I-P-PC Transcript

Hi, my name is Laura Moussa and I'm a reviewer on the Animal Bioengineering and Cellular Therapies (ABCT) Team. At this time, we will be going over the INAD Product Characterization Technical Section. Before we get started, I wanted to say that if you have any broad questions about your product (e.g., what type of submissions are needed), then you can send your inquiries to AskCVM@fda.hhs.gov. That will be routed to the appropriate person within the Center. You can also reach out to our project management team. If you have any issues with eSubmitter itself and require technical help, then you can email CVMeSubmitter@fda.hhs.gov. If you have any questions during the presentation, please put them into the chat box and I will answer them at the end.

Once you open eSubmitter, to open a new submission, you want to click on the left-hand side of the screen under Menu Options: the button called "Create New Submissions". For traditional products, we have used the "ONADE Submissions" template set. For any product that is designed to go to the ABCT Team, we have our own set of templates. You will need to select the "ONADE Animal Bioengineering and Cellular Therapies Submissions" set of templates. There is a description that shows what types of products are appropriate for these templates. Then you click next, input a descriptive name and a file name, and click "Create".

For this demonstration, we will be working in the eSubmitter test environment because our ABCT templates are still under development. This means that they will not be available on the eSubmitter on your computers after this demonstration. They should be available on October 1, 2018. To access the template, I'm now switching over to our test environment.

On the first screen, you will need to select the "Document Type". For a technical section, you will select investigational new animal drug (INAD or I). You will need to identify the product category; there are four checkboxes that you can simultaneously click, and usually only one product category will apply [intentionally genetically altered (IGA) animals, cell-based products (including stem cells), gene therapy products, or other; other products could be combination products, new types of products, or anything that doesn't fit into one of the first three categories].

After you've designated the product category, we ask you to describe the product and identify whether or not the animal comes from a food-producing species. If you identify that the animal is from a food-producing species, you will be prompted to tell us whether or not the animal is intended to enter the food supply. If you say "No", then that questions goes away. The final question will ask "Is this submission for a currently established file or application?". Since this is a technical section, you will have already submitted your INAD A submission, so you will click "Yes" and you will enter the document number.

The next screens are for administrative information. On Screen 2.0, you are requested to input information about who owns the file, whether it's a US institution, and then contact information. On Screen 3.0, you are requested to identify the Responsible Official and choose their role (institution/company representative or regulatory agent) as well as input contact information for that person. On Screen 4.0, you will input information regarding who is putting the information into eSubmitter, including contact address, phone, and reference numbers.

On Screen 5.0, you will select "Major Technical Section (P)" as the submission type and "Product Characterization" as the classification code in order to pull up the appropriate

template. Next you will select the review division; it should be coming into the ABCT Team. The next question is “Is this information intended to amend a submission currently pending and under review by CVM?” The very first time that you submit your product characterization info to CVM, you would click “No”, but afterwards if you receive communication from the Center asking for additional information to be submitted while it’s still under review, you would then select “Yes”, and subsequent questions would pop up.

This is the Product Characterization template. On the left-hand side, you can see there is an outline of all the screens in the template. You can see that they are based on product type, so most of the time you won’t see all the sections activated. Whatever product type you did not select will be grayed out.

In Screen 1, for both cell-based products and IGA animal products, you will be able to tell us what type of information is provided in the submission. You are allowed to submit one piece at a time, multiple pieces, or all pieces, depending on what you have available at the time of submission. For cell-based products, you can submit the product overview, product characterization plan, manufacturing summary, donor selection, or comparability plan information. Again, these are checkboxes, so it’s not either/or decision, it’s an and decision. For IGA animals, you will provide us with molecular characterization of the intended genomic change and molecular characterization of the animal lineage. For gene therapy and other products, there are no options to specify since we don’t routinely see product characterization for these product types. We wanted to be able to have the ability to submit this information if it was needed. Next is a field to input the summary of the information provided in the submission. You are also allowed to attach a cover letter; you can see by the absence of the blue dot that a cover letter is not required. It is often helpful for a reviewer to have one though.

On Screen 2, we are asking what type of letter you are seeking from the Center. If you are not submitting all of the pieces simultaneously, then you would select “Submitted Information Acceptable; Technical Section Incomplete”. If you are submitting all pieces simultaneously or you are submitting the final piece, then you would select “Technical Section Complete”. The next question is whether this is in response to an incomplete letter. If this is the first you are submitting this information, then you click “No” and there are no more questions on this screen and all subsequent screens are required. If you have previously submitted this information and received an incomplete letter, you would click “Yes”. The template will then prompt you for some administrative information regarding whether or not shortened review time was offered and the submission number(s) of the previous submission(s). You will also attach your technical section incomplete letter. Also, all the subsequent sections will become optional to allow you to answer only the questions that are associated with the incomplete letter comments.

