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Electronic Submission of Adverse Event Reports to FAERS Using ICH E2B(R3) Standards
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>> OPERATOR: Recording in progress.

(Background talking.)

>> SURANJAN DE: Nobody is on for the FDA meeting page. The event is going to give them a link.

(Background talking.)

>> SURANJAN DE: There is a problem.

All right. It's 9:00 o'clock.

All right.

All right. Good morning, everyone. And welcome to the first April meeting in 2023. So we are excited to discuss Reporting Premarket and Postmarket Safety Reports to FDA Using ICH E2B(R3) Standards. My name is Suranjan De. And I am the Deputy Director of regulatory science in Office of Surveillance and Epidemiology in CDER FDA. So welcome, everyone.

If you would -- 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 we can go to the next slide.

This is my disclosure.

And go to session overview. So what we will go over today. This session will review requirements for submitting safety reports for INDs, IND-exempt BA/BE studies and approved drug and therapeutic biologic products excluding vaccine, we are not going to be talking about vaccine using the ICH E2B(R3) format. Submission methods

and mechanisms. 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 reporting of IND and postmarket safety reports to be submitted in ICH E2B(R3) format we will let you know when that will happen and the implementation. And via FAERS through the gateway or through the Safety Reporting Portal. And understand the detail regional data elements that are key for postmarket, 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 will 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 kept some time at the end to talk about questions answered 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 with postmarket safety reports. I will also be talking about reporting mechanisms, some implementation plans.

So I am the Deputy Director of Regulatory Science Staff in Office of Surveillance and Epidemiology in CDER.

And later in the afternoon after lunch we are going to are -- we will have two more speakers.

One will be Veronica who will be talking about the IND safety reports and how they can be reported using ICH E2B (R3) standards she's a director of bioinformatics in Office of New Drugs in CDER.

And the third speaker is going to be Jung Lee. She will be talking about the IND-exempt BA/BE safety reports and how they are to be reported using ICH E2B (R3) standards. 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. 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, say around 10:15.

Then we will go into talking about the E2B(R3) implementation package.

So this is the regional implementation package that FDA has published on the product submission webpage. And we will talk about this package. It will start basically with sections such as what will be relevant for premarket. What will be

relevant for postmarket 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 through all of the different types of reports is what we will talk just before the lunch break.

Then there will be a lunch break from about 11:45 to 12:30.

And then talk about the postmarket safety reporting.

So here we will go deep dive into the specific elements, the regional elements, for market safety reporting.

Then we will have our speakers for the IND safety reporting.

And our speakers for BA/BE safety reporting for generic drugs.

Next we will talk about the validation and implementation. This will also include things like what other kinds of implementation where we are right now. And what are we doing.

Also talking about some of the rejection and rules we will talk about here with that implementation.

Then we go into a small break, 15 minutes. Then the last two areas we will be talking more about the audits, how FDA has defined audits for the regional data elements. And what are these audits and how these audits are defined.

Then we go into talking about the regional forward compatibility. Now, this is more applicability to postmarket because premarket, you know, it all comes through ECTB today.

So postmarket is the only thing which is an R2. And how can you move to R3?

And then finally, we will summarize everything. And then go into a Q&A.

So that's the agenda for today. And with that, let's type into the first slide under background.

So give me -- giving you a little bit of background, where we were and where we are going towards is that this was about a few years back, about three, four years back we had started doing some work with E2B R2.

And for premarket.

We already had postmarket.

And were planning to do with premarket. And we came into the implementation of FAERS. And during implementation, what we realized was, you know, if you do premarket -- we do R2 with premarket first, and then go to R3, it's a lot of burden.

So our initial plan, just as the slide says, that FDA initially had planned to implement E2B R2 for premarket ICSR reporting then we moved to R3 and now the implementation plan changed and now FDA will implement R3 for both premarket and postmarket safety reports at the same time.

Now, this change was decided based on the complexity to migrate from R2 to R3.

And of course we had suggestions from industry where they all thought it's better to all move to R3 for both premarket and postmarket.

So this change pushed the timelines as there were dependencies like update to technical specifications and clearance of the final guidance, which is a 745A.

Also we had pulled out data specific technical. To make sure all of the regional elements that we have for the premarket safety reports defined and set and published.

And 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 different events in the vendor timelines.

So with that, we had to come with a new date. We are still in the process of implementation. So a new date for voluntary 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 sponsors that, it's about two years to implement from their side. So you will have ample time to do the implementation.

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 -- standards that are supported. So standards that are supported, the standards that FDA will support is E2B(R3) for premarket. Both R2 and R3 for postmarket.

At some point they will retire the submission of postmarket reports in R2 format. And this date is yet to be decided.

And this will be -- and this date will be decided based on house companies move over from R2 to R3. So based on that we will decide a date and communicate that date.

Then additionally, information about E2B(R3) testing and implementation will be made available on the FAERS electronic commissions page.

We're going to talk about the implementation. What we're talking about is with E2B(R3), you will want to test with the agency. So the information about that testing will be made available.

First testing will typically be done using the page rate and you will have most of the companies I think sponsors do have a preproduction or a test account. And the same test account can be used to do the testing. Except that the routing ID will have some change, especially for premarket. And I will talk about what routing IDs are or AS2

headers are. But that's 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 these words regional extensions are mentioned. What does it mean? It refers to FDA's data elements and terminologies supported in the ICSR file in addition to the ICH E2B(R3) data elements. So many times you will hear me talking about core ICH elements so these are the elements that were defined by ICH. And regional extensions or regional requirements are the specific requirements that FDA has.

Next as is -- is as we go through the implementation, here is a recommendation we want to give you. The recommendation is whenever you create the XML file, the data element, there is a value called displayName. We recommend that to facilitate human and computer system identification and understanding, if you can put the displayName with the name of the field, it will really help us in understanding, you know, if there was any issue with XML. And understanding that XML.

So a small example is given at the bottom in the left corner. Where we display the ethnic group so the display name of ethnic group basically displays the name of the field.

And lastly, this is one of the very important things you need to remember is the PADER or the SER, what would be you submit to FDA.

This is the submitted portion of the safety analysis. This descriptive portion must be submitted using eCTD so it cannot be submitted using FAERS. I have gotten many questions asking about the PADER, will that change, and the answer is no, that is not going to change, you will continue to submit the descriptive portion through eCTD.

The E2B(R3) ICSRs will come to FAERS. So please 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 will -- you may get the first but will not get the second acknowledgement. And that will be something that will go nowhere.

Okay. All right.

So moving ahead, acknowledgements.

So acknowledgement -- the two acknowledgements that you will get, the first acknowledgement is the FDA's Message Delivery Notification which we in short call this as the MDN. Which comes from the gateway.

And the second acknowledgement will be the acknowledgement that you will get that FAERS has processed the data of the XML file. The first. And the second acknowledgement will come after that. We have said that we will send you the acknowledgement within 24 hours of your submission.

You know, again, if you could get acknowledgements sooner.

But it all depends upon the size of the file. As we all know E2B(R3) XMLs have now increased in size as part of an embedded, you know, attachments and of course how many ICSRs are you sending in a batch? Based on all of that, we're saying within 24 hours you should get an acknowledgement. But you could get it sooner.

There's 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 warning error message or comment so the maximum length I think was 250 characters we have extended that to 2,000 characters so we can accommodate more messages if there were issues with the points. ACK.B.r.7. We have issues and warnings, we will go over those in one of the slides. But basically the errors will be the file will be rejected. And warnings means we will give a warning but we will still accept a file. Hoping that sponsors will correct the data in the next follow-on.

Okay.

And for information on all ICH and regional extensions, please refer to the E2B(R3) Core and Regional Data Elements and Business Rules. Now, I will basically pause the slides here. And kind of go into -- go into explaining to you a little more about what the E2B(R3) Core and Regional Data Elements and Business Rules are.

