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FDA CBER OTP Town Hall:
Cell Therapy Chemistry, Manufacturing, and Controls

June 8, 2023

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DR. MELANIE EACHO: Good morning, everyone. Thank you all for joining us for today's Office of Therapeutic Products town hall. Today's event is hosted by the Office of Therapeutic Products (OTP) within the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA).

My name is Melanie Eacho. I'm the Branch Chief of the Cell Therapy Branch 1 in the Office of Cellular Therapy and Human Tissue CMC. I will also be your moderator for today's event. As you all know, today's town hall is focused on chemistry, manufacturing, and controls (CMC) of cell therapy products. Our conversation will also cover tissue-engineered medical products regulated by OTP. We look forward to answering your questions about these important topics.

Some of you may have joined us for previous town halls, including our December 2022 town hall, which also focused on CMC of cell therapy and tissue-engineered medical products. For those of you who have joined us before, welcome back. For those of you who are joining us for the first time, welcome and thanks for attending today's event.

Before we share more details about today's OTP town hall, I also want to remind all of our attendees that FDA is hosting its 2023 Regulatory Education for Industry (REdI) conference this week. For anyone interested in more information about the work we do at OTP, we encourage you to join this important event. CBER sessions begin today at 1 p.m. ET. Registration is free, and we will add a link to that event in the chat box for anyone who is interested.

Before we begin, I want to share some background about the OTP Town Hall series. OTP launched its virtual town hall series in 2022 to engage with product development stakeholders and researchers. These town halls have a question-and-answer format with a goal of providing regulatory information to stakeholders to help advance development of OTP-regulated products. All other recordings from previous town halls are on FDA.gov, and we encourage you to watch them for additional information.

Please note that this town hall is being recorded. The recording and event materials will be posted on FDA's website in the next few weeks. We will also provide a transcript. Closed captioning for this event is available directly in Zoom. If you have a question, please type your question 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 questions from the audience during today's event. We will do our best to address as many as we can today, but please note that FDA is not able to comment on or answer questions regarding specific investigational products or drug applications. Also, we will not address any questions considered out of scope for the event. Lastly, please use the chat box if you are experiencing technical difficulties.

As many of you are aware, FDA requires sponsors to provide chemistry, manufacturing, and control, or CMC, information as part of an investigational new drug (IND) application. CMC information should describe product manufacturing and testing to assure safety,

identity, quality, purity, and strength, including potency of the investigational product. During today's town hall, subject matter experts from OTP's Office of Cellular Therapy and Human Tissue CMC, or OCTHT CMC, will answer questions related to CMC for cell therapy and tissue-engineered medical products.

I'd like to take a moment to introduce today's panelists. We have Dr. Matt Klinker, who is the CMC reviewer in Cell Therapy Branch 2 in the Division of Cell Therapy 1; Dr. Liz Lessey-Morillon, who is a CMC reviewer in Cell Therapy Branch 1 in the Division of Cell Therapy 1; and Dr. Bao Nguyen, who is a CMC reviewer in Tissue Engineering Branch in the Division of Cell Therapy 2. Thank you to all our panelists for your time today.

We will now move to the Q&A portion of today's town hall. We will begin by answering questions submitted during the registration process, followed by responding to your questions submitted during today's event. As a reminder, you can submit a question for our panelists in the Zoom Q&A box at any time during the event, which can be found at the bottom of your screen in Zoom. We will try to address as many questions as we can, but please remember we're 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 under public commenting period or under revision of final guidance document publication.

We hope you can stay on with us for the entire time, but would also like to reiterate that the town hall is being recorded so you can visit the full discussion after it is posted on our website. Let's begin with our first question.

Please define what "phase-appropriate CMC" means.

DR. LIZ LESSEY-MORILLON: Thank you for the question. We use the term *phase-appropriate CMC* to keep CMC and product development aligned with the clinical studies. As the clinical program moves forward, so do our expectations for product development. For example, the amount and types of data expected with an original IND submission is not the same as for a marketing submission. Phase-appropriate expectations allow for sponsors to start clinical studies while they are still characterizing the product, and determining clinical attributes, so that the product will be sufficiently controlled and the manufacturing process well-established before a study is intended to support a marketing application. Thank you, Melanie. Back to you.

DR. EACHO: Thanks, Liz. Next question I'd like to ask Bao.

Can allogeneic cells collected outside of the U.S. be used in clinical trials within the U.S.? What type of testing is necessary?

DR. BAO-NGOC NGUYEN: Good morning, everyone. Thanks, Melanie, for that great question. We do actually get that question often, just as clinical trials are becoming more global. Yes, we do allow allogeneic cells from donors outside the U.S., as long as they can follow and meet the donor eligibility requirements as outlined in 21 CFR 1271 subpart C. As stated in those regulations, donors should be screened and tested for things like HIV-1 and -2, hepatitis B and C virus, syphilis, and the West Nile virus. Then they should also be screened for Creutzfeldt-Jakob disease and Zika virus, but I'll elaborate more on that

screening in a minute.

When it comes to donors outside of the U.S., we sometimes have some concerns about donor testing laboratories, because they often don't have the appropriate Clinical Laboratory Improvement Amendments (CLIA) certification or access to FDA-licensed, approved, or cleared donor screening tests, which we do require for all donors of allogeneic cells. So to address those concerns, we do recommend that manufacturers of allogeneic cells outside of the U.S. send some donor specimens to an appropriate laboratory in the U.S. for testing to meet donor eligibility requirements outlined in those regulations.

To provide some clarification on the topic of screening for Creutzfeldt-Jakob disease, we have recently gotten some inquiries on FDA guidance that was published in May of 2022 regarding recommendations on reducing the risk of transmission due to Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease in blood and blood component products.

Sponsors have asked us if that specific guidance applies to products within our office in OTP. We do want to clarify that this guidance does not apply to donors of human cells, tissues, and cellular and tissue-based products, which we refer to as HCT/Ps, reviewed in our office, but only applies to blood and blood component products. So screening for Creutzfeldt-Jakob disease is still required for all donors of HCT/Ps like allogeneic cells.

Similarly, as I said earlier, we also require screening for Zika virus for all donors of HCT/Ps. We have also gotten some inquiries on this screening, and FDA has two guidance documents that we recommend to sponsors. The first one is titled "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by HCT/P-Based Products," and that one was published in May of 2018. The other guidance is called "Important Information for HCT/P Establishments Regarding Zika Virus Transmission Risk in the World," which was published in 2019. According to both of those standards, the donors of human cells and tissues should be considered ineligible if they have any risk factor of Zika virus, because, unfortunately, the virus is still a relevant communicable disease as defined in the regulations, specifically under § 1271.3. We know that the Zika virus is readily detectible in human cells and tissues, even if it's not detectible in circulating blood. For those reasons, the Zika virus screening is still required for donors of HCT/Ps.

I hope this information is helpful to clarify the necessary testing and screening for all donors of HCT/Ps, whether they're located within or outside of the U.S.

Thanks, and back to you, Melanie.

