UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FDA CBER OTAT Town Hall: Cell Therapy Chemistry, Manufacturing, and Controls

December 7, 2022

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DR. STEVEN OH: Good afternoon. Thank you all for joining us for today's OTAT town hall. Today's event is hosted by the Office of Tissues and Advanced Therapies, or, as we usually say, OTAT, within the Center for Biologics Evaluation and Research at the Food and Drug Administration. My name is Steven Oh. I am the Deputy Director for the Division of Cellular and Gene Therapies here at OTAT, and I will also be your host for today's town hall meeting.

As you all know, today's town hall is focused on cell therapy chemistry, manufacturing, and controls, or CMC, including tissue-engineered medical products regulated by OTAT. We look forward to answering your questions about this important topic.

OTAT launched the virtual town hall series to engage with product development stakeholders and researchers to discuss topics related to OTAT-regulated products. These town halls have a question-and-answer format, with the goal of providing regulatory information to stakeholders to advance drug development. Today's town hall is the second event in the series. As some of you may know, we held our first town hall in September, with a focus on gene therapy CMC, and that recording is live on FDA.gov.

Before we begin, I would like to share a few notes. This town hall is being recorded. The recording and event material will be posted on FDA's website in the next few weeks, and we will also provide a transcript. Closed captioning for this event is available directly in Zoom. This event is a question-and-answer format discussion. If you have a question, please type your question directly into the Q&A box in Zoom. The Q&A box can be found at the bottom of your screen in Zoom. We appreciate the questions submitted in advance and look forward to seeing your questions today. We'll do our best to address as many as we can today. Please note that FDA is not able to comment on or answer questions regarding specific investigational products or job applications. Also, we will not address any questions that we consider out of scope with the event. Please note that we have great questions and answers lined up from the previous pre-submitted questions, and I'd like to also make it clear that, if you are experiencing technical difficulties, please use the chat box in the Zoom function.

Now we'll get started with today's event. As many of you are aware, FDA requires sponsors to provide CMC information as part of an investigational new drug application. CMC information should describe product manufacturing and testing to ensure safety, identity, quality, purity, and strength, including potency, of the investigational product. During today's town hall, subject matter experts from OTAT's Division of Cellular and Gene Therapies will answer questions related to CMC for cell therapy product development, as well as tissue-engineered medical products. I would like to now take a moment to introduce today's panelists: Dr. Melanie Eacho, Chief of Cell Therapies Branch; Dr. Laura Ricles, Chief of Tissue Engineering Branch; Dr. Irina Tiper, Team Lead

in Cell Therapies Branch; and Dr. Zehra Tosun, Team Lead in Tissue Engineering Branch. Thank you to our panelists for your time today.

We'll now move to the Q&A portion of today's town hall. We'll begin by answering questions submitted during the registration process. We will then respond to questions that you are submitting during today's event. As a reminder again, you can submit a question for our panelist in the Zoom Q&A box at any time during the event, which can be found at the bottom of your Zoom screen. We'll try to address as many questions as we can, but please remember we are not able to discuss questions regarding specific investigational products or drug applications. We will also not be able to discuss questions related to our draft guidance documents that are under public comment period or under revision for final guidance document publication. We hope you can stay with us for the entire time, but we would also like to reiterate that the town hall is being recorded, so you can visit the full discussion after it is posted in our website. And one final note: We did receive some questions about gene therapy CMC, and as that is not the topic of today's town hall, we do encourage you all to visit the recording from our gene therapy CMC town hall, which was held in September, for more information.

Let's begin with our first question. The first question is for you, Zehra.

How can I evaluate CMC readiness prior to starting an early-phase clinical study?

DR. ZEHRA TOSUN: Thanks, Steven. We strongly recommend that sponsors engage the Agency prior to submitting an IND application through our pre-IND or INTERACT meeting. Information about this meeting types can be found on OTAT's website. We recommend that sponsors address the comment communicated to them in their IND and, preferably, provide a table in their IND which contains all of the pre-IND or INTERACT comments—and when and how they address the comments in their IND. We strongly recommend that sponsors ensure their original IND submission is complete upon submission. For assistance in procuring the CMC section of our IND, you may use the cell therapy guidance titled *Guidance on CMC Information for Human Somatic Cell Therapy INDs* while preparing your CMC section. To assist in applying current good manufacturing practices in the manufacturing of the investigational drug products used in phase 1 clinical trials, you may refer to *Current Good Manufacturing Practice for Phase 1 Investigational Drugs* guidance, located at FDA's website.

Back to you, Steven.

DR. OH: Thank you, Zehra. The next question is for Laura.

Can the Agency discuss some commonly observed CMC-related issues that have potential to lead to a clinical hold for a first-in-human phase 1 study?

DR. LAURA RICLES: Thanks for that question. The grounds for imposition of a clinical hold of a phase 1 study under an IND are outlined in 21 CFR 312.42. For CMC, the most common hold reasons are related to safety, and include that human subjects are or would

be exposed to an unreasonable and significant risk of illness or injury and the IND does not contain sufficient information required under 21 CFR 312.23 to assess the risk of subjects of the proposed study. The reasons for these holds might include not providing sufficient information to describe the manufacturing process, using reagents which are not demonstrated to be of sufficient safety or quality, not conducting donor eligibility determination according to 21 CFR 1271, and not conducting appropriate solvent testing. Testing on the product may also be insufficient, including not performing appropriate safety testing or insufficient information provided on the assays to conduct such testing. Another commonly observed CMC-related issue is insufficient safety information on delivery devices and data demonstrating that the delivery device does not affect the safety or quality of the drug product, which is referred to as device compatibility. In today's town hall, we will go over some of these topics in more detail.

