De, MS, MBA

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Location Remote Meeting

Baltimore, MD 21201

Reported by: Richard Livengood

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A P P E A R A N C E S

List of Attendees:

Suranjan De, MS, MBA, Deputy Director Regulatory Science Staff (RSS), Office of Surveillance & Epidemiology (OSE), CDER, U.S FDA

Y. Veronica Pei, MD, M.Ed., MPH, Lieutenant Commander, U.S Public Health Service, Associate Director of Biomedical Informatics, Office of New Drugs (OND), CDER, U.S FDA

Jung Lee, R.Ph., MPH, Safety Officer, Division of Clinical Safety and Surveillance, Office of Safety and Clinical Evaluation, Office of Generic Drugs (OGD), CDER, U.S. FDA

Kelley Simms, PharmD, MS, BCPS, Regulatory Policy Analyst Regulatory Affairs Staff (RAS), OSE, CDER, U.S. FDA

C O N T E N T S

P R O C E E D I N G S

THE REPORTER: This is Tuesday, April 4, 2023, at 9:00 a.m.

MR. DE: All right. It's nine o'clock.

All right. Good morning everyone and welcome to the first ECOM meeting in 2023.

So we are excited to discuss reporting pre-market and post-market safety reports to FDA using ICH E2B(R3) standards. My name is Suranjan De, and I am the Deputy Director of Regulatory Science and Office of Surveillance and Epidemiology in CDER, FDA. So welcome, everyone.

If you don't have the link to the site, you can go to the FDA meeting page and you will see the Zoom link there to be able to connect, so.

Okay. So we can go to the next slide. This is the disclosure as well as the second overview.

So what I'm going to be able to talk today, certain review requirements for submitting safety reports for IND-exempt BA/BE studies and approve drug and eligible biologic products, excluding

vaccine, we're not going to be talking about vaccine, using the ICH E2B(R3) format and submission records and the -- and we will highlight the regional extensions and talk a little bit about the implementation plan.

Today's objective is to recognize that FDA will require the working of IND and post-market safety reports to be submitted and ICH E2B(R3) format. We can let you know when that all will happen in the implementation and that via FAERS, the Gateway or through the safety reporting portal and understand the detailed regional data elements that are key for post-market IND and IND-exempt BA/BE safety reporting. Okay.

So before we go, I go into introducing the speakers, I want to communicate some housekeeping items. This meeting is for about six hours from 9 to 3 p.m. We going to have two short breaks and one lunch break. And you can submit your questions in the chat or through the Q&A throughout the meeting and we will address them during the Q&A time at the end. So

we have got some time at the end to talk about questions and answer or response to your questions.

All right. So who are today's speakers? So first, I am Suranjan De. I will be talking about mostly on the regional requirements and specifically the post-market safety reports. I will also be talking about the reporting mechanisms, some implementation plans. So I am the Deputy Director of Regulatory Science Staff in Office of Surveillance & Epidemiology in CDER.

And later in the afternoon after lunch, we are going to have two more speakers. One will be Veronica. She is going to be talking about the IND Safety Reports and how they're to be reported using ICH E2B(R3) standards. She's the Associate Director of Biomedical Informatics in office of New Drug in CDER.

And the third speaker is going to be Jung Lee. She'll be talking about the IND-exempt BA/BE Safety Reports and how they're to be reported using ICH E2B(R3) standards. So and Jung Lee is a

Safety Officer in the Division of Clinical Safety and Surveillance, Office of Safety and Clinical Evaluation in the Office of Generic Drugs in CDER.

Okay. So here is the outline for today's meeting. So we have a packed agenda. We are going to be talking about some of the regional implementation of E2B(R3). And then, also talking about submission methods and mechanisms. After which we will take a 15-minute break, so around 10:15. Then we go into talking about the E2B(R3) implementation package. So this is the regional implementation package that FDA has published on the page of the FAERS Electronic Submission webpage, and we will talk about this package and will start basically sections such that, you know, one will be relevant for pre-market, one will be relevant for post-market and so on.

Then we will talk about the common regional extensions, so again, the regional extensions will be the regional changes and we'll go into all the different types of report is what we will talk just

before the lunch break. There will be a lunch break from about 11:45 to 12:30.

And then talk about the post-market safety reporting. So here we will go deep dive into the specific elements, the regional elements for post-market safety reporting. Then we will have our speakers for IND Safety Reporting and our speakers for BA/BE studies safety reporting for generic drugs.

Next, we will talk about the validation and implementation which will also include things like, you know, what are the plans of implementation where we are right now and what are we doing. And also talking about some of the rejection and warning rules we will talk about here with that implementation. Then we go into a small break, 15-minutes.

And then, the last two areas we will be more talking about, you know, the OIDs and how FDA has defined OIDs for the regional data elements and what are these OIDs and how these OIDs are defined. Then we go into talking about the regional forward

compatibility. Now this is more applicable to post-market because pre-market, you know, it's all comes through ECTB today. So Post-market is the only thing, which is in R2, and how can you move to R3. And finally, I will summarize everything and then go into our Q&A. So that's the agenda for today and with that, let's dive into the first slide under background.

So to give you a little bit of background in where we are, where we were and where we are going towards, that is this was about a few years back, about three, four years back, we had started doing some work with E2B(R2) and for pre-market. We already had post-market. We were planning to do with pre-market, then we came into the implementation of FAERS and during the implementation what we realized was, you know, if you do R2 with pre-market first and then go to R3, it's a lot of burden.

So our initial plan, as the slide says, that we had initially planned to implement E2B(R2) for pre-market and CSR reporting and then move to the R3.

The initial plan changed and now FDA will implement E2B(R3) for both pre-market and post-market safety reports at the same time. Okay.

Now, this change was decided based on the complexity to migrate from R2 to R3. Now, of course, we have got some submissions from industry where they all thought that it's better to all move to R3 for both pre-market and post-market.

So this change pushed the timelines as there were dependencies like update and clearance of the final guidance, which is a 745A. Also, we had to update the technical specification, so to make sure that all the regional elements that we have for the pre-market safety reports were all defined and set up and published.

Of course, we were dependent on vendor timelines to make sure that the regional requirements are in the tool. As we all know, everybody uses vendor tools today to do their safety reporting and manage their safety database, so we are all dependent on our vendors. So yes, we did have the dependence on

the vendor timelines. And so with that, we had to come with a new date.

We are still in the process of implementation, so a new date for quality reporting will be communicated soon on the Electronic Submission webpage. Unfortunately today, I cannot give you a date, but as we are working through the implementation, we will provide you a date as we come closer with our implementation.

But remember that, any kind of implementation, such implementation, once the Agency FDA implements and our sponsors had over two years to implement from their side, so you will have ample time to do the implementation, so. So once we have a date -- a fixed date, we will definitely communicate that date.

All right. So next, let's talk about the regional implementation. There are some important items that we need to discuss in the regional implementation. And so the first item is a standard status supporter. So standard status support, the E2B

standards that everyone supports is E2B(R3) for pre-market, both (R2) and (R3) for post-market.

At some point, when people were gathering the submission of post-market reports in (R2) format and this data's yet to be decided. And this will be, this data will be decided based on how soon companies move over from (R2) to (R3). So based on that, we will decide a date and communicate that date. Okay.

Additionally, the information about E2B(R3) testing and implementation will be made available on the FAERS Product Submission page. We're going to talk about the standard implementation. What we're talking about is how do you prepare with E2B(R3). You will want to test with the Agency. And so the information about that testing will be made available.

This testing would typically be done using the Gateway, okay. And this Gateway you will have, most of the companies, I think, sponsors do have a pre-production, or a test account and the same test

account can be used to do the testing, except that the login ID would have some change, especially for pre-market, and I will talk about what those login IDs are or the AS2 headers are. But that is what will be posted. Some of the information has already been posted on the technical documentation, which you can always look at.

One definition is we call as a regional extension. So every time you will see in every technical specification document, this word, "regional extensions" are mentioned. What does it mean? It refers to FDA's data elements and terminologies submitted in the ICSR file in addition to the ICH E2B(R3) data elements.

So many times, you may hear me talking about four ICH elements, so these are the elements that were defined by ICH and regional extension, or regional requirements are the specific requirements that FDA has.

Next is, as we move through the implementation, there is a recommendation we want to

review. And the recommendation is that whenever you create an XML file, there is, you know, a data element. There is a value called display name. We recommend that to facility human and computer system identification and understanding, if you can put the display name with the name of the field will really help us in understanding, you know, if there was any issue with XML and understanding the XML. So a small example is given at the bottom in the left corner where we display the ethnic group, so the display name is ethnic group basically displays the name of the field. Okay.

And lastly, this is one very important thing to remember, things appear, are the -- are, you know, the SUR what would be you submit to FDA. This is the scripted portion of the safety analysis. The scripted portion must be submitted using eCTD. Okay. The scripted portion cannot be submitted through FAERS. I have had many questions asking about the FAERS, you know, will that change? And the answer is no. That is not going to change. You will continue

to submit the scripted portion to eCTD. But E2B (R3) ICSRs will come to FAERS, so please know, remember that. And this is very important and just making sure that we all understand. And please do not submit the E2B (R3) ICSR, which are those XML files to the eCTD. You may get the MDN first, but you will not get the second acknowledgement and that will be something that, you know, that can go nowhere.

Okay. All right. So moving ahead, acknowledgements. So acknowledgement of -- the two acknowledgements that you will get, the first acknowledgement is the FDA's message, delivery notification, which we in shop call this as an MDN, which comes from the Gateway. And the second acknowledgement will be the acknowledgement that you will get after FAERS has processed the data of XML file, has passed and processed, and the second acknowledgement come after that. We hope to -- we have send the second acknowledgement within 24 hours of your submission. You know, you could get acknowledgement sooner, but it all depends upon the

size of the file, as we all know it to be (R3) XMLS have now increased in size as part of embedded attachments and, of course, how many ICSRs are you sending in a batch. Based upon that, we're saying that within 24 hours you should get an acknowledgement, but you could get it sooner.

There was one change in the acknowledgement message that we have updated as a regional need or a regional extension. That's the data element ACK.B.r.7, which is for error or warning message or comment. So the maximum length, I think, was 250 characters. We have extended that to 2000 characters so that we can accommodate, you know, more messages if there were issues with the files. And also that we have errors and warnings, and we will go over what those errors and warnings in one of the slides, but they're basically that errors means, you know, the file will be rejected, and warnings means, you know, we will give a warning, but we will still accept the file. Hoping that sponsors will correct the data in the next follow up. Okay?

And for information on ICH and regional extensions, please refer to the E2B (R3) for regional data elements and positions. Now, I will basically pause the slides here and kind of go into -- go into explaining you a little more about what the E2B (R4) regional and data elements in business rules are.

So here, this is an Excel spreadsheet. And this Excel spreadsheet, and all of this document is available on the FAERS on the Product Submission page on FDA.gov. This is an Excel spreadsheet listing all data elements, their attributes, their conformance, the business rules, the rejection and warnings and the x-facts. This document is the key document for implementation. This document, also you will see that the ICH data elements has a source -- sorry. The data elements has a source that will say either ICH or FDA.

If it says ICH, the piece is set-up up for ICH data elements. If it says FDA, that means it's a regional data element. Every -- has an element number and an element description. The element number

that starts with a prefix of FDA has other FDA regional extensions. But also there are some data element which are the core ICH data element in conformance with they after due to regional extensions or regional needs, and they are usually -- yeah. And they are usually noted in this particular spreadsheet.

Also, this data elements spreadsheet also list down all the observation codes for the regional elements. It will also list the rules, which are the warning rules, rejection rules, and it'll tell you what the message for these -- if these rules are not complied with, what kind of message will you get. And exactly that the message that will come in that data feed, ACK.B.r.7. And it will tell you the different messages for each of the rules. And then there are some standard messages that you will also see, which talks about, you know, if a data feed was required but was not submitted, if a data feed did not comply to a list of observation codes, or a data feed went when the value was created and what's in the specification. So those are some general rules that

you will see in this document. And also, rules that this document is the key document for this implementation, because everything about the data in this document is there. And also out recommendation would be also that as you are doing an implementation, if you find anything that is -- that the grid will not be -- proper -- may not be set-up right or maybe the message is not very clear, please let us know and we will work through this with you to, you know, update this because we are in the process of making sure that as we go through we correct things, we have to correct things, and then do it right. So this is a very important document for everyone to use.

All right. The FDA data element conformance, as I said already, and one most important thing is that we have got many questions asking that when we will accept the country code of EU. And as things are going -- getting -- looks like difficult with the EU where they do not want to disclose some of the data elements, the country code UE is acceptable to FDA. We have to have spot of our codeless value

and for different data points where country code is used, yes, EU is acceptable. Okay.

We also have got messages from, as we talk about the country code, EU, we also have got messages that EU coming up with all these rules. How would -- how will that impact FDA. As we go through this, we also working with the -- and this all started with vaccine reporting, but we are working with the EU to come up with some kind of resolution for these types of -- for these types of rules where things have to be adapted to send to other regulators, including us. So we are working with them and hopefully we'll come with some solutions very soon. So until then, you know, whatever you have, keep submitting that to us.

All right. The controlled terminologies. So controlled terminologies. So these are kind of dictionaries and -- and kind of are also, you know, data -- data that we use in our ICSRs. And we also look at, you know, some of the, you know, attributes and like codeless observation codes for

which we use controlled terminologies. So these are the list of controlled terminologies that FDA's using, so we have it in CIA Enterprise Vocabulary Service -- Vocabulary Services.

Now this is used, particularly for many of our regional elements that we have and that's where we point at the relevant two. And as we all know that controlled terminologies are used because we as ICH or FDA, to not want to keep controlled terminologies because if there's any change, we have to worry about that change, versus if we have standard organizations who manage these terminologies we respond to them, and they have the responsibility to manage those terminologies. So in set-up, EVS as a set-up is mostly for our regional elements that we have used. Each of the terminology, actually datapoint, data element, you know, they will have you see a C code to start with the alphabet capital C and then a number. So every reference on the technical specs of the spreadsheet, if you see that C code, that means it has been taken from NCA EVS.

We all know by drug, which we use for coding our events, our tests, results, pre-existing conditions and so on and so forth. You have UCUM codes in the measures. So that is, again, we use the UCUM codes. EDQM for a lot of our administration and dosage form. Then we have device for our code, the ProCodes that we use. Then we have device common codes, that is also we are using, so we have the IND and the FDA codes so any of those codes can be used.

Then we have the Global Substance Registration System, which is the GSRS, so we using the unique codes from there for the substance ids. And then, of course, we use a Structured Product Labeling, so this is something that is used for mostly the post-market reports so this is also, we will go into this Structured Product Labeling, so I will also recommend that, you know, this will have a Structured Product Labeling as your submitting because based on the name that you submit with the SPL, that's the naming you use to populate our dictionaries and the make sure that when the reports come in, ICSRs, we

call to that product and many times we do see that the name in the Structured Product Labeling does not match with the name that has been submitted with the ICSR. So this is a request to the sponsors that please have them check and that and make sure that the ICSRs that you submit and the product names that are in the ICSRs match with the names that are in the SPL that are submitted.

So I scheduled in a few views of the controlled knowledges are noted and defined in the relevant section of the technical specification. Okay?

All right. Go to the next slide. Okay. Here we will talk about submission methods and mechanisms. So with submission methods and mechanisms and this is a very important topic here, because as we go into implementing E2B (R3) for pre-market, you know, we have to have come up with new, you know, mechanisms of solution. So we actually have three methods. So here's the first method option A, which is via database-to-database transmission. So we call

this a database-to-database transmission is nothing but you submitting through the Gateway. Okay. So you would have a sponsor, the sponsor would submit and XML, and E2B XML, which would come to the Gateway. And the Gateway will send the first ACK, which is the center of the picture that you see, ACK 1, which is the MDN, which will be sent back to the sponsors.

This XML file is sent to FAERS and the FAERS database will process that and send an acknowledgement number 2. This acknowledgement 2 is then, it can be sent to the Gateway by to -- from FAERS and then the sponsors would be able to get that acknowledgement 2 and the loop is closed. So this is the first submission mechanism that we will have. Now, this mechanism is already available today with post-market safety reporting. We will use the same mechanism for pre-market safety reporting, so we don't have to learn anything new, except that we have to have the right routing lead so that we know that pre-market goes to certain, post-market goes to a certain location and pre-market will go to a different

location. So that they can pick it up and recognize that it's a pre-market report or post-market report.

All right. Now, companies or sponsors do not have, you know, do not have the process of connecting database-to-database through the Gateway. The can use option B, which is via the Safety Reporting Portal. Okay. So Safety Reporting Portal is where some submitters enter the ICSR manually into a web-based form. Okay. And submit. In such case as soon as you hit on the submit button, ICSR basically, in general in the back end, that means that you do this in the back end in XML and then send to the Gateway and the same process happens, but in such case the acknowledgement is basically an email that you will get from the Safety Reporting Portal to say that the report was submitted successfully, here's the report information and that's very good that you can keep for all that that you have submitted the report.

Now, Safety Reporting Portal. The only problem -- difference between Option A and Option B is that you can only submit one report at a time in the

Safety Reporting Portal because that's a web-based form. Okay. Now, the in Safety Reporting Portal, you can also upload attachments, so that's not a problem, and also requires some kind of registration. So unless you have registered and received the credentials, you cannot submit to the Safety Reporting Portal. For database-to-database also, you have to send the certificates and all that that you have to do.