So here, this is an Excel spreadsheet.

And this Excel spreadsheet, and this document is available on the product submission page on FDA.gov.

This is an Excel spreadsheet listing all data elements, their attributes, the conformance, the business route for rejection and warnings and the XPaths.

This document is the key document for implementation. In this document you will also see that the ICH data elements has a source the electronic -- the data elements has a source saying ICH or FDA if it says ICH it means the core ICH data elements if it says FDA that means it's a regional data element.

Every element has an element number and an element description.

The element number that starts with a prefix of FDA has FDA regional extensions.

Also there are some data element which are the core ICH data element. And conformance. The regional extensions or regional needs.

And they are usually noted in this particular spreadsheet.

Also, this data -- this spreadsheet also lists on all of the Observation Codes for the regional elements. It will talk about the rules, which are what are the warning rules, rejection rules. And it will tell you what the message for these -- if these rules are not complied with, what kind of message will you get. And that -- exactly the message that will come in that data field B.r.7. And it will tell you the different messages for each of those rules.

And then there are some standard messages that you will go also see, which talks about, you know, if a data field was required but was not submitted. If a data field, what did not comply to a list of Observation Codes. Or a data field value was greater

than what's in the specification.

So those are some general rules that you will see in this document. And also, note that this document is the key document for the implementation. Because everything about the data element of this document is there.

And also our recommendation was it would be that as you're doing an implementation, if you find anything that is -- that -- it may not be set 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 you go through the current things, we rectify things and do it right.

So this is an available document for everyone to use.

All right. The FDA data element conformance, as I said, may vary.

And one of the most important things is we have got many questions asking that will there be a country code of EU. And as things are getting -- it looks difficult with the team who they do not want to disclose a lot of the elements. The country code EU is acceptable to FDA. We have that as part of our core values. And for different data points where country code is used, yes, EU is acceptable.

Now, we also have gotten messages as we talk about the country code EU, we also have gotten messages that is about, you know, with EU coming up with all of these rules, how would -- how will that impact FDA?

As we go through this, we are also working with the -- and this all started with that same 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 redacted to send to other regulators, including us.

So we are working with them. And hopefully they will come with some solutions very soon.

So until then, you know, whatever you have, people keep submitting that to us.

All right.

The controlled terminologies.

So controlled terminologies. So these are kind of dictionaries.

And kind of are also data that we use in our ICSRs.

And we'll also look at some of the attributes and like code lists or Observation Codes for which we use controlled terminologies. So these are the list of controlled terminologies that FDA is using.

So we have the NCI Enterprise Vocabulary Services. Now, this is used typically for many of our regional elements that we have. And that's where we point the data element to. As we all know control terminologies are used because we as ICH or FDA do not want to keep controlled terminologies. Because if there's any change, we have to worry about that change. Versus if we have standards organizations who manage these terminologies, we just point to them. And they have the responsibility to manage those terminologies.

So NCI EVS, as I said, is most of the for our regional elements that we have used. Each of this terminology actually data point, data element, they will have you will see a C code, it will start with the ACK alphabet of capital C and then a number. So everything on the technical specs if you see that C code it's done by NCI EVS. We all know MedDRA we use for coding our events, our test results, pre-existing conditions, so on and so forth.

You have UCUM codes, measures. So again, we use the UCUM codes.

EDQM for administration and dosage form and then we have the device codes that we use, we also have the Device Product Codes. That is also we are using.

So we have the INDR 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 use 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 postmarket reports.

So this is also -- we will go into this Structured Product Labeling. So I will also recommend that, you know, please look at the Structured Product Labeling as you're submitting. Because based on the name that you submit with the SPL, that's the naming we use to populate our dictionaries. And then make sure that when the reports come in, the ICSRs, we go 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 please to the sponsors make sure you check that to make sure the ICSRs that you submit and the product names that are in there the ICSRs match with the names that are in the SPL that is submitted.

So ICH elements that use FDA-controlled terminologies are noted and defined in the relevant sections of the technical specification.

Okay.

All right. We'll go to the next slide.

Okay.

So here we will talk about submission methods. And mechanisms.

So the submission methods and mechanisms, this is already an important topic here. Because as we go into implementing E2B(R3) for premarket, we have to have -- come up with new, you know, mechanisms -- excuse me; mechanisms of submission.

So we actually have two methods. So here is the first method, Option A, which is via database-to-database transmission. So a database-to-database transmission is nothing but you're submitting but through the gateway.

So you have a sponsor. The sponsor would submit an XML, an E2B XML which would come to the gateway.

The gateway will send the first ACK which is in the center of the picture if you see ACK1 which is the MDN which will be sent back to the sponsors.

This XML is sent to FAERS. And the FAERS database will process that. And

then -- and send an acknowledgement No. 2. And this acknowledgement 2 is then taken -- sent to the gateway from FAERS. And then the sponsors are able to get that Acknowledgement 2. And the loop is closed.

So this is the first submission mechanism that we will have. So now this mechanism is already available today with postmarket safety reporting. We will use the same mechanism for premarket safety reporting. So we don't have to do anything new. Except that we have to have the right ones so we know that premarket -- postmarket is going to a certain location and premarket will go to a different location. So that FAERS can then pick it up and recognize that it's a premarket or postmarket report.

All right.

Now, companies or sponsors who do not have -- do not have the process of connecting database to database through the gateway, they can use Option B, which is via the Safety Reporting Portal.

So Safety Reporting Portal is where submitters enter their ICSR manually into a web-based form.

And submit.

In such case as soon as you hit on the submit button, your ICSR basically gets generated in the backend, it's in the backend of the XML and sent to the gateway and the same process happens. In such case the acknowledgement is basically an email that you get from the Safety Reporting Portal to say the email was submitted successfully here is the report information and that's the record that you can keep for you have submitted the report. Now Safety Reporting Portal the difference between -- the difference between Option A and Option B you can only submit one report at a time in the Safety Reporting Portal because it's a web-based form. In the Safety Reporting Portal you can also upload attachments so that's not a problem.

Also requires some kind of registration unless you register and receive the credentials you can't do the Safety Reporting Portal for database to database you also have to send the certificates and all that you have to do. One thing I want to point with Option A is Option A has got the web trader, which you can use for testing and especially I would want to mention this for typically the tool vendors. Many of our tool vendors have asked FDA hey can we test E2B(R3) when FDA is implementing this we always have a challenge we never give the web trader accounts they were just given to the sponsors so I have a verified and scan requests for the trader hub so there is a process of requesting which is available on FDA.gov.

And users can -- vendors can actually request for a web trader account and can submit E2B(R3) standard XMLs which we can then test in FAERS.

Please note that web trader can submit things at a time but please know you will only get an account for testing reporting -- testing purposes only not for production. For testing purposes only. What we saw is if one vendor -- if vendors can test then vendors tools are used by sponsors so indirectly we are also able to test from different

sponsors.

So going to the next slide.

Option A and Option B, as I said, submissions -- submitters who have database-to-database transmission capability, may directly submit ACKs in format using the Electronic Submission Gateway. And Option B, you will require the registration. You have to receive the credentials. And typically when you do registration, you will fill out a registration form which will ask for your organization information, who the users are going to be, who will be submitting data. It will also ask you which products you will be reporting. Then eventually we will make sure the products are in our dictionary and then you will get login credentials. It normally takes about five to seven business days. To get the login credentials so if you are planning to submit through the Safety Reporting Portal, please plan ahead.

So that you can get your credentials on time.

To 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 our web-based form. And submit.

