G23-168-B
Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonization (ICH) E2B(R3) Standards
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[Lunch Break]

[Recording in progress]

>> SURANJAN DE: Welcome back. We're at 12:31. With the outline, we have now completed the background, regional implementation of E2B, the submission of methods, we talked about the implementation package. There were questions on the spreadsheet, and I opened the spreadsheet for you to see what it looks like, what are the components of the spreadsheet. We talked over some of the common regional extensions. Some are pre and some are postmarket and now we'll talk about postmarket safety reporting extensions, what they are and we'll first start with the transmission identification.

You may have seen this table previously. We have talked about N.1.4 and 2 R3. I'll go over again and again these particular data elements after we are in line with the headers because we thought the files would be rejected.

In this table I have highlighted for postmarket and in here you have the AS2 header, CDER, and XML files, very important to note this down.

Going into some of the specific elements we have for the postmarketing, a data element we added as a regional extension. It's under the reaction event as reported.

The feeling is called required intervention. It's FDA.E.i.3.2h. Oftentimes this is used for verification errors because they require intervention. This is a Boolean data type.

It's very similar to the Boolean fields that we have for the criteria like death, life threatening, hospitalized and so on. You have the conformance as required for this relevant. The values allowed, true and NI. And for premarket safety report this will almost always be submitted as NI. You have other elements to talk about the seriousness. This is the required intervention data element.

Next, we have device information. And this could be repeated as necessary.

This section started with FDA.G.k.12.r and here are the elements. The first element is defining if there was a malfunction. If it's a combination product, that element is way ahead. You're saying it's a combination product, now you say is it a malfunction or not. The observation code value is a C code, it's true or false and it's conditional required.

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

Next is if follow-up, what type of follow-up it is. We have this data element. Observation code is a C code. This is an optional data field.

It's an optional field, there's no business rules.

Device problem code, this is an important field. The observation code is C54451 and there's a link there. This link takes you to all of the device problem codes that you can mention and this could be IMDR or the FDA code. This is required if the malfunction is true. This is a business rule.

FDA will only validate the format. One or more codes can be required. Then we have device brand name. It's a free text. It's conditional required. You're saying it's a combination for that report. Then device brand name and common device name either can be null -- however, if the value is null, device product code is required.

Common device name. Inn text field is free next. If you don't have it, you can submit NI. This is a conditional required field. We say if the combination product report indicator is true, then you need to provide the device brand name and the common device name. If either is not available, then you provide the device product code.

Okay. Device product code. That is available on the link, all of the device product codes.

Again, conditional required.

If both device brand name and common device name are blank or null -- or NI, then the value for the device code is required. You have to at least see what the device is.

So you have three fields to understand what the device is. Then everything is about the manufacturer of the device. The device manufacturer name, the device manufacturer address, city, state, country. These are all optional fields. You can use alpha numeric.

For the country field you can use EU.

Device usage, this is observation code C54595. It's an optional element. And then device lot number is an optional element. Now I'd like to invite Veronica to talk about IND safety report. I guess everyone is waiting to hear that.

>> Y. VERONICA PEI: Thank you, Suranjan. We're going to spend the next few minutes talking about reporting IND safety reports to the FDA using the ICH E2B(R3) standards.

This is a brief overview, comparing the current process to the new process. You can see in the existing process sponsors of clinical trials are required to submit IND safety reports as per 21CFR. If the process, they're submitted in PDF format. It results in labor-intensive reviews, it doesn't allow the tools for data visualization and there's no universal tracking system.

However, in the new process, this will allow the use of visualization and analytic tools for review and tracking because the data will be structured and actionable.

FDA will also leverage existing processes in use for postmarket safety reporting such as the ICH E2B data standards and FDA gateway. Implementation of this new process will comply with federal regulations 21 CFR 312.32.(c)(1)(v).

This required change format under 745A of the FD&C Act.

This change will be effective 24 months after publication of the final guidance and after the effective date, FDA will only accept safety reports in the new format.

The goal is toll begin voluntary submissions by the end of this year. FDA will publish on FAERS website 30 days prior to the voluntary submission. This is a snapshot of the FAERS webpage and in preparation of the safety reports in the E2B(R3) format, FDA has posted relevant documents on this website.

The link is on the bottom of this slide and there's a number of resources listed.

FDA will conduct remote meetings. I'm sure you're familiar with this slide, this is a reminder, this table highlights the attribute values that must be used when submitting CDER and CBER IND CSRs. The header define the gateway folder where the XML files will be routed. FAERS will verify the values of N.1.4 and N2R3. If those values do not align, your submission will not be accepted and you'll receive a negative acknowledgment. In this case, a resubmission with the corrected routing ID will be required.

Not all IND safety reports will go to FAERS. You can see from this table it outlines where to submit different types of IND safety reports.

The top three rows show the three types of IND safety reports that must be submitted to FAERS and these are the ones that include the individual ICSRs. Findings from other studies, findings from animal or invitro testing or increased rate of occurrence of serious suspected adverse reactions should continue to be submitted in the EC TD format.

First, you will no longer need to submit 1571 and the cover letter when submitting electronically.

You will not need to submit the same safety reports for cross-reported IND separately because now we have a mechanism that allows you to do that.

You will also receive immediate acknowledgment if your report is accepted or if there are errors which you need to resubmit the report.

Other benefits include submitting ICSRs directly and eliminates the need to send ICSRs to your regulatory affairs.

We're going to talk about example scenarios to illustrate how you would submit the safety reporting for INDs in the premarket space.

First scenario, we're just talking about simple, submitting a safety report to a primary IND.

