

**UNITED STATES DEPARTMENT OF HEALTH AND  
HUMAN SERVICES Food and Drug Administration**

**FDA CBER OTAT Town Hall: Gene Therapy  
Chemistry, Manufacturing, and Controls**

**September 29, 2022**

*Note: This document is not official FDA guidance.*

# FDA CBER OTAT Town Hall: Gene Therapy CMC

## September 29, 2022

**DR. WILSON W. BRYAN:** Good morning, everyone. Thank you for joining us for our first 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 Wilson Bryan, and I am pleased to welcome you here today as we launch our new OTAT Town Hall series. Before we get started with today's town hall, I want to take a few minutes to share some announcements and information about OTAT.

The Office of Tissues and Advanced Therapies is one of the program offices within the Center for Biologics Evaluation and Research at the FDA. OTAT regulates a wide variety of products, including gene therapies, cell therapies, plasma protein products, xenotransplantation, and some devices. OTAT's mission is to promote public health through a collaborative, science-based process to help ensure medical products are safe and effective. Because of the recent growth of OTAT, and the growth that we expect in the coming years in the gene and cell therapy space, I am pleased to announce some updates to our office.

Over the next several months, OTAT will become the Office of Therapeutic Products, or OTP for short. OTP will be a super-office, with six sub-offices, including a dedicated Office of Gene Therapy CMC. This restructuring will enhance OTP's and CBER's capabilities to focus on our commitments to advance drug development and fulfill the FDA's mission of protecting and promoting public health.

As you have heard, today's town hall is the first in a new virtual series. OTAT is launching this virtual town hall series to engage with product development stakeholders and researchers to discuss topics related to OTAT-regulated products.

The town halls have a question-and-answer format, with the goal of providing regulatory information to stakeholders to advance drug development. We will cover a variety of topics at these town halls. As you already know, today's topic is gene therapy chemistry, manufacturing, and controls.

Before I pass it over to the moderator for today's event, I would like to share a few notes. This town hall is being recorded. The recording and event materials will be posted on FDA's website in the next few weeks. 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 will do our best to address as many questions as we can today, but please note that we are not able to comment on or answer questions regarding specific investigational products or drug applications. Also, we will not address any questions that we consider out of scope for the event.

Lastly, please use the chat box if you are experiencing technical difficulties. The chat box for technical difficulties, the Q&A box if you have questions to submit to the panelist. I'd now like to introduce Dr. Steven Oh. Dr. Oh is Acting Director of the Division of Cellular and Gene Therapies, who is the moderator for today's event. Steven?

**DR. STEVEN OH:** Thank you, Wilson. And good morning, everyone. Welcome to our town hall, where today's topic will be gene therapy chemistry, manufacturing, and controls, or CMC for short. As you know, the FDA requires sponsors to provide information about CMC as part of investigational new drug applications, or INDs; biologics license applications, or BLAs; and new drug applications, or NDAs. For gene therapies and other biological products, the CMC information should describe the sponsor's commitment to perform manufacturing and testing to assure product safety, identity, quality, purity, and strength, including potency.

During today's town hall, subject matter experts from OTAT's Division of Cellular and Gene Therapies will answer questions related to CMC for gene therapy product development.

I'd like to now take a moment to introduce today's panelists: Dr. Denise Gavin, who is Chief of Gene Therapies Branch 1; Dr. Kimberly Schultz, who is Chief of Gene Therapies Branch 2; and Dr. Anna Kwilas, Team Lead in Gene Therapies Branch 2. Thank you to 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. We will then respond to questions

that you are submitting during today's event. Due to the high volume of questions we received during registration, we will extend today's town hall by an additional 30 minutes. We hope you can stay on with us for the entire time, but I 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. 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 note: We're not able to discuss questions regarding specific investigational products or drug applications. We'll also not be able to discuss questions related to draft guidance documents under public commenting period or under revision for final guidance document publication.

We'll start with questions submitted in advance. We'll start with a question for Denise.