As Zehra mentioned, we strongly recommend that sponsors engage the Agency prior to submitting an IND application through a pre-IND or INTERACT meeting and address FDA's comments in their IND submission. We do strive to resolve hold issues with sponsors during the 30-day review period of the IND. We will frequently send information requests to the sponsors with requests for clarifications or additional feedback and we recommend that, during the original IND review period, sponsors submit information request responses in a timely manner.

Thanks and back to you, Steven.

DR. OH: Thank you, Laura. I think the next question is for Irina.

If I use GMP-grade reagents, isn't that sufficient to support their safety? What are the general expectations on reagents used to manufacture products under an IND?

DR. IRINA TIPER: Thank you, Steven. That's a fantastic question. There is a lack of clarity regarding expectations for reagents in the production of cell and tissue-engineered products. The terms *Good Manufacturing Practice (GMP)* and *Current Good Manufacturing Practice (CGMP)* are used widely, but the exact meaning of the terms in different contexts can be unclear. For example, reagents such as purified antibodies, cytokines, growth factors, and serums might be described as GMP grade. GMP is not a grade, but a series of controls used to help ensure manufacturing consistency for the production of safe and effective products. Such controls include well-defined written procedures, adequately controlled equipment in the manufacturing environment, and accurately and consistently recorded data from manufacturing, including testing. Any reagent supplier can call their facility a CGMP facility or say that a reagent is manufactured under CGMP, even if it isn't. Some facilities may incorrectly believe they're in full compliance when, in reality, they're not. Please note that FDA does not typically investigate whether a facility meets FDA expectations of full CGMP compliance for FDA-regulated products until a pre-licensure or post-licensure inspection is performed where there is a for-cause inspection. Therefore, in instances of reagent manufacturers who claim to have CGMP facility, FDA may not have inspected these facilities—because FDA does

not typically inspect facilities of reagent manufactures—and therefore cannot ascertain these claims. Reagents used in the manufacturing of cell and tissue-engineered products are not required to be manufactured under CGMP unless they are also a licensed product for therapeutic purposes. However, the safety and performance of reagents should be established to ensure consistency of drug manufacturing and safety of drug substance and drug products. The evaluation of reagent safety and performance is typically achieved through risk assessment and qualification of all reagents. In some cases, a certificate of analysis provided by the reagent supplier to FDA may be sufficiently detailed and include results of comprehensive testing such that no additional information is needed. In other cases, drug developers may need to provide to FDA additional detail about how the reagent is generated, which may necessitate additional testing being performed to assure adequate safety and quality. Research-grade reagents can be used in some cases in drug manufacturing if they are sufficiently qualified.

The following are some general recommendations for reagents. Specifications are determined by the nature of the material and the needs of the manufacturer. A manufacturer may rely on vendor information for confirmation of purity, strength, and quality if they perform a specific identity test and the manufacturer has confidence in the supplier. If documentation for a reagent is incomplete, testing for the incomplete attribute of the component should be performed. We recommend that you investigate approaches to verification of reagent and excipient identity during your clinical studies as outlined in 21 CFR 211.84(d)(2). We expect that you conduct at least one identity test on each lot of reagents in addition to maintaining a reagent qualification program and supplier audit. If the vendor of the reagent has a regulatory file with FDA, a cross-referenced letter from the holder may be provided in the IND. For human- or animal-derived reagents, documentation should include information on sourcing and test results for adventitious agents as appropriate.

Back to you, Steven.

DR. OH: Thank you, Irina. The next question is for Melanie.

What are some differences between autologous and allogeneic donor eligibility considerations?

DR. MELANIE EACHO: Thanks for the question, Steven. For general eligibility for starting materials in the manufacturing of cell therapy products, it's a three-point CMC-related hold issue that we encounter, as Laura mentioned earlier. For cell therapy products manufactured with autologous donor material, donor eligibility determination or screening and testing per 21 CFR 1271 is not required; however, you must include the applicable required labeling. For example, for autologous products your label should include the statement "FOR AUTOLOGOUS USE ONLY." In addition, you must also include the statement, "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" in your label if you are not performing all applicable donor screening and testing for 21 CFR 1271 such that there was contact with the donor material during manufacturing especially and you're

aware of the potential dangers with handling of the starting material. Additionally, we recommend that you include a minimum of two unique identifiers for autologous therapies to minimize potential for mix-ups. For cell therapy products manufactured with allogeneic donor material, the two label requirements that I just mentioned do not apply. However, you are required to perform donor eligibility determination; that includes screening and testing per 21 CFR 1271.

I would like to point out that screening and testing are two different components. Screening entails reviewing relevant medical records and asking questions on the donor's medical history and their relevant social behavior so that a risk assessment can be made regarding potential communicable diseases and even potentials for communicable diseases related to previous xenotransplantation exposures. Testing is performed on the specimen from the donor, typically blood, using FDA licensed, approved, or cleared test kits according to the manufacturer's instructions for use in a CLIA-certified lab or equivalent as determined by CMS, the Centers for Medicare and Medicaid Services.

Some pitfalls, I'd like to point out to watch out for. You might typically see incomplete testing of diseases as required by 21 CFR 1271—this is just to reiterate this common issue. Donor specimen collection outside of the seven-days window before or after starting material recovery is also an issue that we see; there are certain exceptions, however. Not using proper FDA licensed, approved, or cleared test kits at a CLIA-certified lab for donor testing is also something that we look out for. We understand that this may be difficult for donors from or in foreign countries, but this is still a requirement, and one workaround may be that you could ship the test specimen to a lab in the United States. Another question or related issue that we see is pooling of cells or tissues from different donors; this is prohibited per 21 CFR 1271. This includes placing cells or tissues from different donors in a single container during manufacturing or even for the final product. If this is something that's a part of your manufacturing process, we ask that you inform us early, such as under an INTERACT or pre-IND, so that we can give you some feedback on potential exemption request requirements. I also want to just point out that CJD and Zika are screened only—not tested—for donors of HCT/Ps. This is different than the updated guidance for blood and blood components, so just pointing that out. For more detailed information, please refer to our 2007 guidance document on eligibility determination for donors of HCT/Ps.

