Environmental Impact Technical Section submitted under a P-submission

Now I'm going to demonstrate the, walk through the eSubmitter report for the P-submission which is your Environmental Impact technical section. And a lot of this, I'm going to basically repeat what I just said for the X-submission for certain things for recording purposes, so these two presentations can be stand along recordings. But if you have questions, please feel free to go ahead and just write your questions in the chat box and I will answer them when I am done.

Ok. So in this presentation, I am going to walk you through how to submit a claim of categorical exclusion, an environmental assessment, and any supporting information under the Environmental Impact technical section. In this demonstration, I will be demonstrating submitting under an INAD file as an example, but again, similar to the X-submission, the same things apply if this were submitted under a JINAD. There is one additional screen to complete for JINADs which is to fill out the RLNAD proprietary name, established name, and sponsor, but everything else is going to be the same.

I would also like to point out that if you submit your Environmental Impact technical section under a traditional NADA or ANADA, currently, the templates don't exactly match what they are in the P-submissions. But that should be, or will be, updated very soon so that the screens in the NADA and ANADA templates will look exactly the same as this. So if you were in another demo, one of these breakout rooms, or someone else is, rely on this presentation on how to fill out a Cat Ex or your Environmental technical section.

So again, on screen 1.0, you would fill out the document type and document number. And select yes that it is an established application. On screen 2.0, you would indicate whether you are a U.S. company and fill out your firm's information, typically from your address book which would be right here. If you are not a U.S. company, you will also fill out screen 3.0, which I can show you from here, which is information about the U.S. Agent. But for now, we're just going to assume that we are a U.S. company. And this information was demonstrated this morning so we've already pre-populated the template. And the same thing goes for the responsible official which I pulled out from an address book. And I selected yes that the submitter is the same as the responsible official.

So screen 6.0 gets into the submission type you'd be submitting. First you would select "Major Technical Section", which is a P, from this drop-down. Then you would select "Environmental" as your technical section. And again, this is different from the X-submissions because this is your technical section now. And the division of scientific support is the only review division to which you can be submitting. And again, for these purposes, I will assume that it is not an amendment.

On the next screen, screen 1.0 is under this “Environmental Technical Section” and you’ll see it’s the I/P/NP template and it gets into the submission type you’re going to be submitting. First, I’ll walk though how to submit a Cat Ex, and then I will come back to this screen and demonstrate how to submit an EA and then again on how to submit a supportive submission.

To submit a Cat Ex, first check the claim of categorical exclusion box like I have here, as the type that you are submitting. In the parentheses it has the 21 CFR 25.33, which is the part of our regulations that lists the classes of actions for animal drugs that are categorically excluded. The specific citations under 25.33 are on the following page, so we will get to those shortly.

If you are submitting a Cat Ex or an EA with or without study reports, and a Cat Ex, if you select any of these, you’re always going to select “Technical Section Complete” as the final action letter that you are requesting. The “Submitted Information Acceptable; Technical Section Incomplete” would only be selected when you submit supporting information.

The next question asks if this submission is in response to a previous technical section incomplete letter. If you answer yes, then you would need to answer yes or no to whether CVM offered you a shortened review time with the resubmission of the technical section and, if so, you would need to include the submission number. Otherwise you would just select no. For JINADs, this would be the last question on this page. You’ll see this question right here, this new one. This is a new submission, this is a new question that will be added to eSubmitter as of October 1 as part of the ADUFA reauthorization. And this covers instances when we need to reopen a technical section, the Environmental technical section because the conditions of use reviewed for a completed technical section is different from what will be on the label. And then you would have to resubmit a claim of categorical exclusion, but we would be able to review that within sixty days if your other submissions have already been, your other technical sections have already been submitted.