DR. EACHO: Thanks, Bao. That was very helpful. Liz, I'd like to ask you the next question.

What are the general requirements for a donor eligibility exemption request?

DR. LESSEY-MORILLON: Exemptions or alternative requests to 21 CFR Part 1271, subpart C and D, which include exemptions or alternative requests to donor eligibility and exemption requests to allow pooling of materials from multiple donors, should contain either information justifying the request, the requested exemption from the requirement, or

a description of a proposed alternative method of meeting the requirements.

The request must be accompanied by supporting documentation and relevant valid scientific data about the mitigated risk of communicable disease transmission. The request should also include a detailed description of the manufacturing process, include procedures for donor screening, testing, and making the donor eligibility determination, in-process and final product testing that is performed during the manufacturing process to mitigate the risk of communicable disease transmission. The request should also specify the patient population and indications for the study and justify why the mitigation strategy is sufficient for the proposed patient population and indication. We strongly recommend that a donor eligibility exemption or alternative request be submitted at least 90 days prior to the submission of an IND to allow adequate time for review and to send any requests for follow-up or additional information that might be necessary. If there's not a granted exemption request prior to the IND submission, then the IND submission will go on hold.

Thank you, and back to you, Melanie.

DR. EACHO: Thanks, Liz. I'd like to welcome Matt for the next question.

Is it acceptable to manufacture a cellular product using material collected from a CMV-reactive donor? What about from donors reactive for other viruses, such as HSV-1 and -2 or HHV-6, -7, or -8?

DR. MATTHEW KLINKER: Thanks, Melanie. Good morning, everyone. Let's start by talking about CMV reactivity first. If you're making an allogeneic product and that product is derived from a leukocyte-rich material, then your donors must be tested for reactivity to CMV. While CMV reactivity is certainly something you need to consider carefully when assessing potential donors, CMV reactivity alone does not necessarily mean that a donor must be considered ineligible in all circumstances.

If you're considering using material from a CMV-reactive donor, it's important to think about how this may affect the risk your product poses to those receiving it. There are several things you may want to consider in assessing this risk. First, the specific isotype of the anti-CMV antibodies can give you some indication as to the current infection status of that potential donor. If the anti-CMV antibodies are IgM, this may suggest an active infection. But if they are IgG, then the anti-CMV reactivity you see may be more likely to be the result of a previous exposure to the virus.

Additionally, you should think about your intended target population and the risk that exposure to CMV poses to them specifically. If your target population is immunocompromised or otherwise might be at higher risk of having serious complications from CMV, then you should probably think about using only donors who are not CMV reactive or possibly implementing some additional risk mitigation steps. Those might include things like testing the starting material or the product itself for the presence of CMV by PCR or other methods.

Finally, keep in mind that most FDA-approved or FDA-cleared donor testing kits for CMV test only for the presence of anti-CMV antibodies. They can't distinguish between IgM or IgG reactivity, and they don't test for the presence of the virus in the test sample itself. So

if you plan to use these other types of testing kits, whether they be PCR test kits or isotype-specific reactivity tests, you should look carefully to make sure those tests are suitable for your intended purpose, because we will expect you to provide that information and your justification for using those kits in your IND.

In regard to donors with reactivity to other viruses, this may also pose an increased risk to subjects, but there may be some circumstances when this could be acceptable. As with CMV-reactive donors, the key factor here is that you can show that the risk to subjects receiving your product is not unreasonable. Again, you should assess the risk that exposure to the specific viruses in question may pose to individuals in your specific target population and implement additional risk mitigations, such as the PCR testing or other types of testing that I already mentioned, if such mitigations are warranted.

In either case, we will evaluate the risks on a case-by-case basis, so it's very important that you clearly explain your justification for using these donors and why your risk mitigation approach is adequate in your IND submission. For more information on how to determine donor eligibility for cell therapy products, we recommend that you see the 2007 FDA guidance document called "Eligibility Determination for Donors of HCT/Ps."

Back to you, Melanie.

DR. EACHO: Thanks, Matt. I'd like to direct the next question to Bao.

What manufacturing and testing steps should be considered when creating a master cell bank? When is genetic stability testing of a cell bank needed?

DR. NGUYEN: Thanks, Melanie. So let me address that first part of the question first with a bit of background introduction. Manufacturers often create master cell banks to ensure the adequate supply of their cell material. These cell banks consist of a large number of cells that have been derived from therapeutic-producing cell lines and are then cryopreserved. Through cryopreservation, these cell lines can then be stored for a long period of time, depending on the cells' stability, therefore eliminating the need to continuously culture and maintain the original cellular material. The types of cell banks that can be created are either master cell banks and/or working cell banks of various sizes depending on the manufacturer's needs. Working cell banks are generally derived from the aliquot of a master cell bank and then can be further manufactured into the final drug product.

In terms of generating these cell banks, we recommend extensive characterization of the master cell bank, as well as the working cell bank, to ensure the safety of those cells. Testing for the master cell bank should include adventitious agent testing, including human infectious disease agents and even for specific viruses, in the event that animal-derived materials are utilized in the production of that cell bank. The adventitious agent testing should be PCR-based and test for species-specific viruses. We also recommend the use of transmission electron microscopy to evaluate the master cell bank for viral particles. Lastly, we also ask for in vitro and in vivo adventitious agent testing to demonstrate that there are no viral contaminants in the master cell bank. For the working cell banks, we recommend sponsors test for things like viability, mycoplasma, identity, and in vitro adventitious agent testing.

Now to the part of the question about genomic testing: we generally recommend this testing be performed on cell banks of continuous cell lines and genome edited cells to confirm that the cells are able to maintain a normal karyotype throughout the long storage conditions. Cell lines that are cultured extensively often accumulate mutations during cell expansion.

While we are not prescriptive of the type of test method that you should be conducting for genomic stability testing, there are some options including G-band analysis, genetic fingerprinting, or some other sensitive methods. But whichever method you do choose, we ask that you justify and provide qualification information for that method. We also recommend that you utilize and justify your testing samples that are used for karyotyping analysis, and that you set an appropriate acceptance criterion to be set for potential karyotyping deviations. Genomic testing can be conducted on a one-time basis to assess genetic stability of the cell line at the end of the production.

Going back to the topic of cell banks again, we do highly recommend, when you first come to FDA during the INTERACT or pre-IND meeting, that you try to outline how you will create and maintain your cell banks, including your testing plans, the size of the cell banks (for example, how many vials are created and how many potential patients can be treated per vial), and any test results you may already have collected up to this point in your product development. This will give us a chance to give you proper feedback on the adequacy of your cell bank and if any additional testing is necessary prior to initiating studies in subjects.

One last important point I want to make is that master cell bank and working cell bank testing that I just described should be conducted even after the donors of the cells have met the donor eligibility requirements as outlined in 21 CFR 1271. The cell bank testing should be conducted on the cell banks independently from donor eligibility testing, so please keep in mind that just providing evidence that the donor eligibility requirements have been met is not sufficient to demonstrate the safety of the cell bank and that you need to plan to incorporate the necessary cell bank testing as well.