Back to you, Steven.

DR. OH: Thank you, Melanie. For the next question, I'd like to ask Laura.

What are FDA's recommendations on establishing and refining acceptance criteria for final product release specifications?

DR. RICLES: Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product must be provided in your IND, and this is outlined in 21 CFR 312.23. We do acknowledge that, early in development, a complete

understanding of appropriate process controls may be limited, and that specific controls might be added or even refined during the product's life cycle. However, the initial IND submission should describe and justify the controls which are implemented to ensure adequate quality and manufacturing consistency, and we recommend that the products be as fully tested as feasible in early stages of development. Specifications should be appropriate to the stage of product development. For example, for early-phase clinical studies we recommend that assays be in place to assess drug product identity, quality, strength, and purity, and then for later-phase studies more detailed product characterization and potency should be included. Acceptance criteria for release testing should be established and justified based on data from lots used in preclinical or earlier clinical studies, lots used for demonstration of manufacturing consistency, stability studies, and relevant product development studies. For products in the early stages of clinical development, FDA recognizes that few specifications will be finalized and some tests may still be under development; however, for any given stage of development, the testing plan submitted in an IND should be adequate to describe the physical, chemical, or biological characteristics of the drug product necessary to ensure quality and safety. Drug product specifications should be further refined as part of product development, and we recommend that sponsors tighten acceptance criteria as appropriate based on manufacturing experience as clinical development proceeds. For a licensure, final specifications based on validated assays must be in place to ensure the safety and effectiveness of the product, and the specifications must include the general biological product standards as outlined in 21 CFR part 610.

Thanks, and I will turn it back to you, Steven.

DR. OH: Thank you, Laura. I'm going to go back to Melanie for the next question.

Is it acceptable to use products manufactured from engineering runs in clinical studies?

DR. EACHO: Use of a product manufactured from successful non-GMP engineering runs in clinical studies may be permissible in early phase if you can provide adequate justification on the safety and quality of the batch and whether there are any differences in the manufacturing process for that engineering run versus the intended clinical run. Just remember that we rely on your engineering run data as one evidence to demonstrate that you can manufacture the product meeting your prespecified product attributes, so the hope is that your engineering runs will produce batches that will be of clinical quality.

Back to you, Steven.

DR. OH: Thank you, Melanie. Next question is for Zehra.

Are potency assays required as lot release attributes during first-in-human clinical studies, such as phase 1 studies?

DR. TOSUN: Good question. General recommendations for potency testing and regulatory requirements are outlined in the 2011 potency guidance. Potency applies to all stages of

clinical development but is not required until clinical studies intended to provide the primary evidence of effectiveness to support the marketing application. Your potency assays may not be completely defined early in the development, when product and process knowledge is limited. Your potency assays should become progressively more comprehensive as you accumulate manufacturing experience, product characterization data, and clinical data. For first-in-human studies, you may provide the description of your general plans for product characterization, including your description of your initial product critical quality attributes, potency assay development plans during clinical development, and a quality type of product profile in your initial IND submission.

Back to you, Steven.

DR. OH: Next question is for Irina.

What are the biggest pitfalls that a company should avoid when considering design of potency assay(s)?

DR. TIPER: Thank you, Steven. This is a fantastic question and a continuation of our potency discussion. The biggest pitfall to avoid is not starting early, not employing an incremental approach to potency assay development, and not establishing specifications for potency assays. Incremental approach generally entails developing multiple potency assays and evaluating which one should be validated as product development progresses. Not all potency assays can be validated, and some potency assays may not fully reflect the biological activity. That is why it's important to start early and to evaluate multiple potency assays. We recommend not only developing multiple potency assays but also considering using multiple potency assays for product release to better reflect the proposed mechanism of action, or the MOA. Because the ability to measure potency is fundamentally related to product characterization, you should initiate potency assay development by the way of product characterization during preclinical and early clinical investigation to obtain as much product information as possible. We do not recommend evaluating this data for informational purposes only, unless you have no confidence in the reliability of the assay or cannot yet interpret the significance of the data. For measurements of biologically relevant activity related to the proposed mechanism of action, it is preferable to establish at least a wide range of an attribute for product potency than to potentially allow for release of the product with no measurement of their relevant biological activity.

Back to you, Steven.

DR. OH: Thank you, Irina. I have another question for Zehra.

If a product has a complex and multifaceted mechanism of action, is a potency assay matrix required or desired by FDA to address all mechanisms of action?

DR. TOSUN: Good question, Steven. We recognize that identifying product attributes related to potency for cell-based products can be challenging due to complex or poorly

defined mechanisms of action. The 2011 potency guidance outlines phase-appropriate, flexible approaches and tries not to be too prescriptive because cell therapy products are so diverse and complex. As products advance in clinical development, the expectations are that the potency test should be refined to measure relevant biological activity of the product. Per the regulations, the test should demonstrate the product is capable of effecting a given result. In many cases, a single biological or analytical assay may not provide an adequate measure of potency. If one assay is not sufficient to measure the product attributes that indicates potency, then an alternative approach could be used, such as developing multiple complementary assays that measure different product attributes associated with quality, consistency, and stability. Such a collection of assays is imported as an assay matrix. Because cell therapy and tissue-engineered medical products usually have multiple potency-related critical quality attributes (CQAs), your potency assurance strategy could typically include multiple assays, each of which quantitates a potency-related CQA. These assays may be physical assays, chemical assays, or bioassays.

Back to you, Steven.

DR. OH: Thank you, Zehra. The next question is about—again—a potency assay, and I'm going to go back to Irina for this question.