One thing in which I may want to point with Option B is, you know, Option A has the web-trainer which you can use for testing and especially I would want to mention this for typically the tool vendors. Many of the tool vendors who have asked FDA that, "Hey, can we test E2B (R3) when FDA's implementing this?" And we always have challenge that, you know, we never give, you know, traditional account to vendors. Always traditional accounts was given to, you know, the sponsors. So I have verified, and vendors can request for the traditional account. So there is a process of requesting, which is

available on fda.gov and users can actually request for a traditional account and can submit E2B (R3) standard XMLs, which we can then test in FAERS. Please note, that web-form account you can submit one XML at a time but please note that you can only get an account for testing purposes only. You will not get an account for production. Only for testing purposes. I think the advantage here what we saw was if one vendor, you know -- vendors can test the vendors tools are used by sponsors so indirectly, we are also able to test, you know, from different sponsors, so.

So going to the next slide, submission with XML. I added Option A and Option B as listed. Submissions -- submitters, listed as database-to-database transmission capability, may directly submit ICSRs in XML format via the Electronic Submission page. And Option B you will require registration, you will have to receive the credentials and typically when you do registration, you will fill up a registration form which will ask you for your organization information, who the users are going to

be, who will be submitting data. It will also ask you for on which products you will be reporting and then eventually, we will make sure that those products are in our dictionary, and then you will get a login credentials.

It normally takes about five to seven business days to get the login credentials. So if you are planning to submit to Safety Reporting Portal please plan ahead so that you can -- you can get the credentials on time. You request for this credential, I think I have an email address, which I'm going to show that to you in the later slide.

Submitters enter the ICSR information manually into a web-based form and submit. So you will see a screen, you will see, you know, what type of reporting you're filling in, if it's a post-market or a pre-market and then we go to a form to enter the details of what the report, the patient, the suspect products and so on and so forth. The events and so on and so forth.

You can upload an attachment. Again,

the very important thing is please do not upload E2B (R3) XML or XML attachment through Safety Reporting Portal. It will -- that will not ger processed. So please do not upload right there. And also, as I said, please do not send the XMLs to the eCTD as a document. Okay?

Submitters ISCR uploaded into FAERS database, so which means once you submit, that data goes into FAERS and gets loaded into the FAERS database.

All right. Very important, highlighted here in yellow. Okay. Do not submit ICSRs via both options. Always stick to one option and here why is why I said, sometimes how sponsors have a situation where their database may be down or the Gateway may be down and they will then send to us information saying that, "Hey, our Gateway, we are not able to send, our database is up, but we're not able to send a file so for which can we get an account to Safety Reporting Portal and be able to participate through the Safety Reporting Portal?" Now, that creates a problem

because once you submit to the Safety Reporting Portal that report will go in FAERS, and then the next follow up you will try to run through the database from database, when the connection is up and running, you will submit to that. Now, that creates multiple versions in our database. So we say that please do not use both methods, unless -- unless there is a dire situation where your database in your organization -- a database in your organization is down due to attack and that -- and that you are not able to operate your database. In such case, we may give you, it's not guaranteed, but we may give you the option to use the Safety Reporting Portal to submit, you know, and process your reports.

If you have a situation where your gateway isn't up and running but your safety database is up and running, in such case an electronic safety reporting rule mentions that you can use physical media, which means you can take your XMLs, load it on a CD and, you know, mail it to us and we will process those XMLs. Same thing would happen once we go to E2B

(R3), if you have that same situation. Okay. But please, please do not use both methods or both options to submit your reports. Always stick to one option.

Okay. So some other areas about on the Safety Reporting Portal. So companies who would want to use Safety Reporting Portal, and especially, you know, we have seen CROs using Safety Reporting Portal, we have seen some sponsors who have low volume reports who don't want to invest on the Gateway -- Gateway and use Safety Reporting Portal. So advantage here is Safety Reporting Portal are intended for sponsors and CROs without infrastructure for direct -- do not have infrastructure, for direct database submission. So and individual reports only, so you will basically submit individual reports one at a time. You cannot do a batch.

It can be used for both commercial and research findings safety reportings or as we go into post/pre-market safety reporting. It can be used for both commercial and research. This is not available for vaccine reporting. So it is not intended for

vaccine reporting. Please keep that in mind.

If you are a CO, you will need to have separate accounts for each sponsor or license holders, all right, so that you can separately submit their safety reports. Now, one nice part about SRP is once you have submitted a report, let's say you submitted an initial report, now, you have follow up report. You can continue working initial report and say, "Hey, I will now create a follow up." So all the information from the initial report is copied over to the follow up report and now the follow information that you have, the new information, you just update and submit. So you don't have to re-enter the report from scratch, and it also keeps track of how many reports were submitted for a case, that means for an individual patient, and all the tracking is kept on the Safety Reporting Portal.

So Safety Reporting Portal are there for post and pre-market. Of course, we are still working on the pre-market screens. So they are maintained separately. So when you go into Safety

Reporting Portal, you will be asked that -- asked that up front, you will be asked if you are submitting a report for -- for post-market or pre-market. And then it will take you to the right path to submit a pre-market or a post-market report.

What you do next, you complete an online form. Right? And as I mentioned, do not upload into E2B (R3) XML file in SRP. Okay. And you have heard me mentioning this so many, many, many times, because we do see happening. And so we do not want that you will submit an E2B (R3) XML to the Safety Reporting Portal and nothing happened and tomorrow you may -- you may be under -- under an inspection and the inspectors may ask about those specific reports. We have not processed them, so please make sure that you do not upload E2B (R3) XML through SRP.

You can take down my email and keep that for records because SRP, your submission is as soon as you hit the submit button is your submission done. So you, after that, it's not -- it's not your

problem, it's FDA's process to -- to, you know, pass the report and making sure it's put into FAERS. So as you submit you will create email account with same ACK, saying here is the report that you submit.

All right. Next slide. All right. So we are doing some changes for SRP. So SRP as we know is based on MedWatch 3500A. There are some changes that has come to the specific 3500A based on the last reauthorization. So some of those changes to get included in the 3500A. So we performed some update to include pre-market questionnaires. So everything in SRP, we call it as a questionnaire or we call it as, in short, we call it as rational questionnaire for RQ. And when the time post-market questionnaire updates on what we are doing is to accommodate the E2B (R3) structure. Because, as you know, that the current SRP for postmark a questionnaire that we have has datapoints that fit into the (R2) but doesn't fit into the (R3). So there are some changes we have to do to the questionnaire to make sure it follows direct into the (R3) structure so that we can get the data into

FAERS.

And of course, pre-market questionnaires are being developed right now. And then once this is ready, as I said, the availability for SRP and E2B (R3) via the Gateway for pre-market submissions will be available at the same time. So when we are ready with E2B (R3) at the same time, we will also be launching the ESRP post/pre-market questionnaires so that companies can actually use that.

As always, SRP is free. There's no adverse cost to use. And to request for an account for SRP you will submit an email to the FAERSESUB@fda.hhs.gov. So this is one email address pretty much everybody knows because we do get a lot of questions here. So this is the email address you will use for request for SRP account.

Now, there was a question that came if SRP comes in, you know, will that have any action to be required by existing SRP users? No. For existing SRP users who were using -- are users who are using

SRP for post-market reporting, there is no change for you. Now, you as a user also want to report on pre-market, well, you will have access to report on pre-market, you know, same data points. That means you will get a pre-market questionnaire. If you don't have any -- any INDs to be reported and you're only reporting on post-market, you just continue the way you continue today and there's no action or change required from your side.

All right. So let's go into the Gateway submission. And so we all know that for Gateway submission we submit the post-market safety reporting. You have the AE2 header and the routing IDs. We do not need any change to those values. We are keeping those values as is, we don't want to destruct anything, and we want to keep as is.

Now, we going to have pre-market safety reporting. And when we have pre-market safety reporting, we have pre-market safety reporting for both CDER and CBER. All right. So because it's for CDER and CBER, we have to separate that out for CDER

and for CBER. Now post-marketing, we do have, you know, we do have therapeutic binarities and all that, we really don't want to disrupt anything, we want to just keep it as is. Of course, vaccine reporting is now here and we're not talking about that here. They are separate reporting for to theirs.

Pre-market, you have a CDER, you have CDER and CBER. Now, what we are not saying here is for pre-market CDER we have now we have two new data attributes and log-in IDs for pre-market safety reports. And the pathway, it's two pathways, that allow separation for pre-market and post-market. Within pre-market the A and B have two separate pathways, one for CDER, one for CBER. And also we -- we understand that for CDER and CBER we had to do it separately because we also realized that some, mainly numbers, are the same for CDER and CBER, and so we want to make sure that they are separated out. So as a sponsor, you would know that it is a CDER ID or a CBER ID, and accordingly you will set-up the AS2 header to right drop in ID and submit.

Now, very important, rejection. Will occur if pre-market reports incorrectly submitted to post-market pathway. And post-market reports incorrectly submitted to the pre-market pathway. Now, this login ensures doing this rejection is that we then do not publish a pre-market report publicly. It's the only way to making right. Okay. Then pre-market report will not be published publicly, and we want to do that. We do not want pre-market reports to be published publicly. So please keep a note that, yes, we will reject if we submit a pre-market report incorrectly to the post-market and post-market report to the pre-market pathway.

Some of the login IDs, all the informations are here in the ESG Appendix J, AS2 login IDs and I have the link there. And you should be able to see those values for XML files and for login IDs and those values are available in that link.

So this is a very important slide and as I go through the different post-market and pre-market, these values that you see for post-marketing

and for pre-marketing CDER and CBER, and initially for IND-exempt BA/BE will show up, you know, regularly in these different slides just to make sure that you all understand the relationship here and how this to be submitted.

Okay. Next. So the approach of how we triage things here, so you have a pre-market and then your pre-market ICRS submission responses submit that. ICRs sponsor submission, if you look at it you have the AS2 header which says, this is just an example. So you have the AS2 header which has the destination which says CDER, and the XML file is the pre-market. CDER will be login ID, if you use it, the that's the login ID. When that file comes and it goes to FAERS, we look throughout and make sure that within is the FAERS datapoint N.1.4 as the value ZZFDA_PREMKT, and N.2.r.3 says it's a CDER_IND. And, of course, the other two fields are basically some examples of IND number and so and so. But that is very important that when you submit through the Gateway that those headers, we are expecting that the XML file has N.1.4

AND N.2.r.3, those values there. Okay?

Now, the next one is if it was a CBER one, then you see there the destination says CBER, the XML file says pre-market CBER, and the login IDs would say FDAS pre-market CBER. So what we expecting is the XML file would have and run for as ZZLP_PREMKT, so that tells me it's a pre-market and within pre-market, N.2.r.3, tells me CBER ID, that means I know what this is for, CBER. And similarly for post-market and you will have destination as CDER and when it comes to filling in the XML file, expect ZZFDA and CDER. So for post-market ICSR destination is same for CBER. CBER we are not in any kind of differentiation there.

And this type of submission, this way of submission is important so that we can submit out the pre-market and post-market report and I believe, eventually, I will be define what the IND number is because our review as medical officers get these reports based on the IND number. So here is what we have for the post-market side. So it is very important that this relationship is maintained all the

way from the sponsor submission to the XML file and so that we do not have to reject it.

Okay. All right. So now, this is a very important table. See if we can get one down. So we will be talking about the section N.1, which is a ICH ISCR transmission identification. Two important fields here. N.1.4, the previous slide we talked about N.1.4. What is N.1.4, it's a batch receiver identifier and we talk to N.2.R.3, and that is a message receiver identifier. So this table is a very important table. So let me go over this table and try to explain this table -- what this table tells you.

So this table explains the attribute values that must be used in submitting the CDER IND ICSRs, so INDs that are for CDER. CBER IND ICSRs, INDs that are for CBER and the CBER IND-exempt bioavailability and bioequivalent ICSRs, strictly post-market ICSRs. So there are four rows here, but the top three rows are for pre-market and the last row is for post-market.

So this is not showing the entire

relationship between the AS2 header and the E2B data field. The code to data value field that we have. So the AS2 header on the routing ID defines the ESG folder where the XML files will be routed to. So as soon as you say the AS2 header or routing ID, the -- our Gateway exactly knows where to drop the XML file, which folder to drop the XML file. Once the XML files are dropped in the folder, that's when FAERS will go and pick it up from those folders and process them, general acknowledgement and sent it back to the Gateway.

So when things imports the XML file from the folder. Okay. Where CDER ID or ID-exempt are stored. Right? FAERS will verify that the value for, anyone for an N.2.r.3 are ask for the values in the table. So what does that mean? That means that let's say a sponsor is submitting a CDER ID ICSR through AS2 header. So yes, that's the header that's like a part of the envelope, and in the front of the envelope it says that this destination is CDER, and the XML files is PRMKT_8 and this for PREMKT_CDER.

Okay. Great. And within that envelope, there is a letter. The letter is the XML file, and that XML file has got the values in there N.1.4 and N.2.r.3. Now, if N.1.4 says ZZFDA_PREMKT AND N.2.r.3 says CDER_IND, everything looks good. Okay? There will be no rejections. But let's say the AS2 header was for CDER ID ISCR and now, N.1.4 says ZZFDA_PREMKT but N.2.r.3 says CBER_IND, then you will get a rejection because you plan to submit an IND -- CDER IND. So the envelope it says CDER IND, but inside the envelope, the letter says it's a CBER ID, so you will get a rejection.

Same if you try to take the CBER AS2 header or login ID, let's say you have a routing ID that says FDAS PREMKT CBER, N.1.4 is standard for all the three types of pre-market that say ZZFDA_PRMKT. But if you say CDER IND or login ID which is FDAS PREMKT CBER, you will get a rejection because you're trying to submit a CBER IND datapoint, which is in the envelope, which is all the envelope, but inside the envelope, the letter says CBER IND and so it does not

match, it's unknown, it will rejection. And same for how it happen for post-market versus pre-market. You could submit through AS2 header data which says AS PREMKT CDER, then we will be submitting N.1.4 as ZZFDA and N.2.r.3 as CDER, you're going to get a rejection.

Now, all these type of rejections and, you know, exceptions have been set-up up, but keeping in mind that by no means in no way pre-market reports are published publicly because we all know post-market reports are published publicly as we water, and we do not want this to happen with pre-market report. Now, and also responsibility lies on the sponsor to maintain this because we can do so much with our check at the FDA but if sponsors or the manufacturers who are submitting the reports do not take care of this, you know, something may fall through the crack because as much as test and as much as rules you apply, you know, that still could be some reports that can fall to the crack and mess up potential on to both sides, you know? Well towards maintaining these rules and set-up this and combine to these rules.

So I have some rules here which I want to mention here that is, please note that if message receiver identifier, which is the data element N.2.r.3, is CDER. Okay. So N.2.r.3 is CDER then the batch receiver identifier data element, N.1.4, must be ZZFDA. So there is also a rule, a rule looking at the AS2 headers where it has come to which folder versus N.1.4 and N.2.r.3, but also there are rules between the ICH data element N.1.4 and N.2.r.3. But these values also note are not the mixed values or observation codes, these are values which we are imposing on me asking as a regional extension to use in N.1.4 and N.2.r.2, because we all know N.1.4 and N.2.r.3 are like free text data fields. So please make sure that these values are appropriately in there because if you have a -- have a mistake with the alphabets or a typo, you know, that can create a rejection. So please make sure that those values are appropriately set up.

So as I said that there are checks between the data elements, which is N.1.4 and the

N.2.r.3. If you have CDER, make sure it's ZZFDA. If it is ZZFDA, then make sure that N.2.r.3 is CDER. Okay. This is very important.

Submitting the message receiver identifier N.2.r.3, if it is CDER IND or CBER IND or CDER IND-exempt BA/BE, then the batch receiver identifier data element, N.1.4, must be ZZFDA_PREMKT. These are some new values that we have come up with and vise versa, that if you have ZZFDA as N.1.4, the N.2.r.3 must be one of the values of CDER and this IND, CBER and this IND and CDER IND-exempt BA/BE. It cannot be CDER. Okay?

Again, as I said that this business rules has been defined to make sure that the different way that you assure that the pre-market and post-market reports are clearly delineated within the pre-market reports and not published publicly. A few reports that I'll make on the slides, this is a very important slide and, you know, this whole set-up has to be -- has to be put in a way so that if you don't go in a main theme, this set-up, you will start

getting -- you will get rejections. Now, let's say you have a batch of ICSRs and in that batch, you know, please make sure that you have -- try to make different batches for post-market and different batches when you have pre-market for CDER, pre-market for CBER ad pre-market for -- pre-market for IND-exempt.

You can submit all together, but I think we would -- we would prefer that you submit them in different batches, don't mix the CDER with the CBER or the CDER with the CDER IND-exempt BA/BE. And definitely do not mix pre-market with post-market. Having the different batches also helps us and -- and then that all the batches that you have here, that you submit in batch, you know, try to keep the batch size small because the bigger the batch sizes, it's going to take more time so that means your acknowledgements will come probably later. It won't come sooner, so if you can, let's say you have, you know, 300, 400, 500 files to send, send batches of let's say, a hundred, you know max of 200 and send them as like three or

four batches so you will get acknowledgements sooner and faster and so on.