Back to you, Melanie.

DR. EACHO: Thanks, Bao. I'd like to direct the next question to Liz.

What are some specific current good manufacturing practice, or CGMP, requirements for cell products during phase 1, 2, and 3 studies?

DR. LESSEY-MORILLON: Because cell therapy product attributes can directly affect the manufacturing process, the manufacturing process must be well-established and controlled at all stages to ensure the cell therapy products meet all of the appropriate standards. The FD&C Act requires drugs, which include biologics and investigational products, to comply with CGMPs. However, there is flexibility with applying specific CGMP regulations described in 21 CFR Part 1211 for phase 1 studies. Phase 1 studies are exempted from many of the CGMP requirements in Part 211. Many of these CGMPs are designed for final-stage commercial products. Following CGMPs for phase 1 studies occurs mostly through well-defined and written procedures, adequately controlled equipment and manufacturing environments, and accurately and consistently recorded data from manufacturing, including

testing.

A controlled manufacturing process is critical and required to maintain the quality and safety of cell therapies. For example, most cell therapy products cannot be terminally sterilized and rely on aseptic processing. The appropriate controls for aseptic processing in the manufacturing process should be in place to ensure the product is free of microbial contamination at all stages of manufacturing. Therefore, aseptic process simulation studies are a part of the controls for aseptic processing that should be in place for a new manufacturing process or new facility. This is particularly important for cell therapies that will be administered based on a rapid microbial contamination test, while the final sterility test results are still pending. It's worth noting that CGMPs do not apply to the collection of the donor material. CGMPs start with a manipulation of the starting material, either at the manufacturing site or a third-party establishment.

For cell therapies in phase 2 and phase 3 clinical studies, and for any subsequent phase 1 clinical trials after the initiation of phase 2 or phase 3 studies, we expect CGMP regulations described in Part 211 to be in place. For more information, there is an FDA guidance from July 2008, titled "Guidance for Industry CGMPs for Phase 1 Investigational Drugs," available on the FDA website.

In addition to CGMPs, there are also current good tissue practices (CGTPs), which are outlined in 21 CFR Part 1271, that apply to cell therapy products at all stages of clinical development.

Thank you, Melanie, and back to you.

DR. EACHO: Thank you. Matt, for the next question:

What product attributes should be considered during development of a potency assay?

DR. KLINKER: Thanks, Melanie. This is a great question. Potency assay development is maybe the most significant challenge for developers of cell therapy products, so I'm glad we got a chance to talk about these issues. First, let me just say that we know that this is hard. We know that these are very complex products and that this complexity can make controlling their potency very challenging. Also, we expect that you'll continue to learn about your product's attributes during development. It's generally okay if there are some question marks about product potency during the early stages of development, but you don't want to ignore these challenges, and the best way to meet them is simply to start early.

In trying to identify attributes that may be related to potency for your product, you may start by considering what you know about the product's mechanism of action (MOA) in the context of the intended clinical indication. Then use that knowledge to try to determine what attributes are necessary to mediate your product's intended therapeutic effect. These attributes will likely be different for every product, but hopefully you understand your product better than anyone else and are in the best position to figure this out. Use any source of information that's available to you. This could include things such as data from early manufacturing runs, results from non-clinical studies, as well as just general knowledge you can obtain from published peer-reviewed studies.

In some cases, a product's MOA may not be clear or well-characterized, especially during early stages of development. This is especially true for complex products. So if this is true for your product, then you should consider implementing what we call product characterization tests early in development. These are tests that assess product attributes for informational purposes, and this approach allows you to evaluate multiple attributes that may be related to product potency to determine which of them are truly important. But even if you think you have a good idea of how your product works, you should still think about product characterization. Cells do lots of things, and biology is complex and often unpredictable. The more you know about your product, the more likely you are to find attributes that are truly important to its potency. I know this approach can sound daunting, but keep in mind that it's often not necessary that these product characterizations be fully qualified or validated during early development, but they should be suitable for their intended purpose.

I would also encourage you to not just focus merely on one specific product activity, but to think bigger and consider potency-related attributes more broadly. For example, if your product needs to persist in recipients after administration, then you may consider testing for attributes associated with viability or maybe attributes like low immunogenicity that may help your product stay around longer.

Additionally, potency tests conducted at the time of lot release can't by themselves make sure that your product is potent at the time it's delivered. Really, it's the potency of the product at the time of administration that really matters. So you should make sure that your product is compatible with all excipients and the container closure you intend to use, and it's also very important to know that your cells are not damaged by the procedures used for preparation prior to administration or by the method of delivery. Cells can be surprisingly sensitive to these things, so it's worth checking before you start clinical studies.

I will end this answer with a reminder that, before you initiate pivotal studies or phase 3 studies or what we like to refer to as studies intended to provide primary evidence of efficacy to support a marketing application, we will expect you to have at least one meaningful quantitative potency assay in place. So to make sure you have that, as I said before, start early.

Melanie, back to you.

DR. EACHO: Thanks, Matt. Don't go anywhere. We have several potency assay-related questions in this series. For the next question:

How should acceptance criteria be determined for potency assays?

DR. KLINKER: Thanks. This can also be a real challenge for these very complex products. So determining what attributes to measure for potency is important, obviously, but it's also critical that you set appropriate acceptance criteria for that attribute. As I mentioned earlier, it's okay if you're still learning about your product during those early stages of development. That being said though, measuring and controlling your potency as early as you can is certainly the preferred approach. This allows you to give a more consistent product in your clinical studies and it helps avoid CMC-related delays later in product development. We generally recommend that you set acceptance criteria for potency

tests even during these early stages of development, even if they are relatively permissive at that time.

For first-in-human studies, acceptance criteria can be based on your manufacturing capabilities and on the potency of lots used in any supporting nonclinical studies. But as development progresses and you begin to collect clinical data and gain experience from manufacturing, you should re-evaluate your acceptance criteria as needed to ensure that your dosing is consistent both within and between clinical trials. By the time you reach pivotal or phase 3 studies, hopefully you'll have quite a bit of data available that can help you set acceptance criteria for these crucial studies. At this stage, you should consider all available manufacturing and clinical data that you have and then refine and tighten your acceptance criteria to ensure that the product you're giving in these pivotal studies is consistently potent enough to mediate the intended therapeutic effect.

Finally, the acceptance criteria that you propose in a marketing application should be determined by the potency of the product lots that you used in the supporting clinical studies. Your product specifications more broadly should be sufficient to ensure the continued potency of your products in a commercial setting. That's one very important reason why it's so crucial that you have your potency assay in place before you start those efficacy studies, so you know what an effective product looks like. It can be very challenging to set acceptance criteria for a commercial product if you didn't test the product in efficacy studies for lot release.

Melanie, back to you.

DR. EACHO: Thanks, Matt. One more potency-related question to you, Matt:

Is it necessary to demonstrate that potency tests measure an attribute associated with clinical outcomes?