So you will see a screen. You will see what type of reporting you're filling in, if it's a postmarket or premarket then we will go through the form to enter the details of the report, the patient, the products, so on and so forth, the events and so on and so forth. You can upload an attachment. Again, very important, please do not upload E2B(R3) XML attachment through Safety Reporting Portal.

That will not get processed. So please do not upload that there. And also as I said, please do not send the XMLs to the -- via eCTD as a document. Okay? Submitters upload into the FAERS database. That means once you submit the data post into FAERS and it gets loaded into the FAERS database.

All right. Very important. Highlighted here in yellow.

Do not submit ICSRs via both options. Always stick to one option.

And here why I said. Sometimes sponsors have a situation where their BA/BEs are down or the gateway would then be down and they would then send us information saying that hey our gateway we are not able -- our database is up but we are not able to send the files so far which can we get an account in Safety Reporting Portal so we can submit 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 -- not database. Your connection is up and running, you will submit through that. Now, that creates multiple versions in our database. So we say that -- please do -- we say please do not use both methods. Unless, unless, there's a dire situation where your database in your organization, safety database in your organization is down due to an attack. And that -- and that you are not able to operate

your database in such case, we may give you -- we may give you the option to use the Safety Reporting Portal to submit 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 the electronic safety reporting rule mentions that you can use physical media, which means you can take your XMLs, burn it on a CD. And mail it to us. And we will process those XMLs.

Same thing would happen with E2B(R3) if you have that same situation.

But please, please do not use both methods -- both options to submit your reports. Always stick to one option.

Okay.

So -- okay. Is some more areas about the Safety Reporting Portal. So those who want to use Safety Reporting Portal especially we have seen CROs using the Safety Reporting Portal. We have seen some sponsors who have low volume reports, don't want to invest on the gateway.

And use Safety Reporting Portal.

So the safety the reporting portal is intended for sponsors and CROs without infrastructure for direct -- who do not have infrastructure for direct gateway-to-gateway submission.

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 INDs safety reporting. So as we go into -- INDs safety reporting so as we go into that it can be used for both commercial and research. This is not available for vaccine reporting so it's not intended for vaccine reporting, please keep that in mind.

If you are a CRO, you will need to have separate accounts for each sponsor or license holder.

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 have submitted an initial report, now you have a follow-up report. You can actually go to your initial report and say, hey, I want to now create a follow-up.

So all of the information from the initial report is copied over to the follow-up report. And now the following information that you have, the new information, you just update and submit.

So you don't have to re-enter the report from scratch.

It also keeps track of how many reports are submitted to a case, that means for an individual patient.

And all the tracking is kept on the Safety Reporting Portal. So Safety Reporting Portal and therefore post and premarket, of course we are still working on the premarket screens. So they are maintained separately.

So when you go into Safety Reporting Portal, you will be asked that -- upfront you

will be asked if you are submitting a report for a postmarket or premarket.

And then it will take you to the right path to submit a premarket or a postmarket report.

What you do there, you complete an online form.

And as I mentioned, do not upload E2B(R3) XMLs via SRP.

And you have heard me mentioning this so many, many, many times. Because we do see it happening.

So we do not want that you will submit an E2B(R3) XML through the Safety Reporting Portal and nothing happen and you may be under an inspection and the inspector may ask about those specific reports. But we have not processed them.

So please make sure you do not upload E2B(R3) XML via SRP.

You will get an acknowledgement by email and keep that for your records.

Because SRP, your submission as soon as you hit the submit button is your submission done.

So after that, it's not your problem. It's FDA's process to parse the report and making sure it's put into FAERS.

So as you submit, you will get an email acknowledgement saying that it is the -- saying here is the report that you submitted.

All right. Next slide.

All right. So we are doing some changes to SRP.

So as you know SRP is based on MedWatch 3500A.

There are some changes that have come to the 3500A based on the last reauthorization. So some of those changes will get included in the 3500A.

So we performed some updates to include premarket questionnaires. So everything in SRP we call it as a questionnaire.

Or we call it as -- in short we call it rationale questionnaire for or RQ.

And in the current postmarket questionnaire updates that we are doing is to accommodate the E2B(R3) structure.

Because as you know, that the current SRP for postmarket questionnaire that we have has data points that E2B(R3) doesn't fit into. So there are some changes we have to do to the questionnaire to make sure it follows that E2B(R3) structure. So that we can get the data into FAERS.

And of course premarket questionnaires are being developed right now.

And then once this is ready, as I said, that the availability for SRP and E2B(R3) via the gateway for premarket 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 SRP post -- premarket questionnaires. So that companies can actually use that. This SRP is free. There's no added cost to use.

And to request for an account for SRP, please submit an email to the FAERSESUB@FDA.HHS.gov. This is one email address pretty much everybody

knows because we do get a lot of questions here. So this is the email address we use for requests for SRP account.

Now, there was a question that came, now, SRP comes in won't that have any action to be required by existing SRP users? No, for existing SRP users who are using -- users were using SRP for postmarket reporting, there's no change for you.

Now, you as a user also want to report on premarket. Now you will have access to report on premarket safety reports. That means you will get a premarket questionnaire.

If you don't have any INDs to be reported and you are only reporting on postmarket, you just continue the way you continue today. And there's no action or change required from your side.

Okay.

All right.

So let's now go into the gateway submission.

So we all know that for gateway submission, we submitted postmarket safety reporting, we have the AS2 header and the routing IDs, we are not doing any changes to those values. We are keeping those values as-is. We don't want to disrupt anything. And we want to keep as-is.

Now we are going to have premarket safety reporting.

And when we have premarket safety reporting, we have premarket safety reporting for both CDER and CBER.

So because it's for CDER and CBER.

We have to separate that out for CDER and for CBER.

Now, postmarketing we do therapeutic biologics and all of that, we don't want to -- didn't want to separate those things we want to keep it as-is. Of course vaccine is not here. And we are not talking about that here. They are a separating reporting. But for premarket you have CDER and CBER.

Now, what we are saying here is for premarket CDER, we have -- now we have two new attributes and routing IDs for premarket safety reports.

And this allows separation of premarket and postmarket. Within premarket the -- they have two separate pathways, one for CDER, one for CBER.

And also we realize 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 will know is it a CDER IND or a CBER IND. And accordingly you will set the AS2 header to the proper ID to submit.

Now, very important, rejection will occur if premarket reports incorrectly submitted to the postmarket pathway.

And postmarket reports incorrectly submitted to the premarket pathway.

Now, this, what it ensures during this rejection is that we -- we do not publish the premarket report publicly.

We will maintain the right.

Then premarket report will not be published publicly.

And we want to do that. We do not want premarket reports to be published publicly.

So please keep a note that, yes, we are going to reject if you submit a premarket incorrectly to the postmarket and postmarket incorrectly to the premarket pathway. The routing IDs, all of the informations are here in the ESG Appendix J, AS2 routing IDs. And I have the link there. And you should be able to see those values for XML files. And for routing IDs. And those values are available in that link.

So this is a very important slide. And as I go through the different postmarket and premarket, these values that you see for postmarketing and for premarketing CDER and CBER and even should be for IND will show up. Regularly in these different slides. Just to make sure that you all understand the relationship here and how it is to be submitted.

Okay.

Next so the approach of how we triage things here, so you have a premarket. And then -- a premarket ICSRs submissions or sponsors submit that.

Once the sponsor's 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 a destination which says CDER and the XML file is the AERS premarket CDER and the routing ID if you use a routing ID then that's the routing ID. When that comes and it goes to FAERS, we need to also make sure that within the FAERS data point N.1.4 has the value ZZFDA_PREMKT. And N.2.r.3 says it's a CDER IND and obviously the other ones are examples of IND numbers so on and so forth.

But that is very important when you submit to the gateway, that those headers, we are expecting that the XML file has N.1.4 and N.2.r.3, those values there.