Also that with this particular rule here, as I said, these AS2 header and login ids will be available on the Appendix J, but there will be one for testing and there will be one for production. I think the ones that are for testing will say something of TST or TST something like that, but those will be used for testing and we will want to make sure that as you submit through the testing site or to the testing web trader or we want to test this scenarios with you all, so we will during the testing period, we want to test that some putting in using a login id of CDER IND or some reading as CBER in the XML files gets you rejection. So you want to test that. And also we want to test the positive side that you submitted with the right routing ID, with the right N.1.4 and N.2.r.3. You are getting a positive acknowledgement. Same thing we will want to do for the post-market, you want to interchange those values and make sure you get the right rejections and also get the right values so

that you get the right acceptance, so.

And with that, I think I am probably four minutes before time for a break. So I guess we take the break, but we come back at 10:30. Well, it was not that bad. Four minutes, I guess it's okay. So we will resume at 10:30, so anyone has any questions, please start putting the questions in the Q&A so that we will start looking at those questions and answer them at the end. All right? Thank you and see you at 10:30.

(Off the record.)

MR. DE: All right. So we're back from a break. Hope everybody can hear and see.

So before the break, we talked about a bit of the background, we talked about some regional implementation guidelines. We went over the submission methods and mechanisms, and we did talk about, you know, specifically the table that I spent a lot of time on, very important table. And then, you know, certain things about -- we talked about there are two options, Option A, Option B, for tests and for

basically, for testing we will only use Option A for database-to-database, which is the Gateway for testing. Option B, is basically a website, and online form. That will be posted, and we are not doing any testing with the companies there. That will be directly posted.

Now, after this break until lunch, we will talk about the E2B (R3) implementation package. The implementation package, this is where I will try to coordinate to the spreadsheet and if we have some Q&As on the spreadsheet, so I'll try to go into the spreadsheet and try to show you how the spreadsheet looks like and help you navigate through that spreadsheet. Okay.

So the E2B (R3) implementation package actually has four documents. One is the FDA Regional Implementation Guide. This is a PDF document. The purpose of the technical specification document is to assist submitters transmitting the electronic submission with attachments, so it gives you some details about what terminologies have we used and what

some kind of, you know, rules that we will have. So you can talk about the Gateway set-up, ESG set-up.

We talked a little bit about attachments, what are we accepting, what are we not accepting, you know. It talks about something on a combination product. So it gives you an overview about the transmission and it need to be (R3). So it describes the technical approach for submitting ICSRs and for in completing the regionally controlled technology and for implementing regional extensions that are not in the ICH Implementation Guide. So that is what the -- the first document is. Okay. So this documents, as you see, these are all links because you see that in blue. These links, if you click on it, actually then takes you to -- it opens the document for you, basically. And these documents are also available on the FAERS Electronic Submission webpage.

The second document, which I have talked about this document previously, which is a very important document, which is the FDA E2B (R3) Core and Regional Data Elements and Business Rules. So this

whole document provides, of course, version 1.3, just because we had some updates. Soon we will have version 1.4 -- soon we will have version 1.4 and the purpose of -- the reason why we will have 1.4 is there are some changes that we had identified during an implementation, and it will be encountered in that. There was a few new ones here and there that we have identified that we are needed in the document. It should be posting very soon in a week's time.

So this document provides list of all ICH and FDA Regional Data Elements, data element attributes, conformance, business rules, X files and acknowledgement attributes. And some of the regional data elements in this documents that detail, sponsor detail in the FDA Regional Implementation Technical Specification, planning to be out soon, which is the first document at the top.

So let's try to open the Excel file, which is the second document. And to open the second document, we should have to do an R-Tab and the Excel file will be opened. It's R and Tab. So R-Tab and

you go to the Excel. And is the Excel being shared?

UNKNOWN: Yes, it's being shared.

MR. DE: Okay. So thank you. I need to see that, sorry, excuse me. I need to see -- it's not coming up here.

All right. So right now we have the Excel spreadsheet that is shared. If we look at the Excel spreadsheet, there are certain columns here called field identification. And just if somebody in the Q&A can say that they are able to see the spreadsheet, I would really appreciate that because we will go a little bit into the spreadsheet. Great.

So in the spreadsheet, first few columns are field identification. So it will tell you the source and it will say if that source is a source for FDA or that source is a source from ICH. It gives you the field identification, the field data element number, so if you see the element that starts with FDA, that means it's a regional data element. Then it gives you the data element name, and then, if you scroll to the left, on the bottom there, the scroll

bar, yes. That it gives you the data field type. Field type will tell you what is the maximum length, what is the data type, which is A for Alpha and N for numeric. The values that are allowed and then it goes into if that was an FDA specific data element then you would probably not see anything under Column H, which is conformance and Column I, which is ICH business rule because those are ICH conformance and ICH business rules.

You will also see column J where under post-market, this data field is required, and it give you some post-market business rules for that particular data field. And the next columns, which is L and M are for pre-market business rules. And for pre-market is the conformance is required or not required, and where the conformance is for the data element, which is a regional extension and then it lists rules for that. And then when you go to column S and P. S says it's FDA regional data element.

Then the next few columns are nullflavor applicable, so it tells you if nullflavors

are applicable or not. And if it is so, which ones are applicable. It gives you the OID for that particular data field, which is the object identifier and that's pretty much about it. And then it tells you which HL7 data element it actually uses in Column AE.

So that's what this particular Excel spreadsheet will talk about. Similarly, it will show you, you know, other the data elements in there. And let's go into the Read Me Tab that in this spreadsheet. At the bottom you see Read Me on the left-hand side of the tab. The first tab. Yes.

So what this says that this spreadsheet provides the comprehensive view of the ICH elements, so every time it will tell you what it is, so this tab, which is number one, which is revision history. In this spreadsheet, the revision history will tell you about the changes to this document. Okay. And so this information includes the document version number, date and version description. So let's go into the revision history tab at the bottom where you have Read

Me, beside that. And so this is how the revision history tab looks like. So we have a revision number, we have a revision date, and the revision description. So right now, version 1.3 we posted in January of 2023. We going to have one probably posted this month, in next couple of weeks' time, and it will list all the changes that we have had since the previous version.

So let's go back into Read Me Tab again. So the next tab after version history is the ICSR data and data element. This is where this tab lists all ICSR data elements and their attributes. And for the comments ICH is further divided to provide, you know, conformance and, you know, data type, data length. We have a difference choosing between post-market and pre-market because sometimes the rules are different. And also further divided the conformance and the business rules. So one thing to note here, the absence of required data element will result in a negative acknowledgement, as we have said -- I've said before, and be rejected.

The nullflavors are used to explain the reason for the lack of the data on the required data element and must be used for specific required data elements as defined, if the data element value is blank.

In case of additional required data element, if the condition is true, then the absence of conditional required data element will result in later acknowledgement and be rejected, unless appropriate nullflavor is used. So as you saw that there is some nullflavors, like not applicable, no information, asked but unknown. So sometimes you will have data fields where you may not have a value. It's a required field, but do not have a value. In such case, the data element will tell you that use nullflavors and that nullflavor is applicable and certain data element must be used. Okay?

Okay. Going down this, you will have -- I have a legend I have put for that particular tab, which is ICSR data element for source. So this column defines a source of the data element. Okay. For

regional extensions, it's marked as FDA. Then you have the data element number. This column defines a unique identifier for the data element and these numbers, wherever you see the prefix with FDA, these are the general extensions again. Data element name, they give a name for the data element. Right? Standard names for ICH are already there. One is the max length, so it tells you -- it defines the length of the data element, the data values -- the values that are allowed for the data element and the conformance. So conformance is -- conformance can be required, conditional requirement optional. So the conditional required -- the conditional required data elements are required if condition mentioned in the business rule is satisfied. Right? So that's how we have to be used.

Business rules that these columns define the business rule for the regional data element or any deviation for the full ICH to E2B (R3) business rule. Then Q&A is, these are the columns that define any question and answer associated with the data

element. We are going to have some question and answer so we kept that column so that in future, if we have questions and answers on specific data elements other than updating the spreadsheet, we can have it in the Q&A and wanted to put the question and answer to the Q&A question.

Nullflavor applicable, as I said, these are nullflavors. And field OIDs are basically the OID value for the data elements that are some regional OIDs and then some, you know, ICH OIDs.

So we see the ICSR Data Element Tab. So next tab is actually, the Rejection and Warning Tab. So before we go to the Rejection and Warning Tab, let's read through the Read Me what that tab is about.

So this tab lists business rules for the regional data element and for any deviation from the ICH or E2B (R3) business rules. The checkmark under the column rejection, if not met, indicates that the ICSR will be rejected if the business rule is not met with the header message in the acknowledgement.

The checkmark under the column warning if not met, indicates that the ICSR will be accepted even though the business rule is not met, with a warning message in the acknowledgement.

Then we have two columns for header ID and header description columns and that describes the error code and descriptions of the error and if rejection error starts that with a R and warning error ID starts with a W. So let's go to the Rejection and Warnings Rule Tab. So if we look here and we should go all the way to the top, you will see that here's the columns. So there are certain things here where there are some common things that says if the thing was required. Then you have a standard list that says this standard number is required but not provided. If you have a few letter observation value is incurred and so this line number contains an invalid value. If you have exceeded the max length, it will say that that number contains value that exceeds the max length.

So similarly, now you have some data

elements, other data elements are listed here and if you see the columns that the business rule is mentioned. If you have a check mark where it says rejection if not met, so which means that for that particular data element, which is N.1.4, if that is not met, then there is an error message that you are going to get. And that error message will be listed in that, you know, ACK.B.4.r.B.8 or B.4 something, which I talked about when you change from 250 characters to 2000 characters. So these are the rules. So as we scroll down, actually, you will see that there is some where the check mark is under the column E, which is warning. So let's go down and we should find some, yes. So there is one which is a warning here. So in this case, we may not reject the file, but we still give you a message hoping that the next time you will correct that and not get that warning message anymore. So this will list all this and all the error descriptions that you see, that is the information that you will see in the acknowledgement file. Okay. We are not sending the

error code; we are sending the error description in acknowledgement file. So it will be easy for you to read through. Okay?

Now let's go back into the Read Me Tab. Next we have the X files. So these are the tabs that list the X files based on the HL7 model for both the ICH and the regional E2B element. X files are also defined for data elements where nullflavor is applicable. So let's go to the X Files Tab. So if you see all these, these are basically the X files. So that X file specifically we will verify to make sure that the data elements falls in the right location, the right data element is used, and these are the X files that we will be using. Wherever you see the source as FDA, those ones is the X files that we have defined based on the HL7 model and those X files needs to be used appropriately for accessible submission. So that's the X files.

So finally, the Read Me Tab is the Acknowledgement Tab. So this tab lists the element for acknowledgement. So going into the

acknowledgement tab, this is the acknowledgement tab and if you scroll down, it takes you back to the bottom, we will see that the data element was changed from 250 to 2000 characters. Further, the last column row states 2000 in red. So that was previously 250 and we have changed to 2000 characters, as I mentioned previously. So in here, nothing else has changed. The message will still be the same message that was coming to you. And we will be ACK.B.r.7 which has changed to 2000 characters, so. So this is how that spreadsheet needs to be read. If you find any kind of, you know, ambiguity in the spreadsheet, please inform us at faersesub@fda.hhs.gov and anything that you find, we will really highly appreciate if we catch any issues, right now than later. Okay?

So with that, we will go back into the slides, and can we confirm that the slides -- folks can see the slides and the slides are shared. Okay.

So we talked about this particular document, the second document which is the heart of this whole implementation. The third document is

forward compatible rules. I will go over this in another set-up of slides. This spreadsheet -- I have taken the spreadsheet and I made those columns -- the spreadsheet columns and I put some slides at the end of this presentation just to -- for -- I think we talked about that in the opening, that there will be a section that we found (R2) to (R3) forward compatible and that's what we'll talk about this spreadsheet. I will review the spreadsheet, but I have the tables already in the slides, so well will talk about that then there. Then next is IND ICSR in similar instance. So one of the instance, these is the list of scenarios provided. As XML instructs us and acknowledgement examples based on FDA (R3) Technical Specification document. So this will add all the regional elements also. It's a .zip file and the .zip file has a Read Me.txt file describing the different scenarios. So there are seven or eight scenarios, I believe, and the Read Me and .txt file will tell you about each and every scenario. There will be a scenario relating to combination services, there will

be a scenario relating to IND Safety Reporting. There will be a scenario relating to IND-Except BA/BE. There will be a scenario between column is like a metal file, which means it has got, pretty much, all the elements in there. So likewise, we have all the scenarios that can be used and looked at by testing and so on. So we have provided some instance files, which again, those instance files are different from those instance files filed from ICH because this instance files actually has the regional elements in there. So -- so keeping that in mind, these instances are documented and posted. Okay.

So with that, now we will go into some common regional extensions. When I say common regional extensions, these are common regional extensions applicable to our Excel reports. So -- so let's get into each and every section of this common regional extensions. Okay.

All right. Section C1, this is identification of a case safety report. Now, in the document on regional extension, just know that there

will be some elements that are new elements that are being as defined. There are some elements where some business rules have changed and there are some elements where we may have changed the conformance. So going into Section C1, identification of the Case Safety Report, the change here is the business rule. So you have to send the case safety report with just C.1.1. This is a standard ICH data element. The business rule is that use the same sender safety report unique identifier for all previously submitted reports. We will always use the same identifier for data elements. And for data element C.1.1, that was a sign to the initial ICSR when submitting follow up and post follow up throughout the lifecycle of the case. The reason we have put this business rule is because this the value of this particular data field makes the initial and follow up reports in our database. Okay. So having the same number makes a new follow up and the next follow up and the next follow up. So that is why this particular data point is important. More details about this is provided in the previous

document of the technical specification. And reasoning also has been given there.

The next data element is C.1.3, that stands for type of report. Type of report then is a rule here, as we say that if the batch receiver identifier, just N.1.4. We talked about this field so many times now, is easier here in this pre-market, then the type of report C.1.3 must be two reports from starting. Okay. Makes sense, right? Because it's a pre-market report and two is, value two is report from -- it's also provides another level of security from not publishing this report. Okay? So now you see the two, three levels of security that we are putting in so that we cannot publish this report publicly.

Now, again, you can have everything this, but the content in the report is all -- let's say you submit; the people are reading a post-market report. Our sponsors know it's a post-market report -- pre-market. That's something which we cannot know, make sure that and catch that and not publish it. Because data point with discreet data

values -- and say that it's pre-market or post-market report, but the content of the data -- and the content of the data in like the product name and all that is all about pre-market, then, you know, that is something which would be very difficult to track and not publish. But from the perspective of making sure that pre-market report will not get published, we talked about the login IDs. That's why we have separate from post-market and pre-market.

We talked about converting (R4) into (R3) in relationship with between the login IDs. SO that is another level of check that we are doing. And finally, this is like the third level of check that we are doing to make sure that this is not published yet. Okay?

All right. Next is the local criteria report type. So in the local criteria report type, this is a new data element because with FDA we need to know if it's a 15-day report or it's a not expected report. And then we have five day and 30-day report for combination process and then we have a seven-day

report for IND. And IND has both seven day and 15-day. So we define a new data element and previously we had a local criteria report in (R2), but that was a value data field that I can add more values, but that field know has become a, what do you call it. A Boolean, true or false, and experiment report. We used to use a value for the experiment report and that's become a Boolean, so now, we had to have a new data element, which is called a local 30-day report, FDA C.1.7.1. The length is one, the data type is numeric, the conformance it is required, and the observation code values, which is C.5.4.5A. Again, the C, I talked about it, it's NCI EVS values. So one will be for 15 day to non-expedited, or 5 day, 5 to 30 day and 6, 7 day. So you may wonder why there's not value 3. Because we used the value 3 basically for our direct reports that we get directly from consumers and health care professionals. So we reserve that for that.

Any kind of rules are available in that spreadsheet, which we showed you, which is E2B (R3) --

that link is there that will open that spreadsheet, but we already showed that, I'm not going to go into that. I have extracted out some of the rules from the spreadsheet and if we arrow down, here are the rules. So let's take a look at them. So in this particular data elements let's go over some of the rules. Many of the rules apply because of combination products. Because combination products are for post-marketing. We don't have anything for pre-market. If combination product report indicator. So there is a data field, which is a regional data field, called combination product report indicator which immediately saves these reports on the combination portal.

If that was true, then that's the case fulfil, the local criteria for an expedited report. That means if it will fill like area for expected reporting. And that is also true, then observation code value must be 1 or 4. That means we're saying, it's a combination product, it used for experiment criteria. So value of 1 and 4 is what? 1 it could be a three-day, and 4 is a five-day. Right? So when you

have 1 and 4 will be allowed.

The combination product report in the value is 2 that means that it's a combination product report and it did not fulfil experiment criteria, so it just falls on no information and then we would use 2 out of 5, which means, 2 means its non-expedited and 5 means it's a 30-day report. Okay?

If combination product indicator is false, that means not a combination product report, and doesn't fulfil expedited criteria and then for post-market, the value must be 1 which is for 10-day report. And of course, if you have the combination product indicator is false, that means it's not a combination product report and it does not fulfil expedited criteria, then the value alone is 2, which is non-expedited report. These rules apply to make sure that it was about right and set-up right for us.

On the pre-market side, the 15 day and seven-day experiment report, if the field, which is false, and the expedited criteria is true then the report type -- type of report is report for study and

observation value allowed is 1 or 6. 1 being 15-day or 6 means seven-day report. All right.