DR. KLINKER: Thanks. Linking a product attribute to clinical outcomes can be a good indication that the attribute is relevant to potency, but this is no simple feat. Federal regulations have quite a bit of flexibility regarding potency tests. Just to be clear, they do not require that an attribute measured by a potency test be associated with clinical outcomes. But for products with MOAs that are not well-characterized, evaluating potential potency attributes for associations with either nonclinical or clinical outcomes can be a useful way to help you figure out what attributes are meaningful. It's important to remember, however, that a statistical relationship alone should be supported by additional data establishing a mechanistic relationship. It really has to make sense why this attribute would be related to potency.

If you have questions about how to go about demonstrating your potency attributes are meaningful or any of these other potency-related topics we're discussing today, I encourage you to refer to the FDA guidance document from 2011 called "Potency Tests for Cellular and Gene Therapy Products."

Melanie, back to you.

DR. EACHO: Thanks, Matt. Potency is very popular, and I have one more potency-related question, this one to Bao.

How can potency be evaluated for a tissue-engineered product, like a cell-seeded scaffold?

DR. NGUYEN: Thanks, Melanie. Happy to continue that discussion on potency, but this time, as you said, we'll focus on tissue-engineered products. Evaluating the potency of a tissue-engineered product that contains multiple components can definitely be more complex, and we understand that developing such a potency assay or matrix is complicated.

These products, like described in the question, can consist of different components, like cells seeded within or on a scaffold. These products can sometimes have multiple modes of action, which may need several different potency assays to evaluate specific critical quality attributes or biological activity.

For tissue-engineered products, it's most important to keep in mind that all potency assays, whether it's a single assay or an assay that's part of an assay matrix, are evaluated on the final product. In this example, that would be the product consisting of cells on a scaffold.

That means that the entire final product should be evaluated for potency. It's not sufficient to just evaluate the cells, even if you think that the cells provide the main mode of action or provide the critical quality attribute in this therapeutic product. That is because the cells interact with the scaffold, and vice versa. The cells are affected by the scaffold, while the scaffold could also impact how the cells function. That means that the cells could potentially behave differently on the scaffold, specifically in 3D, than when the cells are in suspension in a solution or even just seeded on a 2D surface. So it's critical that the potency assay for tissue-engineered products utilizes the product in its final form with all of its components prepared and formulated together.

Thanks, and back to you, Melanie.

DR. EACHO: Thanks, Bao. Now moving to some stage-related questions, or phase-stage-related questions. For Matt:

How do analytical procedure expectations for late-stage clinical studies differ from those for early-stage studies?

DR. KLINKER: Thanks, Melanie. In general, the level of qualification you need for a particular analytical procedure is going to depend on the intended use of the assay. If the assay is related to safety or is necessary for controlling the dosage of your product, then we would generally expect that the assay be qualified even at early stages of development. For example, if a particular cellular impurity in your product may pose a risk to study subjects, then you should demonstrate that the method you're using to measure it for those cells is appropriately controlled before your product is used in clinical studies.

In the early stages of development, there might be some flexibility in how thoroughly developed or qualified an assay needs to be, provided that it's not related to safety or dosing. But if an assay is worth doing, it's usually worth doing well. Assays that don't

measure what you think they measure or assays with high variability or little robustness — these simply waste resources and they don't really provide any meaningful control of your product. So even at early stages of development, it's worthwhile to understand how your assay performs and have confidence that it's suitable for what you're using it for. That's why we generally recommend that you evaluate assay performance at all stages of development, even if qualification of the assay is not strictly required to proceed.

By the time you start pivotal studies, however, most or all of your assays should be qualified because it's absolutely critical that the attributes of your product used in your pivotal studies are measured reliably. You will need this information so you can set specifications for your commercial products, and if your assays don't provide reliable information of the attributes of the product used in your pivotal studies, then it becomes challenging to set suitable acceptance criteria.

Finally, before you submit a BLA, all assays should be validated and demonstrated to be suitable for their intended purpose. But even though validation is only required at these very late stages of development, it can still be very helpful to think about how you will validate your assay, even way back when you were designing it. Many developers struggle with validating assays, as these are complex and inherently variable products. Sometimes complicated assays are just simply necessary to measure their attributes. But if you can limit the sources of variability in your assay by designing it thoughtfully from the start, this may make it easier to validate the assay later in development.

Back to you, Melanie.

DR. EACHO: Thanks, Matt. Next we have a set of questions on comparability, which is another popular topic of questions that we received. These questions are to Liz.

What type of comparability is expected when multiple changes occur simultaneously for an improved process?

DR. LESSEY-MORILLON: A risk assessment is needed for all manufacturing changes to determine if the change has the potential to negatively or positively affect product quality. The risk assessment should include an evaluation of various product attributes and process parameters to assess the product quality as they may relate to the safety and effectiveness of a product and select sensitive analytical methods that can detect meaningful differences in product quality. The more changes that are occurring at the same time, there will be an increased risk that even small changes will impact product quality. An analytical comparability study is required for significant changes to the manufacturing process to demonstrate that product quality and safety have not been affected. Depending on the exact changes, multiple small changes occurring simultaneously can be considered significant.

The risk assessment and potential impact to the product should determine if a change is significant, thus requiring an analytical comparability study.

Analytical comparability study design should address the risks identified in your risk assessment. As part of the risk analysis, you should determine the most appropriate process time points to detect a change in quality attributes. This may entail evaluating the product at multiple stages of manufacturing, such as in-process or final product. Please note that

depending 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 the comparability assessment.

To determine the amount of data necessary to support a manufacturing change, it's important to consider the stage at which the manufacturing change occurred. In early development, a comparability assessment will generally focus on demonstrating that product safety remains unchanged, whereas safety and efficacy is required for changes for a study intended to support a marketing application. We recommend that the commercial manufacturing process is established and well-controlled prior to initiating clinical studies that are intended to provide the primary evidence of effectiveness to support a marketing application.

Changes made to the manufacturing process may also affect the stability and expiration dates of the product or intermediates and may require additional stability studies as well.

Thank you, Melanie, and back to you.

DR. EACHO: Thanks, Liz. Another comparability question for you:

Regarding comparability, can FDA elaborate on the sample size expectations to statistically power the data analysis for analytical comparability studies?

DR. LESSEY-MORILLON: Thank you, Melanie. This is a challenging question to answer because it will depend in part on the comparability study design, the manufacturing process change, sources of variability in the manufacturing process, and known product attributes. There should be enough lots to allow for a meaningful statistical comparison. The selected number of lots should be justified, in particular when there are external constraints that limit the number of lots possible.

Designing the comparability protocol to control for areas of variability can reduce the required sample size. In general, we recommend a prospective side-by-side comparability study directly comparing the pre-change and post-change product to eliminate variabilities that can be introduced when using historical data, including differences in analytical methods and changes in the process, other than the change proposed. This is particularly valuable when the starting source material is variable. We recommend you consider splitting the same source material to manufacture the pre- and post-change products for the comparability evaluation.

Thank you, Melanie. Back to you.

DR. EACHO: Alright, Liz. One more question on comparability.