There’s going to be a whole other presentation that will be available by video that will be available soon that explains this process of reopening the technical section so I’m really not going to go into that today. But basically, what this question, that’s what this question has to deal with. It says, “Have you or CVM identified changes to the conditions of use that would affect your Environmental Impact technical section complete for a pending proposed action?” So basically, did your conditions of use change after received the Environmental Impact technical section complete letter and before the drug was approved? If the answer is yes, then it will ask you has CVM has offered you a sixty-day review time with the resubmission. And there’s a hint box here that basically explains what it means. You’re basically saying that CVM has contacted you and you’ve received a letter stating that upon resubmission, you can get a sixty-day review time. If this, if you, if we didn’t have that conversation or you didn’t have a completed technical section, then you would just answer no. And most of the time, the majority of the time, you’re going to answer no to this question. These are kind of for one off instances that we have.

So screen 2.0, again, is the product description. This was also discussed earlier this morning and just when I did the X-submission briefly, and again there are a few important things to point out. For the purposes of an environmental review, it is important that you fill out the information exactly as you expect it to appear on the product label. And that's again because we're evaluating the potential for environmental impacts to occur, and the dose, duration, frequency, indication, and species are important to our review because these parameters dictate how much drug will be entering the environment. If information provided in the eSubmitter report does not agree with information that we receive from the target animal divisions, because we always verify with the target animal division before we close out a submission, a technical section, then we could ask, we'd either ask for an amendment or it would be a refuse to review. So we just ask that you fill this out as accurately as possible.

And again down here, you have the CAS number to enter, and to work in the question that we already had, if it doesn't have a CAS number yet, we, it would be helpful if you can enter, include some place in the submission, a structure, a chemical structure, or a molecular weight and a chemical name, which should also be entered with the established name.

This screen also allows you to attach a file, and typically, you should not need to include information for the drug product on this page. But again, if you don't have a CAS number, you might be able to add something. But it does allow you in the event that you need to.

This again takes us to screen 2.1 in which you enter information regarding your drug and whether or not it will be manufactured using recombinant DNA technology. If you select no, then you'd have no other questions to answer and if you select yes, you then you have to answer the next question which is whether or not the manufacturing facility of the API located in the U.S. And the reason for this question is to determine whether there could be environmental impacts in the U.S. from the manufacture of the genetically engineered drugs. And if we don't, we don't evaluate environmental impacts that may occur from the manufacture of the drug in another country. So if the answer is no, you do not need to answer any other questions. But if you answer yes, you would need to include the location of the facility or facilities. Even if only part of the manufacturing is done in the U.S., you should provide the information for that part of the manufacturing process. I do know that there are some drugs in which they manufacture part of it in another country and then finish the manufacturing process in the US. So just include whatever information you can and we prefer, it would be better to have more information than not enough information because then we would have to ask for an amendment.

So if you answer yes that the location, the facility is in the U.S., then you must answer the remaining questions on this page, which ask you to identify the recipient organism or cell line, indicate whether the organism is a known pathogen, and describe how the drug will be modified and why. You could also provide reference materials such as literature articles if they directly pertain to your

compound and modification process. Finally, the last question asks you to describe the specific biosafety standards and biological containment measures followed at the manufacturing facility as a way for us to verify that the labs are using adequate precautions for the biosafety level of the drug.

At the top of the screen it states that we would prefer that you provide the information directly into the eSubmitter template rather than referring to attached documents. But if you cannot enter all the information in this page or in Section 7.0 at the end, you can certainly provide that information in an attached document.

And as discussed with the X-submission, we are aware that some information may not be available to you because it is proprietary information. This information may be available for CVM to review in a DMF or VMF. If this is the case, you would need to obtain a letter of authorization from the DMF or VMF holder that will give you a right of reference to the information in the files. You should submit one copy of the letter of authorization along with the Cat Ex and include the file number and relevant page numbers. And this may go along with the question that was asked earlier about, you know, if the information is in an A-quad or another submission, if you have a right of reference letter in, submitted under a different submission, you can refer to that right of reference letter because a lot of this information you might need to submit for manufacturing, but if you can include it here, there's some things that, you know, we would like to keep the submissions clean in the event that things change from the time you previously submitted the information. So we don't always have to keep crossing between submissions so that's our way to ensure that we are still reviewing the same thing and you the sponsor have not changed any of the conditions of use along the way.