So the next data element, if that's the case fulfil local criteria from an expected report. C.1.7, this is already existing field. You know, there is more guidance now than a rule. Specified data -- so this field actually says you are specifying one of the case from this, the regional specification on expected reporting. If this, if the local criteria report file is seven-day or 15-day or five-day, they're considered expedited reports then C.1.7 must be true. Another rule is if local criteria report type is not expedited or a 30-day, they are considered non-expedited, the C.1.7 must be false. In fact, things that could reject it, initial submission with nullflavor and 9 will be rejected. So you cannot submit a report, an initial report with the value of no information for the data field. That's the case for the expected criteria from expected report then the report will get rejected. Okay, so.

All right. The next data element. The

next data element will be a FDA C.1.12, so we'll show the next slide. So the combination product report type indicator, I just mentioned about this field. So this is a regional data element, FDA C.1.12. This data element is a Boolean element, so which means, it doesn't have a max length. The data that is Boolean. But it look true or false. No information in NI. The conformance is required of this. Right? So which means you either have to say in combination report have to say false or NI. NI was given because sometimes you don't know if it was truly a combination product or not.

So NI is given whether or not you know it's a combination product and you say false. If it's a combination product you say true. The observation code as a C code, if you see that. When I say C code, it has starts with alphabet C. The code number, and that means it has been taken from NCI EVS. And the business rules for this is how to decide it's a combination product or not. So to decide it's a combination product or not, you will have to look at

the rules as defined in the post-market -- post-market safety reporting for combination products guidance for industry and FDA Guidance.

So this is posted. This link if you click will take you to the guidance and this is an FDA Guidance that was posted and based on this guidance you will decide should it be a true, should it be a false, should it be a no information ACK. It will be a decision that you will make based on this guidance. Okay? So this is what the combination product import indicator is.

So going into the next thing is a reporter statement. So this is again a new data element that was added in FDA C.2.r.2.8 and the max length is hundred. The data type is alpha numeric. The conformance is required, and the values allowed again, is taken from NCI -- sorry. This needs to be -- this is 5 point here. The value -- there's no values allowed here. This should be -- this shouldn't be related. Please do not take that values alone in consideration. The max length is hundred, data type

is alpha numeric, and conformance is required, and the value alone must be only nullflavor, which is not asked, NASK. So the values allowed will be only nullflavor, NASK. And I'm going to update the slides before we post it. And the reason being that it's an email address, so if the email address was not asked then -- then you just say, you know, not asked. And if you don't have the -- you would just say not asked.

So one important note of all this particular data element is that when submitting the nullflavor response, also include the telecom prefix with the value attribute. Currently reference the latest telecom type as shown in the example. If you see telecom type, you know, you have the value, it says mail to: and the email address up in the corner. If you don't have it, you say nullflavor, NASK, and the value is basically says mail to, because you don't have, and you've not asked anything. So that is an example, so that is how you need to report that data. This is the same type of process that we have also for base reporting. That has email address and if you do

not have an email, then this is what -- how you would report. Okay?

Next is Section C.3.3. So information on sender. You have these data elements were optional and FDA has made the state elements required. So this is the sender of the report, so who is sending the report to FDA. We want to know that because based on this sender information and our compliance works, that was who was send in the report, who's the responsible party for sending the report, so we want to know this information so that we know who is actually sending this report. So that's why this information -- the conformance was changed from optional to required. Okay? And these are all the elements of the sender.

Next, let's get into patient characteristics. Okay. Patient characteristics. Patient name, by any method you want. Data elements stays the same, but there are some business rules that we have put down. If no patient is involved, especially like on a compounding product report, medication report, then you can use a nullflavor NA

for patient name. For non-patient products report having malfunction with no adverse event, you can use the nullflavor NA for the patient. We all know that reporting you need at least minimal for data elements, patient being one. From a technology perspective, we are checking this so just having a nullflavor actually makes it easier for us to do the check. So and it also satisfies that the patient is not applicable in such situations.

For combination product we can rename a function on a batch of combination products with no name. So there was a batch of combination products and there was a malfunction. So in such case the batch could be used in multiple patients and in that ask for you to submit one report and the patient name or initials be, and you mention the values summary there. And then it would go into IND Safety Report when we talk more about IND Safety Report after lunch, there's a concept of aggregate reports and in such case when there's an aggregate report for aggregate report, use the value aggregate in the patient

initial.

And lastly, the rule is if the type of report is true, which means, especially for aggregate reports, so it means 2, report from starting, the IND number, adverse event occurred is provided and what's the IND number for adverse event provided? You will hear that regional elements in IND when IND Safety Reports are being discussed.

And Identification number of the report, which is linked to the safety report. But this is an aggregate reporting, you have -- you have the aggregation of all the other IND individual safety reports. That's again, you will hear that, you know, how, especially aggregate reports are to be reported in the IND section. And also important just because of the patient name and initial, if those three fields are populated with those values or populated with specific values, then B1 must have the value aggregate. So it's like the cross-check business rules that we are -- we are having here. Okay?

Next we go into race code. And before

we go into race code. Okay. So race code. So this is a new data element, patient race code, which is alpha numeric 10. Conformance is required and values allow again a C code, which means, it's taken from NCI EVS. These are the values here. They also have C codes. It does -- race code is used in many other types of forms that we have in the United States, and the business rule is must be provided as a nullflavor NA, when patient is like a summary or aggregate. And of course, if you don't have the value of the race for the patient, then you can use unknown mask or other -- if you're masking something or if you don't know, just -- you know, you have unknown. So that's what you will be using for the race code. And we have that as NSA code, which is FDA.C.1.12. So in such case you have maximum 10, alpha numeric, it's required. It again, has a C code, which means it's taken from NCI EVS. It has nullflavor like unknown, NASK, no information, NA. How can you use NA when you submit the report as is about combination product with multiple patient and aggregate and so you can use NFR.

Those types. Okay.

All right. Then we have GK, which is drug information. Now that a drug can be repeated, right? So the categorization of drug rules. This is an important field, G.k.1. So there was some business rules with this particular drug role data point. And the business rules are for post-market, for pre-market and so on. These two.

But first, CSRs. The first product under section G could have the data element answered as 1 or 3. Unless, the report has at least one device in the report where malfunction is true. In which case, the observation rule value would be 1, 3 or 4. Okay. 1, 3, or 4. 1 stands for suspect, 3 for interacting and 4 for drug administered. Right?

So what we are saying here is we would want to that the first product, we always the suspect product, the interacting product on the drug in case of combination products. And then you have number 2, which is concomitant, that could be the product that can come later in the XML. So basically, your

information, kind of, if you're reporting, becomes the first product in the list. So if you look at these group here, if you have a combination products and combination products has a malfunction, okay. But the malfunction, there was no adverse event, there was just a malfunction, then in first will be on a similar device, then you could use the value 4 which is drug administer. That's you have 1 or 3. You must have at least one product, at least one product must be reported with an observation core value of 1 or 3 or 4, which is suspect, interacting or drug administer. And as I said for, yeah, 1,3 or 4. For pre-market ICSRs. Okay.

For IND ICSRs, we only have the observation core value of 1, 2 or 3. So 1 means suspect, 2 means concomitant and 3 means interactive. At least one report must be reported with observation code value of 1 or 3. It's very important to do that. The other serious piece, which one of your companies work as the first in the list. Okay?

For IND-exempt you can use the value 1,

2, 3 or 4 and you will still have a combined products and at least one product must be reported without the core value of 1, 3, or 4. Because when you have IND-exempt you need, you could have the test drug, you could have the reference drug and so on. So the value of 4 is also used.

So we have a new field on the other characterization of drug code. Why was this field used? Because it's a concept of similar device. So this is a concept of similar device, you know. Anything to an existing observation code value, like for example we have the characterization of the drug. We really cannot in IC need to be up on 3. You can just go ahead and enter the observation core value. You can just go ahead and enter observation code value if you had existing list of observation code values. And the reason is I could add a value of, let's say I characterization of the drug role and it had four values, and I added a fifth one. The fifth one I got at a similar device. You know somebody else; some other region may call the value 5 as something else.

Some other region may call the value 5 something else. So it's not concomitant to add a value to an existing list unless the standard organization has, you know, endorsed that and has included that into the core values on the observation code.

So a bit of advice, this is specifically for -- specifically for combination products, actually. Its maximum length is one, it's numeric and conformation is conditionally required. And when it is required it's because similar device, observation code value 1 must be provided in combination concomitant code indicator is 2, malfunction is 2 and characterization of drug is 4. That is drug was not administered. So that means you're talking about a combination product because as I'm talking with a similar device. So you have a divide and you're talking about a similar device, that means that the device would have been administered so add value of 4 to all these three "criterias" have to match up and have to be true. So to say that it's a similar device. So that's the conditionally required

code in this particular field. All right?

Next, so we have common regional extension for drugs, GK. So these are some important areas that I would say let's focus on right now because of the data that we typically get, and we have to go back to sponsors to get things correct. So the data element G.K.2.1.1b, medicinal product identifier, MPID, you would want to start using this data element. In (R2) we never had this, but now if you want to start using this, if available. So which means, MPID you use the FDA NDC code, not your drug code, and should be used as a regional MPID. Okay? Use either only the first two segments of the NDC or the full NDC as the regional MPID in the ICSR. And we take care of if you only send the first two segments of the full thing.

But if you stop sending, again, this is an optional data element. But we would request that we would recommend to start using this because when it comes to, you know, IND and all that, you know, we might start using the MPID as the NDC code as the

MPID. So and also it gives FDA facts to pinpoint to the exact product that we are looking for once we know the NDC code, so when known, please supply the NDC code in the data element Medicinal Product Identifier.

Next, data element is GK.2.2, which is medicinal product name as reported by the primary source. Okay. So this the first report name. So FDA validates the medicinal product name as market in the United States negates the the available structure, product, everything. So I mention that previously during the local technologies and vocabularies that we're using. Structured properly it really is very important because that's the name we use to validate the medicinal product name. And many, many, many times we see sponsors have one name that we have submitted the structure product labeling, but then when the actual ICSRs come the name has some variations. Also, in the name it's a name. So don't try to use a trend into the name, you know, and those kind of values into the name. When your name got approved by the Agency and what you submitted at

structured product labeling, use that name in the ICSR.

If the medicinal product name is not provided but the active substance name is known, then provide the active substance name as it appears in the FDA's Global Substance Registration System. So how the substance was approved, that name you must use and that's what you will provide, you will get in the FDA's GSRS which is available publicly for you to use. If you have foreign product trade names, let's go write that foreign product trade name in this particular field, G.k.2.2.

Then we have the G.k.2.3.r.2b, which is a substance and specified substance termID. Now, the termID that you have, we are recommending to use the FDA's GSRS unique code, 'cause then it also helps us to directly pinpoint that substance that was registered. Right?. And the name, of course, is the name of the substance then. So that should always be populated, we expect the termID, that should always be populated, but if you have the termID and it is

available, then use the FDR GSRS. Okay.

But what happens if it's a foreign product? So if it's a foreign product then go ahead with that substance name as it appears on the FDA's GSRS. Okay.

The FDA's unique rules are updated monthly and can be obtained from FDS GSRS in your list. These type of rules, you know, and suggestions and recommendations that we are giving, it only helps us in validating the product because, you know, we as the Agency, we have to look at product across the United States and what is marketed in the United States. Right? And manufacturers are looking only at their portfolio of their products that they market. But we are looking at every product that is marketed in the United States. So it becomes very important for us to make sure that we're also validated because eventually we have to do a search on those products to make sure we're getting the right, you know, cases from the products, we are receiving the right identification, so again, we do have close to 2.3

million reports that we receive every year. And of that come close to 2.5 to 3 percent report do fail because name did not match on the SPL, or the active ingredient did not match the GSRS name and the products fall out which means now we have to take manual steps to validate those products and then process them to maybe make available to the viewers. So it's additional effort, additional cost, additional steps and also additional time. So if industry can focus through making sure that the names are validated by them to SPL, making sure that that's the name they were using or the name that they're using are from GSRS, it will really help us.

Next, here is we have the drug information again from GK. This is where you have the authorization and the application number, GK3.1. So there are some rules here. Some of these rules are specifically applied for post-marketing, but also can be used to be pre-market, especially if you're using a post-market study drug. Because many of you mention what the MPID or NDA number probably is. So in this

we have, if you have a human drug or a biologic product, the application type could be IND, NDA, BA/BN, is used by CBER and in the recommended format is this, NDA with a number. IND with a number. BA with a number and BN with a number. If a biologic product which is BLA, then you have a BLA with a number.

Prescription drug product marketed without an approved application, no application then you submit that as 000000, six zeros. And non-prescription drug product marketed without an approved application, so is not ARES, no application then it will submit them as six nines. Okay. And if you're compounded product marketed then you have the word comp 99. Some of these things actually help us to help see this report both ways. Wo we have a compounding rule. So if you send comp 99 then we have appropriately notices about the compounding product and the needs to go there because the compounded product is not really approved, you're mixing things. So and then you can add a dictionary of products, so

sending these values appropriately actually helps us.

Now, the question comes where do you submit the IND number? So if you see down here it says for IND and IND-exempt BA/BE Safety Reports. That reporting on marketed drug product on biological products being evaluated under an IND or IND-exempt BA/BE. Do not list the IND with the pre-ANDA number in this field. Okay?

Use data element FDA C.5.5a and this is a regional element and FDA C.5.5b, which is again a regional element for IDN and IND-exempt BA/BE, respectively. These two attributes of these data elements bring with respect to bring the IND and the IND-exempt BA/BE talk. That will happen after lunch. But these two data elements are regional elements that has been set-up because these two data elements actually defines where the report is going to go, report review.

Next we have the data element Pharmaceutical Dosage Form TermID. Right? So we are asking to use the observation code C54456. If you go

into NCI EVS, you will be able to search for C54456. If not available, then use EVP Report. Okay. For those in this field, we actually have that pharmaceutical dosage form. If you don't have it, then use the EVP report. Make sure that you're submitting either one, all right?

Same with route of administration. You first look at C54456 as the observation code, the C code in NCAEVS. The value there, the list of values are there but the values that you are intending to use in this report is not available there, then you can use the EVP report. And if none of them are available then, and I think there's a free text field also available for you to submit in that free text field. Okay?

All right. So the next data element under drugs, GK, is every additional information on drug would repeat as necessary. So this is the regional element that we have inter-used. Used to provide characteristics associated with a product. The maximum length is 2, that the data is alpha

numeric, and the conformance is condition required and the allowed values are 1 for test, 2 for reference, 3 for bulk ingredients, 4 for bulk ingredient with human prescription compounding and 5 for approved drug from a manufacturer exclusively for private label distribution and we have a nullflavor. But this typically could be used that if you had a, you know, a compounding, as we mentioned it, this is going to be also set-up to 4 as we mentioned, with observation as com 99. This can be also set-up to 4. But this field is mostly the, I mean, for the IND-exempt BA/BE study. You will see that in later presentation, but I'll just mention the rule here and the rule here is if pre and the number, where it works, even that part, which is a regional data element. If this is present, that means I know this is for IND-exempt. Then the observation code value 1 or 2 must be used to describe the drugs in the IND-exempt BA/BE study. And the drug rule is either test drug or a reference drug. And then you can use nullflavor element for all of the drugs or if information is not available. So this is a important

thing. Now, that reminds me of another rule that if you have N.1.4 or N.1.3, and 1.4, which we talked about which has, you know, ZZFDA_PREMKT and N.2.r.3, which is IND-exempt BA/BE, if you have that then the rule is the pre-ANDA number, the date occurred, must be present. Right? Because you're telling me that you are reporting about an IND and BA/BE, so that must be present. Or if this pre-ANDA number the day after is present, then we will try to check to see that -- that N.1.3 or N.1.4 has the ZZFDA_PREMKT and the N.2.r.3 says IND-exempt CBER and this IND-exempt BA/BE. So that rule will also apply to make sure that we don't fall through the cracks and publish this report publicly. Okay?

All right. Then we have another, bigger field called FDA Specialized Product Category. This is mostly for combination drugs. This is used to provide characteristics associated with a combination product, so FDA.G.k.13.r. The data length is 10. The data max length is 10. The data type is alpha numeric, conformance is optional, and we are using the

C codes. So this also helps, really helps us to define this as a combination product between a drug or a biologic, which is a type 6 or is it, you know, pre-filled drug delivery device system, like a syringe, example patch, et cetera, which is a type 2 on a convenience scale, which is a type 1.

Giving these values actually really helps our team here of the reviewers here to can report it into, you know, what type of product that is. You know, you just say the product, but then these extra attributes actually help us to, you know, to the right investigation that we need to do. So the C codes again, there are C codes that way you have NCIEVS, it's taken from there. And these are all the values that we had used for this particular field, FDA Specialized Product Category. Okay.

And next, submission rules. So we did talk about some, I showed you the spreadsheet, but this is a section in the technical specification about submission rules, so I wanted to, you know, talk about a few of the submission rules, what they are and what,

you know, how they need to be issued and complied to that so that we can prove the quality of the data. So submission rules is defined conditions resulting in a data acknowledgement and not accepted by FAERS if not met. We also have the E2B (R3) code and regional data elements -- oh, before I go over the second bullet, the first bullet, Conditions Resulting in Negative Acknowledgement and it's not accepted, so you could also have got a safety acknowledgement, God forbid, and then error messages. And FDA accepted. Right? Because they are warnings. So it's still a rule, but that rule will be taken as a warning so that we would like -- we would expect that next time, you know, the submitter saw, fixes the data and submits it. Okay.