Now the next one is if it was a CBER one, then you see there the destination says CBER. The XML file says market CBER or it would say premarket CBER. So what we are expecting is the XML file would have N.1.4 as ZZFDA_PREMKT so that tells me it's a premarket and within premarket N.2.r.3 tells me it's a CBER IND that way I know it's CBER. Similarly for postmarket, you would have destination as CDER when it comes to the XML file you expect ZZFDA and CDER so it's the same for CDER and CBER, there's no kind of differentiation there.

And this type of submission, this way of submission, is important. So we can submit the premarket and postmarket report.

And ideally eventually identify what the IND number is. Because our reviewers' medical officers are getting these reports based on the IND number.

Now, yes.

So here is what we have for the postmarket site.

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 that.

Okay.

All right. So now this is a very important table. If you can click one down.

So we will be talking about the Section N.1. Which is the ICH ICSR transmission identification.

Two important field here N.1.4 the previous slide we talked about in 1.4. This is a Batch Receiver Identifier. And we talked about N.2.r.3 and that's the 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 displays the accurate values that must be used in submitting the CDER IND ICSRs so INDs that are for CDER and INDs that are for CBER and the IND-exempt available ICSRs so there are four rows here, the top three rows are for premarket and the last row is for postmarket.

So this is not showing the entire relationship between the AS2 header and the E2B data field. The core data value fields that we have.

So the AS2 header or the routing ID you'll find the ESG folder where the XML files will be routed to.

So as soon as you say the AS2 header or routing ID, then our gateway exactly knows where to drop the XML file.

Which folder to drop the XML folder.

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.

Generate the acknowledgement. And send it back to the gateway.

So when FAERS imports the XML file in the folder, okay, where CDER IND or IND-exempt are stored, FAERS will verify that the value for N.1.4 and N.2.R.3 are the values in the table. What does that mean? That means let's say a sponsor is submitting a CDER IND ICSR. Through AS2 header way.

So yes, that's the header. That's like the -- part of the envelope.

And then the front of the envelope it says that its destination is CDER. And the XML file is premarket underscore -- this is underscore CDER. Okay, great.

And we take that envelope that is -- within that envelope there is a letter. The letter is the XML file.

And that XML file has got two 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 that AS2 header was for CDER IND ICSR.

And now, N.1.4 says ZZFDA this is for premarket. But N.2.R.3 says CBER_IND.

Then you will get a rejection.

Because you're trying to submit a CDER IND to the envelope that says it's CDER IND but inside the envelope the letter says it's a CBER IND.

So you will get a rejection.

Same if you try to take the CBER AS2 header routing ID let's say you have routing ID that ZZFDA premarket CBER then it's standard for all of the types of premarket that says ZZFDA premarket.

But if you say CDER IND, or routing ID which is FDA premarket CBER, you will get a rejection because you are trying to submit a CBER IND report which is on the envelope but inside the envelope says CDER IND so it does not match so it will give you a rejection.

And same will happen for postmarket versus premarket.

You could submit through AS2 header which says market CBER then you are submitting N.2.R.3 and N.1.4 as CDER, you will get a rejection.

Now, all of these types of rejections and acceptance have been set up to -- by keeping in mind that by no means and no way premarket reports are published publicly. Because we all know postmarket reports are published lately every quarter. And we do not want this to happen with premarket report.

Now, 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 manufacturers were submitting the reports also do not take care of this, something may fall through the crack. Because as much as tests and as much as rules you apply, you know, there still could be some reports that can fall through the crack. And until both sides, you know, will -- you know, maintaining these rules and setting up these and complying to these rules.

There are some rules here which I want to mention here 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, there's a rule looking at the AS2 headers where it has come to which folder versus N.1.4 and N.2.R.3 but there are rules between the ESG 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 asking as a regional extension to use in N.1.4 and N.2.R.3 because we all know N.1.4 and N.2.R.3 are free text data fields.

So please make sure that these values are appropriately in there. Because if you have a -- if you have a mistake with the alphabets or a typo, that can create a rejection. So please make sure that those values are appropriately set.

So as I said that there are checks between the data elements, which is N.1.4 and N.2.R.3.

If you have CDER, make sure it's a ZZFDA. If it's ZZFDA, then make sure that

N.2.R.3 is CDER.

This is very important.

Similarly 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. Again these are some new values we have come up with.

And vice versa.

That if you have ZZFDA as N.1.4, the N.2.R.3 must be one of the values of CDER_IND, CBER_IND and CDER IND-exempt BA_BE. It cannot be CDER.

Again, as I said that this business rules has been defined to make sure that the different way you show up in the premarket and postmarket reports are clearly delineated in the premarket reports -- and the premarket reports are not published publicly.

A few other points I'll make on this slide, this is a very important slide. And you know, this whole setup has to be -- has to be put in a way so that if you don't maintain this setup, you will start -- you will get rejections.

Now, let's say up a batch of ICSRs.

And in that batch, please make sure that you have -- try to make different batches for postmarket and different batches where you have premarket for CDER, premarket for CBER and premarket for IND-exempt.

Here you can submit altogether. But we would prefer that you submit them in different batches. Don't mix CDER with CBER or CBER with CDER IND-exempt BA/BE. And definitely do not mix premarket with postmarket. Having them in different batches also helps us.

And then that all the batches that you have here, a submitted 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. They won't come sooner.

So if you -- let's say you have 3, 400, 500 files to be sent, send them in batches of let's say 100, max of 200. And send it as like three or four batches. So you will get acknowledgement sooner and faster and so on.

Also, with this particular rule here, as I said, these AS2 header and routing IDs will be available on the Appendix J. There will be one for testing. And there will be one for production.

I think the ones that are for testing will say some kind of TSD or TESD. 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 trigger, we want to test these scenarios with you all.

So we will during the testing period want to test that submitting and using a routing ID of CDER IND for submitting a CBER in the XML files gets you a rejection. So we

want to test that.

And then also we want to test the positive side that you submitted 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 postmarket. We 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 4 minutes before time for a break. So I guess we take the break but we come back at 10:30. I was not that bad. 4 minutes, it's okay.

So we will resume at 10:30. So if anyone has any questions, please start putting your 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.

(Break.)

>> OPERATOR: Recording stopped.

(Standing by).

>> OPERATOR: Recording in progress.

>> SURANJAN DE: All right. So we are back from our break. Hopefully everybody can hear and see.

So before the break we talked a little bit about the background. We talked about some regional implementation guidelines. We went over the submission methods and mechanisms.

And we did talk about specifically the table that I spent a lot of time on.

Very important table.

And then certain things about -- we talked about there are two options, Option A, Option B, for tests. And basically for testing, we will use Option A for database to database which is the gateway testing.

Option B is basically the website or online form. That will be posted. And we are not doing any testing with the companies there. But that will be directly posted.

So now after the break until lunch we will talk about the E2B(R3) Implementation Package.

With the Implementation Package, this is where I will try to go into the spreadsheet and we had 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.

So the E2B(R3) Implementation Package has four documents.

One of the FDA regional implementation guide. This is a document so the purpose of this technical specification document is to assist submitters with the transmitting submission with attachments so it gives you some details about what terminologies that we use. And what are some kind of rules that we have. So it will talk about the gateway settings. ESG settings.

We will talk a little bit about attachments, what are we accepting, what are we not accepting, you know.

It talks about some subjects on combination product.

So it gives you an overview about the transmission in E2B(R3).

So it describes an approach for submitting ICSRs.

And for incorporating its regionally controlled technology. And for implementing regional extensions that are not in the ICH Implementation Guide.

So that is what the first document is.

Okay. So this document, as you see, these are all links. Because you see that in blue.