We're going to draw your attention to this new data element called IND number where the AE occurred. This is to capture the primary IND number. The max length of the field is 10 and the data type is numeric and the business rules for this element are described on this slide. The data field is required when you're submitting an IND safety report.

So in the second scenario, the sponsor IND is -- you're submitting an ICSR with the cross-reported IND. You're going to need to include the cross-referenced IND number. Note, this data element can accommodate more than one cross references IND number and the business rules and the performance for this data element is also listed on this slide so I'm not going to repeat them.

In the third scenario, we'll talk about reporting from aggregate analysis from several ICSRs, there's a couple of elements that are important here.

The first one, you'll notice you need to submit the aggregate analysis under its own unique safety report identifier, this is submitted as data element C.1.1. You'll also need to include a parent IND and you'll submit that under FDA C5.5.A and the D1 value must be denoted as aggregate. You also need to include all of the DSR that make up the aggregate analysis using C.1.10.r.

In this scenario, the sponsor is investigating drug A versus an approved drug B.

So you know that for suspect drug A you will use the company code, the established name, or the preparatory medicinal product name under the element ID G.k.2.2. If the proprietary name is not available, you must at least submit the active substance name and it's important to distinguish between the company code versus the proprietary medicinal name.

Now, in this scenario, you have two trials -- or two arm trial. Both drugs are approved, however, you're conducting a trial where the approved drug A is being studied to support a new indication.

So here you'll note that you need to submit two reports to FAERS. You need to submit one under the IND and one in the postmarket. Next slide.

Here we're going to discuss reporting of causality for IND safety reports. This outlines the data elements needed for reports of causality information. You will need to include the source of the assessment, the method, and result. The business rules are also listed here.

I want to highlight a couple of other IND regional requirements. The first is that you need to include the study name. This is where you would submit the study ID along with the abbreviated trial name.

The study ID should be the same value used in the ECT submission, for an aggregate report, the study type where the reaction was observed, the value must be one which indicates clinical trial.

This is the other element, study type or reaction occurred, you must submit this information.

Another one is the element date of death. If the element death, which is in the Ei32a, if that's true, you're required to submit the date of death at D.9.1. Now I will pass this on to Jung Lee. Thank you.

>> JUNG LEE: Next slide.

Hi, my name is Jung Lee.

I'm from the division of clinical safety and surveillance. I'll be presenting on BA/BE study and safety reporting for generic drugs, here are the objectives, I'll be briefly covering the generic drug pharmacovigilance overview and Bioavailability/Bioequivalence studies and safety reporting requirements and processes.

The key characteristic of a generic drug pharmacovigilance is that it's a collaborative progress. We engage with different offices within CDER as listed on the slide as well as -- [inaudible]. Not only is it across all of these offices, but it covers the entire lifecycle of the generic drug. The flow of information covers the bio-IND safety report as well as the IND-exempt BA/BE study.

I'll review the safety variation of the new drug application safety issues.

[Indiscernible]

The safety reporting requirements are different for BA/BE studies conducted under an IND and those not conducted under an IND. Those under IND must meet the safety reporting requirements under 21 CFR 320.31 and 32. Sponsors are required to submit an IND safety report for an event that meet the following conditions: Serious, unexpected, and suspected adverse reactions. BA/BE study not conducted under an IND must meet the IND exemption under 21 CFR 320.31. Must meet the expedited safety reporting requirements under 21 CFR 320.32d3. This slide covers the current generic drug premarket and postmarket safety report submissions.

What I want to emphasize here is that generic drug premarket safety reports are still submitted in form FDA 3500A. But IND safety reports are required to be submitted via E2B. These premarket reports contrast with postmarket reports that are submitted to FAERS database in E2B through database-to-database transmission or the safety report portal.

FAERS enhancement will bring opportunities for electronic submission.

The IND safety reporting requirements under the 745Aa have already been covered by Veronica.

Sponsors have two options of submitting; one is through submitting throughout the electronic submissions gateway and the other is throughout the safety reporting portal.

Sponsors can begin the voluntary submissions in the E2B(R3) format. The date to be published will object the FAERS website. Requirement 24 months after the final guidance publishes.

Bio IND safety reports am meet the electronic ICSR reporting requirements under 745A(a) of the FD&C act.

Options for submission, currently form FDA 3,500 A email.

Once FAERS II enhancement for premarket is available, E2B format is an acceptable form of notification to the FDA for an SAE required under 12 CFR 320.

If a company is using voluntary electronic submission of IND-exempt BA/BE safety reports, we'd like to recommend the following. These are stated in the FDA regional implementation guide for E2BR3 electronic transmission of individual case safety reports for drug and bi-logical products guidance for industry technical specific occasions document.

I also listed additional resources and hope you find them helpful.

The next step in this process is to prepare your IT system for E2B(R3) submission.

If you do not already have a FAERS account, please create one and use the contact information for creating an account with a FAERS electronic submission coordinator.

Next thing to remember is the preassigned and the number. This number can be requested via the CDER NextGen portal. It's ideal to have this pre-IND number ready.

Now that you have your system ready, all of the information you need and ready to submit your safety report, at this point I can't emphasize enough the importance of correctly identifying

ICSRs from IND-exempt BA/BE studies, first of all by complying with the business rule for submission path. There are FDA defined header attributes and routing IDs.

Please use the information on this table to specify these submission paths for IND-exempt BA/BE safety reports. Please include message CDER identifier and batch receiver identifiers.

These business rules are created to differentiate between pre and postmarket ICSRs and to ensure premarket reports are not published publicly and to make the safety reports available to the [indiscernible]. In addition to complying with the submission path business rules, please indicate the type of report in data element C.1.3 to indicate this is a report from the study.