Can a potency assay matrix employ one quantitative validated assay including specifications and one qualitative assay, though non-validated, for Phase 3 and BLA?

DR. TIPER: Thank you, Steven. As we discussed, in many cases a single biological or analytical assay may not provide adequate measure of potency. A potency matrix includes assays that give a quantitative readout, such as units of activity, and/or a qualitative readout, such as pass/fail. Please be aware that a qualitative assay should be accompanied by one or more quantitative assays; it cannot be used instead of a quantitative assay. Similar to a quantitative assay, you should validate all the parameters relevant to your qualitative assay and provide a rationale for those parameters that you determine are not relevant. Naturally, without a quantitative data, demonstrating accuracy and precision for a qualitative assay could be challenging; however, with proper assay design with sufficient replicates, you should be able to demonstrate adequate assay consistency. Section III.C of the *Potency Tests for Cellular and Gene Therapy Products* guidance outlines general points on validation of qualitative assays. Please plan to validate the assays prior to the conduct of clinical studies that will assess product efficacy for licensure.

Turning it over back to you, Steven.

DR. OH: Thank you, Irina. We have a couple of comparability questions, and I'm going to go to Zehra for the next question.

What type of manufacturing changes require comparability studies, and how should a sponsor assess if a manufacturing change is clinically relevant?

DR. TOSUN: Thanks, Steven. Risk assessment should be performed for any change, and it should be determined if there is a potential to affect product quality first of all. Therefore, not every change requires comparability studies. We recommend that the sponsors evaluate the potential of various product attributes and process parameters to affect the product quality as they may relate to the safety and effectiveness of the product, and select sensitive analytical methods that can detect meaningful differences in product quality. The comparability study design should address the risks identified in the risk assessment. In addition, as part of the risk analysis, you should determine the most appropriate process time points to detect the change in the quality attributes; this may entail evaluating the product at multiple stages of manufacturing. It is possible that comparability study results may not be sufficient to establish product comparability. Sufficiency of your comparability evaluation depends on the type of change and your level of understanding of product quality attributes as predictors of clinical safety and efficacy. The inclusion of additional characterization tests or preclinical studies may be necessary to support comparability. For some products, animal models may be used to demonstrate that the product has the desired biological effects and to provide supportive evidence for comparable biological activity of the pre-change and post-change products.

Back to you, Steven.

DR. OH: Thank you, Zehra. The next question is for Laura.

What are FDA's expectations for technology transfer to a new manufacturing facility where process changes, including scale-up, are implemented?

DR. RICLES: Thank you for that question, Steven. Zehra just nicely went over some of the expectations for comparability assessments, and we have found that most development programs include changes in manufacturing during process development, such as a change in the production process or a change in the manufacturing facility—for example, from an academic facility to a commercial facility or from a facility outside the United States to one inside the United States. Comparability is a topic of great interest to many of our sponsors, and we are developing a guidance document pertaining to comparability assessment, which has been announced on the CBER guidance agenda, so please look for this draft guidance to be released in the future. At this time, we recommend that you apply the basic principles described in ICH Q5E; specifically, a risk assessment should be conducted to identify the impact of the proposed change and to inform the level of studies needed to support the change. It's important to remember that the goal of a comparability study is to demonstrate a lack of an adverse effect on product quality to be able to combine the clinical data generated with the pre-change and post-change products. Consequently, the level of risk for introducing changes increases as you move into later-phase clinical studies. Therefore, we recommend that changes are implemented as early as possible.

We do consider technology transfer to a new facility and scale-up to be changes, especially if implemented in late-phase clinical studies, and would expect the

comparability assessment to be conducted in addition to developmental studies and risk assessment to support the change. The developmental studies and risk assessment should allow you to rank different product characteristics and determine the type of evaluation that should be performed, such that a study can be designed to address the risk identified. I'd like to emphasize that release testing alone is generally insufficient to assess comparability, and additional characterization testing or in-process testing should be conducted to demonstrate that there is no adverse effect on product quality using analytical testing. The extensive analytical evaluation needed in comparability studies generally increases with the stage of clinical and product development and should be supported by knowledge of critical quality attributes, accumulated manufacturing experience, and further understanding of the mechanism of action. Understanding the impact of manufacturing changes on product quality is essential for determining risks to product quality and for subsequent design of comparability studies. It should also be noted that technology transfer to a U.S. facility is not required prior to conducting investigational studies or for commercialization. Manufacturing and process changes should be implemented at the discretion of the sponsor; however, we do recommend that changes are implemented as early as possible, such as prior to conducting clinical studies intended to provide the primary evidence of effectiveness, and before clinical studies are completed. We also recommend that sponsors engage with FDA prior to conducting comparability studies, such as through formal meetings and by submitting comparability protocols prior to initiating the studies as an amendment to their IND.

Thanks, and back to you, Steven.

DR. OH: Thank you, Laura, for that response. The next question is for Melanie.

What is required to demonstrate product stability throughout the clinical trial phases, especially when there is limited product availability for the study?

DR. EACHO: Thanks, Steven. First, I want to note that stability data is required in all phases of the clinical trial under the IND; this is to establish the shelf life for your product and to demonstrate that the product remains within acceptable limits for the duration of the clinical trial. So, one should provide preliminary data on product stability to indicate whether the product or components are likely to remain stable for the duration of the clinical trial, including for the start of the baseline study. During the IND stage, we recommend that you develop and initiate a stability protocol to collect adequate data to establish a dating period, storage conditions, and shipping conditions for timely submission in a license application. How we design the stability study protocol, in terms of the number of batches, frequency of data point collection, test conditions, is all dependent on the unique nature of your product and expected product stability, so we ask that you provide clear justification on your stability study design plan. For cases when you may have a limited amount of product available for stability studies—for example, with autologous products—you can conduct your stability study with another lot, perhaps manufactured with the same process dedicated for stability testing. We recommend that

you design and provide a study plan emphasizing justifications for all the parameters, such as the number of batches, frequency of data points, the conditions that you're studying or that your product will be exposed to, and any other parameters for our review, and we ask that you provide that for our review as needed and provide feedback if you have any questions.