Alright, and now I'm just going to assume that this is "no" to make it easier that it's not made by rDNA.

OK. So section, screen 3.0 pertains only to Cat Exs. So the first question is to specify which type of action this claim applies to. So it can be, we're just going to say that it's an NADA, but it could be a supplement, a conditional, or for indexing. So this would be an NADA. Then you must specify which section of the CFR for claims of categorical exclusions that your proposed action qualifies. The wording in this template is the same as the wording that is in the regulations. And sometimes a drug will qualify under multiple citations, but you can only choose one in these in these templates.

Only when you select 25.33(a) will this other section right here become active because there are several examples in the regulations that fall under a which is the no increase in use. If after you read the options (a)(1) through (a)(7), if your proposed action doesn't fit exactly under one of these examples, you can choose this "unclassified", which just means that the action does not increase the use of the drug, but the examples listed don't apply. And if you choose unclassified, as I did here, you will have to provide an explanation in this box here as to why there would be no increase in use. So this becomes mandatory once you hit unclassified. See that mandatory button disappears. And then here you have, the hint box to the

right of the text box which defines what is considered an increase use, as it is described in the regulations.

For most claims of Cat Ex, you wouldn't need to include any additional information. This includes actions under, if you look here under (d)(1), (d)(2), and (d)(3). You don't need to add anything else. Those are for nonfood animals, anesthetics, and non-systemic topicals or ophthalmic drugs. However, there are some citations that do require additional supporting information. You will know which ones require additional information because you will see the blue mandatory dot next to file attachment section. So this would include 33(c). You see here this dot became active. That means you have to attach a file. Also (d)(4), which is for drugs for minor use and minor species, and (d)(5), which is drugs intended for use under prescription or VFD for therapeutic use. So you will have this mandatory button in which you would need to attach a file. For the purposes of this demonstration, so that we don't have any issues coming up, I am just going to select (d)(1).

Now, by the time you are ready to submit your Environmental technical section, you should have already come in for a pre-submission conference to discuss what is needed to fulfill the requirements of the technical section. At that time, we'll let you know what information is needed when you submit as specific Cat Ex so I'm not going to go into that, those details today.

If you do choose to include a cover letter with your submission, you can include it here. But if you do, please verify that the citation in the eSubmitter report and the cover letter are the same. Again for the, more so with the technical section, we receive submissions that cite different Cat Exs in eSubmitter and the attached cover letter. Since the information in the eSubmitter form is the official record, we would potentially assume that's what you mean, but if there are different citations in the attached documents, we don't know which one you are actually requesting. So this is when we would call and ask for an amendment or we could potentially refuse to review the submission.

And again, at the bottom of the page is the required certification statement that you must check. It states that you certify that the action requested qualifies for the Cat Ex and that to the best of our knowledge, no extraordinary circumstances exist that may significantly impact the quality of the human environment. And then it refences the regulations under 25.15(d) and 25.21. And then it also states that it should be based on a reasonable search of information, which could include any environmentally related information that that you own or is in the public literature. So you should determine whether there could there be the potential for serious harm to the environment at the expected level of exposure. And we do that as well when we review these. And then there's a hint box that also explains what's considered to be extraordinary circumstances, as they are defined in the regulations. So this certification is required for all Cat Exs that are submitted and the box must be checked for you to complete your submission.

And then the last screen is screen 7.0 which is where you can include any additional information that may be needed for this submission.

So this would be the end of this submission. You would hit the green right arrow up here one more time and it will let you know if you have reached the end and all is good, or if you have an incomplete submission. If it is incomplete, you can go to the output tab and select missing data and validation issues report. Check OK in the box and another window will open up in your browser and list where the issues lie.

And then you are done.