Please include pre-ANDA number in your submission. This is FDA regional data element with max length of ten, numeric data type and the conformance of conditional required. Meaning if the type of report is two, indicating this is from a study and the message with CDER identifier is CDER_IND_EXEMPT_BA_BE, this becomes a required element according to the business rule. Remember, this pre-ANDA number must be valid.

It's also important to identify the drugs the subject was exposed to.

In in G.k.2.2 titled money did national product name as reported by the primary source -- report the proprietary name of the product and G.k.2.3.r.1 is used to report the drug substance name.

It's important to characterize the role of the drug in G.k.1. You can select the values for the rule of the drug.

1 for suspect, 2 for concomitant, 3 for interacting, and 4 for drug not administered.

If subject signed the consent form for IND-exempt on accident and was hospitalized before the study drug was administered, because of the outcome of hospitalization that accident would count as a serious adverse event that must be reported to the FDA.

This would be the case that where drug not administered value can be used.

FAERS and FDA regional data element title FDA additional information on drug. This is data element with maximum length of two, numeric, and conditional required. If FDA C55b is present, then the observation code must be used to describe the drug's rule in the IND-exempt BA/BE study. This is required and important for us to understand the drug exposure. In this presentation I have highlighted data elements required to submit the IND-exempt BA/BE safety

reports but there are other elements required. I highly recommend refers to the technical specification document for more information on other ICH and other regional data elements.

Sample XML files are made available at the FAERS website. Please take a look and let us know if you have questions. Please review acknowledgments and notifications as you start submitting the electronic safety reports. In case of rejection, it will include the reason for rejection of the submission. The FAERS electronic submission coordinator is available for any issues.

I would like to end this presentation with the encouragement to the companies who are considering voluntary electronic submission of IND-exempt BA/BE safety reports by reviewing the advantages listed in this slide.

First of all, the premarket safety reports will not be in public space. There are two user specific requirements that are available in the public portal.

Secondly, for efficiency purposes, most of the companies with approved products already have a pharmacovigilance system in place. The chances are high you're company has the IT system to support this submission.

The premarket safety reports will be required in electronic format, but it makes sense to have all safety data in one submission method, including IND-exempt BA/BE safety reports.

With the added benefit of automated confirmation of receipt.

Another advantage of submitting IND and BA/BE safety reports in electronic format is supporting generic drug pharmacovigilance, this will improve generic drug signal detection and enhanced data management and analytics.

I would like to end the presentation with acknowledgment to my division. Thank you for joining us and looking forward to engaging with you during the Q&A session.

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

>> SURANJAN DE: Thank you, Jung. So with that, we will get into the next area of the presentation, which will be the validation and implementation.

So when we talk about validation, what we're talking about here is how do you validate your XML file that you've generated, test it, make sure the files will be accepted. Maybe you've

generated your first XML file, now you want to test that. So how do we do all of that? So we go into some of the specifics.

The mechanism to validate E2B, provide a mechanism for industry to validate the regional E2B(R3) XML files. The mechanism can be used to pre-validate prior to production submission. And it will had been available to everyone via a public URL. The URL will be posted to the FAERS electronic submission webpage.

I'll show you the next screen as to what the validator looks like.

But it's a place where you can upload a file and test the file.

These are not stored with us. It's for temporary validation and it will tell you all of the issues the file has or it will say the XML is valid which means when you submit through the gateway, the file will be accepted.

In order to do that basic validation, let us see how the validator screen will look. Here is the mechanism to validate E2B. On the screen there is a browse button. When you click on the link, a page will open up which will say you can validate. You can browse and pick the XML file you want to test. Source should say FDA underscore R3, which means we're using the R3 structure. With the regional elements of R3. The XML file is shown here. And then you will have a button which will say "validate." You will probably not have the converted XML. We're not providing that. We're just providing to validate. You'll have a validate button. You will see the list of issues that the XML file has. On the screen you see at the bottom it displays the list of issues that that file will have.

If there are no issues, it will say it's a valid XML and then you'll go to submit this.

Now, again, remember that when you're using this validator, it's something that you will use for a temporary period of time. We don't want you to before every submission go to the validator and validate it because you will have so many submissions and this can only validate one at a time.

So the idea here is that you will probably go back and fix the issue in your database so this doesn't happen for the ICSR you just validated and for future ICSRs. This is more of checking everything is good so that you can have a process running and you won't have to come to this validator anymore.

This validator will be more used in the first timeframe and once you have corrected everything, you probably won't have to come to this validator anymore.

This will give a way for you to test rather than emailing us and depending on FDA to respond back every time. This validator will help you to expedite your validation.

With this the next thing is we go into some of what the implementation plans are and where we are.

We have published the regional specifications. We published on April 2022 and there's a link below here. We also had updates in August of 2022, I believe, and then updates in January again. Because as we're implementing the spreadsheet, the regional specifications are updated. The data rules and attributes are still the same.

We're enhancing both of the tools that we have, which is the LSMC and RXLogix tool to include regional extensions, because of R3 and regional elements, they all have to be updated. Also, some downstream system enhancements. That work is now in progress.

The set up is completed for inbound and outbound folders. So the set up for ESG is completed. We have yet to start the system testing because I think that just probably may have started because we just got a release batch from the tool vendor.

We're starting the testing to fix identified issues. It started to happen, and it was a continuous process. As we find issues, we'll go back and forth to the vendor to make sure the issues are fixed. Then we want to do peer industry testing with a few companies.

We cannot do more than 8 or 9. We have identified a few. The validation tool, which we saw in the previous slide, will be available very soon. I believe that testing is going on for the validation tool right now. That will be available. You can do as much testing as you want. Even if you have not been invited to do specific testing, you can do as much testing as you want.