Thank you. Back to you, Steven.

DR. OH: Thank you, Melanie. The next question is for Laura:

How should sponsors handle manufacturing deviations, including product lots that do not meet lot release specifications?

DR. RICLES: Manufacturing deviations should be investigated to identify the root cause, and appropriate corrective actions should be taken to avoid repeat occurrences in the future. Appropriate change control procedures should be in place to manage risks associated with these corrective actions. Sponsors should provide a description of the risk management and change control procedures for how to address manufacturing deviations in their IND. If a product lot does not meet lot release specifications due to manufacturing deviations or otherwise, the product should not be released. In cases where the subject is at significant risk, such as the subject has already been conditioned to receive the product, the sponsor may consult with FDA for potentially administering the out-of-specification product to the subject. For licensed products, FDA requires reporting of certain deviations and unexpected events in manufacturing in accordance with 21 CFR 600.14, 606.171, or 1271.350.

Thanks, and back to you, Steven.

DR. OH: Thank you, Laura. The next question I have is for Zehra.

At what point does manufacturing at the clinical site become manufacturing that requires additional final product release testing?

DR. TOSUN: Thanks, Steven. If you perform additional manufacturing steps at the clinical site, we may consider these additional manufacturing steps to qualify as substantial manipulations that are required to prepare the final drug products. Therefore, these steps may be subjected to manufacturing controls and Good Manufacturing Practices. We also recommend that, during the investigational phases, you establish an approach to eliminate additional manipulation steps, such as washing of thawed product at the clinical site after the product is released and distributed from the manufacturing site.

Back to you, Steven.

DR. OH: Thank you, Zehra. And thank you to all who submitted questions during the registration process. We will now spend the remaining time today answering your live questions. The first question we have is for Melanie.

What are FDA's thoughts on the use of noncellular placebo that is just the excipient for cell therapy product trial to mirror appearance, viscosity, et cetera?

DR. EACHO: Thanks for that great question. As a placebo will be used in an investigational study, we request typically that you provide full manufacturing details regarding the noncellular placebo, even if it's just the excipients, and that if it's an approved drug that's already on the market—for instance, HSA—that you provide us with that information: the package insert, COA, the information on the approval of that particular excipient. But whatever the placebo it is that you are using in your investigational study, we request that you provide as much full manufacturing information as possible and that you also use the highest quality readily available, especially for clinical use.

Back to you, Steven.

DR. OH: Thank you, Melanie. The next question we have is for Irina.

Will the agency accept the use of irradiated mouse fetal cell lines as a raw or ancillary material for immune cell expansion if (1) there is a validation to prove no residual fetal cell remains in the final drug product, and (2) it has been tested for infectious agents in the COA?

DR. TIPER: Thanks, Steven. For murine fetal cells, there is a risk of murine adventitious agents; therefore, to support the use of murine fetal cells, you would need to provide information on the provenance and information on test methods used for adventitious agent testing. Additional information to submit is all the reagents and their safety used to grow the murine cells, such as whether fetal bovine serum was used. Please note that for irradiated fetal cells you need to provide data using a relevant assay with appropriate controls that adequately demonstrate the irradiated cells do not proliferate. These data should demonstrate that the cells are rendered incapable of proliferation but still maintain their desired characteristics after irradiation. You would also need to describe the irradiation conditions that are used. This information should include but not be limited to dose of irradiation, temperature, type of container used for irradiation, location of the irradiator, and the program for maintenance and calibration.

Back to you, Steven.

DR. OH: Thank you, Irina. The next question we have is for Zehra.

With regards to comparability studies, if a process improvement is made that results in an increase in product quality, the new process might not be comparable but would be better. Would a comparability protocol be framed as comparable or better in terms of acceptance criteria?

DR. TOSUN: That's a great question. As I mentioned earlier, comparability exercise starts with a risk assessment. If your risk assessment determines that a comparability study is

required, we always recommend that you provide us with a comparability protocol to assess the effect of the change on the product quality. In that situation, you can include a justification and rationale for the proposed change, a timeline for implementation of the change, and the risk assessment that we just talked about to determine whether the change has the potential to negatively and—as asked in this question—positively affect the product quality. So, when we talk about positive product quality, we recommend that you evaluate the potential of various product attributes and process parameters that affect product quality as may relate to the safety and effectiveness of the product. To reiterate, again, we recommend that you select sensitive analytical methods that can detect meaningful differences in product quality. I would like to also add here that, to detect that change, we also recommend a description of statistical methods evaluating comparability, if appropriate in your situation, to detect meaningful differences in product quality attributes.

Back to you, Steven.

DR. OH: Thank you, Zehra. The next question we received today is for Laura.

Is it possible to use source cells that are from non-U.S. donors if donor screening and testing are performed outside the United States?

DR. RICLES: Thank you for that question. Melanie did outline some of the requirements earlier in the town hall in terms of allogeneic donor screening and testing. So, to reiterate, all allogeneic donors must be screened and tested according to 21 CFR 1271, and these requirements include conducting appropriate donor testing, collecting the donor specimen for testing at an appropriate time, using FDA licensed, cleared, or approved test kits to conduct the testing, and reporting testing in a CLIA-certified lab. In addition, the donors must also be properly screened by reviewing relevant medical records for risk factors and clinical evidence of relevant communicable disease agents. All of these requirements are applicable for non-U.S. donors as well and, frequently, testing labs outside the United States are not CLIA-certified or do not have access to appropriate test kits. In these situations, we recommend that sponsors send donor samples to a U.S. testing facility which is CLIA-certified and is appropriate in terms of the type of testing they conduct and the test kits. When doing this, sponsors should ensure that the donor specimens are properly stored and shipped. So, in summary, non-U.S. donors who are tested outside of the United States can potentially be used, but the sponsors would need to demonstrate in their IND submission that they comply with all of the expectations and requirements in 21 CFR 1271.