The E2B code and regional data element and business rule. So this is mainly the same documents, you will see multiple times the same documents is with us for two. In this case, I have not put a link here, but put a link in many other places. This is a spreadsheet that I went over with you. And that defines the conformance and the rules

for each data element. Right? If there is different data elements, you know, some data does not have any rules but the rules that are there are all defined in the spreadsheet, and we saw that. And where will we see them in that spreadsheet? The tabs that says Rejection and Warning Rules. That list, the rejection rules, that will result in a negative acknowledgement and warning rules that will notify a warning, but result in a positive acknowledgement. So when you hear warning and a positive acknowledgement, you know, you want to say it's positive, so I did. You know, but the main core data in good quantities so that we can do better review, and you know, we would request that the warning rules are also looked at the by the submitter and corrected in the subsequent submissions. Okay.

And finally we have the forward compatibility. I have a whole different set-up of slides which will come at the end which will talk about the forward compatibility. But know that forward compatibility is something where if you had

something you would move to a forward compatibility, so which means we have today post-market, which is submit in an (R2) format, yes. We follow that to (R3). So pre-market, we don't have (R2) format. Okay. So there is nothing to follow up there for forward compatibility because we go to (R3). Because as we said, we are directly jumping into (R3). So with that, you will find those forward compatibility rules are not applicable to pre-market safety reports. If we ever use (R2) first that we had ultimately planned, yes. We will have had forward compatibility for pre-market safety report, but now we are not. So we are straight jumping to (R3) so there is nothing to talk about forward with the pre-market, only the post-market.

So the forward compatibility rules list the data elements and the rules to be applied, so if you have X and now, that field is now Y and one of the rules from (R2) to (R3), in (R2) it X and (R3) it was Y. Right?

And of course, please do not forget

about that Appendix B, the ICH Guide, about forward and backward compatibility, should be there for the data elements and sources for ICH. So you still have to look at that. The one forward compatibility that we are talking about are for regional elements only. Okay. So we will go over some of those elements in later slides.

So with that, I think we are almost time at 11:44, so we will now go into a lunch break and come back at 12:30 and go over the next few topics. So I think I am probably doing good at timing.

So if you have any questions, please do submit your questions through Q&A. We have somebody here monitoring those questions. And with that, we will take a break, 11:45 and we will be back at 12:30. Thank you.

(Off the record.)

MR. DE: All right. Welcome back. We are 12:31 and so we're back from our break. And with the outline we now have completed talked about

background from key items on the regional implementation of (R3). We talked about submission methods and mechanisms. Then right before this lunch break, we did talk about the implementation package and as I said, there was some questions that we had on the spreadsheet and I opened the spreadsheet for you all to see what the spreadsheet looks like, what the contents of the spreadsheet and the tabs that we have on the spreadsheet, which is the core regional and core and regional data elements.

We talked about some of the common regional extensions, which some were pre and post and some were for post market. And then now, we will talk about some of the very specific post-market safety reporting extensions, what they are, and we will first start with the transmission identification identifier -- identification.

So again, you have seen this table previously. We have talked about in 1.4 and N.2.r.3 and I am going over this again and again, reason being, this particular, you know, this particular

sections on this particular data elements have to be in line with the AS2 headers, because without that, the files will get rejected. And so in this particular table I have highlighted all post-market, because we are talking about the post-market facts and business rules, and here you have the AS2 header as CDER and then you have the XML files, which is FAERS, and for the login ID, you have FDAFAERS and 1.4 will be ZZFDA and into (R3) will be CDER. So again, very important to note this down.

All right. So going into some of the specific elements we have for the post marketing, we have a data element which we added as a regional extension. This element is under the reaction and event. That's it, so reaction and event as reporter, and the theming is called required intervention. So it's FDA.E.i.3.h.2. Most of this type of data, this data element value is used for medication errors, because there was some required intervention, and this is a Boolean data type. It does look and feel very similar to the Boolean fields that we have for the

seriousness "criterias", like death, life threatening, hospitalized and so on. So you will have the conformance as required for this element. The values are alone are either true or no information, NI. So if you don't have any information for that case, for the required intervention, you can submit as NI. And for pre-market safety reports, this element will almost always be submitted as NI. You have other data elements to talk about the seriousness. So, this is the required intervention data element. Okay.

Next, we have device information. So that alone we have device information. And this could be repeated as necessary. This section start with FDA.G.k.12.r and you have other elements. So the first element is identifying if there was a malfunction or not. If it was a combination product, that element is way ahead of which we have talked about. But now you say it's a combination product, now you're talking about the device information to say first is it a malfunction or not. So the observation code value is a C code. It's a true or a false and it

is conditional required. Why is it conditional required? If you have the local criteria report type as 5, which is a 30-day, and malfunction is -- then malfunction must be true for at least one suspect product. So that is a rule conditional requirement for this.

So next is a follow up, make a follow up for this. So we have this data element, observation code again is a C code, taken from ENCEVS. This is an optional data field. This is to audit that we have used data. That's not a business rule, it's just an optional field. There's no true business rules here. Just listed the right there.

All right. Device problem code. This is an important field. The observation code is C54451, and there's a link there. This link takes actually takes you to all the device problem codes that you can mention, and this could be IND RF code or the FDA code, so you can submit any of those codes and we will take it. And this is required if malfunction is true. Okay. This is a business rule. And we will

only validate the format, one or more codes can be provided. But it's free text field, so you can have one or more codes.

Then we have the device by name. It's a free text. If you don't have it, give a nullflavor, NI. It's conditional required. Again, it is set-up because if combination product report indicator is true, that means you're saying it's a combination product report. Then enter the device brand name and the common device name. It will -- can be null; however, if both are null a value of device product code is required. Okay.

Common Device Name. Again, free text field, alpha numeric, and if we don't have this you can submit an NI. Again, this is a conditional required field. The business rule the same as the device brand name where we say that if the combination product report indicator is true, that means this is a report about a combination product, then you need to provide the device brand name and the common device name. If either is not available, then you would

provide the device product code.

Okay. Next slide. The Device Product Code. To begin, that is available it is a 10-alpha numeric, it's available on that link, all the device product codes. Again, conditional required. If put device brand name, the common device name are blank for now. Okay. NI. Then the value for the device code is required. You have a listing of the devices. So, you have three fields basically to identify what the device is. Then every time it's all about the manufacturer of the device, next two fields, so the device manufacturer name, the device manufacturer address, city, state, country. And so these are all actually optional fields, country of use, ISO alpha numeric. You can also use EU, to put there. So as I said, if you read the country field, you can use EU.

Device Usage, okay, this is an observation code of C54595 and EVS and ENCEVS scored the value of 1 to 1.3. It's an optional data element. Device lot number, txt, that's an optional element. And with that, those are all specific data elements

that we have for post-market safety report.

So with that, I would like to invite Veronica, who is going to come and talk about IND Safety Report. I guess the October is waiting to hear back.

DR. PEI: Thank you, Suranjan.

So good afternoon everybody. So we're going to spend the next few minutes talking about the reporting of IND Safety Reports to the FDA using the E2B (R3) standards. And we're going to go through some case scenarios. So next slides.

So this is a brief overview, sort of compares the current process the new process. And what you can see here is that in the existing process, sponsors of clinical trials are required to submit IND Safety Reports as per 21 CFR. And in the current process, the sponsor would submit these in PDF format in the eCTD, which results in inefficient and labor-intensive reviews. It doesn't really allow the use of tools for data visualization and analytic tools for review. And there's really also no universal tracking

system.

However, in the new process, the sponsor will now submit safety reports following the ICH E2B format to FAERS. And this will allow the use of visualization and analytic tools for review and tracking because the data will be structured and actionable. FDA will also leverage existing processes in use for use in post-market safety reporting, such as the ICH E2B data standards and FDA Gateway. So implementation of this new process will comply with existing federal regulations as outlined in the 21 CFR 312.32.

So in order to implement the Electronic IND Safety Reporting process, change in format is required under 745a. Sponsors of commercial INDs must now submit specified IND Safety Reports to FAERS by one of the two listed methods. As you can see here, the first method is through the Electronic Submission Gateway. The second method is through the Safety Reporting Portal. This change will be effective 24 months after publication of the final guidance, and

after the effective date, FDA will only accept IND Safety Reports in the electronic format.

So the tentative goal is to begin voluntary submission by the end of this June. FDA will publish the date on FAERS Electronic Submission webpage 30-days prior to the start of the voluntary submission.

So this is a snapshot of the FAERS webpage and in preparation for the electronic submission of the electronic safety reports in the ICH E2B (R3) format, FDA has posted a number of relevant documents on this website. And the link is provided on the bottom of the slide, as you can see here. And there's a number of resources listed. Additionally, FDA will conduct remote meetings, such as the one that you're attending today, and share communication with stakeholders, such as DIA, to discuss technical specification, implementation and testing plans.

Next slide, please. So as, I'm sure you're familiar with the slide, because Suranjan presented this earlier, this is just a reminder, this

table highlights the attribute values that must be used when submitting CDER and CBER IND ICSRs. So the AS2 header and the routing IDs define the Gateway folder where the XML files will be routed to. And when FAERS imports the XML files from the Gateway folder, it will identify and verify the values of N.1.4 and N.2.r.3, as per the values shown in this table. And if those values do not align, your submission will not be accepted, and you will receive a negative acknowledgement. So in that case, a resubmission with the corrected AS2 header or routing ID will be required.

So not all IND Safety Reports will go to FAERS, and you can see from this table, it outlines where to submit different types of IND Safety Reports. The top three rows shows the three types of IND Safety Reports that must be submitted through FAERS. And these are typically the ones that include the individual ICSRs with narrative reports. The bottom three includes findings from other studies, findings from animals or invitro testing, as well as reports of

increased rate of occurrence of SAEs. Those should continue to be submitted in the eCTD format.

So how would this new process benefit the sponsors? There are some huge potential time savings for the sponsors, and we've tried to list them here. So first, you will no longer need to submit 1571 and a cover letter when submitting electronically. You will not need to submit the same safety reports for crossed-reported INDs separately, because now we have a mechanism that allows you to do that. You will also receive an immediate acknowledgement if your report is accepted or if there are errors which you need to, then resubmit the report.

Other potential benefits include submitting ICSRs directly from your safety database and eliminates the need to route ICSRs to your regulatory affairs division and thus saving time, effort, and money.

Okay. So in the next couple slides, we're going to talk about a few different example

scenarios to illustrate how you would submit IND safety reports in the pre-market space. So in the first scenario, we're just talking about very simple, submitting a safety report to a primary IND. So I want to draw your attention to this new data element called "IND number where the AE occurred." And this is to capture the primary IND number and it's a new regional extension. Now the max length of the field is 10 and the data type is numeric. And the conformance and business rules for this element are described on this slide. But the bottom line is that the data field is required when you're submitting an IND Safety Report.

So in the second scenario, you're submitting a ICSR with a cross-records IND. So in this case, you're going to need to include the cross-referenced IND number in the data element called "IND number of cross reported INDs." And note that this data element can accommodate more than one cross-referenced IND numbers and the business rules and the conformance for this data element is also listed on

this slide, so I'm not going to read through them.

In the third scenario, we'll talk about reporting from aggregate analysis from several ICSRs. So there's a couple of elements that are important here. The first one you'll notice is that you need to submit the aggregate analysis header, it's only unique safety report identifier. And this is submitted as data element C.1.1. Now, you will also need to include a parent IND and you will submit that under the data element FDA.C.5.5a, and the D1 value must be denoted as aggregate. And finally, you're also going to need to include all the ICSRs that makeup the aggregate analysis, and that must be reported using the data elements C.1.10.r.

So in this scenario, the sponsor is investigating drug A versus an approved drug B. So you know that for suspect drug A, you will use the company code, the established name or the proprietary medicinal product name under the element ID G.k.2.2. Now, for drug B, you will report the proprietary medicinal product name along with the active drug

substance name. If the proprietary name is not available, then you must at least submit the active substance name. And it's important to note to distinguish between the company code versus the proprietary medicinal name.

Now, in this scenario, you have a two arms trial. Both drugs are approved. However, you're conducting a trial where the approved drug A is being studied to support a new indication. So here you'll note that you need to submit two reports to FAERS, if report meeting IND and post-market safety reporting requirements. You need to submit one under the IND and one in the post-market.

Next slides. So here we're going to discuss reporting of causality for IND Safety Reports, and this slide outlines the data elements that's needed for recording of causality information. So you can see here that you will need to include a source of the assessment, the method of assessment and the result of assessment, and the business rules are also listed here.

So I want to highlight a couple other IND regional requirements. The first one is that you need to include the study name, and this is where you would submit the study ID along with the abbreviated trial name. The study ID should be the same value used in the study tagging file format of the eCTD submission.

For an aggregate report, the study type where the reaction observed here must be -- the value must be 1, which indicates clinical trial. So this is the other element that I want you to be aware of, is the study type where the reaction occurred. You must also submit this information.

Next slide. So another one is the element date of death. Now, if your -- the element death, which is in the EI.3.2a, if that value is true, then you're required to submit the date of death as D.9.1. Okay.

So now we'll pass this on to Jung Lee to talk about BA and BE study safety reporting for generic drugs. Thank you.

MS. LEE: There's the next one.

Hi, my name is Jung Lee. I'm from the Division of Clinical Safety and Surveillance in the Office of Safety and Clinical Evaluation at the OGD. I will be presenting on BA/BE Study Safety Reporting for Generic Drugs.

Here are the objectives for my presentation today. I'll be briefly covering the generic drug pharmacovigilance overview and bioavailability and bioequivalence study safety and reporting requirements and processes, and will focus on electronic pre-market safety reports from BA/BE studies.

The key characteristic of generic drug pharmacovigilance is that it is a collaborative process. We work with the colleagues at CDRH to handle safety issues regarding generic drug regarding combination products. And we engage with different offices within CDER, as listed on this slide, as well as internally within the OGD to address various generic product safety issues.

Not only is it across the centers, and the offices, the next slide, but the generic drug pharmacovigilance covers the entire life cycle of the generic drugs. In the pre-market phase, the safety issues observed during the BA/BE studies conducted under IND application, referred as Bio-IND studies, as well as the safety reports from BA/BE studies, not conducted under an IND, referred as IND-exempt BA/BE studies, are reviewed. And they inform the safety variation of the abbreviated new drug application (ANDA) safety issues, which in turn support post-market safety review, surveillance, and pharmacovigilance efforts for generic drugs.

Next Slide. The safety reporting requirements are different for BA/BE studies conducted under an IND and those not conducted under an IND. Those under an IND must meet the safety reporting requirements under 21 CFR 320.31 and 312.32. Under these requirements, sponsors are required to submit IND safety reports for events that are serious, unexpected and suspected adverse reactions referred as

SUSAR(s). These regulations require reporting of individual case safety reports and aggregate reports.

The BA/BE study not conducted under an IND must meet IND-exemption under 21 CFR 320.31. These studies are required to meet safety reporting requirements under 21 CFR 320.31(d)(3), which require reporting of any serious adverse events [SAEs] during the conduct of the BA/BE study, regardless of whether the event is considered drug related or not in an expedited manner.

This slide compares the current pre- and post-market safety report submissions and review processes for generic drugs. Pre-market safety reports are also separated by Bio-IND and IND-exempt BA/BE safety reports. This is a busy slide and what I want to emphasize here is that the generic drug pre-market safety reports are both still submitted on Form FDA 3500A in PDF formats. The Bio-IND safety reports are required to be submitted via eCTD and IND-exempt BA/BE safety reports are sent to the OGD's inbox by email, which are then entered into a tracking system

manually and the linkage between initial and follow reports are also done manually.

And these pre-market processes contrast with that of post-market safety reports that are submitted to FAERS database in E2B format via Electronic Submission Gateway through database-to-database [D2D] transmission or via Safety Reporting Portal. The good news is that FAERS II new enhancements will bring the opportunities for electronic submission of adverse events from pre-market BA/BE studies for generic drugs.

The IND safety reporting requirements under 745A(a) of the Food, Drug, and Cosmetic Act has already been covered by Veronica. I'm going to just recap the highlights here. So according to this draft guidance for industry, published in 2019, sponsors of commercial INDs have two options in meeting the electronic submission requirements. One is through Electronic Submission Gateway, via D2D transmission, and the other is through the Safety Reporting Portal. Sponsors can begin voluntary submission in E2B (R3)

format. The FAERS website will. And the requirements for the electronic submission will begin 24-months after final guidance is published. And what I'd like to point out here is that Bio-IND safety reports must meet the electronic ICSR reporting requirements under 745A(a).

As mentioned earlier, the IND-exempt BA/BE safety reports are currently submitted on the Form FDA 3500A to the OGD [premarket safety] mailbox. This option will continue to be available in the future. But once the FAERS II enhancements become available, E2B format will be an acceptable form of notification to the FDA of SAE(s) required under 21 CFR 320.31(d)(3).

Like post-market and IND pre-market safety reports, there will be two options for submitting ICSR's from IND-exempt BA/BE safety reports in E2B(R3) format. One will be via the Electronic Submission Gateway in D2D transmission, which will be the focus of the rest of my presentation. And the other will be via the Safety Reporting Portal.

If a company or person or CRO conducting IND-exempt BA/BE studies chooses to use the electronic submission option to notify FDA, we'd like to recommend the following: First of all, to understand the requirements. These are clearly stated in the FDA Regional Implementation Guide for E2B(R3), electronic transmission of ICSRs for Drug and Biological Products, also known as a Technical Specification Document. Also, note that OGD has published a draft Guidance for Industry Electronic Submissions of Expedited Safety Reports from IND-exempt BA/BE Studies to support this process. I have also listed additional resources and hope you find them helpful.