We will test pre and postmarket ICSRs. We'll have testing in July/August and a second round of testing in October if issues show up.

You can test the E2B validator. There is no limit to that. You can test as many times as you want.

Then basically for the specific industry testing we will be providing progress and all of that. But for everybody else -- I'll repeat the E2B validators will be available. First step is making sure the XML is valid.

Gateway testing, it's the same except you have to route it to a different location.

If you want to send something that you're ready, your XML files are good, now you just want to test the acknowledgments, please let us know through FAERS and we will work with you to get some of those XML files that you can submit through preproduction or test gateway. You should automatically get acknowledgments once you start submitting through the preproduction of the test gateway.

Public communication, we're communicating via the SBIA conference, ePrompt meeting and DIA conferences. We're going to have separate pages for E2B(R3) and separate for R2 so at some point we will prepare R2. There's no date yet. We'll be preparing Q&As for the technical specs, on boarding and inquiries. With all of the communication that we have, we are using those questions to prepare a Q&A.

And we will be posting that sometime as we come close to the implementation date.

Lastly, we have the communication to the FAERS submission page.

We don't have a date yet. We're trying to get something done by the end of this year for voluntary submission of IND safety reports. Sponsors continue to submit premarket and postmarket ICSRs.

Please do not start submitting R3. You can start submitting during the voluntary period.

We'll do E2B(R3) for postmarket and premarket respectively.

Sponsors should notify FDA when ready for the first production submission to FDA in E2B(R3) format.

The first submission in R3 we'll keep an eye on that.

Questions for testing must be sent to the email address with the subject line "R3 testing." Let me tell you what this timeline is saying.

We will have a date when FDA goes live with E2B(R3) and the safety reporting portal. Consider that date as year 0. From that year 0 all of the way to year 2, you have the voluntary

period to submit ICSRs. During that period as we're getting ready, start submitting in E2B(R3) format. This is where you have mandatory ICSR submission via ESG or SRP, year two.

Then you go to mandatory submission using E2B(R3) format or via SRP. End of this year, we're trying to make that year zero. But please don't hold us to that.

We will notify 30 days before when FDA is basically ready to accept E2B(R3).

Now, a few suggestions or recommendations here for all of you, during the voluntary submission period for premarket ICSRs, we recommend that you use the Safety Reporting Portal for submission. We give you an account, you can enter your own safety reporting. It gives you that you have to submit 1571 or the cover letter and eliminated sending the report to your company's regulatory affairs. It's not mandatory but recommended because you have the advantage and we have the advantage that the report is already electronic because if -- if you submit through the -- [indiscernible] -- but then we'll have the data -- and we make sure things are --. During the year 0 to year 2 you can use the Safety Reporting Portal until you're ready to submit through the gateway.

Now, once ready to submit premarket safety report in E2B(R3) format via gateway, you can notify us and we can deactivate the SRP account and then from that point you will be submitting the E2B(R3) XML file through the gateway.

Again, your choice. You can let us know and we will work through to get you an account soon.

It takes about 5 business days. And if every company starts coming like this, we will have some backlogs. When we notify this to you and when we're ready, if you want to submit through the Safety Reporting Portal, please let us know so we can create your account.

So data submission changes that may happen once you move to E2B(R3) for IND safety reports.

This picture shows what is happening today.

You have the sponsor, your submit a regular form through eCTD goes through the gateway, the regulatory submissions and then from there we take that and we will send that thoroughfares, which means that the data has to be entered into the FAERS database. We will have it in FAERS. That's the process that will happen before the first 2 years.

Now, once the 2 years is over, if you have completed or are ready to submit E2B(R3), within that 2 years, this is what will happen.

What will happen is that your sponsors will submit the E2B XML to the gateway and from there it will go to FAERS. Which means you don't have to submit that med watch to the eCTD and it won't go through the submission database because it's already gone to FAERS. We save a step in FDA to not take that and enter it into FAERS because the XML is already gone and the you will get an acknowledgment back. That is a record for you that you submitted your IND safety reports to the FDA.

This will be the process that -- the change that will happen when you move fully into submitting IND safety reports using E2B.

So now going into rejections and warnings.

We want to focus on this because with rejections and warnings, it's important that you are aware of that.

The first thing is, we recommend do not include more than 100 ICSRs in a single batch. It helps us and it helps you all who maybe are filing. It's also easy in transmission, smaller files. It's easy to parse and lower into our database and soon we'd be able to send acknowledgments than having large batches.

If you have, let's say, 300 ICSRs could be sent, three batches with 100 ICSRs, that will make our process faster.

ICSRs in the same batch must have the same sender.

The batch that you have for sender, the sender identifiers, must be the same in a single batch.

You cannot -- please do not use different sender identifiers in one batch.

One batch will have 100 ICSRs.

All batches must be for a common receiver.

Batch all postmark ICSRs together.

Don't put pre and postmarket in one batch and send it to us.

It's important that it doesn't go public.

Separating it out will make it easy for us to catch that and put it in different buckets so they are not mixed.

Do not mix premarket ICSRs for CDER with postmarkets.

Do not send initial and follow-up reports in the same batch.

If you send initial and follow-up, we may see the follow-up first.

If you're sending a batch, that means you're sending a batch at that point -- either you've forgotten about the follow-up and 99 percent of the time I believe when you're sending a completed reporting form to batch, you should not have follow-ups in the same batch. Please keep that in mind.

Next, do not submit nullification or amendment ICSRs as the initial report.

Your amendment report cannot be the nullification report and vice versa. The other specific rejections and warnings, these are regional.

There are rejections that are related to what ICH has said. These ones which you will see are specifically what FDA says, this is extracted from that spreadsheet the ones which are regional, regional extensions.