Thanks, and I'll turn it back to you, Steven.

DR. OH: Great, Laura. Thanks for that response. The next question is for Melanie.

What are some CMC regulatory considerations for the use of cord blood as a starting material for manufacture of cellular therapy products under IND?

DR. EACHO: Thanks for that question. I want to clarify that we do not regulate cord blood intended for nonclinical research uses. However, if you intend to use cord blood as a starting material to manufacture cell therapy products under IND, we ask that you provide certain information. Some of this information includes complete information regarding donor screening and donor testing for the cord blood units, just like any other starting material. Know that the cord blood units must comply with donor eligibility requirements per 21 CFR part 1271. Information on the cord blood collection, storage, and shipping, if you are using standardized or accredited practices, we ask that you include this information in your IND, and also documentation such as certificate of analysis, that describes the testing that had already been performed on the cord blood unit. And as with any cellular starting material, please include information on procedures you have in place to ensure consistency in the handling of the cord blood unit across all manufacturing sites and information such as expiration date, which is based on stability data, should be apparent in the labeling of the cord blood and also in your certificate of analysis.

Back to you, Steven.

DR. OH: Thank you, Melanie. The next question received from today's participants is for Irina.

Does OTAT have any requirements for using U.S.-sourced fetal bovine serum in the upstream manufacturing process?

DR. TIPER: Thank you. For fetal bovine serum, or FBS, you would need to provide information on the source of material and the location where the herd was born, raised, and slaughtered, whether you can verify that the material is from a country where BSE (bovine spongiform encephalopathy) risk is negligible, and any other information relevant to the likelihood that the animal may have ingested animal feed prohibited under 21 CFR 589.2000. For U.S.-sourced FBS, the risk of BSE is negligible, but you would still need to provide documentation that the FBS is coming from cattle born, raised, and slaughtered in the United States. For example, the certificate of analysis can indicate the U.S. origin. In addition to providing the information regarding BSE risk, you should provide a certificate of analysis to document that bovine material has been tested according to the requirements for ingredients of animal origin used for the production of biologics, as described in 9 CFR 113.53.

DR. OH: Irina, I think we are having some audio issues at your end. I'm going to go to the next question, and we hope to fix your audio problem in the meantime. So, the next question is for Laura.

Is an IND required to be filed with FDA if the trial is conducted outside of the United States?

DR. RICLES: To answer this question, if sponsors want to conduct a clinical study outside the United States with no clinical sites within the United States, they are not

required to submit an IND. However, if you would like to use clinical data and especially efficacy data collected from a clinical study conducted outside the United States to support a future marketing application, such as a BLA, to be submitted to FDA, then sponsors can submit an IND, although it's not required. Submitting an IND in this situation would then help ensure that FDA has reviewed the CMC information, pre-clinical and clinical study information, and agrees with the information provided to potentially support a future BLA submission. If sponsors need to make changes to manufacturing processes due to FDA requirements or feedback, then this may require a comparability assessment, and we went over many of the expectations and requirements for comparability earlier in the town hall. So, while not a requirement to submit an IND if the clinical study is conducted outside the United States, it is possible for sponsors to do so and they should consider if that's something that they want to do based off of potential feedback they can receive from FDA to support a future BLA submission.

Thanks, and back to you, Steven.

DR. OH: Thanks, Laura. The next question is for Zehra.

What information do I need to provide to FDA if I'm using a device to deliver the final drug product?

DR. TOSUN: That's a great question. Actually, Laura previously—in the first part of the presentation—touched base on this topic a little bit, because this is one of the commonly observed CMC-related issues, which is insufficient safety information on delivery devices and data demonstrating that the delivery device does not affect the safety and the quality of the drug product. In terms of information regarding the device used to administer the final drug product, some of the information that should be provided in the IND submission I can go through right now. Generally, we ask sponsors to provide a detailed description of the delivery device, and this will include a description of each component, manufacturer, trade name, the principle of operation of the device, pictures, diagrams, engineering drawings, and materials of construction that the devices are made of and identification of—directly and indirectly—the patient-contacting components. If the device will be purchased from a third party, the sponsor should indicate if they will be reprocessing the device in any way, such as sterilization or repackaging. The sponsors also should indicate if the delivery device will be provided to the clinical site or supplied to the end user. In addition, the sponsor should provide information to establish the safety of the delivery device for the proposed clinical use, including biocompatibility, sterility, endotoxins, packaging, shelf life, performance data, and—if applicable—electrical safety, electromagnetic compatibility, and software. If any of this information is contained within a master file submitted to FDA, then sponsors can provide the letter of authorization to cross-reference the master file. On the other hand, if the sponsors are using an FDA cleared or approved device, then they should provide the relevant submission number—this could be a 510(k) or a PMA number—and a comparison of the cleared or approved indications for use and how the device will be in the clinical study. And we recommend

that you provide a risk assessment for any differences between the cleared and approved intended use and the proposed use in the clinical study. We strongly encourage you to obtain a written agreement with the manufacturer of the device so you will be notified of any changes to the device throughout your clinical development. Consequently, this will help to ensure consistent delivery of your product throughout the study. Lastly, we ask that sponsors provide comparability data demonstrating that administrating the drug product using the delivery device will not negatively affect the product's quality and that they understand the quantity of the product that will be actually delivered to the recipients, and this also can be called preliminary dose accuracy data.

Back to you, Steven.

DR. OH: Thank you, Zehra. The next question is for Irina.

What are the meeting and interaction opportunities with FDA?