***What are the major CMC considerations between first in human studies in late phase studies that are intended to support the marketing approval? Are OTAT expectations more strict than other FDA divisions?***

**DR. DENISE GAVIN:** Welcome, everyone. The main concern for phase 1 studies is to ensure the safety of participants. Phase-appropriate CMC expectations were published and outlined in a 2020 gene therapy CMC guidance. This guidance references many FDA and ICH guidance documents. Hopefully, we're consistent with that. For first-in-human studies, the materials used to make the product should be qualified as suitable for clinical use.

We also want to make sure that the clinical material is comparable to the preclinical material so that we can ensure that the preclinical safety data is applicable. The product and the process should be sufficiently described in your IND and supported with data so that we can assess product safety. And as clinical development progresses, the expectation is that product characterization and controls need to increase at the same pace.

Regarding CMC expectations and whether we're stricter than other agencies, CMC expectations for INDs and BLAs are broadly applied across all CBER review divisions. I don't think, in general, our expectations are stricter. However, our consideration of risk-benefit is often complex. About 50% of our products are for rare disease indications with currently no available treatment. Some of the things we consider in our risk-benefit

analysis include the fact that many of these products are often administered [at] one time at very high doses intended to have a long-term or lifetime expression. Since you only get one shot at administration, it's important that you don't have a low quality, which will limit your successful development. Some products also have well-documented toxicities, so we need to consider this also in our risk-benefit analysis.

Many gene therapy studies often include pediatric subjects. When pediatric subjects are included, you need to have a prospect of benefit. Product quality needs to be controlled to ensure that all participants receive a similar product of defined quality.

Another thing that we consider is that recent clinical successes have resulted in gene therapy products being developed at an increasingly accelerated pace with many trials not designed as typical phase 1 studies. Therefore, we really consider the CMC information in the context of a clinical trial design. For instance, if a clinical protocol is listed as a randomized, placebo-controlled, double-blind study for a rare disease in 50 subjects, we're pretty much going to assess the CMC information a little bit more stringently than if it's a typical 3+3 dose escalation study.

There'll be another question on later-phase studies, and Kim will go into that. One of the main things we want for you to keep in mind is that product development should keep pace with clinical development. Thank you. Back to you, Steven.

**DR. OH:** Okay. The next question is for Kim.

***What is the “must-have” and “good-to-have” CMC information for a gene therapy product going into phase 3 IND studies or late-phase studies that intend to support a marketing approval?***

**DR. KIMBERLY SCHULTZ:** Thanks. That's a good question, especially as I think we can all agree we're in an exciting time in the gene therapy field, where there's a number of products that are entering late-stage development. In addition to safety, which is our main concern during early-phase studies, late-phase studies should reflect the planned commercial setting so that you can support interpretation of the clinical study data in order to assess the product's efficacy.

The gene therapy CMC guidance does provide some insight into these phase-specific expectations. But I'm going to highlight what you might consider some must-haves and good-to-haves here.

First and foremost, you must have qualified assays, including a potency assay, in place prior to initiating studies that are intended to provide the primary efficacy data for licensure. And so we do assess that based on the clinical study design, as Denise said. As many times, our products don't have what would be called a formal phase 3 study. And so for these late-stage studies, you should also have appropriate CGMPs in place in order to support the product quality and facility control.

Our general advice is that you should determine where the variability and risk are possible in your process. And then, through that risk assessment, you should ensure that you have the controls in place in order to reduce the variability of your product. And this is going to be assessed on a product-by-product basis. For instance, for a fresh cell-based gene therapy, shipping validation should be conducted in order to support that the product quality is not affected from the time of release to the time of delivery and administration at the clinical site. For an AAV vector, the product should be formulated using a nominal titer so that you can gain experience with the commercial dosing strategy. And that can be part of the interpretation of the efficacy assessment.

Overall, we recommend that you move to the expected commercial configuration prior to conducting this pivotal study. And this will reduce the risk in your developmental process. This includes using the intended commercial manufacturing process at the intended manufacturing facility and using the expected lot release testing strategy. And this will position you to have the maximal data at your disposal to use for your license application. And it's also going to reduce the complications related to comparability assessments that may occur during the BLA review.