We will start with the cell-based products template.

Screen A in the **Product Overview** section is the Referenced File Node. This node is included in multiple sections, so I’m only going to go over it the first time and then I will skip it in subsequent sections since the same questions and business rules apply in every instance. You will be asked if you are using information that’s in another file to support the information in this submission. If you say “Yes”, then you will be prompted to input that information here and provide the submission number(s). As you can see in the help text, the information that you input here must begin with a character (V for VMF, I for INAD, N for NADA, or G for General Correspondence) followed by six digits in order to be validated by the system. You can add up to 100 referenced files. The next

question asks you to provide a summary of the information in the referenced file(s). If you say “NO”, then the sub-questions will go away.

In Screen B, you will provide details on the product overview. You will identify the tissue source, describe what is included in the final product, and designate the category of the cell-based product. You will state the species of the donor and recipient and summarize any manipulations performed on the product. You will be asked whether any genetic modifications were performed during the manufacture of the product. If you say “No”, there are no further questions. If you say “Yes”, you will be be prompted to describe the construct and the technology and to state whether a viral vector was used. If you say “Yes” to the viral vector question, then a further sub-question will populate to capture the assessment for any potential shedding and mitigation strategies. If you say “No”, then that question goes away. Next, you will provide any information on any potential off-target effects. Finally, you will provide the formulation, describe any materials provided with the product, and our sections often end with this catchall question “Provide any additional information”. It is not required.

In the **Product Characterization Plan** section, Screen A is the Referenced File Node (see above).

In Screen B, you will define what constitute a single cell line or product batch, identify the anticipated number of doses obtained from a single donation, and provide the dose/frequency of administration, directions for any end-user manipulations prior to administration, and the proposed directions for administration to the patient. You will state whether the product is single- or multi-use. You will describe any administration restrictions, state the intended population, and list out the proposed safety and effectiveness studies.

In Screen C, you will summarize any information relevant to safety and effectiveness for your product. You can provide any pilot study(ies) and/or literature specific to your product that is available; these are not required questions. You can submit literature that is not specific to your product but is relevant to safety and effectiveness characterization, which is also not required.

The next piece is the **Manufacturing Summary** section. In Screen A, you will first add all the facilities that are used during the manufacture of the product. You add a facility by clicking the green plus sign, then input the name and contact information and describe the facility operations, the facilities/rooms/equipment used to ensure aseptic processing, and the inspection history.

In Screen B, you will provide a description of tissue collection procedures, the collection and receipt personnel, the storage and transport conditions for donated tissue. You’ll describe the acceptance criteria for donor specimens upon arrival at the manufacturing facility and the regulations/guidance/standards followed during tissue collection and early processing.

In Screen C, you will identify the starting material how the batch/lot is defined. You will describe the processing/preparation of the tissues. You will be asked whether or not a drug substance is used. If you click “Yes”, then you will be prompted identify the drug substance, define the number units used to make drug substance batch/lot and define the number of drug substance lots used to make the final product. If you say “No”, these questions go away. You’re next asked whether any cell banks are utilized during the manufacturing process. If you say “Yes”, then you will be prompted to state what

kind of bank is used, how it is generated, and the number of passages between the bank and the final product. If you say “No”, these questions go away, but you will be prompted to answer the total number of passages between the donor sample and final product (if applicable. This is not a required question. Next, you will identify the drug product and describe any hold times, in-process controls, and any reagent or raw materials that are used. You are asked whether any of the raw materials or reagents are from human or animal origin. If you say “Yes”, you’re asked to identify them. If you say “No”, that question goes away. You will also list out the equipment and summarize the aseptic processing procedures. You will describe the packaging for the product for any long-term storage or shipment and indicate if the conditions apply to long-term storage or shipment.

In Screen D, you will describe the final formulation, the container/closure system, and the components of the finished product.

In Screen E, you will summarize the tests conducted on components and reagents of human or animal origin in order to identify potential disease agents, the tests conducted on the drug substance or drug product to demonstrate lack of contamination, and the tests conducted on the drug substance or drug product to support donor eligibility. Then you will state when each test is performed and provide the acceptance criteria for interpreting test results as well as justification for the sampling plan.