Does FDA recommend their review of comparability protocols prior to executing those types of studies?

DR. LESSEY-MORILLON: Yes. We do recommend submitting the analytical comparability study protocol to FDA before executing the study. As I stated, manufacturing changes can directly impact product safety and efficacy. Therefore, the product used in the clinical study needs to be evaluated before and after the manufacturing change. This is particularly important in later stages when the comparability study is being conducted for a study intended to support a marketing application like a BLA. Submitting the protocol ahead of the study allows time for FDA to review and provide feedback and should allow for a more efficient review of the comparability data after the completion of the study.

We also recommend that comparability be established prior to initiating the phase 3 study. For any manufacturing change occurring during or after completion of the phase 3 study, we strongly recommend all comparability concerns are resolved at or before the pre-BLA meeting. Comparability studies are intended to allow the use of clinical data before and after the manufacturing change. If comparability is not established, then the clinical data collected might not be applicable to the BLA, and this could lead to a filing issue for the BLA. If the product turns out to be not comparable, then a new clinical study might need to be conducted.

Thank you, Melanie. Back to you.

DR. EACHO: Thanks, Liz. I'd like to round out the pre-submitted questions. The next two are related to medical devices or delivery devices. I'd like to ask Bao to answer.

How and when should materials that are intended for direct or indirect contact with a patient be tested for biocompatibility?

DR. NGUYEN: Thanks, Melanie. Biocompatibility testing is needed for devices or device components that come into direct or indirect contact with human tissues, like the question says. But this type of testing specifically determines if there's any potential for an unacceptable adverse biological response resulting from the contact of a foreign material with the body. We sometimes see some confusion in the terminology used when it comes to biocompatibility testing, specifically the terms *direct* and *indirect* contact, so I'm just going to take a moment to clarify these two important terms. Tissue contact with the material can be considered direct contact when the material is, for example, touching the surface of the skin or directly getting implanted into the body. That is direct contact.

Tissue contact can be considered indirect contact when, for example, a fluid comes into contact with a device or material and then that fluid is then contacting human tissue. That is considered indirect contact. Once you understand the type of contact a foreign material may have with tissue, we can consider the duration of contact. We generally categorize the contact into three different groups. First, we have limited contact, which is usually less than 24 hours. Then we have prolonged contact, which is between 24 hours and up to 30 days. Then we have permanent contact, which is anything greater than 30 days.

Depending on the degree and duration of contact, we have a list of tests and evaluations that should be conducted to assess the biocompatibility of a material. These revolve around a risk assessment process usually, which considers the device material, intended anatomical location, and the frequency and duration of contact. CBER, along with our colleagues in the Center for Devices and Radiological Health (CDRH), published a guidance document

on the topic of biological evaluation for medical devices, which follows the recommendations outlined in a standard, specifically ISO 10993. We highly recommend that sponsors refer to a table at the end of that guidance document, specifically Table A.1, which outlines all of the necessary biocompatibility testing that's needed for foreign material based on the contact type and duration used in the therapeutic product.

I do have a couple of pitfalls that are often encountered in biocompatibility testing conducted on the materials used in our products. First, several of the biocompatibility tests utilize solvents to extract compounds out of that material and evaluate the toxicities of those compounds. The type of solvent used, whether it's a nonpolar or polar solvent, is very important. But equally important is the ratio of solvents that are used with the test article. The guidance document, along with ISO 10993, clearly outlines the specific parameters for these two things. For most of our products, the ratio is often based on the surface area of the exposed material to the solvents. We recommend that sponsors review those documents carefully to make sure that their biocompatibility testing protocol is done correctly.

Next, sometimes these sponsors utilize materials that have previously been reviewed by FDA as part of a different product. In those cases, we ask the sponsors to make sure they check the intended use of that cleared or approved product to make sure that the material is used in the same way as they wish to use it in their product. For example, if there's a polymer that was previously cleared as part of a device that has limited contact with the tissue, it will have been tested for that intended use. But if that same polymer is now being proposed to be implanted, for example, as a scaffold with cells, it would need to undergo additional biocompatibility testing and evaluation for that new intended use. So it's important that if sponsors want to leverage previously reviewed information, that the information is relevant to this material's new intended use. As a note, FDA does not clear or approve any materials, but we clear devices or products that contain those materials for specific indications for use.

For devices regulated in CBER OTP, biocompatibility testing is generally needed for device constituents of combination products such as scaffolds, for example, in tissue-engineered therapies or for materials used in delivery devices. As outlined in the biocompatibility guidance document, the type of testing required depends again on the use of the devices within the therapy and where and for how long it is in contact with the body. When it comes to biocompatibility testing, it's important to note that the testing should be conducted on the device component only, which in most tissue-engineered products, for example, is the scaffold. So biocompatibility testing should be conducted on scaffolds only, without the cellular or biological components, just in order to assess the biological reaction to that material alone. This ensures that the material or device is tested without the impact of any added biological components that could potentially interfere with the biocompatibility testing.

That's all from me, Melanie. Back to you.

DR. EACHO: Thanks, Bao. One more question regarding delivery devices:

When a biologic product is administered using a delivery device, what are some important biologic-device compatibility considerations?

DR. NGUYEN: Thanks, Melanie. Another great question. Many of our products reviewed in our office do utilize a device to administer the actual final product. We ask that you provide information on the route of administration and any devices that are needed for administration as early as the INTERACT or even a pre-IND phase meeting, depending on how complex that device is. But we'll definitely need that information by the time you get to the IND-phase study. Generally, we ask that sponsors provide a description of the delivery device, and that can include important details like each component that is involved and its function. You should also provide information to establish the safety of that delivery device for the proposed clinical use, including things like biocompatibility like I just talked about, but also sterility, cumulative endotoxins, packaging, shelf life, performance data, and if applicable, even things like electrical safety, electromagnetic compatibility, and software. With regard to the biologic and device compatibility testing, we assess that to see how the device will affect the biological product after simulated administration using a delivery device. We ask that you provide data demonstrating that the administration of that drug product using a delivery device will not negatively affect any of the product's quality attributes, like sterility, potency, or identity. Just as important, we want you to assess the quantity of that product that will actually be delivered to the patient using that delivery device. We generally refer to that as dose accuracy.

Along the topic of using a delivery device, we've also seen submissions utilize 510(k) cleared delivery devices to administer a drug product. While a 510(k) clearance indicates there's some level of assurance of safety and effectiveness for that delivery device, this only applies if the device is being used as intended in the 510(k) application. For example, if there's a needle that was cleared under the 510(k) process for administration of a product into the spine, then its use for administration of that product into the, for example, gastrointestinal space would not be supported by that 510(k) clearance. It's critical that sponsors check the indications for use and intended use of a cleared or approved device, and see how it compares to the proposed use with their biological product. Depending on the cleared or approved use, additional performance or safety testing may still be necessary. One important thing to remember is that even if the device is used per the cleared or approved intended use, the sponsor should still show compatibility testing of that device with their own product. That type of testing often includes sterility and cumulative endotoxins, as well as assessment of the final product after passing through the delivery device for things like viability and dose accuracy.