The next step in this process is to prepare your IT system for E2B (R3) submission -- next slide -- by learning about the specifications for preparing and submitting electronic submissions of ICSRs. If you do not already have a FAERS account, please create one. Here's the contact information for creating an account with FAERS electronic submission

coordinator.

The next thing to remember is to obtain a pre-assigned ANDA number, which is refer as a pre-ANDA number. This number can be requested via CDER NextGen Portal. Instead of waiting until an SAE is observed, it will be ideal to have this pre-ANDA number ready prior to submitting an SAE report or even before recruiting for BA/BE studies.

Now that you have your system ready, all the information you need and ready to submit your safety report, at this point, I can't emphasize enough the importance of correctly identifying ICSRs from IND-exempt BA/BE studies, first of all, by complying with the business rules for submission path. You're familiar with this table today, I'm sure. There are FDA defined header attributes and routing IDs specific for CDER pre-market ICSRs. Please use the information on this table to specify the submission paths for IND-exempt and BA/BE safety reports.

In addition, please be sure to include message receiver identifier with a value of CDER IND

EXEMPT BA BE, and the batch receiver identifier with the value ZZFDA_PREMKT within your ICSR. And please remember that these business rules are created to differentiate between pre- and post-market ICSRs and to ensure pre-market reports are not published publicly and to make IND-exempt BA/BE safety reports available for the OGD reviewers.

In addition to complying with the submission path business rules, please indicate Type of Report data element C.1.3 as 2 to indicate that this is a Report from Study.

Lastly, please be sure to include pre-ANDA number in your submission in FDA C.5.5b. This is an FDA regional data element with maximum lengths of 10 and a numeric data type with the conformance rule of conditional required. Meaning that if the type of report is 2, indicating this is a report from a study and the message receiver identifier is CDER IND EXEMPT BA BE, then this Pre-ANDA Number Where AE Occurred becomes a required data element, according to the business rule. And also, please remember that this

pre-ANDA number must be a valid one for processing and routing.

In addition to correctly identifying and routing the ICSRs, it is also important to identify drugs the subject was exposed to. In E2B (R3) ICH data element G.k.2.2 titled Medicinal product Name as Reported by the Primary Source will be used to report the proprietary name of the product. And ICH data element G.k.2.3.r.1 will be used to report drug substance name. If there's no proprietary name, please report only drug substance name.

And it is also important to characterize the role of a drug in the data element G.k.1. You can select the values for the role of the drug: 1 for the suspect, 2 for concomitant and 3 for interacting drug. You'll also have the element value of 4 to indicate Drug not administered. Occasionally, this situation is observed in the IND-exempt BA/BE studies where the subject experienced serious adverse event without being exposed to a study drug. For example, if the subject was signed the consent form

for an IND-exempt bioequivalence study, has an accident and was hospitalized even before the study drug was administered, because of the outcome of hospitalization, that accident would constitute a serious adverse event that must be reported to the FDA. And this would be the case that where Drug not administered value can be used.

There's an FDA regional data element titled, FDA Additional Information on Drug. This is a data element with maximum length of 2 and a numeric type data with conformance rule of conditional required. So if FDA C.5.5b includes the Pre-ANDA number, any drug exposure is required to have at least one of these data elements listed in this table. 1 for test, 2 for reference, and NA for all other drugs or if information is not available. This data element is unique to the OGD and an important one for us to understand the correct drug exposure in reviewing the pre-market safety reports.

In this presentation, I have highlighted some data elements required to

successfully submit the IND-exempt BA/BE study safety reports. However, as you have heard earlier today, there are a lot of other data elements necessary to make up a successful electronic pre-market submission. So I highly recommend referring to Technical Specification Document for more information on other ICH and regional E2B data elements.

To support this transition sample xml files are made available at the FAERS website. Please feel free to take a look and let us know if you have any questions. Finally, please review acknowledgements and notifications as you start submitting the electronic pre-market safety reports. These will indicate status of submission whether the submissions are accepted or rejected. And in case of rejection, the reason for rejection after submission. Again, the FAERS electronic submission coordinator is available to help with any issues.

I would like to end this presentation with encouragement to the companies considering voluntarily electronic submission of IND-exempt BA/BE

safety reports by reviewing the advantages listed in this slide. First of all, the pre-market safety reports will not be in the public space. FAERS II will use specific data elements to identify pre-market safety reports and sequester them from post-market reports that are available in the public portal. And secondly, for efficiency purposes. If not all, most of the pharmaceutical companies with approved products already have a pharmacovigilance system in place. And if you are here listening to our presentation, the chances are very high your company already has IT systems that support E2B submission of post-market safety reports to FAERS. IND and Bio-IND pre-market safety reports will be required in electronic format. It just makes sense for efficiency purpose to have all safety data in one submission method, including IND-exempt BA/BE safety reports, with the added benefit of automated confirmation of receipt.

Another advantage of submitting IND-exempt BA/BE safety reports in electronic format is supporting generic drug pharmacovigilance. This

transition will improve generic drug safety, signal detection and enhanced data management and analytics both in your own drug safety system, as well as the regulatory environment at FDA.

So with this, I would like to end the presentation with acknowledgement to my division management as well as Suranjan. Thank you for joining us and looking forward to engaging with you during the Q&A session.

And now, I'll give the podium back to Suranjan. Thank you.

MR. DE: All right. Thank you, Jung.

Okay. So with that, we will get into the next area of the presentation, which will be the validation and implementation.

So when we talk about validation, what we're talking about here is how do you validate your XML file that you have generated. How do you test that, how do you make sure that the files are good and will be accepted. So during once, maybe if, you generated your first XML file, you need to be (R3),

which includes the FDA's regional extension, now you want to test that. So how would we do all that and so we go into some of the specifics as to how this can be done.

So the mechanism provided into the (R3), so every rule provided a mechanism for industry to validate the regional E2B (R3) XML files. The mechanism can be used and will be available to -- can be used to pre-validate prior to production submission and it will be available to everyone through a public URL. The URL will be posted on the FAERS Electronic Submission webpage. You can, and I will show you in the next screen, as to how that validator looks like. But the validator is somewhere where you can upload a file and say validate and test the file. But when you uploading the file these files are not stored with us. It's for temporary validation and it will tell you all the issues that the file has, or it will say that the XML is valid, which means, you know, when you submit through the Gateway, the data will -- and the file will be accepted. Okay?

So in order to do that basic validation, let's see how the validator screen typically will kind of look like. So here is the mechanism for to validate E2B (R), either E2B file. So if you look here, that on the screen there is a browse button. When we link, that will be provided on the Electronic Submission page. When you click on that link updates will open up which will say E2B Validator. You can browse and pick the XML file that you want to test and show your source, which will say FDA_R3, which means we are using the (R3), you know, we are sending to the (R3) structure that you have picked. And with regional elements of (R3). The XML file is shown here, what the file is. And then, basically, you have -- you will have a button which will say validate. And you probably will not have the converter XML, because that too actually have -- can also convert and (R2) to an (R3). We will have not be providing that. We just providing to validate your (R3). So you'll have a validate button and as soon as you click on the validate button, you will see the

list of issues that the XML file has and it's in the screen you see here at the bottom, it displays the list of issues that that file have. If there were no issues, it will say it's a valid XML and -- and then you are good to go to submit this.

Now, again, remember that when you're using this validator, this validator is something that you will use just for a temporary period of time. I mean, we don't want you to before every submission, production submission, you are going to the validator and validating it. Because you might have so many submissions and this validator can only validate one XML at a time. Right? So the idea here is that when you are doing your validation, any issues that are identified, you will probably go back and fix that in your safety database so that this issue doesn't happen for the ICSR you just validated and for any future ICSRs that you will generate from there. So this validator is more than way of checking everything is good, so that you have a process running and you probably don't have to come to this validator anymore.

So this validator will be more used through kind of a first-time thing. But once you've corrected everything, you probably don't have to come to this validator anymore.

So then to this will actually give, you know, a way for you to test, rather than emailing us and depending on FDA to respond back every time, this validator will really help you to expedite your validation. Okay?

Now, with this validator, the next thing is we go into what some of the implementation plans are and where we are. Right? We have list of regional specifications, there are certain things that we have here. We published a regional specification. We published on April 2022, and the link below here kind of give you whether it's published. We also have some updates in August of 2022, I believe, and then we had some updates in January, I think, again. Because as we are implementing, especially that spreadsheet of those core and regional elements have been updated. But we are almost there, I mean, there is no major

changes to those. There's one or two business rules, you know, but the data elements are still the same, the active rules are still the same, there's no changes to that.

Any progress, what we have is to investments, so we are enhancing both of the tools that we have, which is the LSMB Tool and the Audit Subject Tool to include regional extensions so that each of these tools is used for, which is to and from -- which is used for case processing that we do. And then, we have the Audit Subject Tool, which is used for data analytics and several -- and because of (R3) elements, they all have to be -- and regional elements, they all have to be enhanced and updated. And also downstream system enhancements because we also have some downstream systems this data goes to that also need to be enhanced. So that role is now in progress. The Gateway is set-up. I think we have completed that for pre-production environments set-up up for routing ID. And set-up up has been completed for inbound and outbound folder, so the set-up up for

ESG is completed. We are now, we have yet to start the system testing because I think that just only may have started because we just got release from the tool, release back from the tool vendor, so we staring the testing, probably not as much as deployed and it fixes our issues and identifies what issues need to be fixed, so that system testing, so that's basically will be happening. It started to happen, and it was a continuous process so as we find issues we will go back and forth with the vendor to make sure that the issues are fixed. Then we want to do some pure industrial testing, which is just with a few companies we want to do in this, just that we cannot do more than eight or nine. We have identified a few, we have got some responses from a few. We will be just testing with them, but again, I said that the violation tool, which we saw in the -- in the previous slide will be available very soon. I believe that testing is going on for the validation code right now, so that will be available. You can do as much testing as you want, even though, you know, you have not been

invited to do specific testing. But you can do as much as -- testing as you want. And we will test both pre and post-market ICSRs for these, some companies with the viable Gateway. You know, testing like times will be late summer, some time in probably July/August, and we'll have also a second round of testing sometime in October if any issues show up and test the E2B validator so as we showed the previous thing that you do validator, you can test there as much as you want in that validator. There is no, you know, there's no limit to that. You can test as many -- as many times as you want.

At the end of the day, we will be basically, especially for those specifications for testing, we will be providing like S progress and all that. But for everybody else, you know, again, I repeat that the E2B validator will be available, and you can go and test that. Because I think the first step will be to make sure that XML file is correct and it's a valid XML file. So that will take some steps to be done.

Gateway testing, it's the same gateway testing, except that, you know, you have to route it to a different location. You know, if you want to send something that you are not ready, you have looked everything through the E2B validator, your XML file is approved, everything is set-up, now it's just -- you want to just test the acknowledgements, just let us know to faersesub@fda.hhs.gov and we will work with you to, you know, get some of those XML files that you can submit through a pre-production on test gateway and have acknowledgements. Because you should already get acknowledgements once you start submitting through the pre-production of the test gateway.

And public communication, we are communicating by SBI Conference, we have G-Prod meeting, which is happening today, we have some BI conferences and our page on the Electronic Submission webpage will be updated. Right now, the way you see the Electronic Submission webpage for FAERS, pre-market at the top, post-market is at the bottom, we're going to have separate pages for E2B (R3) and then --

and then separate for (R2) so that, you know, eventually at some point, we will break out (R2). There's no date yet in regards to (R2), so we'll have two separate pages so that we can redact that page when we redact (R2). And we are preparing Q&As for the technical specs onboarding and any inquiries, so this Q&A, as you are submitting a Q&A here, and with all the communication, the first that we've had, we are using those questions to prepare the Q&A and we will be posting that, you know, sometime as we come close to the implementation date.

Lastly, we actually have the communication go live date that will be communicate to the FAERS Electronic Submission page. We don't have an ETA, we just heard that, you know, we are trying to get something done by end of this year for voluntary submission of IND Safety Reports. But until that date you get, you know, we are ready, sponsors continue to submit pre-market ICSRs and post-market ICSRs in the ECPD and the E2B (R2) format respectively, until FAERS is ready for (R3). So please do not start submitting

(R3). Let us all be ready fist and then you guys, you all can then start submitting during the voluntary period. Okay. So until then, eCTD and E2B, of pre and post-market respectively.

Okay. All right. Next. Sponsors should notify when they're ready for the first production submission. Just as a courtesy so that we all know that you will be submitting so that we can keep an eye on it that you're first submission in (R3), and we all have been done through (R2), but first submission in (R3), we'll keep an eye on that. And all submissions regarding, you know test -- regarding testing must be sent to faersesub@fda.hhs.gov, with subject line asking to be (R3) testing. So that, actually, that helps us that you want to go through some E2B (R3) testing.

Now, if you look at this timeline, so I can give you some points on this timeline what the standard is saying. So we don't have a date. Okay. We don't have a date when FDA goes live with E2B (R3) and the safety reporting portal. Okay. Consider that

date as 00. Okay? Consider that date as 00. So from the 00, to all the way up to year two, you have the volume needed to submit the ICSRs in E2B (R3) format. Because many companies will be preparing for E2B (R3). Some companies may be ready. But during that period, as you're getting ready to start submitting in E2B (R3) format. Okay. Now, you get two years, so you're at two cups, this is where you have mandatory ICSR submission by the ESG or the SRP. And from that point onwards, you have to go into mandatory ICSR submission using E2B (R3) format or by SRP. So this is how the -- would work. Now, when is it 00, when is the 00, as we said? End of this year. We are trying to make that 00, but please don't hold that to us. We're trying our best with all the condenses that we have that, as I said, if we will notify 30-days before when FDA is basically ready to accept E2B (R3). 30-days prior to when we can become ready, yes.

Now, a few suggestions or recommendations here for all of you. It's during the voluntary submission period, for pre-market ICSRs.

Okay. And I'm talking about pre-market ICSRs, you literally can use the Safety Reporting Portal for submission, if you can. Because what it will give you is if you go to the Safety Reporting Portal, we'll get you an account, you can then enter your own safety report ID on what we call is a Manufacturer Control Number or MCN. You can use your own safety report ID. The advantage that it gives you is that you don't have to now submit 1571 or the cover letter and it eliminates sending the report to your company's area prefix. Right? Is not mandated. Let me repeat, it is not mandated. Because you have an advantage and we also have an advantage that the report is only electronic because if at that time you're submitting through the SRP during that voluntary submission period until you are ready, with E2B (R3), but it's a web-based form, we'll have the data -- we'll have the data until, you know, OCR or whatever we do. And data into it and make sure things are coded and all that all that. The Safety Reporting Portal, whose active duties are also a win for us. Okay.

So that is one choice that you have. You can do that. So during that year, you go into year two, you can use the Safety Reporting Portal until you are ready to submit through the Gateway. But once you -- once ready to submit pre-market safety report, you need to be (R3) format via Gateway, then you notify us, and we can deactivate the SRP account. And once you deactivate it, as I said at this time, you cannot submit to both methods at the same time. We will deactivate that account and then from that point onwards you will be submitting the E2B (R3) XML file through the Gateway. Okay.

So in your choice, you can let us know and we will walk through to, you know, get you an account, so. It takes again, as I said, it takes about five business days, so the sooner you could do the better it will be and if every company starts coming like this, you know, we will have probably get into some backlogs so, you know, when we notify this to you and when we are ready, we'll notify this to you, if you want to submit through the Safety

Reporting Portal, please let us know once we have notified to you that we are ready so that we can create your account. Okay?

So data submission change that may happen once you move to E2B (R3) for IND Safety Reports. So the change that will happen is, here's what is happening. So this picture kind of shows what is happening today. You have the sponsor, you submit a letter up front to eCTD, it goes to our Gateway. We have our re-submission database that the data goes to. And then front there, we keep that and we will send it back to FAERS and which means that the network has to be data entered into the FAERS database. And so we will have it in FAERS. So that is the process that will happen before the first two years.

Now, once that two years is over, okay, if you have done -- completed and are ready to submit E2B (R3), within that -- within that two years this is what will happen. So, yes, what will happen now is that your sponsors will submit the E2B XML to the Gateway and from that Gateway, it will still go into

FAERS. So which means, you don't have to submit that MedWatch, just on about the MedWatch, to the eCTD and won't be in on the new to submission database because it's already going into FAERS, like all the post-market reports. And eliminate a step, be save a step in FDA to not take that MedWatch and enter it into FAERS. Right? Because the XML has already come and the XML sending to the Gateway will send you an acknowledgement back to your safety data -- an acknowledgement back which will be in your safety database and two acknowledgements will go there so that is a record for you that we have submitted the (R3) safety reports to at the end. So this will be the process that -- the change that will happen when you move fully into submitting IND Safety Reports using E2B. Okay?

So now, going into rejections and warnings. I want to focus little bit on the rejections and warnings because rejection and warning, that's very important that things will get anywhere rejected and you will all want to be aware of that.

So our saying is we recommend, do not include greater that hundred ICSRs in a single batch. It really helps us, and it really helps us in -- it probably helps you all too. Maybe the file, because it doesn't create a huge, large file. It's also easy in transmission, smaller files. It's easy to parse and load into our FAERS database and then soon I'll be able to send acknowledgements, you know, sooner, quicker, faster than having large batches. So if you have, let's say 300 ICSRs to be sent, you know, send three batches each with 100 ICSRs. And that will also be processing much faster. Also, ICSRs in a single batch must have the same sender. So the sender information that you have, the batch that you have for sender, the sender, what do you call, the batch -- the sender identifiers, it must be the same in a single batch. Right? You cannot -- please do not use different sender identifiers in one batch. Right? So one batch would have 100 ICSRs and they can be from the same sender.