These links if you click on it, it actually then takes you to -- and 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 document provides now Version 1.3 just because we had some updates, soon we'll have Version 1.4.

We'll soon have Version 1.4. And the purpose of this that we have an 1.4 is there are some changes we had identified during our implementation. And we will be incorporating that. There were a few rules here and there that we have identified that we updated in the document. It should be posted very soon, in a week's time.

So this document provides a list of core ICH and FDA regional data elements.

Data element attributes.

Conformance, business rules, and acknowledgement attributes. And some of the regional data elements in this document are also detailed in the FDA regional implementation technical specification. 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 usually have to do an alt tab and the Excel file will be opened.

Alt and then tab.

So alt tab. And you go to the Excel. It's the -- is the Excel being shared?

>> Yes.

(Background talking.)

>> SURANJAN DE: Okay.

Thank you. I need to see -- sorry; excuse me. I need to see it, it's not coming up here.

Share the Excel spreadsheet.

(Background talking.)

>> SURANJAN DE: All right.

So right now we have the Excel spreadsheet that is shared. And if you look at this Excel spreadsheet, there are several columns here.

Identification. 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. Yeah, great. So in this spreadsheet, the first few columns are field identification.

So it will tell you the source.

All right. Say if that source is a source from FDA or if the source is a source from ICH.

It gives you the field identification the field data element number so you see the number starts with FDA dot that means that's an FDA data element. Then it gives you the data element name.

And then Michelle, if you scroll to the left. On the bottom there, the scroll bar. Yes, it gives you the field type.

Field type will tell you what is the maximum length, what is the data type, which is A for alpha, 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 now scroll to Column J where under postmarket this data field is required. And it gives you some postmarket business rules for that particular data field.

And the next column, which is L and M, are for premarket business rules. And for premarket is the conformance required or not required. What the conformance is for the data element which is a regional extension. And the business rules for that. And then we go to Column S and T, S says it's an FDA regional data element. Then the next few columns are nullFlavor applicable to it tells you if nullFlavors are applicable or not. If it is so, which ones are applicable.

It gives you the OID for the particular data field which is the object identifier. And then it tells you which element it actually uses in Column AE. So that's what this particular Excel spreadsheet talks about.

Similarly it will show you other data elements in there. And let's go into the Read Me tab in this spreadsheet. At the bottom we 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 data elements so every tab it will tell you what it is.

So this Tab No. 1 which is history. In this spreadsheet the history will tell you about the changes to this document, revision history.

Okay.

And so this information includes in a document version number, date, and version description.

So Michelle, let's go into the revision history tab at the bottom where you have Read Me. Just like that. So this is how the revision history tab looks like so you have the revision number, you have revision date and then the revision description. So right now is 1.3 we posted it in January of 2023.

We're going to have one probably posted this month in next -- in a week's time. And it will list all the changes that we have had in since the previous version. So let's go back to the Read Me tab again. The next tab after the -- the ICSR data elements and attributes.

The common ICH is further divided to provide conformance and data type. We have a differentiation between postmarket and premarket because sometimes the rules are different. And also for the 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 before and be rejected. NullFlavors are used to explain the reason for the lack of the data on required data element. It must be used for specific required data elements as defined. But the relevant data element is blank. In case of additional required data element, if the condition is true, then the absence of conditioned data required element will result in negative acknowledgement and be rejected unless appropriate nullFlavor is used so as you saw there are some nullFlavors like not applicable, no information, information unknown.

So sometimes you will have data fields where you may have a nullFlavor value. It's important that you have those values. In such case the data element will tell you that use nullFlavors and the nullFlavors that are required -- that is applicable for that data element must be used.

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

For regional extensions it's marked as FDA. Then you have a data element number this has a unique identifier for the data element. And these numbers, wherever you see the prefix with FDA, these are regional extensions, again.

Data element name we give a name for the data element. Standard names for ICH are already there. What is a max length so it tells you the length of the data element, the data element type, the values that are allowed for the data element. And the conformance. So conformance is the conformance can be required, conditional, required optional.

So scrolling down, the conditional required, under conditional required data elements are optional. Required if condition mentioned in the business rule is satisfied.

That's how we have to be used business rules these columns define the business

rule for the regional data element or any deviation from the ICH E2B(R3) business rule.

Then Q&A this is a column that defines the appropriate answer associated with the data element. We are going to have some question and answer. So we kept that column so in the future if we have questions and answers on specific data elements, rather than updating the spreadsheet, we can have it in the Q&A and point the question and answer to that Q&A question.

Null flag applicable. As I said these are nullFlavors. And field OIDs are basically the OID value for the data elements there are some regional OIDs and then there are some, you know, ICH OIDs.

So we can 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 rule.

The check mark 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 check mark 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 error ID and error description columns.

And that describes the error code and descriptions of the error and rejection starts with warning so let's go to the rejection and warning tool tab. So it will be R or W.

If we look here, we should go all the way to the top. You will see here are the columns.

So there are certain things here where there are some common things which says if a field is required then we have a message saying this standard number is required but not provided. If you have a field where the observation value is incorrect so this number contains an invalid value.

If you have a exceeded the max length, it will say the tag number contains a value that exceeds the max limit.

Similarly now you have some data elements, all the elements are listed here. If you see the columns, the business rule is mentioned. If you have a check mark where it says rejection is not met, which means that for that particular data element, which is N.1.4, if that is not met, then here is the error message that you are going to get. And that error message will be listed in that ACK B4 or B8 -- or B4 product something which I talked about which we changed from 250 characters to 2,000 characters.

So these are the rules. So if as we scroll down, actually you will see there are some -- somewhere you will see that the check mark is under the Column E. Which is warning.

Let's go down and we should find -- yes, there is 1, which is a warning here. So in this case we will not reject the file but we will 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 of these. And all of the error description codes you see, that is the information that you will see in the acknowledgement file. We are not sending the error code but we are sending the error description. In the 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 XPaths these are the tabs that list the XPaths based on the model for both the core ICH and the regional E2B element. XPaths are -- X paths are also defined for data elements where nullFlavor is not applicable. Let's go to the X paths tab, if you see all of these, these are all beta the XPaths because we are verifying to make sure that the data elements are in the right location, the right data element is used. And these are the XPaths we will be using wherever you see the source as FDA these are XPaths we have based on the model. And those XPaths need to be used appropriately for a successful submission.

So that's -- that's XPath.

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, I think somewhere at the bottom, you will see that the data element was changed from 250 to 2,000 characters. In the last rule it says 2,000 in red. So that was previously 250 and we have changed to 2,000 characters. I had mentioned previously. So in here nothing else has changed the message will still be the same message to you. And we will be just -- just have the -- B.r.7 has changed because of characters. So this is the spreadsheet that used to be there. If you find any kind of, you know, ambiguity in the spreadsheet, please inform us at FAERSESUB@FDA.HHS.gov. And anything you find we will really highly appreciate if we catch any issues right now than later. So with that we will go back into the slides.

And can we confirm that the slides are -- good. Folks can see the slides. And the slides are shared.

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

The third document is Forward Compatible Rules. I will go over this in another set of slides. This spreadsheet, I have taken the spreadsheet and made those columns in a spreadsheet columns and put some slides at the end. This presentation. Just before I think we talked a little bit in the outline that there will be a section that will come E2B R2 to R3 compatible and that's where we will talk about this spreadsheet. Moving

to the spreadsheet.

But I have the tables already in slides.

So we will talk about that then there.

Then next is the FDA ICSR XML instances. So these are instances, a list of scenarios provided as XML instances. And acknowledgement examples based on FDA R3 technical specification document. So this will add all of the regional elements, also. It's a zip file. And the zip file has a ReadMe.TXT file describing the different scenarios. So there were 7 or 8 scenarios I believe. And the Read Me text file will tell you about each and every scenario what it's about. So there will be a scenario relating to combination products. There will be a scenario relating to IND safety reporting. There will be a scenario relating to IND-exempt BA/BE. There will be a scenario which we call it like a metafile which means it's got pretty much all the elements in there.