Back to you, Melanie.

DR. EACHO: Thank you, Bao.

I'd like to thank you all who submitted questions during the registration process. We'll now spend the remainder of today's event answering your live questions.

For live questions, I would like to ask Liz the first question.

What is the sterility testing requirement for a cell product that has a short manufacturing duration, such as three days, and is to be administered fresh, shortly after final harvest on day three and thus is not amenable to conventional 14-day culture-based testing?

DR. LESSEY-MORILLON: Thank you, Melanie. We understand sterility testing can be a challenge for products that have a limited shelf life (for example, those administered shortly after manufacturing) and that short-shelf-life cell therapies might not be amenable to the conventional 14-day sterility test methods. The expectations for sterility testing of licensed biologics are described in 21 CFR Part 610.12, and we recommend following those approaches for investigational products as well. We do allow both compendial and noncompendial sterility test methods.

For noncompendial sterility test methods in IND submissions, the methods should be qualified to determine if it's suitable for the product and has the adequate sensitivity under the assay conditions. If the sterility test method provides a readout faster than 14 days, which is the conventional sterility test method, then the submitted data should demonstrate the test method's ability to detect slow-growing organisms. Like other noncompendial assays, any noncompendial sterility test method must be validated prior to licensure. We recommend that sponsors submit their proposed validation protocol to FDA for comment before conducting the validation study. I'd also like to point out that if the parameters of a compendial method are changed, such as incubation temperature, duration, or media type, then the method is no longer considered compendial and will need full validation.

Alternatively, it is permissible to use an alternative rapid microbial detection method to release the product for infusion while the final conventional 14-day sterility test results are still pending. This approach requires having in-process testing and an action plan if there is a post-release sterility failure. We do allow greater flexibility with this approach under IND than we would for commercial products. If this approach is intended to be used for commercial products under a BLA, then the proposed approach should be discussed at FDA to determine if it's appropriate for licensure and what additional controls might be necessary, as this will depend heavily on the product, the manufacturing process, and the risk to the patient. Therefore, we recommend that you talk to FDA about all alternative approaches to sterility to ensure agreement with FDA and, particularly, prior to the BLA submission.

Thank you, Melanie. Back to you.

DR. EACHO: Thanks, Liz. I actually have another question regarding sterility for you.

How flexible is FDA regarding the minimum number of samples and volume of samples for final sterility testing, as cell therapies may have small batch sizes? For example, does FDA recommend 1% or 10% of the batch is suitable for sterility testing?

DR. LESSEY-MORILLON: Thank you, Melanie, for the question. Sterility testing should be performed on the drug product in the final container, unless otherwise justified as outlined in 21 CFR Part 610.12. We recognize that for many cell therapy products, there is a limited amount of the final drug product. Due to the amount of product and sterility test method considerations, we don't have specific requirements about the minimum amount of materials or the number of batches that should be sampled. The appropriate sample volume will depend in part on the sterility test methodology. For example, low levels of inoculation can alter the limit of detection for the assay.

We do allow alternative sterility test sampling on a case-by-case basis. For example, if the final volume is insufficient to provide an adequate sample for a sterility test, then we do allow that the product can be tested at a different stage of manufacturing if sufficiently justified. Alternative testing approaches we frequently see are testing of in-process samples, cell harvest, and possibly supernatants, rather than the final product. It is important that any alternative approach be scientifically justified and supported by data and be representative of the final product and capable of detecting contamination in the final drug product, even slow-growing microbes.

We recommend that you talk to FDA about all alternative approaches during development and provide adequate justification for the approach in the IND and BLA submission. Thank you, Melanie. Back to you.

DR. EACHO: Thanks, Liz. Bao, I'd like to ask the next question to you.

During which part of product development is extractable and leachable testing for container closure needed? How should this testing be conducted?

DR. NGUYEN: Thanks, Melanie. That's a great question because we've actually been providing a lot of comments about extractables and leachables to our sponsors, especially those who are coming close to their BLA application. Just to back up a little bit, when a final product is stored in a container closure system, there are different considerations that should be kept in mind. The regulations say that manufacturers need to provide sufficient information on the packaging materials, which include things like how the materials could impact the drug product.

Throughout the drug product development process, we hope that sponsors are thinking about the safety of their container closure system, keeping in mind that testing for extractables and leachables is most critical when the product moves to late-phase studies that may lead to a BLA. We do know that container closure systems and product formulations change throughout the product development cycle due to things like scale-up or scale-out and process improvements, but this makes it even more critical to remember to conduct extractable and leachable testing on the final product during those late-phase studies.

Extractable studies are conducted to evaluate a list of potential leachables in the drug product from a container closure system. The extractable study is performed under exaggerated conditions that include things like solvents with high extracting propensity, higher temperature, and longer incubation time than what usually would be seen in a clinical setting. This is then followed by a leachable study, and those are performed using the actual drug product or a simulated matrix of that drug product where the samples are analyzed for compounds leaching into the matrix due to its direct contact with the container closure material. The leachable study is performed under real-time drug product storage conditions over the product shelf life with multiple points of analysis. After completing those two studies, then you get to the toxicology risk assessment, which is then used to evaluate if any of those chemicals that were seen in the extractable and leachable studies are actually within safety levels. That kind of depends on the proposed route of administration for that product.

One important point I do want to make is that the leachables start to actually accumulate in the drug product or in the product as early as the drug substance just because of the multiple processing steps, especially if there's no purification of that intermediate drug substance. In those steps where leachables can start to appear, this includes things like intermediate filtering, formulation into the drug substance and the drug product, and eventually actually filling into the container closure system. Leaching into the drug intermediate can come from all sorts of different materials, like the tubing, the connectors, the containers if you use any bags or filters, and then of course the container closure system itself. So it's important that when you're assessing the leachables in your product, that you start with the last purification step of that drug intermediate because it can start accumulating throughout the manufacturing process. Keep in mind that the leachables that you see from the container closure really only represent a small fraction of the cumulative leachables in the drug product that have accumulated over time.

Thanks, and back to you, Melanie.

DR. EACHO: Thanks, Bao. I'd like to ask the next question to Matt.

We heard about a new pilot FDA program under PDUFA VII to help cell therapy product sponsors meet their CMC development needs. What is this program about?

DR. KLINKER: Thanks, Melanie. That's correct. Under PDUFA VII, there is a new program that launched. The point of it is to facilitate expedited CMC development of cell and gene therapy products through increased communication with FDA. The program is called the CMC Development and Readiness Pilot Program, or CDRP. It launched on April 1 of this year, so it's still very new. Its intent is to encourage sponsors to prioritize CMC development early to help keep pace with the expedited clinical development programs. And hopefully, if you've been listening to our earlier responses during the session, that should be a suggestion that sounds pretty familiar.