**DR. OH:** Thank you, Kim. The next question is for Anna.

***What is the current thinking about drug compatibility related to delivery devices? In general, would the same acceptance criteria as lot release of the drug product be sufficient for drug compatibility? Does the OTAT consider human factors in using delivery devices?***

**DR. ANNA KWILAS:** Thanks, Steven, and welcome, everybody. The main goal for device/biologic compatibility is to demonstrate that administering the drug product using the delivery device won't negatively affect the product's quality and then also that you understand the quality of the product that will actually be delivered to the patient. Compatibility studies should be collected with the final formulated drug product under the worst-case conditions expected in the clinical trial. That includes, say, thaw

conditions, any dose preparation procedures, duration of storage after preparation, your dose or volume range, a flow rate or pressure, duration of delivery, the temperature, the simulated delivery into the worst-case target tissue anatomy, and other things as applicable as far as risk assessment that's performed to what could potentially affect the compatibility of the drug product with the device.

For vectors, you really want to know if there's any vector adsorption to the device, so you'd think about evaluating your vector titer, so whether it's genome or infectious titer, before and after exposure to the device, or any effect on vector activity — for example, measuring your transgene expression or performing your potency assay before and after exposure to the device. The compatibility data really should inform and instruct the instructions for product handling that's provided to the pharmacy as well as the clinical administration site.

As far as using the same acceptance criteria as lot release for your drug product for the device compatibility study, this is really going to depend on how wide the lot release acceptance criteria are. While the product should meet the lot release acceptance criteria following passage through the delivery device, it may be better to establish acceptance criteria for how much product loss is actually acceptable for you to still maintain your product quality and your intended product dose.

Regarding human factors testing, yes, we do work with the Human Factors group here at FDA when warranted. We generally will request a human factor study to be performed on the delivery device if there are special circumstances involving the actual use of the device or if it's a very specific use of a device. And so for that, like I said, we consult with the group here that specializes in human factor studies. And so that should definitely be discussed early on with the FDA team if you believe there is going to be a need or whether we infer that there'll be a need for a human factor study. We'll discuss that early with the sponsors as well. Thanks, Steven.

**DR. OH:** Thanks, Anna. The next question is for Kim.

*In light of technical and logistical challenges specific to autologous cell-based gene therapies, what is the expectation on formal process characterization? For example, design of experiment type studies?*

**DR. SCHULTZ:** I do expect that process characterization studies are conducted to find manufacturing process for autologous cell-based gene therapies. In most cases, it is appropriate to show that the healthy donor material is representative of the patient's

specific process. And then you can use healthy donor material for these process development studies. And this generally allows for you to explore a wide range of different parameters within the process in order to understand how they affect your manufacturing process. And this can allow you to define the parameters for your commercial process for it to be successful and more consistent when using the autologous starting material.

We do understand that there may be some instances, particularly when the introduced gene replaces a missing gene, but not all attributes may be tested in products manufactured using a healthy donor material. This is most often encountered, for instance, with potency testing. But there are other aspects to the manufacturing process that may be affected.

And so in this case, we would recommend that you should evaluate some small-scale manufacturing studies and see if those can be used to support manufacturing process characterization and allow you to gain the necessary information while maximizing the use of patient-derived starting material. And in these specific cases, it may be beneficial to discuss such limitations with your FDA review team prior to initiating these critical studies.

**DR. OH:** Thank you, Kim. The next question is for Denise.

*In the context of rare diseases, where it may be viewed as essential for clinical data from every study participant to contribute to a determination of efficacy, could OTAT please outline the strategic approach it recommends to sponsors for assuring that CMC development is sufficiently mature to support use of clinical data from every study participant receiving the test article in determining clinical effectiveness?*

**DR. GAVIN:** Sure, I can speak to that. In 2020, we also published a guidance on gene therapies for rare diseases. In this guidance, we outlined strategies that can be used to leverage your clinical data from every subject in order to determine effectiveness. We recommend that sponsors, before they administer any product, that they establish a well-controlled manufacturing process and qualified analytical test.

In that guidance, we also recommend strongly that you plan ahead and you consider the long-term demands of the disease indication when designing your process. Sponsors often make significant changes late in development. This introduces uncertainty in the development program, as analytical comparability is not always

sufficient with complex gene therapy products, because you can't measure certain things like immunogenicity or toxicity. And those are the things that can sometimes occur with late changes.