So likewise we have all of the scenarios that can be used and looked at by testing and so on.

So we have provided some instance files, which, again, these instance files are different from the instance files from ICH.

Because these instance files actually have the regional elements from in there. So keeping that in mind, these standards were developed and posted.

So with that now we'll go into some common regional extensions. When I say common regional extensions these are common regional extensions applicable to all types of reports? So let's get into each and every section of this common regional extension.

Okay. Section C.1 this is identification of a Case Safety Report. Now, common regional extension please know there will be some elements that are new elements that FDA has defined. There are some elements where some business rules have changed. And there are some elements where we may have chains of conformance.

So getting into Section C.1, identification of a Case Safety Report.

The change here is the business rule.

So you have the sender's Case Safety Report which is C.1.1. The standard data element. The business rule is use the same sender safety report unique identifier for all previously submitted reports.

Always use the same identifier for data elements, and for data element C.1.1 that was assigned to the initial ICSR when sending follow-up reports for the life cycle of the case. The report we have put this business rule is because this particular value of this particular data field makes the initial and quality of the reports in our database.

So having the same number is based on the follow-up and the next follow-up and the next follow-up that's why this particular data element is important more details is provided in the document of the technical specifications and reasoning also has been given there.

The next data element is C.1.3. That stands for type of report. Type of report is a

rule here. Is as we say that if the Batch Receiver Identifier, which is N.1.4 we talked about this so many times now is CDER underscore premarket then the type of report must be 2 equals report from study. Makes sense because it's a premarket report and a value 2 is a report from study. It also provides us a another level of security for not publishing this report basically.

Okay. So now you see that -- there are only two, three levels of -- you see there are two, three levels of security that we bring in so we do not publish this report publicly.

Now, again, you can have everything but the content in the report is -- let's say people are submitting the postmarket report, the sponsors submit the postmarket report if everything is on premarket, that's something which we cannot now make sure that we catch that and not publish it. We can now make sure.

Because data points with discrete data values all remark and say it's a premarket or postmarket report but the content of the data in like the product name and all of that is all about premarket, then, you know, that is something which it will be very difficult to track.

And not publish. But from the perspective of making sure that premarket report will not get published, we talked about routing IDs. That's where we have separate from postmarket and premarket.

We talked about N.1.4 and N.2.r.3.

In relationship between the routing 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 publicly. Okay?

Okay. Next is the Local Criteria Report Type.

So in the Local Criteria Report Type, this is a new data element.

Because FDA we do need to know if it's a data report and then we have 5 day and 30 day report from accommodation projects and then we have a 7 day report for IND. Of course IND has both 7 day and 15 day.

So we defined a new data element.

And previously we had a Local Criteria Report Type in R2. But that was a value data field that I can add more values. But that field now has become -- what do you call it a boolean, true or false an expedited report we use a value for that report and that's become a boolean so now we have a different data element which is a Local Criteria Report Type FDA.C.1.1.1. The length is 1. The data type is numeric.

The conformance, it is required.

And the Observation Code values which is C54588. Again, as you see, I talked about it, it's values one will be for 15 day or non-expedited or 5 day, 30 day or 7 day so you may wonder why there's no value 3. Because we use the value 3 basically for our data reports. That we get directly from consumers and healthcare professionals.

So we resolved that for that.

Any kind of rules are available in that spreadsheet which we showed you, which is a

E2B(R3) that link is there that's available on the spreadsheet but we already showed that I won't go through that.

I have extracted out some of the rules from the -- from that spreadsheet. And if we go forward here are the rules for this particular data element. So in this particular data element let's go over some of the rules. Many of the rules apply because of combination products because combination products are for postmarketing, we don't have anything for premarket.

If Combination Product Report Indicator, so there's is the regional data feed caused Combination Product Report Indicator. Which says whether this is a combination product or not.

If that is true, then does the case fulfill the local criteria for an expedited report? That means if it's like if expedited reporting, if that is true then the Observation Code value must be 1 or 4. That means we are saying it's a combination product. And it is -- it's expedited criteria. So value 1 and 4 is what. 1 it's 3 day and 4 is 5 day.

So only 1 and 4 will be allowed.

And if the Combination Product Report Indicator is true, that means if it's a combination product report, but is not expedited criteria so that means it falls in no information that means it falls 2 or 5 which means it's 2 non-expedited and 5 means it's 30 day report if the Combination Product Report Indicator is false that means it's not a combination product report then it's in the expedited criteria then for postmarket the value must be 1 which is a 15 day report. And of course if you have the Combination Product Report Indicator is false that means it's not a combination product report and it doesn't fulfill the expedited criteria then the value is 2 which is a non-expedited report. These rules apply to make sure that it comes out right -- the rules come out right and are set right for us. Now the premarket site for 15 day or 7 day expedited report, if the field, which is you know -- or if it fulfills the expedited criteria is true, then the report type -- the type of report is report from study then the observation value allowed is 1 or 6, 1 meaning 15 days or 6 means a 7 day report.

All right. So the next data element are does the case fulfill local criteria for an expedited report. This is already existing. The rules. There's guidance. -- it's more of a guidance than a rule. Specify whether -- this rule says you're specifying whether the case fulfills the regional specification for expedited reporting.

If this -- if the Local Criteria Report Type is 7 day or 15 day or 5 day, they are considered expedited reports, then C.1.7 must be true.

Another one is -- another rule is if Local Criteria Report Type is not expedited or 30 days -- considered non-expedited then C.1.7 must be false. Important, when things get rejected initial submissions with nullFlavor NI will be rejected.

So you cannot submit a report an initial report, with the value of no information for the data field. If that's the case the criteria will be from an expedited report. Then the report will get rejected.

Okay? So . . .

All right. The next data element.

The next data element will be FDA.C.1.12. So Michelle, next slide, thank you. So the Combination Product Report Indicator I just mentioned this, this is a regional data element. FDA.C.1.12. This data element is a boolean. Which means it doesn't have max length. The data type is boolean. Is it true or false? I have no information. But conformance is required for this. So you say it's a combination you have to say false or NI, NI is given because sometimes you don't know if it's truly a combination product. So NI is given if you know it's not a combination product, you say false if it's not a combination product -- if it is you say true. If it's a C code it starts with the alphabet C with the code number and that means it's 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 if it's a combination product or not, you will have to look at the rules as defined in the postmarket -- in the postmarket safety reporting for combination products guidance for industry and FDA staff.

So this is posted. This link, if you click, it 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, and should it be no information. That will be a decision that you will take based on this guidance. Okay?

So this is what the Combination Product Report Indicator is.

So going into the next thing is a reporter's email this is again a new data element that was added FDA.C.2.r.2.8 the max length is 100 data type is Alpha Numeric the conformance is required and the values again is taken from NCI -- sorry; this needs to be -- this is a typo here.

The values is no values allowed here. This should be -- this shouldn't be related. Please do not take the values allotted into consideration. So max length is 100. Data type is Alpha Numeric.

And conformance is required.

And the value allowed must be only nullFlavor, which is not asked, NASK. So the values are only nullFlavor. NASK. I'll 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 you just say not asked.

And if you don't have the value, just say not asked.

So one important note of all of this particular data element is that when submitting the nullFlavor response, also include the telecom prefix with the value attribute correctly referenced the related telecom type as shown in the example.

You see telecom type. You have the value. It says mailto: and the email address. If you don't have it you say nullFlavor NASK and the value is basically just mailto. Because you don't have -- you're not asked anything. So that is an example. So that is how you need to report to the FDA.