As outlined in the Federal Register Notice, INDs in CBER for products with expedited programs — and that means products with breakthrough designation or RMAT designation — may be eligible to apply for the CDRP program if certain other eligibility requirements are met. The highlight of the CDRP program includes two dedicated Type B CMC meetings, and that's in addition to any other existing meetings. Those are to help sponsors meet product safety and consistency standards for novel products that are designed to mitigate or treat serious or life-threatening diseases or conditions. And ultimately, the goal of the CDRP program is to provide patients with earlier access to new drugs and biologics. For more information on the CDRP program, please refer to the Federal Register Notice published on October 31, 2022, and the FDA website on this program, which you can find by a web search for FDA CDRP.

Finally, if you think your product may be eligible for this new program, we really encourage you to apply and please reach out to us if you have any questions about eligibility or any other aspect of this program.

Melanie, back to you.

DR. EACHO: Thanks, Matt. I actually have another question for you.

Is it a requirement for the sponsor to initiate reagent identity testing in advance of a pivotal trial, or can reagent identity testing be initiated during the pivotal trial with a goal of having a reagent identity test by the time of BLA submission?

DR. KLINKER: Thanks. Good question. We encourage and recommend that you start looking into reagent identity tests during your pivotal studies. But those are not required to start your pivotal studies. So the reagent identity tests are really things that are required at the stage of licensure. At the point of licensure, you should have at least one test in place for each reagent coming in that can confirm the identity of that. Those tests should be validated for licensure. An important point I'd like to make here is that by identity testing, that doesn't mean just looking at the certificate of analysis and confirming that the supplier did identity testing; it's something that should be done to confirm what's on the label of the reagent you're receiving, that that label is correct, and that what is in those containers is actually what you think it is. Just to answer that directly, reagent identity tests are not required to start your pivotal studies.

DR. EACHO: Next question is for Bao.

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

DR. NGUYEN: Thanks, Melanie. We certainly understand that manufacturing deviations do occur from time to time, but we also recommend and hope that sponsors know that they should do their best to adhere to the appropriate steps necessary to avoid, mitigate, and, more importantly, report these deviations to us for review so we can see what should happen next. Manufacturing deviations should be investigated internally to identify things like the root cause, and then appropriate corrective action should be taken just to avoid repeat occurrences in the future. That means that proper documentations are put in place through the entire manufacturing process, so that the root cause can be properly identified through all of the steps.

We also recommend that appropriate change control procedures are put in place to manage the risks associated with each of these corrective actions. Sponsors should provide a description of the risk management change and control procedures for how they will address any manufacturing deviations in their review in their IND so that we can review it and give them any feedback as necessary. If a product lot does not meet the lot release specifications due to some manufacturing deviations or other issues that have occurred, that product should not be released or administered to a patient. In the case where the subject is at significant risk, such as the subject has already been conditioned to receive that product, then the sponsor should reach out to FDA with a description of that deviation, and we can see if it can still be potentially administered, that out-of-specification product for that subject.

For any licensed products, the FDA does require reporting of certain deviations and unexpected events by the manufacturer. Those requirements are outlined in the regulations, specifically 21 CFR 600.14. There's also something in § 606 and § 1271 on the requirements for reporting any deviations to us.

Thanks, and back to you, Melanie.

DR. EACHO: Thanks, Bao. The next question I have is for Liz.

What are the requirements for a cell line for which donor eligibility information may not be available?

DR. LESSEY-MORILLON: If donor eligibility was not tested or screened according to 21 CFR Part 1271, then an eligibility exemption request from donor eligibility is required. In a previous question, I addressed the general requirements for an exemption request. It's worth noting that donor eligibility requirements outlined in 21 CFR Part 1271, subpart C, only apply to HCT/Ps that are recovered on or after May 25, 2005. Thus, an exemption request is not needed for HCT/Ps that were recovered prior to that date.

However, sufficient information needs to be provided to demonstrate safety of the cells. We ask that you provide any available information regarding testing and screening of donor risk factors and for clinical evidence of infection due to relevant communicable diseases. Please provide information on how you ensure patient safety and how you mitigate the risk of infectious disease, either with testing of the starting material, in-process material, or final product adventitious agent testing, for example. Generally, we recommend that material from donors who were properly screened and tested according to 21 CFR Part 1271 are used.

Thank you, Melanie. Back to you.

DR. EACHO: Thanks, Liz. I have another donor eligibility question for you.

What are the differences between donor eligibility requirements for allogeneic and autologous products?

DR. LESSEY-MORILLON: Allogeneic donor eligibility requirements are outlined in 21 CFR Part 1271. You are not required to make donor eligibility determinations or perform during a screening for cells and tissues for autologous use. However, you should consider whether the manufacturing procedures increase the risk of propagation of pathogenic agents that may be present in the donor. If so, you should document whether the donor is reactive or pathogenic for specific pathogens. Also, you should just describe precautions to prevent the spread of viruses and other adventitious agents to persons other than the autologous recipient. For autologous cells intended for autologous use, the label of the product must be labeled as "FOR AUTOLOGOUS USE ONLY" and also "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

Thank you, Melanie. Back to you.

DR. EACHO: All right. Thank you, Liz. Matt, I have a question for you.

When is a validated potency assay required during clinical development?

DR. KLINKER: I guess by the word "required," I will interpret that to mean, "When will we put you on hold if you don't have that?" That's something we don't look for, a fully validated potency assay; that's something you need for licensure. During development, a potency assay that is qualified needs to be in place before you start your pivotal studies. So I guess the answer is a validated potency assay is needed at licensure, but a qualified potency assay is required before you start any kind of pivotal study.
Back to you.

DR. EACHO: Thanks. I have another question related to potency, Matt.

Should potency assays be part of a stability program?

DR. KLINKER: I think I'll just say yes, they should be. If you have it, that is. Late in development, potency testing is an absolutely crucial part of stability testing, one of the most important parts. At that stage late in development, and definitely before licensure, it needs to be part of the stability program.

Earlier in development, there may be some flexibility. If a potency test isn't in place for very early development, then if you just don't have a test, you can't do it for stability, obviously. But I think we would encourage, if you have the potency test, it should be part of your stability program. Just to hit that refrain again, starting early and having those tests early in development and having them be part of your stability program is something that can be very useful later in development and then at the point of applying for a license.
Back to you.

DR. EACHO: Thanks, Matt. I'd like to ask Bao to answer the next question.

Is a pre-BLA meeting required before submitting a BLA?

DR. NGUYEN: Thanks, Melanie. Such a timely question. We're getting more and more sponsors in the field preparing for the licensing applications, so this is a pretty good question. While a pre-BLA meeting is not required, it is definitely highly recommended by us. There are benefits to requesting a pre-BLA meeting to help sponsors have a successful BLA submission. We've really seen what a difference a pre-BLA meeting can make.

The pre-BLA just ensures that the sponsor is aware of all major unresolved issues from a product development program that should be resolved prior to submission of a BLA. It also gives sponsors a chance to identify the studies that they want to use to provide evidence for the product's effectiveness. They can also explain those studies in their current status. The meeting is just a good time to discuss the appropriate methods for statistical analysis needed to analyze those collected data.