DR. TIPER: Thank you, Steven. And I apologize for the earlier technical difficulties. Hopefully, I am back on track now.

There are multiple opportunities to meet and interact with FDA throughout cell therapy and tissue-engineered product development. The conduct of these meetings and additional information is in the guidance document titled *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* from December 2017. SOPP 8101.1, which is available on FDA's website, was recently updated with effective date of October 1, 2022. It is a great resource detailing procedures for scheduling and conduct of regulatory meetings between FDA and sponsors. In the early stages of product development, INTERACT meetings offer an opportunity to meet with FDA. INTERACT stands for INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs. INTERACT meetings are intended to facilitate IND-enabling efforts where the sponsor is facing a novel, challenging issue that might otherwise delay progress of the product toward entry into the clinic in the absence of this early FDA input. Typically, the issue is early in a development program prior to when a pre-IND meeting might be requested and the issue may delay initiation of or progress of IND-enabling study.

Next, pre-IND meetings fall under type B meeting category, which also includes other meeting types such as pre-BLA, among others. Pre-IND meetings are a great opportunity for sponsors to ask specific questions and to receive feedback on the contents of their future IND. There are also type B end-of-phase meetings. Type D meetings are a newly implemented meeting type under PDUFA VII. Type D meetings are focused on a narrow set of issues: they should be limited to no more than two focused topics and should not require input for more than three disciplines or divisions. Type C meetings is any other meeting than type A, type B or type B end-of-phase, INTERACT, or type D meetings regarding the development and review of products. Type C meetings include meetings to discuss early consultation on the use of new surrogate endpoints.

In addition to meetings, amendments are an opportunity to interact with FDA; for example, manufacturing changes should be reported in an amendment. In general, FDA will provide feedback on amendments where warranted.

Back to you, Steven.

DR. OH: Thank you, Irina. The next question is for Melanie.

Is accelerated stability study required for clinical products?

DR. EACHO: The short answer to this question would be no, an accelerated stability study is not required for cell therapy clinical products. However, if you have accelerated stability study for cell therapy products, then you can submit that as part of your supporting evidence in your IND. We ask that you provide clear justification on how the accelerated stability study design supports a cell therapy product. Typically speaking, accelerated testing for cellular products is challenging, as typically would be seen in other products that might be chemical or medical device-based, so we ask that if you have this, you provide that with ample justification. But, again, accelerated stability study is not required for a cell therapy product.

Back to you, Steven.

DR. OH: Thank you, Melanie. I have a next question for Laura.

What are some unique challenges encountered for tissue-engineered products?

DR. RICLES: Thank you for that question. Tissue-engineered products can be very complex and can have some unique challenges, so I'll try to summarize some of the challenges that we see that sponsors frequently encounter with these product types.

One of these challenges is lot release testing. It can be difficult to develop appropriate in vitro and in vivo testing and characterization methods in some cases due to the complexity of the product, such as the 3D structure and the heterogeneity and composition. Because of that, it's very important that sponsors consider the lot release testing that they're performing and that the testing is representative of the entire construct, especially if only a portion of the construct is tested.

Another challenge is that tissue-engineered products often come in very small lot sizes, including a lot size of just one. This can limit the amount of material available for release testing and many times means that destructive testing is not possible, especially if the lot size is only one—one product that's being manufactured. In these cases, it may be that testing cannot be conducted on the actual product that's going to be administered to patients and testing may need to be performed on a different sample, such as a surrogate sample, and sponsors need to demonstrate that the surrogate sample that's being tested is representative of the actual product that's being administered to patients.

Another thing I'll mention—and we have discussed potency assay development earlier in the town hall—and this is also a challenge for tissue-engineered products as well. Frequently, tissue-engineered products have multiple modes of action, and so this may require, in some cases, a potency assay matrix. Of course, the potency assays need to be specific to the product type as well as the indication.

The final challenge that I'll mention is that, frequently, tissue-engineered products incorporate a scaffold construct, which may consist of cells that are seeded onto a scaffold. For these products, the cells and the scaffold need to be evaluated and tested separately as well as following their combination, and the impact of the cells on the scaffold and of the scaffold on the cells needs to be well understood. I'll also mention that in some instances, the scaffold may be considered a device, depending on the material and the function of the scaffold in the final implanted product, and so in situations where a product is considered a combination product, it needs to comply with Current Good Manufacturing Practice requirements under 21 CFR part 4.

Thanks. I'll turn it back to you, Steven.

DR. OH: Great, thanks, Laura. The next question is for Irina.

What are the general expectations on the use of human serum albumin (HSA) as an excipient?

DR. TIPER: Thank you, Steven. In general, we recommend U.S.-licensed human serum albumin, or HAS, to be used as an excipient. As we discussed in the September 29, 2022, Gene Therapy Chemistry, Manufacturing, and Controls OTAT town hall, FDA is becoming more flexible on the expectations for the use of HSA, particularly if the HSA is used upstream in the manufacturing process. We do continue to recommend that you use the safest, highest-quality HSA available, which in most cases would be a version licensed in the United States. Use of the highest-quality HSA is particularly important when HSA is being used an excipient, since it will be directly administered to the patient; however, if you choose to use a version of human blood–derived HSA that is not licensed in the United States in upstream manufacturing, you may be able to do so, provided you are able to submit information supporting that donor eligibility, albumin manufacturing, and appropriate product standards conform to that of the U.S.-licensed products, as described in 21 CFR 640.80 through 83.

Back to you, Steven.

DR. OH: Thank you, Irina. I am going to actually ask you another question. It's a related question it looks like we received today.

Does OTAT have any requirements for using U.S.-sourced fetal bovine serum in the upstream manufacturing process?