This is the same process that we have, also, for FAERS reporting. That has an email address. And if you did not have an email, then this is how you would report.

Next is Section C.3.3.

So information on sender. Here these data elements were optional. And FDA has made these data elements required. So this is the sender of the report. So who is sending the report to FDA. You want to know that. Because based on this, sender information, you know, our compliance works. That is who is sending the report who is the responsible party for sending the report so we want to know this information so we know who is actually sending this report. So that's where this information -- the conformance was changed from optional to required.

And these are all of the data elements about the sender.

Next let's get into patient characteristics.

Okay.

Patient characteristics. Patient name. Or initial D.1.

Data elements still 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 or medication error report, then you can use a nullFlavor NA for the patient name.

For combination product report having malfunction with no adverse event you can use a nullFlavor NA for the patient. We all know that reporting you need at least minimum 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 that check.

So -- and it also satisfies that the patient is not applicable in such situations.

For combination product report having malfunction on a batch of combination products with no AE, so there was a batch of combination products, and there was a malfunction. So in such case this would be used in multiple patients and usually you're asked to submit one report. And the patient name or initial you can mention the value summary there.

And then we will go into IND safety reports and we talk more about IND safety reports after lunch. There's a concept of aggregate reports. And in such case when there's an aggregate report, please -- or aggregate report use the value aggregate in the initial.

And lastly the rule is if the type of report is 2, which means specifically for aggregate reports so it's to report from study, the IND number for adverse event occurred is provided and what is the IND event number for adverse event provided, you will hear that regional element in IND when IND safety reports are being discussed.

And identification number of the report, which is linked to the safety report, this is an aggregate reporting, you have the aggregation of all the other IND individual safety reports, that's, again, you will hear that how especially aggregate reports are to be

reported in the IND section.

The rule just because the patient name and initially if these three things are populated with those values, or populated one with specific values, then D.1 must have the value added. So it's like a cross-check business rule that we are having here.

Next we go into race code.

And -- before we go into race code, so race code. So this is a new data element, Patient Race Code.

Which is Alpha Numeric 10.

Performance 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.

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 null -- the value of the race for that patient, then you can use unknown, MSK or if you're MSKing something or if you don't know, that's the value. So that's what you will be using for the race code.

Then we have the ethnicity code which is FDA.D.12.

So in such case you have max length 10. Alpha Numeric. It's required. It again has a C code which means it's taken from NCI EVS because nullFlavor and unknown MSK, no information, NA, use NA if the report has -- is about a combination product with multiple patients and aggregate. So you can use NA for those types.

Okay. All right. So then we have G be k, which is drug information. A drug can be repeated. So the Characterization of Drug Role, this is an important field, G.k.1.

So there are some business rules with this particular drug role data point.

And the business rules are for postmarket, for premarket and so on.

So these two.

For postmarket ICSRs. The first product under Section G should have the data element answered as 1. Or 3.

Unless the product has at least one device constituent part where malfunction is true in which case the Observation Code value would be 1, 3 or 4.

Okay?

1, 3, or 4.

1 stands for suspect. 3 for interacting. And 4 drug product administered.

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

So basically your -- if you are reporting this becomes the first product in the list.

So if you look at these rules here, if you had a combination product and the combination products device part has a malfunction, but the malfunction -- there was no

adverse event but there was just a malfunction, then it of course could be on a similar device then you could use the value 4 which is drug not administered. You also have 1 or 3.

You must have at least one product, at least one product must be reported with the Observation Code value of 1, 3 or 4 which is suspect, interacting or drug not administered.

Again, as I said, for -- yeah, so 1, 3 or 4.

For premarket ICSRs, -- for IND ICSRs, we only have the Observation Code value of 1, 2 or 3 so 1 means suspect, 2 interact -- 2 means concomitant and 3 means interacting and at least one product must be reported with the Observation Code value of 1 or 3. It's very important to do that. And we also suggest these -- your companies put yours as the first in the list.

For IND-exempt, you can use a value 1, 2, 3 or 4. You can still have concomitant product. And at least one product must be reported with observation value -- Observation Code value of 1, 3 and 4 so if you have IND-exempt you have the addressed drug, the reference drug and so on, so the value of 4 is also used.

So we have a new field called Characterization of Drug Role -- FDA other Characterization of Drug Role. Why was this used, because it's for similar device. So since it's a concept of similar device, you know, adding anything to an existing Observation Code value like for example we have a characterization of a drug, we really cannot in E2B R2 or R3 we can't add an Observation Code value to an existing list of Observation Code values.

And the reason is I could add a value of -- let's say I had characterization of the drug role. And it had four values, I added a fifth one, the fifth one I call a similar device.

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 recommended you add a value to an existing list, unless -- until a standards organization has endorsed that. And have included that into the code values in the Observation Code.

So with similar device, this is specifically for combination products actually. It's max length is 1. It's numeric. And conformance is conditional-required. And when is it required? For similar device Observation Code value 1 must be provided if combination code product report indicated is 2 malfunction is 2 and characterization of drug is 4. That is drug was not administered.

That means you're talking about the combination product. We're talking about a similar dispatches.

So you have a device, you're talking about a similar device that means that device would have been administered so that value of 4 so all of these three criterias have to match up and have to be true. So just say that it's a similar device.

So that's the conditional-required for this particular field.

Next.

So we have common regional extensions for drugs. G.k. So these are some important. So these are some important areas I would very much focus on right now.

Because the data that we typically get and we have to go back to sponsors to get things corrected.

So the data element G.k.2.1.1b Medicinal Product Identifier. MPID. We would want to start using this data element. In R2 we never had this but now we want to start using this.

If available. Which means MPID you use the FDA NDC code, National Drug Code, when known. And should be used as the regional MPID.

Okay?

Use either only the first two segments of the NDC or the full NDC as regional MPID in the ICSR.

Only send the first two segments of the full thing.

But if you start -- again, this is an optional data element.

But we would request or we would recommend to start using this. Because when it comes to IDNP and all of that, we might start using the MPID as the -- the NDC code as the MPID.

And also it gives FDA that -- to pinpoint to the exact product that we are looking for once we know the NDC code.

So when known, please submit the NDC code in the data element Medicinal Product Identifier.

Next data element is G.k.2.2 which is Medicinal Product Name as reported by the primary source.

So this is a Medicinal Product Name. So FDA validates the Medicinal Product Name for products marketed in the United States against the available Structured Product Labeling. So I mentioned that previously during -- I mentioned previously during the medical technologies that we are using Structured Product Labeling 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 Structured Product Labeling but then when the actual ICSRs come, the name has some deviations. Also in the name, it's a name. So don't try to use like strength into the name, you know.

And those kind of values into the name.

Product name got approved by the agency and what you submitted as it's 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 however a substance was approved, that name

you must use. And that you will provide -- you will get it in the FDA's GSRS, which is available publicly for you to use.

If you have foreign product trade names, then provide the foreign product trade name in this particular field, G.k.2.2. Then we have the G.k.2.3.r.2b which is the substance and specified substance TermID. Now, the TermID that you have we are recommending to use the FDA's GSRS UNII code. Because then it also helps us to directly pinpoint to the right substance that was registered. And the name of course is the name of the substance then. So that should always be populated. The TermID. That should always be populated. But if you don't have a TermID, if it is -- if you have it if it's available then use the FDA GSRS UNII.

Now, what happens if it's a foreign product?

So if it's a foreign product, then provide that substance name as it appears on the FDA's GSRS.

The FDA's unique codes are updated monthly. And can be updated from FDA's GSRS UNII list.

So these type of rules -- suggestions and recommendations that we are giving really helps us in validating the product. Because, you know, we as an 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 FDA product that is marketed in the United States.