One of the more important topics is the CMC readiness for BLA. So we talked about that a little bit already today, but for example, how does the commercial manufacturing process compare to the smaller-scale process used during the clinical study? How does that ultimately affect the product comparability? Liz already did a great job discussing aspects of product comparability early in this webinar, and then Matt also just covered the CMC Development Readiness Pilot Program. Both of those things are really important and can help prepare for a really successful pre-BLA meeting.

But while we're on this topic of the pre-BLA meeting, I do want to highlight some of the most common advice that we give to sponsors who are preparing for their pre-BLA. First, it's important to remember that every sponsor only gets one pre-BLA meeting. We want to make sure that sponsors come as prepared as possible because a second follow-up meeting is not going to be possible. From a CMC perspective, we also highly recommend that sponsors provide a comprehensive table of contents of Module 3, which is what the CMC information is coming in. We've seen sponsors just give headings of the HCT/P modules and those are often not descriptive enough. A table of contents with more descriptive headings really allows us to assess the adequacy of any planned BLA submission you want to submit.

As I said earlier, the pre-BLA meeting can also be a great time to identify and resolve any major issues, but it's also important to remember that, when it comes time to submit the actual BLA, all parts of the submission are complete. If you are submitting a BLA, even on a rolling basis, all sections when submitted should be complete. We don't really want to use our valuable BLA review time to ask for major sections of the BLA that are missing and then have to receive those as major amendments to the BLA. Submitting only complete BLA submissions is really important, and applicants should make sure that each section is truly ready to be submitted before doing so.

Another important topic that we do often discuss during the pre-BLA is comparability. We spent some extensive time on this topic already today, but as sponsors really fine-tune the manufacturing process and scale up for commercialization towards the end of their product development, we want to be aware and involved as early as possible during those comparability discussions. Ideally, we would love to see those comparability protocols during the IND studies, prior to the pre-BLA, so that the results of these studies can be discussed during the pre-BLA meeting. That also allows for our clinical colleagues to really understand early on which clinical data will be used to support the efficacy of a BLA.

One last thing I do want to mention with regard to the timing of the pre-BLA request: it takes time to schedule and review that meeting package and even more time for sponsors to make sure they've prepared for the BLA submission adequately. So we do recommend that sponsors submit a pre-BLA meeting request at least four months prior to when they plan to submit their actual BLA.

All right, back to you, Melanie. Thanks.

DR. EACHO: Thanks, Bao, for that comprehensive response. The next question I'd like to ask Liz.

What testing is required if the product is manipulated at patient's bedside, such as washing?

DR. LESSEY-MORILLON: If the manipulations on the product at the bedside are performed in an open system, then we consider these additional manipulations to the product manufacturing steps and should be performed in accordance with CGMP regulations. Due to these additional manipulation steps, sterility and endotoxin testing of the reconstituted final product should be performed.

Additionally, if you will not have control over the cryopreserved final commercial product after you release and distribute to the end user, we recommend that during the investigational phase, you establish an approach to eliminate any additional manipulation steps, such as washing of the product at the clinical site after the product is released and distributed to the manufacturing site. If the manipulations are performed in a completely closed system, then additional sterility and endotoxin testing might not be necessary. Thank you, Melanie, and back to you.

DR. EACHO: Thanks, Liz. Matt, can you answer this next question?

Is it necessary to use GMP-grade materials and/or reagents for phase 1 and 2 clinical studies?

DR. KLINKER: Thanks, Melanie. The quality of reagents and materials you use is really critical to the quality of your product. We generally recommend that you use the highest-quality materials and reagents that are available and feasible for you to use. We frequently see these types of materials and reagents that are labeled with things like "GMP grade" or have statements claiming that they're intended for use in cell therapy manufacturing. I guess in general, those reagents are usually higher quality than maybe similar reagents that are not labeled with that. But the labels themselves, something like for GMP grade, really should be recognized as what it is, as a marketing term. It's not a recognized standard. So even if you're buying reagents that are labeled as GMP grade or intended for use in cell manufacturing, something like that, you still need to carefully look at those materials and make sure that they're appropriate for use in your particular manufacturing process. The information that you provide to us for these reagents that have these kinds of terms is really no different than any other reagent that we would just consider research use only.

That is, that you should provide assurance that the materials are appropriately controlled in the context of mitigating unreasonable risk to people that might receive your product. In most cases, there should be some kind of way of assuring that the materials are free from microbial and viral contaminants, whether it's some kind of sterilization or tested for sterility, and that any animal-derived or human-derived materials are from appropriate sources and are adequately tested for safety. I guess it's hard to give more specific information on types of reagents in this setting, but the 2007 FDA guidance document, the CMC guidance document we have, is a good place to go for more advice and insight into what we look for, for particular types of reagents. The full title of that is "Content and Review of Chemistry, Manufacturing, and Control Information for Human Somatic Cell Therapy Investigational New Drug Applications."

Thanks. Melanie, back to you.

DR. EACHO: Thanks, Matt. Bao, I'd like to ask you this next question.

What are the considerations for a cryopreserved cell therapy product containing DMSO?

DR. NGUYEN: Thanks, Melanie. When we see cryopreserved cell therapy products, that generally means that they contain DMSO, or dimethyl sulfoxide. When DMSO is used as part of the final product formulation, there are a couple of things that we want sponsors to keep in mind.

It's been shown that DMSO reagents can interfere with sterility testing and then potentially produce a false negative test result, where sterility failures are not properly detected in the presence of DMSO. When DMSO is used as a cryopreservation agent, we do ask that sponsors conduct two additional tests — one is bacteriostasis and the second one is fungistasis testing — on samples that include DMSO, just to show that DMSO does not interfere with any of the sterility tests, which are so important for cell therapy products.

It's important to keep in mind that the timing of sterility testing is also important because if a product is frozen before it's administered, then sterility testing should be done prior to cryopreservation. But if a product undergoes any manipulation — and this is kind of what Liz touched on earlier — then for the manipulations, which could be things like washing after thawing the cells, we do request additional sterility and endotoxin testing just to make sure that those additional manufacturing steps do not compromise the sterility of that final product prior to administration.

One other consideration is the stability of the cell therapy product when it's cryopreserved with DMSO. After thawing, reconstituting, and even removing the DMSO, the stability of the cells could still change. We do ask sponsors to consider evaluating the stability of the cellular product after the DMSO has been removed and after the product has gone through one or more freeze/thaw cycles. This type of stability data is best submitted to us during review under an IND. Then we can give you more feedback on that portion.
Thanks, and back to you, Melanie.

DR. EACHO: Thanks, Bao.

I see that we're at the end of the allotted time here. I'd like to thank you all for attending today's OTP town hall. I'd also like to extend a thank you to all our panelists.

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 the FDA website to read the FDA guidance document about cell therapy CMC and find other relevant resources. We plan to host our next town hall meeting later this summer and hope to see you all there.

As I mentioned at the beginning of today's town hall, we do encourage you to join us at the FDA's Regulatory Education for Industry conference, which will resume at 1 p.m. today, actually, in just a few minutes. We hope to see some of you there.

Thank you again for joining and have a great day.