DR. TIPER: Thank you for the opportunity to respond to this question again. For fetal bovine serum, or FBS, you would need to provide information on the source of the material and the location where the herds were born, raised, and slaughtered, if you can verify that the material is from a country where there is a negligible bovine spongiform encephalopathy, or BSE, risk and any other information relevant to the likelihood that the animal may have ingested animal feed prohibited under 21 CFR 589.2000. For a U.S.-sourced FBS, the risk of BSE is negligible, but you should still provide documentation that the FBS is coming from cattle born, raised, and slaughtered in the United States. For example, the certificate of analysis can indicate the U.S. origin. In addition to providing the information regarding BSE risk, you should provide a certificate of analysis to document that bovine materials have been tested according to the requirements for ingredients of animal origin used for the production of biologics, as described in 9 CFR 113.53.

Back to you, Steven.

DR. OH: Thank you, Irina. I'm going to go to Melanie for the next question.

What are the thoughts of FDA as to the necessity for sterility testing during stability studies?

DR. EACHO: Great question. Sterility testing during stability studies would be required at the *t = 0* time point and, at minimum, at the very last time point that you're establishing your stability expiration date or expiry date. But in lieu of actual sterility testing on the final time point, we have also allowed container closure integrity testing at any point other than the initial stability time point. There is a guidance document that is available that is titled *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products* that you can also refer to for further information.

Back to you, Steven.

DR. OH: Thank you, Melanie. I have a question for Zehra.

At what point does manufacturing at the clinical site become manufacturing that requires additional final product release testing?

DR. TOSUN: Thank you, Steven. If you perform additional manufacturing steps at the clinical site, we may consider these additional manufacturing steps to qualify as substantial manipulations that are required to prepare the final drug products. Therefore, these steps may be subject to the manufacturing controls and Good Manufacturing Practices. We also recommend that, during the investigational phases, you establish an approach to eliminate additional manipulation steps such as washing of thawed product at the clinical site after the product is released and distributed from the manufacturing site.

DR. OH: Thank you, Zehra. The next question is for Melanie.

What are FDA's current activities related to supporting standards development with cell therapy, gene therapy, and tissue-engineered products?

DR. EACHO: Thanks for those questions. OTAT is involved in a variety of different standards activities, especially as the regenerative medicine field continues to grow. We recognize the need for standards to help advance product development during all stages, and to provide some direction to sponsors we've published a guidance document in 2019 on the use of standards and product development and also during the review of the regulatory process. It outlines our policy on how voluntary consensus standards can be used by sponsors and also reviewers to make the product development and review process less burdensome. Most recently, in June of this year, we published a draft guidance announcing the standards recognition program for regenerative medicine therapies that will recognize relevant voluntary consensus standards in the field, with a focus on cell and gene therapy as well as tissue-engineered products. The launch of this program is planned for the upcoming year, and we'll provide a regularly updated list of recognized standards for you to access.

Also, since 2017, FDA has been working with the Standards Coordinating Body, which consists of stakeholders from industry, academia, professional societies, and other government entities. Together, FDA and the Standards Coordinating Body have promoted the development of standards of regenerative medicine therapies. The group had published a database and landscape report identifying the needed standards, standards under development, and existing applicable standards. It's a helpful resource for sponsors to look at and also get involved in standards development, and this partnership with the Standards Coordinating Body has also resulted in several webinars for everyone to learn about the use and development of standards.

One last thing that I'd like to note is that standards do not have the force of law like regulations do, which set specific requirement for regulated products. While we do encourage the use of appropriate standards, the use of standards is voluntary, but we have found that when standards are appropriately used you can save time and effort during the lengthy product development process and also in our review.

Back to you, Steven.

DR. OH: Thank you, Melanie. The next question I have is for Laura.

How do I know if my product is a combination product?

DR. RICLES: I know in one of my previous responses I brought up combination products, so to expand on the definition of this a little bit, and how you determine if your product is a combination product. A combination product is defined in 21 CFR 3.2(e), it's considered a product composed of different categories of regulated articles, such as the device and a biologic, and the two articles can be physically or chemically combined; they can be co-

packaged; or they can be packaged separately, but cross-labeled. If sponsors have questions whether they are combination products, they can contact FDA regarding the designation of their product as a combination product, as well as the jurisdiction. Sponsors can also submit questions to the Tissue Reference Group (TRG) and CBER OTAT, or they can submit a pre-request for designation or a request for designation to the Office of Combination Products. And I just wanted to mention that the jurisdiction of a combination product to a lead center, such as CBER, is based on the primary mode of action of the product, any inter-center agreements that we might have, which center has the most relevant expertise and precedence.

Thanks, and back to you, Steven.

DR. OH: Thanks, Laura. The next question is for Irina. It looks like this is going to be a follow-up question to the one you answered already.

This is a follow-up question regarding GMP versus research-grade reagents. Since GMP is not considered a grade, can research-grade reagents be qualified for the use in an IND?

DR. TIPER: Thank you, Steven. I know we're almost out of time, so I would like to make this response as quick as possible. With any reagent, of course it can be qualified for use in terms of documenting safety, its performance, and, as product development progresses, we recommend that you work with the reagent manufacturer to obtain that information on safety of the reagent. You can qualify by looking at the performance of the reagent in your own application. And as product development progresses, we recommend that you work with the manufacturer to move toward selection of a reagent that has been manufactured under GMP conditions.

Thank you, Steven. Back to you.

DR. OH: Thank you, Irina. That concludes this Q&A portion today. Thank you all for attending today's OTAT town hall. We'd also like to extend a thank-you to our panelists and all of those who have worked behind the scenes and backstage. Thank you to everyone.

As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming weeks. For more information, you can visit FDA's website to read the FDA guidance document about cell therapy CMC and find other OTAT and cell therapy resources. We plan to hold our next town hall meeting in February next year, and the topic will be on clinical development of gene therapy products for rare diseases.

With that, I'd like to thank you again for joining. Have a great day.