Batch receiver identifier. ICSR sent to postmarket route should not have the value ZZFDA -- sorry -- yeah. Batch receiver identified, which is saying -- [audio cutting in and out] -- we have rejected that and we're saying ICSR is sent to the postmarket route -- it should be the other way around.

We will say to you that the ICSR that you sent to the postmarket route does not have the value ZZ FDA.

The next one is ICSR sent to the premarket route does not have the value ZZFDA premarket.

The second one is the N2r2 provided is not the same for all reports and does not match is the N.1.3. They need to match and it should be the same for all reports.

Message receiver identified, in this the two rules are if N.1.4 is ZZFDA but the N2r3 is not CDER.

The next one, N.1.4 is premarket but N2r3 is not CDER.

The next one, type of report, N.1.4, but C.1.3 is not two.

We have documents that are to be included. The last one on this slide is does the case fulfill the local criteria -- this said that your initial report cannot have a value of NI because you have to say is it true or false. The initial report cannot have the value of NI.

Other data reports, local data report type. We talked about when these errors will come.

You will get an error if your FDA C171 must be the observation code value of 1 or 4 when FDA.C.1.12 is true and C.1.7 is true. These are some of the data values that will give you a rejection.

There are two warnings here, which is identification number of the report which is linked to the report.

C.1.10 are to be provided when D.1 is aggregated. If you're not provided, we'd give you a warning, but we'd like you to correct it the next time.

Study type -- if you have C.5.4 should be 1 when D.1 is aggregate. That should be there but we're asking you to also have the patient D.1 as aggregate.

IND number where AE occurred, FDA.C.5.5a must be provided when C.1.3 = 2 and N.2.r.3 = "CDER_IND" or "CBER_IND". Same with pre-ANDA number.

IND number of cross reported IND, FDA.C.5.6.r is not provided or nullFlavor is not 'NA' when FDA.C.5.5a is provided. You said the IND number is there.

The next few data elements. Patient name or initial. We talked about the aggregate.

If a patient -- it says D.1 must have nullFlavor NA when FDA C.1.12 is true and, FDA G.k.12.r.1 is true and d E.i.2.1b =10067482 it was not on any patient.

We talked about patient race and ethnicity. We also talked about when you have, you can put it as nullFlavor NA when D.1 is provided. Characterization of drug rule. We talked about the specific rules. Then we have FDA other characterization. We talked about the similar device.

And lastly, in this slide before we take a break is some of the data elements where we have the source of assessment, method of assessment. They need to be provided when you have IND occur. You have the malfunction flag because you're talking about a combination product, you need to let us know if it's true or false. We have the device problem code. And then we have the rules for common device name because if you have a device brand name or common device name, if you don't have brand name you need to provide us with the device product code and

the device brand name and common device name is required when it's a combination product. If you don't have it, we'll submit it as null information and then give us the device product code.

With that, we're at 1:45 and we'll take a 15-minute break and come back at 2:00 and then go into some of the areas with Object Identifiers and forward compatibility and then Q&A. Thank you. We'll join back at 2:00.

[Recording stopped]

[Break until 2:00]

[Recording in progress]

>> SURANJAN DE: Welcome back.

The next two topics are FDA specific Object Identifiers. Going into the next slide, which is the Object Identifiers, let's talk about what this is and how we have set this up for the regional elements in FAERS.

An Object Identifier is a sequence of numbers that identifies an object. The reason I'm saying this is because you will find some Object Identifiers you may not recognize and just to give you what these are, I think it will be useful when you see what they are and what values you need to send into XML.

Each OID corresponds to a node in the OID tree hierarchy. Which is formally defined using the international tell communication union's ITU OID standard X.660. The root of the tree contains the following three arcs: You have 0, that is the international tell communication union, you have 1, which is for ISO and two, which is Joint-ISO-ITU-T. If you look at any of these OID numbers, if it starts with a 2, that means it is a joint value between ISO and ITU.

These examples are written either as a string of digits separated by dots or as a list of named branches.

So to give you an example of MedDRA dictionary of terms, it's identified by the OID 2.16.840.1.113883.6.163 which also represents the branch ‘joint-iso-itu-t.country.us.organisation.hl7.external-code. That means this Object Identifier can be identified if they use this OID number. Every number has some significance, which is that it is two -- starts with a 2, which means it's a Joint-ISO-ITU-T, 16 identifies the country, 840 is the

U.S., 1 is the organization, 113883 is the standard and then you have the code system and then 163 which points to MedDRA.

That means the MedDRA code is OID 2.16.840.1.113883.6.163. Let's go into the HL7 HumanPharmaceuticalsBaseRMIM. This is how we take a regional element and define that. This is a complex model. We looked for how do we define the regional data elements. Going into the type of report, you see the investigation characteristics, that's the class of HL7 with the CE as the data type.

If you look at the data type for this data element it shows an example that you have the code system, which is an OID, and it is a data type which is CE and the value type of the observation would be data type, any, and then CE has been used. It's an ICH report type. Using the same concept we created the regional data element, which is the local criteria report guide. If you look at the local criteria report type, the only difference is the code system says 2.16.840.1.113883.3.989, then you have 5.1.81 and it will tell you what each of these mean. If you go to the next slide, we have another exam of a study registration number.

This is taken from the study registration class. Then you have the root and ID.

This is an example of the Type 2 data type that we have.

Now comes the FDA OID. If you look at this, you see the ICH arc. When we talk about 5.1.2 that stands for ICH arc, then we have 1 which is the FAERS, or if it was used for eCTD, it would be two. That's how the FDA OID has been set up. It goes to the ICH, then the regional specialized, then subregion and then FDA.