So for, so now I'm going to go back and, to screen 1.0 which is the "general information". If you go over here on this environmental technical section tab, I went to screen 1.0, and now I'm going to demonstrate submitting an EA. So if you look over here to the left again, screen 4.0 is for EAs with original study reports, and screen 5.0 is for EAs without original study reports. Although there are separate screens depending on, you know, whether you plan on submitting original study data with your EA, the information on the screens in eSubmitter will be exactly the same. So I am going to click on screens 4.0 and you'll have this information. And if I double click on screen 5.0 you'll have the same exact information. So I'm only going to demonstrate going through one of these.

Again, now again you'll select "Technical Section Compete" as the final action letter you are requesting and then you will select yes or no as to whether the submission is in response to a previous technical section incomplete letter. So if yes, you would just enter the information that's requested here. Otherwise you would answer no. It is more common for sponsors to have to resubmit an EA for a second or a third review cycle than it is for a resubmission of a Cat Ex. But for now, I'm just going to assume that this is the first time we are submitting it.

So then your product description screens 2.0 and 2.1 would still be the same as I just demonstrated for the Cat Ex submission and they are still active in this report so I'm just going to continue to the next screen.

So screens 4.0 or 5.0, depending on if you have original data, is where you would attach your EA and supporting documents. This says, "Have you previously submitted an EA for the proposed action?" We'll check no. And all you will need to do is just include your EA and any supporting documents here, which could be original study reports with copies of the raw and electronic data and any publicly available literature articles that were cited in the EA. So you really only need to upload the documents in this screen and include a cover letter. You can upload PDF, XML, and XPT files. And you can just figure it out here. And how to attach files was demonstrated this morning so I am not going to demonstrate that. But basically, that's all you needed to do for an EA. So compared to the Cat Ex templates, this is a little more straight forward in eSubmitter, although it is not easier to prepare. And then, you again, you have screen 7.0 for comments for anything else you want to note. And that's all you do for EAs.

Now I will go quickly through the supportive submissions. There's a hit box that describes, over here, it describes what may be included in a supportive submission,

which is original study reports, journal articles, technical reports, and other similar types of information. And under this submission type, sponsors typically submit data in order to obtain CVM's feedback on whether the studies and endpoints of the submitted data are acceptable to use in a future EA.

So for this submission type, because you're not submitting a Cat Ex or an EA, you would select "Submitted Information Acceptable; Technical Section Incomplete". You should answer no to this question because this data is typically not in response to a technical section incomplete letter. And everything else again for this should be the same on screen 2.0 and 2.1.

So I'm going to move on to screen 6.0 that asks you what types of data your submission contains. So check all that apply. And "other, unclassified", that could be like a white paper or something. And like submitting an EA, all the information should be submitted as PDF, XPT, or XML files uploaded down here. And you can submit as many study reports at a time as you want and include a cover letter explaining what you want CVM to do during the review of the data. So for example, if you submit a, an acute toxicity test with *Daphnia magna,* you just say that, you know, you are looking to use the LC50 as an endpoint in your future EA. And then when we respond to your, to your submission, our letter will let you know if we agree or not.

And basically, I guess the only other thing I would say is, especially if you submit a lot of data like this, if you submit it in one PDF, we do appreciate when you do bookmark the PDF files for, to make it easier for us to find the data.

And then you, once again, we make it to screen 7.0 and we're at the end of the submission. Oh, and here it says the report is incomplete due to missing information, so we'll go up here and find out what it says. The drug dosage, ok so, it looks like I included, had missed some information. But that's what it would look like.

So if there are any questions, that's everything you need to know on how to submit your environmental impact technical section. If you guys have questions, we're always here to help if you want to shoot us an email or phone call before you submit. And then I can start answering questions.

There are some in the chat box that I will get to. Let's see. And then as you have a question, just put it in the chat box. We'll start with, we'll go back through, there was a question from before: "Is an X-submission required prior to doing studies for all post approval claim extensions?" If you are going to be conducting additional investigations beyond what you were initially doing, like if the dose, duration, and indication, or the species increases, you may need to submit a new Cat Ex so that it covers that use pattern. And if you're not sure ,you can always contact Holly Zahner who is our current team leader. You can contact her, or you can contact your project manager who will reach out to us and ask. Or if you have a question when you come in for a pre-submission conference, you can always include that type question in your, in your meeting materials.