In Screen F, you will describe the quality system and how contract manufacturers are qualified or requalified.

In Screen G, you will describe the batch/lot numbering system, the donor tracking system, and any other applicable tracking systems.

In Screen H, you will provide the release specifications for the drug substance and any of its controlled intermediates as well as the stability specifications for the drug substance. These questions are repeated in Screen I for the drug product.

In Screen J, you will describe the potency assay, justify its use as a quality parameter and its relevance to *in vivo* effectiveness, and provide any preliminary data (if available; not required).

In Screen K, you will describe the shipping conditions, any shipping studies to assess product stability under the proposed storage conditions, and the storage conditions at the end-user facility. You will also provide the stability testing plan to support those conditions.

In Screen L, you are asked if the drug substance is for any amount of time; if you answer “Yes”, you will be prompted to provide the stability protocol (summary or file attachment). The question is replicated for drug product. For both questions, if you say “Yes”, you are prompted to provide the protocol; if you say “No”, the sub-questions go away.

In Screen M, you will provide the information included on the label regarding storage and shipping conditions, product sensitivities, “how supplied” conditions, directions for preparation and administration, the proposed expiry, and the CFR caution statement(s).

In Screen N, you will provide the recall procedures.

In the **Donor Selection** section, Screen A is the Referenced File Node (see above).

In Screen B, we ask to you to list the relevant disease agents and justify each agent. You will also provide information to support any excluded disease agents.

In Screen C.1, you will state the donor eligibility criteria and list the eligible sources for donors and the criteria for donor medical history, vaccination history, environmental history, travel history, and ownership history. You will provide the sample forms used for historical data collection and state the documentation requirements for historical data.

In Screen C.2, you will describe the eligibility requirements for the peri-donation period, state the eligibility criteria for physical exams and daily health observations, and list the general health screening tests. You will state the criteria and timing. Then you will identify the clinical pathology eligibility criteria, list the laboratory(ies) that perform the screening, describe the personnel doing the clinical assessments, and provide the sample form for clinical data collection as well as the documentation requirements for clinical screening data.

In Screen C.3, you will list the tests for relevant disease agents conducted on the donor, the tests to be conducted on the product or source material to support the donor eligibility, and the laboratory(ies) that perform the testing. You will also describe the documentation method for the donor and source material test results, state the criteria for interpreting the test results, provide the test method validation (if it is available). Finally you will justification for any relevant disease agents that are omitted from testing.

In Screen C.4, you will describe the method for making and documenting the final donor eligibility determination and the qualifications of the person who makes the determination.

In Screen C.5, you can attach any additional data collection forms and any data to support donor eligibility for donors requested at the time of submission. If you are not requesting donors at the time of submission, you don't have to put anything here.

In the Comparability Plan section, Screen A is the Referenced File Node (see above). In Screen B, you will state whether you will be using product generated from more than one donation event in the original approval and if you plan to generate product from additional donation events post-approval. Both of these yes/no questions do not activate any sub-questions. You will state the number of anticipated doses obtained from a single donation event, define what constitutes a single cell line/product batch, and summarize the safety and effectiveness data generated from each line or batch. Finally, you will describe the potency assay, including justification for relevance, and the comparability plan.

Next we will look at the IGA animals template.

In the **Molecular Characterization of the Intended Genomic Change** section, Screen A is the Referenced File Node (see above).

In Screen B, you will summarize the intended alteration and provide a schematic of the intended change. You will provide data to support that the genome has been altered as intended. The final question is a catchall to allow the submission of literature articles, R&D reports, or other supporting information; this is not required.

In Screen B.1, you will input each component used to alter the genome of the animal by clicking the green plus sign. Then you will identify, describe, and state the source for each component.

In the **Molecular Characterization of the Animal Lineage** section, Screen A is the Referenced File Node (see above).

In Screen B, you will describe the method used to introduce the regulated article into the founder animal or cell and provide supporting data. You are also asked to provide data to characterize the cell line used to produce the IGA animal (this question is not required; it may be answered if applicable). Then you will describe the characterization results for the founder animal(s) and lineage progenitor(s) and attach the characterization data in the founder animal or lineage progenitor. If you have any data to support the the stability of the alteration, you are asked to provide it. Any supporting data can be attached in the final question.

Next we will look at gene therapy/other products (if it is determined that product characterization information is needed for these products). Screen A is the Referenced File Node (see above). In Screen B, you will summarize the information provided and attach any supporting files; there are no specific questions.

There were no questions during the session.