Some other region, maybe 3 some other region, so that FDA which is two, it's two for FDA. It could be three for some other region and four for some other and so on and so forth. If you go into the next slide, let's look at the joint ISO-ITU, you have the country, U.S. organization which one, heavy, external root, ICH, regional specialized and subregion al. At the end you see the.1, that's the local criteria report type which is specific to FDA and not any other areas or any other region.

Then we have the operator for the device.

The operator for the device, it's.2. So we look all the way, now after the code list, which is 5.1.2 then FAERS is 1 then you have the code list for that local criteria type is 1 and then the

value in that is 1. It tells you these are the values, 1, 2, 3, 4, 5. Then you have the operator of the device, which has a value of 1, 2, 3. Then we go all of the way to dot 2 at the end. FAERS is 1, which is the third number from the right. And then you have one, which is in red, and then.1 which means support list and then 6, operator of the device, is 2. These are the values for -- the OID values. These are called code list values. Then you have name spaces, when you have a name space, the last digit after that one is dot2 and then you have IND number where adverse event occurred. The IND number is joined by 2 -- organization is one, 113883 is the external, 3989 is -- then you have subregion as one, then FDA as two, then FAERS as one, then name space as two, and the last one is one, which means it's for IND number. If you take that same content, the pre-ANDA number is that way. It's dot 2 at the end. If you have an observation code, so you have combination product flag, then the observation code goes as the ICH is 989, region is 5, subregion is one, FAERS is 1 and then dot 3 is observation code. Now we have the combination product flag which is .3.1.

So that is how the FDA FAERS OIDs are set up. If you have new data points, that is how the OIDs will be set up for that.

That's how you expect the OIDs to be defined and to be used.

This is basically all about FDA OIDs so that you have an idea how FDA OIDs are being utilized.

With that, we are going to go into the next topic, which is -- there's been some questions on R2 to R3 regional forward compatibility.

What is this regional forward compatibility? You have been submitting E2B R2 to the gateway. When we move to R3, what are regional data elements that we have in R2 that a submitter needs to take care in R3? It's important for us to know that.

Now, there are also forward compatibility for all of the ICH elements, that needs to be also considered along with the regional forward compatibility. We did not put anything about the core ICH elements, because they're available from ICH. We're going to be talking about the regional forward compatibility and this list of tables that you will see are also available on the FAERS electronic submission webpage.

When I went over the documentation this morning, the implementation packages that you have, one of the documents was that.

So the first few elements, the way this forward compatibility is set up, you have a rule, it shows you what the regional R2 field is, the description of the field, what the R2 values are, and then it goes into what does it map to the regional field R3, the description of the regional field, what the values are, and the comment that tells you how the things need to be mapped.

So let's take a few elements here and go over these elements for forward compatibility.

We have a rule, FDA-01 that says that for element ADOT 1.1 does this case fulfill the local criteria for a report? The values used to be 1 through 5. Now R3 is a Boolean field. In R3 this needs to map to local criteria report type FDA C.1.7.1. It has the values, and you will map 1, 2, 3, 4, and 6. Of course, six is not there -- it should be mapped 1, 2, 3, and 5 to this few field in R3.

Another rule is combination product flag. It's yes or no or it's not set. In R2 it's A .1 FDA 15. In R3, it's a regional element called combination product flag, but it's true or false. The mapping is yes goes to true, no goes to false. If it's not set in R2, then use nullFlavor in R3.

Then study type, here we have 1, 2, 3 then it maps to the same thing. This is a straightforward one.

Next is malfunction. Malfunction flag is yes or no and not set. In R3 it's true or false. Either there was a malfunction or there was not. Mapping, yes to true, no to false. If not set in R2, then set this field value to false in R3.

Then we have correction and additional information response requests, which is if follow-up, what type of follow-up. These are the values. We have separate fields in R2. In R3 we have one field, and you can mention the value. You can repeat it and you can have these values there. So how do you map it? The way you map is if the correction was yes, then you send the value of one.

If additional information was yes, that means you send a value of two. If correction was yes and additional information was yes, then you send correction and additional information as one and two.

Since this is a repeating entity, if the value of R2 field is null or not set, then don't include that in R3 because, again, it's not [indiscernible] -- but if you have yes for one of more of these R2 data fields, then you set it as a repeating type.

So we have the next data elements. Remedial action initiated. In R3 they become repeatable.

Each R2 value is set up as a repeatable value with R3. If there's no value, you don't send them. But if you have a value of yes, let's say you have a recall and then repair or recall and then replace, then you send in the repeatable tag either one and two or one and three. That's what you send in the XML.

Then you have -- let me jump into the evaluation value. It's interesting because we had a field called evaluation value, now we're only asking for device problem. If the evaluation value used to be 01 for device problems, the code type should be 01 and then your value would be actual value of that device problem code.

In R3, we just have device problem code.

So you copy the value of the device problem code where the R2 tag has type R2.1, device problem code.

You can have more than one device problem code. But keep in mind that a device problem code from R2 to R3 is based on the evaluation type of 01, which stands for device problem and the evaluation value, which goes into the field device problem code.

Since we're not asking for all other types of evaluation, we're asking only for the device problem code.

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

We have the field and rule for the manufacturer names, straightforward copy. Device usage is a straightforward copy. Device lot number, straightforward. Operator of the device is to be free text. Now we have the values. In R2, map R2 value of health professional. I think we even though it's free text -- we have health professional and names of patient. So in such case, if you have a database where the operator of the device in R2 was health professionals and in R3 it's 1. And if R2 value is not health professional, only user, then set it to three, which is other.

All right. A sample, this does not require forward compatibility, but I've shown it here because it's a regional field.