All the ISCR batch must be for a common receiver. What do we mean by this? That means

batching all post-market ICSRs together. Okay. Or all of them -- and I'll give an example, all pre-market receiver together. All right. So do not put pre and post-market in one batch and send it to us. Right? Because, like I said, very important that data does not go public. So that's why submitting it out will always make it easy for us to catch that and be put into different buckets, so they are not published publicly. So do not mix pre-market ICSRs for CDER with CBER, or pre-market ICSRs with post-market ICSRs in the same batch. Okay?

Again, I have this data table here. Right? A very important table. So follow this table and submit your batches, also.

All ICSRs must be coded in the latest version of MedDRA, you understand that. Another important area to note on rejection is, do not send initial and follow-up reports in the same batch. If you send initial and follow-up, it will be difficult to know, and we may anticipate the follow-up as initial first. So if you put it in separate batches,

then we know which came first, which came next. Do not send follow-ups in the same case, in the same batch. Right? That means you're sending that batch at that point, you know, in case you have forgotten about the follow-up if you were going to send that, and most, I mean 98 percent of the time, I would believe that, you know, when you're sending that and completed the report and follow the batch, you know, you should not have two follow ups in the same batch. So please keep that in mind. Okay?

Next, do not submit modification or amendment ICSRs in the initial report. If you have a modification, it can't be the initial report because only have the initial report we will know that you are sending a modification. Right? So do not send modification or an amendment. In the way we have the initial report, you will not know about an amendment so your amended report cannot be the initial report and your modification report cannot be the initial report. Okay?

So there are other regions where, you

know, specific rejection and warnings, but these are many reason there are rejections that are related to what ICH has said. These ones, which you will see now, are specifically what FDA says. So this has -- was extracted from that spreadsheet, the ones which are regional. Okay. That is regional extensions.

So back to receiver identifier, we talked about that, that ICSR sent to post-market route should not have a value ZZFDA. Should not have the sent to -- sorry. Yeah. Back to receiver identifier, which is saying that ICSR send to -- so that there has come we have rejected that and we're saying that ICSRs were sent to post-market route, it should be other way around. So oh, they're saying to you that the ICSR you send to the post-market route does not have the value ZZFDA, so that's why this error shows up. The next one say the ICSR sent to the pre-market route does not have the value ZZFDA and is called pre-market. That's why this error has shown up.

Then the message receiver identifier, so N.2.r.2 provided is not seen SR reports and does

not match with N.1.3. So the N.1.3 is basically the message that sender identifier, I believe. So they do match, and it should be the same for all the reports. They have a message receiver identifier. In this are two rules that if N.1.4 is ZZFDA then N.2.r.3 is not CDER. That's why the error message came and then similarly, you have N.1.4 is pre-market, ZZFDA is pre-market, but N.2.r.3 is not this, these values. So that's where it errors have shown up.

Then you have type of report. If N.1.4 is pre-market, then you know C.1.3 must, is not 2. It should be 2 clearly, you know, it says removed from study. Documents held by the sender must be put here as C.1.6.1 is true, we have documents that are to be included and the last one here.

The last one I want to show on this slide is that the case footprint and criteria. We talked about this, we said that your initial report cannot have a value of NI, because you have to say does it contain criteria, true or false. The initial report cannot have the value of NI.

Other regional -- some other data points, local criteria report type. So the local criteria report type, we don't know when these errors will come. So you will get a error if your B.S.e.1.7.1 must have the observation code value of 1 or 4, when in a B.S.e.1.12, which I think is combination product, and C.1.7 is true. So these are some of the data values that checks will happen for the local criteria report value and get you a rejection.

There are two warnings here, which is identification number of the report, which is linked to the report, so Veronica talked about the links reports for aggregate. So should be, so C.1.10 simply provided when B.1 is aggregate. Will -- not able to give you a warning, but we would like it to. Correct it the next time.

Study medical reaction. So if you have C.5.4 should be 1 when B.1 is aggregate. So I think there is an alternate rule saying that if you have type of report is report from study, then you still

need to have the study type which should be 1, clinical trial. So that should be there, but then we are asking you to also have the patient D1 as aggregate.

ID Number as adverse encounter, very important here. It's C.5.5a must be provided when C.1.3.2 is report from study and N.2.r.2 is CDER IND or CBER IND. Same with the pre-ANDA number. And IND number for cross-reporter IND. So if it's not provided, if this particular field is not provided our nullflavor is not referred to as NA. When you have the IND number, the participant number there, the participant number is provided. So if you don't fill this field up and you don't say it's not applicable it will get an error because you said it is NI, you said that IND number where it wasn't even occurred is there.

So next field we have elements is patient initial. We talked about the aggregate. We did talk about, oh. There's on important thing. If a patient it says, D1 must have a nullflavor NA when FDA

C.1.12. which is, I think, this is for accommodation products, is true. And FDA G.k.12.r.1 is true. That means is non-function and E.i.2.1.b is report to that Med Report, which is no adverse event. So which means there was no adverse event, there was only malfunction. It wasn't a combination product, so D.1 must use the nullflavor, NA. Because it was not of any patient. It was a non-function that happened and there is no patient involved.

Date of death, we talked about patient race and ethnicity also. We talked about that when you have, you can put it as nullflavor NA and the D.1 is provided as NA, some on your aggregate that means there's no patient here or there's a group of patient here.

Characterization of drug rule also we did talk about. The specific rules here. Right? And then we have -- and then we have FDA other characterization.

We talked of the similar device and lastly in the slide before we take a break it is about

some data elements that we have like the source of assessment, the method of assessment. I mean, they need to be provided when you have -- when you have IND event, adverse event occur. Value is there and then you have it's a report from study, then you have to provide these values. Then we'll have the malfunction flag because you're talking about the malfunction then you're talking about a combination product, so you need to let us know if it is true or false. We have the device problem code, because if malfunction, you have to let us know what these problem codes are then we need to have the rules for the common device name because as we talked about the rules, if we have to have -- if you have a device brand name or common device name, it you don't have, actually, common device name or brand name you need to provide us with the device product code and also the device brand name and device common device name is required when it's a combination product. But if you don't have it, you will submit it as no information, but then give us the device product code.

And so with that, we are at 1:45 and we will take a break of 15-minutes and come back at 2:00 p.m. and then go into some of the areas with OIDs and forward compatibility and then eventually close up with Q&A. Okay? So thank you and we will join back at two.

(Off the record.)

MR. DE: All right. So welcome back.

The next two topics are talking about FDA specific object identifiers so going into the next slide, which is the object identifier, let's talk about -- let's just -- you know, let me talk about what this is and how we have set-up this up for the regional elements in FAERS.

So an object identifier is a sequence of numbers that numerically identifies an object. And the reason I'm saying this is because you will find some object identifiers you may not recognize and just to give you what one of these identifiers are, I think it would be useful when you see the X fact what the identifiers are and what values you need to send in

the X amount of those identifiers.

So each of OID corresponds to a known in the product tree, in the hierarchy. So it is formally defined using the International Telecommunication Unions added to you for each standard X.6.6.0. The rule of the tree contains the following three -- you have zero that is the International Telecommunication Union, you have 1, which is for ISO and 2 which is joint ISO and ITU. So if you look at any of these value numbers, if it like starts with a 2 that means it was a tree and is a joint value between ISO and ITU. These numbers are written either as a string of digits separated buy dots or as a list of named branches. So to give you an example of MedDRA it should be of those. If identified by the OID 2.16.840.1.113883.6.163. So what does it mean? That means that this object identifier in the Union guide could identify anyone if they use this OID number. And the OID number, every number has got some significance, which is that it is 2, starts with a 2, which means it's a joint ISO and

ITU. 16 identifies the country, and 14 is U.S. 1 is an organization. 113883 is an HL7 standard. And then you have external code system, which is 6. And then you have 163 which points to MedDRA. So which means that the data point it says MedDRA code was OID will be 2.16.840.1.113883.6.163. That is how this has been set-up up.

So let's go into the HL7 the UN pharmaceutical base. This is a bit informal and from here we went into identifying how will be identifying specifically that element, that regional element and define that. Right? So this is a huge complex model. So in that complex model, we look for and how do we define some of the regional data elements. So going into the next slide, going into like the type of report you see the investigation characteristics. That's the class that we took, the HL7 with the CE as the data type. Okay? If you look at the data type for this data element, the type of it, it shows as an example. We already have the type of reports. It shows as an example that you have the core system,

which is a OID, and it is a data type which is CE, you know, and the value type would be, OBS in observation would be in a data type any and then the use of the C, C for this instance has been used. So as I said, it's an ICH report type and we just showed you the type of report, C.1.3 because using that same concept we, you, we created the regional data element, which is a local criteria report type. So if you look at the local criteria report type, the only difference is the code system that we have, it says 2.16.840.1.113.883.3.989. Then you have .5.1.2.1.1.1 and we'll tell you what each of these actually means.

And so going to the next slide, we have another example of study administration number and we're showing, you know, what the root is and what the extension is, so which is taken from the study's registration class and -- and then that you'll have the instance added to five, which is an extension STN the UID rule that we have. This is just to give you an example of and the type 2 data type that we have.

Now, comes the FDA point, and if you

look at this, you see the ICHR. So when we talk about 5.1.2, up to 989, we are all clear that this stands out all the way up to ICH. Then we have the regional specialized, which is 5. Then we have the sub-region 1 FDA, which is 2. And then after FDA, we have using if for FAERS, which will be 1 or if it was used for eCTD, it will be 2. So that is how the OID, FDA OID, has been set-up up. So it goes all the way up to ICH, then it has the regional specialized in sub-region and then FDA. Some other region, maybe 3, some other region maybe 4, some other region -- FDA region 5, so that FDA which is 2 is 2 for FDA, it could be 3 for some other region and 4 for some other and so on, so forth. All right?

But if you go into the next slide. Okay. So in here, now, let's look at the entire thing, which goes all the way up to 5121. So you have the joint ISO/ITU. You have the country, the U.S., 840. Organization, which is 1, HL7 which is 113883. External group uses 3, ICH 989, regional specialized is 5 sub-region 1, FDA 2, FAERS 1. Now, we have a

data element called local criteria report type. Right? So that local criteria report type is .1. So at the end you'll see the .1, that's the local criteria report type. So now we know that why that OID is there because it's the regional feed and looking at all that, we'll exactly know that this local criteria report type is specific to FDA and not any other group or any other region.

But then, they have the operator for the device. So the operator for the device, if you look at, it's .2. So we go through all the way. Right. Now, you have the code list, which is 51 -- 512 and FAERS is 1, then you have the code list for that local criteria report type is 1 and the value in that is .1. So when you go to that .1, it tells you that these are the values, 1, 2, 3, 4, 5. Then you have the operator of the device, which has a value of 1, 2, 3. How do you define that value, 1, 2, 3, that we go all the way up to .2 at the end, which takes us to the value. So which means 5 becomes -- so FAERS is 1, which is the third number from the right. And then

you have 1, which is in red, then .1, which means a support list, and then 6, operator of the device is 3. So these are the values for that, the OID values for those three. When you have -- these are part codeless values. Then you have names pieces. So when you have a names piece, the last digit after that 1 is .2 and then you have IND number where adverse event occurred. So .2.1, then becomes that OID for IND number where it was to have occurred. So which means the IND number for this report number is 2 is joined by ISO/ITU, country is 16, U.S. 840, organization is 1, 113883 is the HL7 code, the external use rule is 3989, it is for ICH. The regional specialized is 5, then you have sub-region as 1, then you have FDA as 2, then you have FAERS as 1, then you have name space as 2 and then the last one is 1, which means it's for IND number and -- number. So if you take that same concept, the pre-ANDA number that occurred is goes that way. So it's .2 at the end for that.

If you have an observation code, so you have combination product flag. Right? Observation

code of true or false, then the observation code goes as the ICH is 989, then you have a regional specialized as 5, sub-region as 1 and FDA is 2, FAERS is 1, and then .3 is for observation code. So .1 is codeless, .2 is name space, .3 is observation code. And now, we have a combination product fact which is .3.1. We have the single use device which is .3.2, and so already we will have for remedial action .3.3. So that is how the FDA FAERS OIDs are being set-up up. So tomorrow if you have any other new data points, that is how the OIDs will be set-up up for that. So that is how you will expect the OIDs to be defined and to be used.

All right. So this is basically all about FDA OIDs as the keeper of this knowledge that I wanted to share so that you have an idea how FDA OIDs are being utilized. Okay.

So with that, we are going to go into the next topic which is, there's been some questions, on (R2) to (R3) regional forward compatibility. So what is this regional forward compatibility? So you

have been submitting into E2B (R2) through FAERS, through the Gateway. When we move to (R3) what all regional data elements that we have in (R2) that a submitter needs to take care in (R3). Right? So it is very important for us to know that. Now, there are also forward compatibility for all of the ICH data elements that needs to be also considered along with the regional forward compatibility. We did not put anything about the core ICH elements because they are already available from ICH. We've been talking about basically the regional forward compatibility and this list of tables that you will see in the next few slides; they are also available on the FAERS Electronic Submission webpage and then they go, remember what this morning -- the documentation of the packages, the implementation packages that you have, what document was that. Okay?

So the first few elements, the way this forward compatibility is set-up up, the table, that you have a rule, it shows you what the regional (R2) field is, what the description of the field is, what

the (R2) values are and then it goes into what does it map to the regional field (R3), the description of the regional field, what the codeless values are and the comment that tells you, you know, how the things need to be mapped. Okay.

So let's take a few elements here and go over these elements for forward compatibility. So we have a rule, FDA01. That rule says that for element A19 and (R2) element does at least fulfill locale criteria for expected report. The values used to be 1, 2, 4, 5, 6, 15-day, expedited, five day, 30-day, seven-day. But now, what has happened is that this field now in (R2) now in (R3) is a Boolean field -- now that this needs to map to in (R3). In (R2) this needs to map to the regional extension field called local criteria report type, FDA.C.1.7.1. It has those values, I think that the values are called expedite, non-expedited now. But still, the value is 2. And we map 1, 2, 4, 5 and 6. Of course, 6 is not there. Sorry. That's -- we're not doing E2B (R2) for pre-market, so 6 is not there. So when I do 4 and 5

should be mapped to 1, 2, 4 and 5 to this new field in (R3). Okay.

Another rule is combination product flag, so it's yes, no. In (R2) it's not set-up, which means empty in (R2). In (R2) it is A.1.FDA.15. In (R3), it's become a Boolean field and it a regional element here called combination product flag, but it's two-fold. So the mapping is yes goes to true, no goes to false. If it is not set-up in (R2), then use a nullflavor, NA, in (R3). Okay.

Then study guide. So again here, you have 1, 2, 3 then it goes to -- maps to the same thing. Study type, here, 1, 2, 3. This is a straightforward one.

Next one is malfunction. So malfunction flag that we have in (R2) is yes, no and not set-up. Like in (R3), it's true or false. Either there was a malfunction or there was no malfunction. For mapping yes to true and no to false. If not set-up in (R2), then set-up this field value to 4 and not 3. Okay.

Then we have, you know, correction and additional information response request. So we just say follow up or type of follow up. That's basically the field, so these are the values. We usually have separate tings for these fields in (R2), but in (R3) we have just one field and you can mention the value, I think you can repeat any of these in (R3), you can repeat it and you can have these values there. So how do you map it? The way you map it is if correction was yes, then you send a value of 1. If additional information was yes, that means you send the value of 2. So if correction was yes and additional information was yes, then you will send the necessary -- you will send correction and additional information. Right? As 1 and 2.

Since this is a repeating entity, that could be marked with values, each (R2) value as set-up up as repeatable values within the (R3) entity. If the value of (R2) field is null or not set-up, then don't need in (R3), you know, because it's not mandatory field. So but if you have a yes, if you

have yes for one or more of these (R2) data fields, then you will send it as a repeating type. Okay.

So we have the next few data elements where they were in (R2), they were all separate data elements, which is that remedial action initiator. In (R3) they become repeatable, same as the previous data element that I talked about. You could have markable values, each (R2) tab value is set-up up as a repeatable value with (R3) and if you just -- there's in no value -- if the answer is no or not set-up, you know, you don't send them. But if you have a value of yes, let's say, you had a recall and then you repair and then recall and then replace, both of these, then you will send in repeatable type in a 1 or 2 or a 1 or 3 and that's all you will send us in the XML.

Then you have, let me jump over into the evaluation value. So the evaluation value is interesting because we had a field called evaluation value, which now we only asking for device problem code. So if your evaluation value used to be 01 for device problems and used to be evaluation value 01 in

relation to code type, should use to be 01. And then you see evaluation value would be actual value of that device problem code. So we have a type and a value in (R2). In (R3), we just have device problem code. So you copy the value of the device problem code, when the (R2) tag has an evaluation type as 01, device problem code. Okay?

And later going, this is a repeatable field, so you know, you can have more than one device problem code. But to keep in mind that a device problem code from (R2) to (R3) is based on the evaluation type of 01, which stands for device problem. And the evaluation value will be the value which will go in the field device problem code. So since we are not asking for all other types of evaluation. We are asking only for the device problem code. Okay.