So it becomes very important for us to make sure that products are validated. Because eventually we have to do a search on those products, we have to make sure we are getting the right cases from the products, signal identification.

So again, we do have close to 2.3 million reports that we receive every year.

And of that close to 2.5 to 3% report (audio cutting in and out) because the name did not match the SPL or the active ingredient did not match the GSRS name. And the products fall. Which means we have to take manual steps to validate those products and process them to make it available to the reviewer. So it's additional effort, additional costs. Additional steps.

And also additional time.

So if industry can work this through, making sure that the names are validated by them through SPL, making sure that that's the name that they are using or the name that they are using contain GSRSs, it will really help us down the line.

Next area is we have the drug information. Again, the G.k. This is where you have the Authorization/Application Number, G.k.3.1. So there are some rules here. Some of these rules are specifically applied for postmarketing. But also can be used for premarket. Especially if you're using a postmarket study drug. Because if you mention what the ANDA number or NDA number probably is.

So in this we have -- if you have a human drug or biologic product, the application

type could be ANDA, NDA, BA, BN as used by CBER. And the recommended format is this. NDA with the number. And ANDA with a number and BA with a number and BN with a number. You have a biologic product which is BLA, then you have BLA with a number. Prescription drug product marketed without an approved application, RX no application then you Smith it as 000000, six zeros and nonprescription drug product marketed without an approved application non-Rx no application then submit it as six 9s if you're compounded product marketed then you have the word COMP99. Some of these things actually help us to kind of see this. So we have a compounding rule. So if you have COMP99 then we know this is a compounded product and it needs to go there because the compounded product is not preapproved. You are mixing things.

So it really can affect the products. So setting these values appropriately actually helps us.

Now, the question comes, where do you submit the IND number?

So you see down here it says for IND and IND-exempt BA/BE safety reports that are reporting on marketed drug products or biological products being evaluated under an IND or IND-exempt BA/BE do not place the IND or pre-ANDA number in this field.

Here is data element FDA.C.5.5. This is a regional element and FDA.C.5.5b this is a limit for IND and IND-exempt BA/BE respectively these two attributes of these data elements are with respect to the IND and IND-exempt BA/BE doc and that we'll talk about after lunch.

But these two data elements are regional elements that have been set. Because these two data elements actually defines where the report is for review.

Next we have the data element pharmaceutical dosage form TermID.

Right? So we are asking to use the Observation Code C54456 so people in these areas you will be able to search for C54456. This is the EDQM code. This is what we're using this for. Because in SPL we actually have that pharmaceutical dosage form. If you don't have it, it's in the EDQM code. Make sure that you're submitting at the one.

Same with route of administration. You start -- you first look at C54456 as an Observation Code, the C code in NCI EVS. If a 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 EDQM code. And if none of them are available, then -- and I think there's a pretext field, also, available for you to submit. In that field test -- pretext field.

Okay.

All right. So the next data element under drugs G be k is FDA additional information on drug coded repeat as necessary.

So this is a regional element that we have introduced. Used to provide characteristics associated with a product.

The maximum length is 2. The data type is numeric. And the conformance is

conditional-required. And allowed values are 1 for test. 2 for reference. 3 for bulk ingredient. 4 for bulk ingredient for human prescription compounding. And 5 for unapproved drug product manufactured exclusively for private label distributor. And we have a nullFlavor.

For this -- this typically could be used if you had a compounding as you mention there this can be also set to 4. As was mentioned in the authorization as COMP9 this can also be set to 4 -- COMP99. But this field is mostly made 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-ANDA number where adverse event occurred which is the regional data element, if it is present, that means I know Social Security for IND-exempt, then the Observation Code value, one of two must be used to describe the drug's role in the IND-exempt BA/BE study. And the drug role is either test drug or reference drug. Then you can use nullFlavor NA for all of the drugs if the information is not available. So this is an important thing. Now, that reminds me of another rule that if you have N.1.4 or -- N.1.4 which we talked about ZZFDA_PREMKT and N.2.r.3 which is IND exempt BA/BE, if you have that, then the rule is that the pre-ANDA number that occurred must be present. Because you're telling me that you are reporting of non-IND or BA/BE so that might be present or this preANDA number where it is present then we will try to check to see that N.2.r.3 -- or N.1.4 has ZZFDA_PREMKT and N.2.r.3 says IND-exempt CDER_IND-exempt BA/BE so that rule will also apply to make sure that we don't fall through the cracks for this report to be public.

All right. Then we have another data field called FDA Specialized Product Category.

This is mostly for combination products.

This is used to provide characteristics associated with our combination product.

So FDA.G.k.13.r.

The data length max length is 10. The data type is Alpha Numeric. The conformance is optional. And we are using the C codes.

So this also helps really helps us to define this is a combination product between a drug or a biologic which is a type 6 or is it a refilled delivery drug device system which is a patch et cetera which is a type 2 or a convenience kit which is a type 1, giving those values actually really helps our team here or the reviewers to kind of hone into what type of product that is. If you just say the product, then these extra attributes actually help us to the right investigation that we need to do. So the C codes are again, they are C codes where you have NCI EVS it's taken from there. And these are autonomic values that we use for this particular field.

FDA Specialized Product Category.

Okay. And next.

Submission rules. So we did talk about some. I showed you that spreadsheet.

But this is a section in the technical specification about submission rules. So I wanted to talk about it a little bit with the submission rules, what they are. And how they -- they should comply to that so we can prove the quality of the data.

So submission rules is define conditions resulting in a negative acknowledgement and not accepted by FAERS, if not met.

We also have the E2B(R3) Core and Regional Data Elements and Business Rules -- 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 for accepted acknowledgement with error messages. And it could be accepted. Right?

Because they are warnings. So it's still a rule. But that rule we are making this a warning. So that we would like you to respect that next time, the submitter fixes the data and submits it.

Okay. The E2B Core and Regional Data Elements and Business Rules, so this is again the same document. You see this multiple times the same document is referred to. In this case I've not put a link here. But there's a link in many other places. This is the spreadsheet that I went over with you. And that defines the conformance and the rules for each data element.

If there is different data elements, some data do not have any rules. But the rules that are there are defined in the spreadsheet. And we saw that. And we see in that spreadsheet it 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 if you're wanting a positive acknowledgement, we always say it's positive. So right there.

But really I mean to make our data good with good quality so that we can do better review, you know, we would request that the warning rules are also looked at by the submitter and character in the subsequent submissions.

And finally we have the forward compatibility.

I have a whole different set of slides which will come at the end which will talk about the forward compatibility.

Know that forward compatibility is something where if you have something if we move to forward compatible. So we have today something that's submitted in an R2 format, yes, we forward that to R3.

For premarket, we don't have an R2 format.

Right?

So there is nothing to go there for forward compatibility to go over to R3 because as we said we are directly jumping into R3.

So with that you will find this forward compatibility rules are not applicable to premarket safety reports. If we have R2 first that we ultimately planned yes we will

have forward compatibility for premarket safety report but now we are not. So we are straight jumping into R3. So there's nothing to talk about forward with the premarket. Only the postmarket.

So they list the data element rules to be applied. So if you have S and now that field is now Y, one of the rules from R2 to R3 where R2 it was S and R3 it's Y.

And of course please do not forget about that Appendix I (B) to the ICH guide for forward and backward compatibility. It should be referenced for the data elements whose source is ICH.

So you still have to look at that. The one forward compatibility that we are talking about 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 good at timing.

So if you have any questions, please do submit your questions to the Q&A. We have somebody who is monitoring those questions.

And with that, we will take a break. 11:45. And we will be back at 12:30.

Thank you.

(Lunch break).

>> OPERATOR: Recording stopped.