There will not be, for instance, R2 does not have the patient race code element. When you're transferring the data, you can use the nullFlavor unknown.

And then submit that for the follow-ups, if you're able to get direct value, then you can use the value. But for data, let's say you have already a case in the database, now you have the patient race code, and you don't have a race code, send it as unknown and we should be good to go.

Same thing with ethnicity code. You send the value of unknown if you don't have the value.

Required intervention, since you don't have the value, you send it as NI, no information.

Now you have it in R3, in the follow-up you use the value N in that case and then you have the characterization of the drug role. Since that in R2 has a value of 1, 2, 3, and 4, we did not have -- drug not administered, we have a value of similar device in R2, that now goes to FDA other characterization of drug role. When you do the mapping of R2 to R3, you map the R2 value of similar device to 1 in R3 and since G.k.1 is required, set the value to 4, drug not administered.

Which means your G.k.1 will be 4, drug not administered, but in a case where you have a similar device is one.

If you have a case where characterization of the drug role in R2 was 4, you will migrate that to FDA other characterization of drug role as one, similar device, and make G.k.1 as drug not administered.

With that, we go into our summary and let's see what we talked about today.

Today we talked about implementation of E2B(R3) for both premarket and postmarket report at the same time.

It will be both for SRP and [indiscernible] all happening at the same time.

Next, we have new date for voluntary reporting will be communicated on the FAERS electronic submission web page. Next, we talked about E2B(R3) code and regional data elements and business rule, the document for all core ICH and regional extensions, this was the Excel spreadsheet where you were able to see all of the different tabs in there.

You did see what tabs are for what purpose.

You saw the X path tab, the elements tab, the rejections, warnings, and the acknowledgment.

We talked about using our controlled terminologies like EVS. We covered many times the separate submission path and business rules, IND versus IND-exempt, BA/BE versus postmarket it's a very important table so the submissions don't go public, especially for premarket reports.

We talked about submission methods and mechanism based on AS2 header and routing ID. Next, we discussed regional extensions. So we went into many of the data elements, almost all of the data elements which including rules that were different, conformance that were changed. All of these were discussed today for IND, IND-exempt BA/BE, and postmarket safety reporter. The E2B validators, should be able to use that to do your testing as you're developing. As you generate your XML you can test it during the testing phase.

I also mentioned, vendors if they wanted to get in to do their testing, they can request for a testing web created account where you can test through the validator first and then you'll test your gateway through those routing IDs, and you should be able to do that through the test account.

Please let us know if you have issues in requesting the test accounts. It's straightforward. It's on the website how to request for the test accounts.

Then we have regional specific rejections and warnings. We had the rules for rejections and warnings and went over the list. These are regional specific.

There are code ICH-specific rules, but what I talked about today, it's regional. Code, you have to go into the implementation guide.

Gave an overview on the FDA OIDs and the regional extensions, how the FDA OIDs are set up, what the numbers are.

And if the future if we have new regional extensions or new data points, that is how those OIDs will be used and how those OIDs will be set up.

Of course, we will go into the regional model to look at the data point that is used to define that field and then the OIDs will come along with it.

And of course, if there are any observation codes, then we will first look at the standards organization to make sure the observation codes are there because we create our own.

Lastly, we went over the R2 to R3 forward compatibility on regional elements.

We went over some of those specific ones where you need to keep an eye on when you're moving from R2 to R3, when you do your submissions -- do the testing with R3 making sure that the forward compatibility rules are in line. Also, please make sure that along with the forward compatibility rules that the regional elements that we talked, please do not forget the elements.

Once you're moving to R3, we're not going back to R2. We're not doing backward compatibility of things, we might use backward compatibility for internal purposes, to make sure certain data points are populated from the respective -- for example, the data elements of event level we want to roll up at the case level. That's where we may use it.

But please, from a submission perspective, if you move to R3, we're not going back to R2.

The R2 to R3 forward compatibility is only applicable for postmarket safety reports.

With that, we will -- the next slide is some of the references. These are all of the documents that we have.

These are accessible at these links; you can download them and look at them.

With that, we will take a short break -- we'll come back at 2:40 to start the Q&A that you have been submitting throughout the day. All right? Thank you. And see you in 4 minutes.

[Break until 2:40]

[Recording stopped]

[Recording in progress]

>> SURANJAN DE: All right. So we are back.

And we will start with some of the questions that we have for IND safety reporting that Veronica, I asked you to repeat the question and then we'll give a response.

>> Y. VERONICA PEI: Could you please confirm that for IND cross reporting, sponsors will submit only one report to primary study IND and all INDs in the report that requires cross reporting, is that correct? The answer is yes.

The second question is, for the date of death -- and if you remember, that element is D91, you advise that if results in death, that element is EI23A and that is true, then date of death is required. However, it was not mentioned that the nullFlavor is accepted for this value. Is the nullFlavor accepted? The answer is yes, correct. The date of death is required if the death value

is true, but it's not -- you don't -- if you have a null value such as MS K masked or ASQU, which is ask unknown and the MASK, you can use those three null values for the date of death.

Another question is, record regarding analysis of certain events for IND reports, is there a specific data element? There is no specific data element for the analysis of similar events. The second part of the question is -- refers to where to report this information.

And we would recommend that you report this information in the narrative portion of your submission.

>> SURANJAN DE: Next I'll request Jung to answer some of the questions that she has that has asked.

>> JUNG LEE: Thank you. The question is, how do I identify the product name for a study? You should use the drug substance name, the non-priority name and the priority name in GT22. The name should fit within the established character length.

The second question is what study drug should be identified in the IND E study reports. You should report all drugs to which the subject was exposed.

