CLAIMS OF CE FOR INVETIGATIONAL USE (X-SUBMISSION)

My name is Kristen Beckhorn and I am a reviewer on the Environmental Safety Team. In this presentation, I will walk you through how to submit a claim of categorical exclusion for investigational use of a drug under an INAD or JINAD. In this demonstration, I will be using an INAD as an example, but the same things apply if this were submitted under a JINAD. There's one additional screen to complete for JINADs which is to fill out the RLNAD proprietary name, established name, and sponsor. But everything else is the same so we are going to skip that for this presentation.

So if you see here on screen 1.0, you would enter the document type. I am going to do an INAD and the file document number. With the exception of opening a new INAD or JINAD, you would always answer yes to the question asking if the submission is for a currently established file or application. And then you can move to the next screen, screen 2.0. You would indicate whether you are a U.S. company and fill out your firm's information and typically this would be in your address book which you can download from right here. If you are not a U.S. company, you also fill out Screen 3.0, which is information about the U.S. Agent. And if you look over here on this outline screen, if we went to 3.0, you'll have the U.S. Agent and U.S. employee information to fill out. But for this demonstration, I am just going to say that I am a U.S. company. Filling out this information was demonstrated this morning in the morning session, so what I've already done is I've already put all this information into the template to save time.

On screen 4.0, it asks you for the contact information of the responsible official which I also pulled from an address book. And then on screen 5.0 it asks if the submitter is also the same as the responsible official. If so, then you wouldn't have anything else to do. But if you select no, then you would have to fill this out and all these mandatory blue dots would come would show up meaning you would have to answer that. And again, this was also demonstrated this morning, so I'll just skip over this and assume that the submitter in this scenario is the same as the responsible official.

And now screen 6.0 gets into the submission type you're going to be submitting. First, you would select for we're walking through your X-submission which is an Environmental Evaluation for Investigational Use. So you would select that. And this should be one of the first submissions you submit under the INAD file after requesting to open the file, which is your A-quad. And you know, as a reminder, this is not your Environmental Impact technical section which is a P-submission. The X is required when you will be using your drug for clinical investigations in animals under the INAD or JINAD. So this submission must be submitted in order to maintain your investigational exemption.

So next you would select whether you would be selecting a Cat Ex or an EA. Most of the time it will be a Cat Ex. If an EA is needed, you'll likely already know that

before you submit the X-submission. The EA for investigational use is less common so I'm only going to demonstrate submitting a Cat Ex here.

You only have one option to submit to a review division and that is HFV-160. And we will assume this is not an amendment.

So now we get into, if you look over on the left, you'll see this tab which says categorical exclusions. It's your I/X/CE submission. And this is a general information on screen 1.0 and really there's nothing for you to do here. So this screen is to verify that you are submitting a Cat Ex under 21 CFR 25.33(e), which is for investigational use of a drug under the INAD or JINAD. There's no other Cat Ex citations for this option for an X-submission and so there's really nothing for you to select here. In the fine print on this screen it just says is that with this submission, you're claiming a Cat Ex under 33(e) from the requirement to prepare an EA for investigational use under the JINAD. And that, you know, the Cat Ex is ordinarily granted except when extraordinary circumstances could exist. And in the case that extraordinary circumstances exist, that would be when you need an EA.

So moving on to screen 2.0. This is the product description that would need to be filled out. This also was filled out this morning so if we click on the drug, if you see this is already, this template is already filled out. There's just a few important things to point out.

For the purposes of the environmental submission, it is important that you fill out the information as accurately as possible. We realize that you are submitting an X-submission it is going to be early in the development process and you may not know the exact dose, duration, or indication. But please provide as much information as you can. And if you don't know the exact dose, you can enter a range or a dose that is up to whatever the max value might be.

The X-submissions also ask you to enter a CAS number because the environmental review is based on the potential for environmental effects of the chemical once they enter the environment, and not necessarily the formulated product. So when we do our review too we also look up CAS numbers.

This screen does allow you to attach a file. Typically, you should not need to include additional information in an X-submission, but this is always a case by case basis. And so, you would add that information here. If you were going to attach a cover letter, that would be on screen 3.0 and I'll walk you through that when we get there.