The next question says “How would CVM have offered a 60-day review, informally, phone call, etcetera?” So this is a little bit outside the scope of this presentation. It will be, just briefly, it will be an informally via phone call but then you will get a letter, a formal letter that will be documented in your INAD file so that it is in your file that we offered this. And this will beginning, again, on October 1. And so what will happen is we will verify that, if something comes in that says it is a 60-day review time for a resubmitted Cat Ex, we’ll verify in our documents in the INAD file to see if that submission, if there is a submission that exists that says that we offered it to you. It would probably be a Q-submission, which would be a sponsor-initiated letter sent to you that would offer you that. So it would be formal.

The next question. “Can we provide additional explanation about target animals? The specific wording in the drop down does not match the wording that appears on the label in many cases.” That is an excellent question because we often have that issue arise. So let me go back to where it is. in cases like that, let me find my product description, hold on. Ok. in a case like that, what I would say is you would select the common name, like cattle. And then. Or let me see. Hold on. Cattle. There was an… I think there was something. Swine. I’m sorry. Hold on a second. You can provide that information someplace. I think we’ve had questions internally about this and it will be addressed at some point. I just don’t know if it’s going to be addressed by the time things roll out on October 1. I would put that information, you can actually add that information under, include it as part of the proposed indications for use or in one of the sections on screen 7.0, where you can include that information. I feel like I’m missing something because I know there was something where you could put, you could do something different. Other. Oh, here we go, “Other unclassified”. That’s what I was looking for. It would be okay for you to select “other unclassified” and add it in here because then once you do that you can specify it in that box, right here. Ok.

“Can the recombinant DNA manufacturing question be answered in the EA or does it have to be done in the text boxes in the eSubmitter?” If it’s in an EA, if you do need an EA, it can be in the EA. But if you can fill out the information in here, then that would also be helpful. And basically, it would almost be a copy and paste, I think, from, the location of the facility, that could be a copy and paste. The identification, and maybe, maybe for an EA you might be able to say “see EA”. But most of the time, these things do come in for a Cat Ex. So I’m going to say possibly. I don’t want to give a definite answer for that yet. I would have to double check before I say yes or no for certain on that. I apologize for not being able to answer that.

“What is meant by original study reports?” So original just means proprietary study reports that were sponsor-funded studies that were not available to the public, to the public such as, you know, study reports that were, that were funded by the sponsor and are not part of public literature.

Next question. “What is the recommended approach to finding out what data the CVM needs to receive in electronic format for a given study, or should this be

included in the study protocol?" That, this is a question that is kind of outside the scope of this presentation. I think it's not just for environmental that you would need electronic data so that would be something you would need to ask, we can ask, send a question to askCVM and get an, I believe it's in eSubmitter. Hold on. Let me find where there's a CVM eSubmitter email that you can send that question to.

"Does CVM want a submission table of contents when multiple files are being attached?" The answer is, we would greatly appreciate that. So, please.

And the next question is, "how much detail is expected in the box for biosafety containment?" Something for that, if you're following, if you see here, it says describe it. We have RAC guidelines, CDC guidelines, international guidelines. You don't necessarily have to contain, provide every step that's taken, but we need to, if you can say that they are following RAC guidelines and/or CDC guidelines and the biocontainment level, that should be sufficient. And if we do have additional questions, we will reach out to you once we get there because we might be able to find that additional information. And if you can refer to. Provide as much information as you can in the box, and if you need to refer to, you know, if you've submitted some of this information with CMC or some other submission, you can refer to that submission number and we will try to look for it there as well, so you are not duplicating your efforts.

Alright and that was the end of the questions. Are there any other questions? We can sit here. Is there, at two o'clock, they're going to be doing a demonstration on how to do the I/P/EF, which is the efficacy template. So we have another five minutes. If not, everyone can take a break until two o'clock.