How do I classify the subject's from exposures? Each of the subjects drug exposures should fit into one of the qualifications, past drug therapy, drug exposure during study and follow-up period.

For the past drug therapy, this should include any drug the subject was taking prior to studying that was discontinued.

For the enrollment and follow up period, these drugs should include the test drug, reference, placebo, vehicle or other drugs such as [indiscernible]. [Indiscernible]

Question four, what are the appropriate descriptions data elements for reporting drug exposures that occur after enrollment? There are three important key components to remember when reporting the drug exposures, one is the name of the drug, give us the proprietary name or substance name. Second, gave us the role the drug played. And the third and last component mentioned was the additional information. Is this drug a test or reference drug? If unknown or neither, flag it as NA.

The next question is, what does no exposure mean for purposes of electronic submission for these expedited safety reports? A subject has no exposure to a study drug if the [indiscernible] prior to study drug exposure.

Event meets FDA's expedited reporting experiments. To report without study exposure, select G.k.1 and drug not administered or G.k.2.2 for proprietary name and 2.1 for [indiscernible]. That's all for me. Thank you.

>> SURANJAN DE: Thank you, Jung.

So I will go into some of the questions, there is a lot of nullFlavors -- null values on the backward, forward compatibility, will the spreadsheet be directed -- yes, the null values are conditional because you're doing backward, forward compatibility. There are values that may be a mandatory field. You have to have a value. There's where you use nullFlavor. Please confirm if we can submit -- there's a reference to submit.

Will you accept XML files with nullFlavor? Yes.

For a small business sponsor that has an ESG account but does not have in-house [indiscernible] capability, they'll be able to submit ICSRs through SRP.

Then can we upload an XML file in SRP instead of manually. No. That will not get processed. The purpose of SRP is you can submit a report, so they are structured.

One thing I did not mention is -- yes, all of the slides, all of the presentations and the recording will be posted on the FDA's meeting page. They all will be posted within three to four business days.

So we will have them there. The slides will be there and the presentation will also be there.

Is there any work been done to sync the fields and required field between FAERS and med watch? Yes, many of the fields have been harmonized, they're using the same codes. Without that, we really cannot import the data into FAERS because sometimes you will have -- of course med watch comes in different flavors, one is for consumers, one is for manufactures.

Submit a med watch that we have mapped to FAERS. We have been doing this activity and most of them have been all harmonized.

Do we have -- okay. If we don't have patient name -- should we not report this? Because if you have a malfunction and there is no AE, that means that the event did not occur -- in that case, we will make it consistent to use NA for the support.

And then regarding medicinal product name, presumably it would be preferred to use the reported data description.

True. But please make sure for your local trade name or product description line matches with the XPL or with the active ingredient name.

It's challenging to get NDC codes. It's true, but if it's available, please report to us and if you're able to ask that and get that, please report to us.

It's not a mandatory field. The product name is mandatory. If you have it, please submit it.

Regarding the combination products, would this be centered for this combination product -- the answer is yes. There are questions on additional data requirement for R3. No. Anything that has been listed today and is in this spreadsheet of the core and regional data elements are the data elements and if they have been -- if conformance says required, it's required. Those would be the mandatory data elements. Every element listed in there is available there.

So when would you need to use the R2 to R3 forward compatibility? If you're submitting postmarket safety reports today in R2 format and then you move to R3 format, you'd need to use the forward compatibility.

When will FAERS reporting in lieu of eCTD/ESG submissions, be required for safety reports for investigational agents?

Check with the FAERS electronic submission webpage. FDA is ready from that point on wards you will get 2 years to prepare yourself and then submit in a shorter timeline from year 0 to 2 you can use SRP and once you're ready with XML, we will deactivate the SRP account.

Do submitters have to have a FAERS and ESG account? No. If you're submitting through the safety reporting portal, yes, you need to have an account created for the Safety Reporting Portal. There is one question that says can we send EDQM terms, please send the SPL first.

After the voluntary period is over, the FDA will no longer accept R2? Or will both R2 and R3 be accepted for a period of time after the mandatory date?

No. After the mandatory date, we will want to move on over to E2B(R3) so that we don't have to maintain two versions because companies are given almost 2 years. Should be enough time for us to get E2B(R3). As I said, with R2 to R3, we will go over that, once we move to R3, we move to R3.

Is there a field limitation for narrative? If so, if narrative goes over limit, will it be automatically truncated?

Yes, it's 100,000 characters and if it's over, yes, it will get truncated. But you could -- we also have sender comments and reporter comments. You may -- you could also use that but mention that additional comments are mentioned in the sender's comments and then we can work it out that way.

There is also another question, A or B will pilot testing be done on? A.

Is there a fee associated with the ESG portal? If you have to do a back submission, there's a certificate that has to be shared with the FDA. The certificate as I understand costs some fee. That's why a lot of organizations have not gone into that but if you use web creator, which is free, you can do one forward submission at a time, that is free. If you use the Safety Reporting Portal, the submission is one CSR at a time, which is also free.

With that, we are -- any additional questions that you have, we will request you to submit to the docket and we will work on addressing those questions.

If any other questions we have, we will also send that in the docket. With that, I would like to thank everyone who attended this webinar, and we hope we've given enough information and good information for you to start your work in implementing E2B(R3) for submissions to FDA.

We are also going in FDA in full speed in trying to implement E2B(R3). So with that, our next talk is going to be at the annual DIA and then one next meeting will be in November of this year.

With that, I would like to end the meeting.

And thank you all for attending and providing your questions to this webinar. And thank you to our other two guest speakers, Veronica and Jung Lee, thank you for your presentation.

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

Thank you.

[Recording stopped]