So, what do you need? We also want you to think in advance what you need your process to do. Do you really need large-scale production, or could smaller batches be sufficient? For instance, is a large-scale, 200- to 2,000-liter scale vector needed for a small rare-disease population? Can the process that you design actually meet future clinical demand? You think about the current population and then the precedents of the disease and how much you're actually going to need.

One of the other things you can think about when you're designing your process is the route of administration. If you're going intrathecal, you'll be constrained by volume, or if you're going IV, you may be constrained by immunogenicity concerns. You need to think about your formulation early and how that's going to affect the route administration.

If scale isn't an issue because [of] it being a rare disease and maybe you need much lower titer or much fewer doses to treat the population, you may want to focus on impurity removal. This may reduce the need to adjust the process later in development to reduce toxicity. These considerations in designing your process early in development can help you with being able to use that data from every patient.

One of the things we think that you could do to help you gain process control early in development is to leverage knowledge you have from other similar products you've manufactured from preclinical lots, from small-scale development studies, as Kim was mentioning, and engineering runs. These runs should all look at process variability. You can gain a lot of information from these small-scale runs. You can also tweak the process in those development environments where it's low risk so you can understand which critical process parameters affect product quality, if you really need to have this process under control before you start a clinical trial, if you're going to use every single subject.

And then you may want to look into the possibility of developing multiple clinical lots so that you can understand variability in the product and how it affects the clinical trial results. And this could also help you set commercial specifications so that you're developing both the product and the clinical trial at the same time.

One of the most important things for getting ready for a trial where you want to use the data from every subject is to make sure that your analytical methods are under control. Variability in the methods can cause a big problem when you're trying to interpret the clinical data. You won't know whether the product is variable, the process is variable, or it's just inherent variability due to the disease. Early qualification of assays to characterize the product are critical to program success.

One of the most important things you need early on in development, if you're going to use the phase 1 study information to support a licensure is to demonstrate potency early. You need a suitable potency test early, and we'll talk a little bit more about potency later today. But it's important that you study multiple product characteristics while you're developing your process to gain an understanding of which product attributes are related to activity. And while developers have many considerations when developing their products, including cost, FDA recommends that product quality be a top priority at all phases of development. Thank you. Steven?

**DR. OH:** Thanks, Kim — Denise, sorry. The next question is actually for Kim.

***Since gene therapy products are complex and may have limited manufacturing data, what are the expectations around setting commercial specifications with limited experience?***

**DR. SCHULTZ:** Thanks, Steven. We generally recommend that commercial lot release criteria should be based on lots that are shown to be safe and effective during the clinical study. And this approach will allow you to evaluate correlations between product attributes and clinical outcome. And to this end, we really recommend that you use multiple lots during your clinical study, if possible, even if one lot would be able to treat everybody in those pivotal studies.

And so one way to facilitate this would be to conduct PPQ runs and use those PPQ runs during the pivotal study. And so then you're really getting more bang for your buck with those lots. These data should be used to determine the commercial lot release criteria and to ensure product consistency and quality.

And so that's really describing the ideal situation. And we realized that this may not be possible for all products, especially those made for rare diseases. And so this is where our conversation becomes much more product-specific. And as Denise mentioned, you can consider leveraging data from multiple drug substance lots in relation to your drug

product or design your manufacturing process to allow more drug product lots to be used during the clinical study.

And really, if you believe that the amount of data that's going to be available to set the commercial lot release criteria is going to be a problem, particularly for your product, and we encourage you to come in early and talk to your review team so that we can formulate a plan on how to move forward to get the most information possible in order to set the commercial lot release criteria.