So this next screen is screen 2.1, which is about recombinant DNA technology. You shouldn't, you don't have this screen on any other submissions that you submit other than environmental submissions. So this will ask you the information regarding whether your drug will be manufactured using recombinant DNA technology and the first question ask you if it is. And if the answer's no, then you have no other questions to answer on this screen. You'll see that all of these are grayed out. But if you answer yes, that it would be made by rDNA, then you'll have

to answer the next question which is "Is the manufacturing facility of the API located in the U.S.?" The reason for this question is just to determine whether there could be environmental impacts in the U.S. from the manufacture of the genetically engineered drugs. So we don't evaluate environmental impacts that may occur from the manufacture of the drug in another country. And so if it's manufactured outside of the U.S. and you answer no, then you don't need to answer any other questions on this page. But if you answer yes, then you would need to answer the next question which asks you to locate the location of the facility and then whether or not the API is produced commercially or in bulk by you or the intended manufacturer. Now this question right here is only in the X-submissions. And the reason for this question is that we expect the investigational use of a drug to be limited and localized. And if the drug is already being produced commercially or in bulk, then we would anticipate that the investigational use of the drug would not result in significant environmental impacts beyond what might already exist.

So if the answer is yes, that it is being currently manufactured, then you have no more questions on this page to answer. But if you answer no, then you would need to answer the remaining questions which asks 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 provide reference materials such as literature articles, too, if they directly pertain to your compound and modification process.

And finally, this last question down here 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 this screen, at the top of the page, you'll see that 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 4 of this template at the end, you can certainly provide the information in an attached document.

And we're also aware that some of the 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. And so, if this is the case, then you will 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. So 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 that would be, you know, if you can't fill out these information because it's proprietary. But for now, for ease of this demonstration, I'm just going to go back and say that my drug is not manufactured with rDNA.

On screen 3.0, you'll again see the information that pertains to the specific Cat Ex that you are requesting, which is the same as on screen 1.0. So right here in this next section, you do have the op, the ability to attach a cover letter here as well. It is not required if you enter everything into the template, but if you do include a cover letter or other attached documents, we do recommend that you try to limit the content in the letter to information that can't be directly entered into eSubmitter report or the eSubmitter form because one big issue that we encounter with cover letters is that the Cat Ex citation or drug information in the cover letter does not match what's entered into the eSubmitter. So when this happens, we tend to ask for amendments or we could refuse to review the submission because we are not really sure exactly which information you're actually relying on for your submission.

And then down below here, is the required certification statement that you must check. It basically just says that to the best of your knowledge, no extraordinary circumstances exist that may significantly impact the quality of the human environment. And the it references the regulations under 25.15(d) and 25.21. And then it just states that the certification should be based on a reasonable search of information which would include any environmentally relevant information that that you own or that you have searched and found in the public literature. So if there is a potential for serious harm to the environment at the expected level of exposure, then that's when an EA might be needed. There's a hint box over here that basically explains what is in the regulations for what extraordinary circumstances are and some examples.

And then the last screen is screen 4.0 in which you can include any other additional information that may be needed for this submission. And then basically this is the end of your submission. You would then hit the green arrow one more time and it will let you know if you reached this submission, the end, if you reached the end and everything is good, or if you have an incomplete submission. If it is incomplete, and you get a red, you don't get this exclamation point, you can just go to this output tab and then select the "missing data and validation issue report". Select "OK" and then another window will pop up in your browser and it will list whatever issues would be missing here. And so right here it just says that there's no missing data. And basically, that's all you would need to do to submit an X-submission.

They showed how to demonstrate how to package the submission when you're done so I'm not going to go through that now. There's the recording from this morning. And I'll take some questions if there are any. And otherwise we can go move on in a couple minutes to the P-submission and how to submit your Environmental Impact technical section.

OK so I have one question that says what if a CAS is not yet assigned? If there is no CAS number assigned yet, that is, answering the CAS number is not mandatory. And sometimes we there are some types of drugs that don't have that and you can just say unassigned at this time. By the time you submit your, your environmental technical section, you should have one at that time. And we have had this come across too where there's been no CAS number which is, let me go back to find that.

If you look here, there is, the CAS number is not mandatory, if I can find it. But what you can also do is you can attach a structure or a structure or the molecular weight or any other information that you have. So if you look right down here its's not considered mandatory in the event that there is not a CAS number.

Any other questions? OK.