So the next few fields that we have here is, we have the brand name, that's a straightforward copy. We have the common device name and the product code, which is a straightforward copy.

We have the field rule for the manufacturer names, which is also straightforward copy. Device usage, again, it's a straightforward copy. Device lot number, again, straightforward copy. All taken off the device.

The operator of the device used to be a free text. Now, we have the values. So in (R2), map (R2) value of health professional. And we used to have free text, but we had, I think in (R2) we had still said even though it's a free text, it's an auditable list of the use of values of health professional and names or patient. So in such case, if you have a database for the operator of the device in (R2) was, you know, health professional, then in (R3) they become 1, if it is a lay user/patient, then it becomes a 2. Okay. And if (R2) value is not health professional or lay user, then set-up it to 3, which is other. Okay?

All right. Some more data fields. This does not require a forward compatibility, but I have shown it here just because it's a regional field.

Okay. So there will not be -- since (R2) does not have the patient race code data element compared to (R2) from (R3), when you are transferring the data you can use the nullflavor unknown. Okay? And then submit that for the follow ups. If you're able to capture the value, then of course, then you can use the value, which are here. But for data, let's say, you have already a case in the database, now you have the patient race code, and you don't have race code, send it as unknown and we should be good to go. The same thing with ethnicity code. That you send the value of unknown if you don't have the value.

Okay. Before I inter-mention, since you don't have the value, you know, from (R2) to (R3) you send it as NI, no information. And that's how you map something. (R2) does not have this, now you have your (R3) source to move your case of the follow up that you are submitting in (R3), we use the value NI in that case.

And then you have the characterization of the drug rule. Since that in (R2) has a value of

1, 2, 3 and 4, Okay. We did not have, you know, drug not administered, we had a value of 4 with similar device in (R2). That similar device now goes to FDA other characterization of drug, as similar device. So when you do that mapping from (R2) to (R3), you will map the (R2 value of similar device to 1 in (R3). And since G.k.1 is required, set-up the value to 4, drug not administered. So which means, your G.k.1 in such case will be 4, drug not administered, but any case where you had a similar device, regular value is 1.

So in summarizing the last one, if you have a case where characterization of the drug rule in (R2) was 4, you will migrate back to FDA other characterization of drug rule as 1, similar device, and make G.k.1 as drug not administered. Okay.

So with that, we go into a summary and let's see what we talk about today. Okay.

So today we talked about inter-relation of the E2B (R3) for both pre and post-market report at the same time. So whenever the increment and the day comes it will be both for post-market and pre-market.

Okay. And it will be both for SRP and Gateway, all happening at the same time. Okay.

Next, we have the new day for voluntary reporting will be communicated on the FAERS Electronic Submission webpage.

Next is, we talked about if the FDA regional code, regional -- sorry. We talked about E2B (R3) core and regional data elements and business rule, the document for all four ICH and regional extensions. So this was a document that Excel spreadsheet that we opened up where you were able to see all the different tabs in there, you did see all of, you know, what tabs are for what purpose. You saw the X file tab, you saw the actual elements tab, you saw the rules, the rejections, the warnings and so and so for the acknowledgment and all that that you saw in that document.

We talked about using controllable vocabularies, like EVS, GSRS and EDQM and so on. We expounded many times on the separate submission pack and we hold on on the separate submission pack and

business rules for IND versus IND-exempt, pre versus post-market, so many of my colleagues, who are also presented, they showed you that table, so it's a very important table to make sure that the table is followed and is aligned in your submission so that reports don't go public, especially for pre-market reports. Okay.

We talked about submission methods and mechanism based on AS2 header and routing ID.

All right. Next, we discussed also regional extensions, so we went into many of the data elements, almost all of the data elements, actually. We talked about extensions that included the data elements, which included any rules that were different, any -- any things, and conformance that were changed. All the rules were discussed today for IND, IND-exempt BA/BE and post-market safety report.

All right. We went into talking about validation and implementation. We talked about the E2B Validator, and I will repeat again that E2B Validator, once posted, you can use it when it is

posted and you should be able to use that to do your testing as you are developing and as I said, as you deliver XML, you can test it during the testing phase. And I also mentioned that, you know, the vendors, if they want to get into, want to do the testing, they can request for a testing web created account, which then you can test through the validator first, making sure their XML is all valid and then you can test your Gateway. For those developing IDs and you should be able to do that through the Web Creator test account. Okay.

Please let us know if you have any issues requesting those test accounts. You should -- it's straightforward. It's on the internet, it's on the fda.gov, how to request for those test accounts. E2B Validator, as I said, will be posted on the FAERS Electronic Submission web page. All right.

Then we have, we went over the regional specific rejections and warnings. So we saw all the different rules that we have for rejection. All the rules that we had for warning, and we went over the

list. And as I said, these are regional specific. There are code ICH specific rules, but what I talked about today is regional. For the core ones, you have to get into the Implementation Guide, look at the core rules. Today, FDA just talked about their regional specific rules.

We went through overview on the FDA OIDs, the regional extensions. How the FDA OIDs are set-up up, how those number are. Why those numbers are that way. And in future, if we have any new regional extensions or data points, new data points, that is how those OIDs will be used and that is how those OIDs will be, basically set-up up.

Of course, we will go into the HL7 more to look at the right location, the right data point that is to be used to define that field, you know, what type of data point, data field, but then the OIDs will come along with it. And, of course, if there are any observation code, then we will first look at the standard organization to make sure the observation codes are there before we create our report. Okay.

And lastly, we went through the (R2) to (R3) forward compatibility and regional elements. We went over some of those specific ones where we need to keep an eye on when you are moving from (R2) to (R3) when you, you know, do your submissions, do the testing with (R3) making sure that the forward compatibility rules are in line. Also, please make sure that along with the forward compatibility rules, that the regional elements that we talked about, please do not forget the core and ICH elements that are in the Implementation Guide of ICH, so you need to also look at that. One thing that we are not doing is once we're moving to (R2) to (R3), we are not moving back to (R2). We are not doing a backward compatibility of things. We might use some of the backward compatibility just for our internal purposes, just to making sure that certain data points are kind of populated from a perspective of, like for example, the data elements of seriousness, which is at the event level, we would want to roll it up at the case level, so how do you do that. So that's where we may

use it. But please, from a submission perspective, we're not going from -- if you move to (R3) you're not going to (R2) back. Okay.

And the (R2) to (R3) forward compatibility is only applicable for post-market safety reports. So that's where we today -- so with that, we will just the next slide is some of the references. These are all the documents that we have and so many places you have seen these document names wrote down, so these are accessible, we will add these links. You can go and download them and look at them.

So with that, we will take a short -- we'll come back at 2:40, it's 2:36. We'll come back at 2:40 to now start answering question and answers that you have been submitting throughout the day. All right? Thank you and we'll see you in four minutes.

(Off the record.)

MR. DE: All right. All right.

So we are back, and we will start with some of the questions that we have for IND Safety Reporting. And so far, that Veronica, I ask you to,

you know, repeat the question and then give a response.

DR. PEI: Okay. Thank you.

The first question is, "Could you please confirm that for IND cross-reporting, sponsors will submit only one report to primary study IND and list all INDs in the report that requires cross-reporting. Is that correct?" And the answer is, yes.

The second question is, "For the date of death, and if you remember that element is D.9.1, you advised as if result in death that element is E.1.3.2a, and if that value is true then date of death is required. However, it was not mentioned that the nullflavor is accepted for this value. Is the nullflavor accepted?" And again, the answer here is yes. It is correct. So just to clarify it, so the date of death is required if the death value is true. But it's not -- you don't have -- if you have a null value, such as MSK mask or ASKU, which is ask unknown and the NASK not asked, you can use those three null values for the date of death.

Another question is, "Regarding analysis of similar events requirement for IND Safety Reporting, is there a specific data element where this information should be provided?" So the answer to that question is, no. There is no specific data element for the analysis of similar events.

The second part of the question is, refers to, "Where to report this information?" And we would recommend that you report this information in the narrative portion of your submission.

MR. DE: All right. Thank you, Veronica.

So my next, I will request Jung Lee to answer some of the question or give response to some of the questions that she has -- that has been asked specifically to the IND-exempt BA/BE.

MS. LEE: Thank you, Suranjan.

So the question is, "How do I identify the product name for a study drug?" The submitters should use the drug substance name (the non-proprietary name) in the G.k.2.3.r.1 and proprietary

name in G.k.2.2 to answer the question. The name should fit within the established E2B character lengths.

The second question is, "What study drug should be identified in the IND-exempt BA/BE study reports?" Submitter should report all drugs to which the subject was exposed using the appropriate E2B data fields referenced in the Technical Specification Document.

The next question is, "How do I classify the subject's drug exposures?" Each of the subject's drug exposures should fit into one of the following classifications: first, Past Drug Therapy, second, Drug Exposure During Study Enrollment and Follow-up Period. For the Past Drug Therapy, they should include any drug the subject was taking prior to study enrollment that was discontinued prior to study initiation. These drugs should be reported using the E2B data element D.8.r, Relevant Past Drug History.

Secondly, for the Drug Exposure During

Study Enrollment and Follow-up Period, drug exposure during study enrollment may include the test drug reference, placebo, vehicle and/or other drugs (such as an allowed concomitant drug) administered to the subject during the study or protocol-defined follow-up period.

Question number four, "What are the appropriate descriptions of data elements for reporting subject drug exposures that occur after enrollment in the BA/BE study?" As in my presentation, there are three important key components to remember when reporting the drug exposures. One is the name of the drug. Give us the proprietary name or substance name if there's no proprietary name. Second of all, give us the role of the drug played. Was it a suspect drug, a concomitant drug, an interactive drug or was no drug administered at all? Third and the last component mentioned was, "Is this a test or reference drug?" If unknown or neither, then let us know by flagging that as NA.

And the next question is, "What does no

exposure mean for purposes of electronic submission of these expedited safety reports?" A subject that has no exposure to a study drug if the subject experienced an SAE after study enrollment but prior to study drug exposure. Such an event meets the FDA's expedited reporting requirements. To report an SAE that occurred without any study exposure during IND-exempt BA/BE study, the submitter should select G.k.1 4 = Drug not administered, with G.k.2.2 for proprietary name [if available] and G.k.2.3.r.1 for [test] drug substance name, and FDA.G.k.10.a.r, number one for test drug.

That's all for me. Thank you.

MR. DE: All right. Thank you, Jung.

So this is Suranjan, and I will go into some of the questions, so.

Question number 1, "There is a nullflavors, non-values on the backward/forward compatibility mapping Excel under the BA/BE material. Will the spreadsheet be corrected, or the null values are intentional?" Yes, the null values are

intentional because you're doing a forward/backward compatibility review, so you know, sometimes a value cannot be appropriate or the value cannot be transferred back or, you know, there are values that the field may be a mandatory field. So you have to have a value, so that's why you use a nullflavor.

The second question is, "Please confirm if we can send picture or articles as E2B (R3) attachment to the FDA?" Yes. The technical specification document says that, and you could submit that. Also, it has a reference that you could submit.

"Will there be accept XML files with nullflavor?" Yes, the E2B (R3) will accept XML files with nullflavor. Again, this is only for E2B (R3), E2B (R3). If it doesn't have a file, will accept nullflavor.

Okay. "For a small business sponsor that has a ESG account, but does not have in house XML capability, are they able to submit ICSRs through SRP?" Yes. They will be able to submit ICSRs through SRP.

Okay. "Then, can we upload an XML file in SRP, instead of actually entering it manually?" No. Please do not do that because that will not get processed. The whole purpose of SRP is you have the screens where you can submit to the -- that you can submit other work, so they are structured.

One thing that I did not mention is part of the questions that have come over the slides today. Yes, all the slides, all the presentations and the recording will be all posted on the FDA's meeting page where you have the Zoom link. So they all will be posted within three to four business days. And so we will have them there, the slides will be there and the entire talk, the video, the presentation will also be there.

All right. Okay. "Is there any work being done to sync the fields and required fields between FAERS and MedWatch?" Yes, we have done. I mean many of the fields that we have for like, especially for VAERS and FAERS have been harmonized. We're using the same observation code, the same data

element and so on. The both fields have also been harmonized between MedWatch and FAERS because without that, you know, we really cannot get -- import the data into FAERS because sometimes you will have MedWatch, I mean the first MedWatch comes in different flavors, one is for consumers and health care professionals, one is for manufacturers.

Manufacturers really, from our perspective of IND Safety Reports, is manufacturers. Submitter MedWatch that we have mapped to FAERS, so yes. We have, doing this activity and most of them have been all harmonized.

Okay. "If you do have a patient name or initials for malfunction report without AE, should we not report this?" Because if you have a malfunction and there was no AE, you know, that means that the event did not occur on the patient, so in that case we will just make it consistent, we use NA for this -- for this report.

And then, "Regarding medicinal product name as reported, presumably it would be preferred to

use the coded product description followed by the trade name from company product library, rather than the verbatim?" True. But please make sure that they're your local trade name on a product description from the company product library matches with the SPL that you have submitted or with the active ingredient name that is in the GSRS.

There was a question about NDC codes, "You know, it's challenging to get NDC codes." Yes. Totally agree. "It's a challenge to get an NCD code. We may not get NDC codes for continuous reports." But what we are saying here, is if it is available the please report to us and if you are able to ask that and get that, please report to us. It is not a mandated field, you know, the product name is for post-marketing is mandated. So it's again, that if you have it, please report it.

"Regarding the specialized product category for combination product, would it just be entered or any combination product?" And the answer is yes.

Okay. Okay. So let's see.

Okay. I guess there is a question. "Is there additional mandatory data collection requirement for (R3)." No. Anything that has been listed today and is in the spreadsheet of Core and Regional Data Elements are the data elements and if they have been, if conformance is been set-up required, that means it's required. So that -- those will be the mandatory data elements. There may be some data elements that is conditionally required, based on another data element, so every element that is listed in there is available there.

"So when would we need to use the (R2) to (R3) format compatibility if you are submitting post-market safety reports today and then you move to an (R2) format and now you move to (R3) format?" You will need to use that forward compatibility document.

"So when will FAERS reporting in lieu of the ESG submission be required for safety reporting on investigation agent?" Again, as we said in the presentation that you should check with the FAERS

Electronic Submission webpage. The date will be, you know, we -- when FDA is ready from that point onwards, you will get two years to prepare yourself and then submit in a shorter timeline that from year 00 to year two, you can use SRP to submit while you are working on your Gateway submission or your XML. And once you're ready with your XML, then you can start submitting XML and we will deactivate the SRP account, so.

"Do submitters need to have FAERS and ESG account?" No. There's no specifically FAERS account, but there's an ESG account for submitting electronically. So but if you're submitting through the Safety Reporting Portal, yes. You need to have -- you need to have a -- a account created for Safety Reporting Portal.

There is one question which says, "Can we send EDQM terms instead of SPL?" We clarified that. You know, please try to send the SPL down first. If you don't have the SPL down, then send the EDQM down.

Okay. "After the voluntary period is over, the FDA will no longer accept E2B (R2) or will both (R2) and (R3) be accepted for a period of time after the mandatory date?" No. After the mandatory date we will want to move on over to E2B (R3) and so that we don't have to maintain two versions because, you know, companies are given almost two years from the day we go. That should be, you know, should be enough time for us to do that, you know, to get E2B (R3). So as I said, with the document (R3), we will go with that. Once we move to (R3) we move to (R3). We don't want to go to (R2) back again.

Okay. "Is there a field limitation to narrative? If so, if narrative goes over the limit will that automatically be truncated?" Yes. There is a field called narrative, which is 100,000 characters. And if it is goes above 100,000 characters, yes, it will get truncated. But you could -- we also have sender comments and reporter comments. You may -- you could probably also use it but mention in your narrative that additional comments are mentioned in

the sender's comments and then we can -- we can work that out that way.

So there is also another question is, "Which option, A or B, of reporting can valid testing be done on?" And you will basically for option A, valid testing will be done on.

"Is there a fee associated with ESG portal, or everybody can use the platforms?" The ESG Gateway Portal actually, if you have to do like a batch submission, there is a one stop certificate that has to be shared with the FDA. The certificate, actually, as I understand, costs some fee. That's why a lot or organizations, smaller organizations have not gone into there. If you use Web Creator, which is free, you cannot do batch submission. You can do one file submission at a time. That is for free and doesn't cost anything and if you use the Safety Reporting Portal, that also, the submission is one sub file at a time, or one ICSR at a time, which is also for free.

All right. So with that, we are -- any

-- any further -- any additional questions that you have we will request you to submit to the docket of the FR notice for this particular meeting. So you can submit to the docket, and we will go through to addressing those questions.

If any other questions that we have, we will also go back through to respond to you through the docket.

So with that, I'd like to thank everyone who have attend this e-prompt webinar. And for all of us, we hope that we have given enough information and good information for you to start your work in implementing E2B (R3) for submissions to FDA. We are also going in the FDA in full speed in trying to implement E2B (R3). So with that, our next talk about E2B (R3) will be at the Annual DIA and then the one next e-prompt meeting will be in November of this year.

So with that, I would like to end the meeting and thank you all for attending and providing your questions to this webinar. And thank you to our

other guest speakers, Veronica and Jung Lee. So really, thank you for your presentation.

And you all have a wonderful evening and a wonderful week.

Thank you.

(Whereupon, the meeting concluded at 4:49 p.m.)

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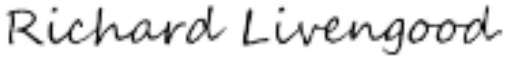

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