**DR. OH:** Okay. Thank you, Kim. The next question is for Anna.

*On what basis does the FDA require the use for U.S.-licensed HSA and not allow the use of EU-licensed HSA, as an ancillary material in the manufacturing of gene and cell therapy products? Neither HSAs are manufactured from plasma collected in countries with TSE-related risk (UK, France, and Ireland), and both utilize a similar questionnaire to verify if the donor stayed in TSE-related risk countries in the relevant years.*

**DR. KWILAS:** Thanks, Steven. This is a question that we get a lot. While we do consider other factors — so not just TSE risk but factors such as viral inactivation reduction processing steps, whether FDA-approved tests were used to test the donor material, and whether testing was performed in CLIA-certified labs, other than — like I said, other than just TSE risk, the FDA is becoming more flexible, 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 that's licensed in the U.S.

This is particularly the case whenever the HSA is used as an excipient, since it will be directly administered to the patient. However, if you do choose to use a version of human blood-derived HSA that is not licensed in the U.S., in upstream manufacturing you may be able to do so, provided that you're able to submit information supporting that donor eligibility, including donor screening and donor testing. The albumin manufacturing and the appropriate product standards do conform with that of U.S.-licensed HSA product, as described in 21 CFR 640.80 through 83.

We're really happy to become a little bit more flexible on this, and hopefully that will alleviate some issues that some sponsors have been having. Thanks, Steven.

**DR. OH:** Thanks, Anna. The next question is for Denise.

***What is the FDA's position on performing identity testing as a requirement for raw material release to manufacture gene therapy products in clinical phases? Can risk assessment be used to support not performing identity tests for some materials?***

**DR. GAVIN:** That's a good question. And we had several versions of that question come in. And so I'll try to address that.

During phase 1 studies and early investigational studies, sponsors may follow the phase 1 GMP guidance, which outlines CBER expectations for phase 1 studies. This guidance gives you information to focus on how the manufacturer's quality unit controls and documents operations in the facility, as well as how product quality is maintained. In this case, a risk assessment may be used to qualify materials. However, if critical materials such as plasmids or cell banks, which really are not verified — it could jeopardize the manufacturing process and delay clinical development, so mix-ups do occur, and we can trust, but we recommend that you also verify.

By the time you start your phase 2 studies, there's an expectation that manufacturers will operate under the GMPs outlined in the 21 CFR 211. Compliance with GMP requires that materials such as components and container starting materials — raw materials used in the manufacture of the drug product — when they come into the GMP facility, are tested to verify identity. This is 211 84-D:1, to use Anna's vernacular and conformity to specifications that for purity, strength, and quality; this is 211 84-D:2. Specifications for raw materials and plasmids and such are determined by the nature of the material and the needs of the manufacturer.

As an alternative to some of the conformity of the specifications in the regulations, a sponsor may rely on vendor information for confirmation of purity, strength, and quality. And this is if they perform a specific identity test, so if you do identity testing, and that the manufacturer has confidence in the supplier.

How is confidence gained? Confidence is gained through a prior history of quality assurance and testing verification of specific vendors. Manufacturers may perform a risk assessment as part of your vendor qualification, but please keep in mind that you still need to verify identity. Thank you.

**DR. OH:** Thank you, Denise. Next question is for Kim.

***Do QC reagents used in the release testing of drug product lot have to be GMP grade? Can research-grade QC reagents support late-stage drug product testing?***

**DR. SCHULTZ:** Thanks, Steven. Controlling the QC lab is just as important as controlling the manufacturing space. In this case, the reagents that are used in quality control testing should be well-controlled and fit for their purpose. This means that they should be qualified for use prior to your incorporation into the QC lab operation. In general, assay controls should be increased as you progress through the different phases of your clinical development. To support this, you may determine that higher-quality reagents are needed to support consistent assay performance or the in-house qualification of reagents are sufficient to support assay performance.

The controls may be incorporated on many levels to support the consistent and successful quality control testing. For instance, you can incorporate system suitability controls that confirm the consistent assay performance with each run, and this can help to make sure that your reagents are functioning properly.

Furthermore, as we move into assay validations, you should include robustness studies to understand how perturbations in the normal assay methods impact assay performance. And while robustness should touch on a number of different points within your assay control and the different parameters in which your assay can function — but it's really important that these robustness studies also evaluate the impact of different reagent lots and how that may affect your assay performance. Thanks.

**DR. OH:** Okay. Thanks, Kim. The next question is for Anna.

***For induced pluripotent stem cells, if the gene editing is done in a research lab that is not a GMP-like environment to generate a gene-edited clone, which will then be used to produce the GMP-grade master cell banks tested for the cell bank requirements and then differentiated into an iPSC-derived cell therapy products, will that clone be considered acceptable for use in phase 1 clinical studies? Could the same master cell bank be used to produce clinical materials to support phase 2/3 trials as well as to support commercial manufacturing if the product is approved?***

**DR. KWILAS:** Thanks, Steven. We did get a lot of questions about induced pluripotent stem cells. I'm going to hopefully be able to answer a few of them today. We'll start with this one.

In theory, yes, you may be able to use a clone derived under non-GMP conditions to make a master cell bank under GMP conditions that can be used throughout your clinical development and possibly commercial manufacturing. This is really going to be dependent on whether you can provide sufficient information on the controls that were in place when and where the initial genome editing and cloning was performed.

For those who have submitted files, you'll notice we ask a lot of questions about this. And so we really want to see the quality of the materials, standard procedures, and adequate segregation that was used during those initial steps of editing and to produce that original clone and to test the clone as well. If sufficient information can be provided, then there shouldn't be an issue with using that clone throughout development.

Kind of as a little caveat I'll add to this is, I think that sponsors really need to consider whether they're going to need to perform these steps more than once, whether they think they're just going to be able to have to manufacture one master cell bank and that's going to be good to go for their clinical development and for their future commercial as well. If you don't think so and you think you're going to have to manufacture more than one master cell bank from multiple different clones or from the same clone, again, these are things that we'll need to consider when we're asking for this information as to how many times are you going to have to go back and do these processes during clinical and commercial development. And so those are conversations that we'll have on a product basis. Thanks, Steven.

**DR. OH:** Thanks, Anna. I think we have another question for you, Anna. It might be somewhat related.

*The question is, all allogeneic induced pluripotent stem cell-derived gene therapies, sponsors would like to understand the quality and documentation required for research-use-only-grade gene-editing reagents. For example, CRISPR reagents, guided RNA, lentiviral vectors, or plasmids. If research-use-only gene-editing reagents are used in the gene-editing step of the iPSC and certain testing details of the manufacturing process for these reagents are not available to support the IND, would the lack of documentation and testing of gene-editing reagents be a clinical hold issue?*

**DR. KWILAS:** Thanks, Steven. In addition to having lots of questions about iPSC, as I know we have a lot of questions about reagent quality and things associated with that. And so FDA really doesn't recommend the use of research-only reagents or materials anywhere in the manufacturing process of a clinical product, for obvious reasons. This

really comes down to whether a sponsor can provide sufficient information on the controls in place for the manufacturer of these critical materials and starting materials and reagents to assure that the quality of these materials are appropriate for the development of a clinical product, even for the early stages of product manufacture, such as in this case of manufacturing the initial iPSC clones.

For this type of product, that would include brief descriptions of the manufacturing processes for these materials, the appropriate quality control testing, in addition to a CoA, which we generally always get for these materials. We may be able to be a little flexible if they're used in this instance — say, for example, used once to make iPSC clones, and then the clones are further manipulated. However, this will depend particularly on the testing that's performed as part of clonal selection and then also as part of master cell bank qualification.

In this case, we really do recommend that you provide this information on your testing plans, not necessarily in detail, but testing plans for each stage of this type of multistage product manufacturing and justifications for the testing that's performed on the materials as well as the clones and then the master cell bank early on in product development — for example, in an INTERACT meeting or pre-IND meeting — and that way we can ensure that sufficient information is going to be provided in your IND to avoid a clinical hold. Thanks.

**DR. OH:** Thanks, Anna. The next question is for Denise.

**Could OTAT comment on the expectation for starting material plasmids used to make factors such as drug product or for genetically modified cells in relation to GMP status at the time of BLA, including whether the level of details to be provided in the BLA is equivalent to what is expected for a drug substance and whether qualification of analytical method used for release of plasmids would be deemed acceptable?**

**DR. GAVIN:** Thanks, Steven. I guess there seems to be a theme about materials coming into the GMP facility and what our expectations are. I can continue on this.

The U.S. regulations do not require that plasmid starting material be made under strict GMPs, nor that the level of detail for these materials is the same as a drug substance. For instance, you put the plasmids' starting material information into a subsection of Module 3 for the drug substance in the controlled materials. This just kind of gives you a hint about how much detail would be there. You need to keep in mind that the plasmid

quality is critical to drug product manufacturing, and the individual manufacturer should set standards as needed for all the materials that come into their facility. This helps them ensure that they can reproducibly make their product.

Part of the question was qualification of methods. Methods used at the vendor should be determined to be suitable for use and to ensure that the quality of the plasmid meets predefined specifications. These specifications are generally determined by the GMP manufacturer with plasmid quality attributes in mind that we would normally expect for a plasmid. Qualification of assays is often sufficient for starting materials, but individual manufacturers, again, may have their own expectations for assay validation or qualification performed by vendors. We recommend that these concerns be outlined in the quality agreement with your suppliers.

Also, if the plasmid vendor has a master file, it may be cross-referenced in an IND or BLA if the master file has sufficient information in it to support control of the plasmid quality and the ability to manufacture a licensed product. This is important that you have sufficient information to cover that.

While the plasmid itself does not need to be made in a GMP environment, the vectors do. Therefore, the vector manufacturing site must comply with GMPs, and I discussed earlier — and I think several other panelists have as well — the starting material coming into the facility to manufacture the drug substance/drug product must be tested to verify identity and conformity with specifications for purity, strength, and quality. I already mentioned the reg, so I won't go there.

As previously outlined, the facility may rely on a vendor for qualification, but they must verify identity. Responsibility relies at the GMP facility to ensure that only materials of specified quality are brought into their facility. And the quality and testing of incoming materials will be verified at inspections. Keep that in mind. Thank you.

**DR. OH:** Thank you, Denise.

**DR. GAVIN:** BLA inspection.

**DR. OH:** The next question is for Kim.

***What facility controls are expected for manufacturing of phase 3 biologics? Does FDA inspect manufacturing facilities?***

**DR. SCHULTZ:** Thanks, Steven. I think everybody can see that we did get a lot of questions related to CGMPs, and so I'll continue on that theme as well.

The OTAT is consistent with the rest of the FDA, in that phase-specific CGMP are expected for all phases under a clinical study. And so there is an FDA guidance that explains the CGMP expectations for phase 1 studies, and so we would recommend that you would consult that, and then we do expect an increasing amount of information and control is provided as product development progresses.

And so specifically for late-phase studies, as I have said earlier, it's really ideal to manufacture what you would expect or are going to propose for your commercial process. And that really relates to CGMPs as well. There should be proper control as defined in the 211s. And this will help ensure both product safety and quality. The 211s go into specifics on a number of things, including proper material control, environmental monitoring, segregation and tracking, change controls, deviation investigations, written procedures, quality control, quality assurance — I mean, it's all there.

I also would like to point out that many of the studies use product that's made using a contract manufacturing organization and contract testing organizations. And so it's important to understand that as the sponsor of the IND, it's your responsibility to make sure that GMPs are being followed there and that the data that's going to be collected from that product is going to be able to support your studies and your interpretation of your clinical study data.

And so as far as inspections though, we generally conduct inspections of manufacturing facilities during the BLA review period. And so at this time, we would be looking into the CGMP control at the manufacturing facility deviation, reporting, and control in the manufacturing process itself.

And then, following licensure, the FDA does conduct surveillance inspections, biennial inspections, or additional inspections if it's warranted. And this can be for a number of reasons, including if there's a supplement to a BLA that would introduce a new manufacturing facility. Thanks.

**DR. OH:** Thank you, Kim. We'll go to the next question, which is for Anna.

***Please clarify that only 21 CFR 1271 and not full GMP would apply to the collection of allogeneic cellular starting material.***

**DR. KWILAS:** Thanks, Steven. As Kim mentioned, to kind of follow along with our discussion of GMPs, in the case of allogeneic cellular starting material, that's correct — that you will need to adhere to 21 CFR 1271 Subpart C, although you will not need to collect the material under full GMP conditions. We do recommend that you implement standard procedures for the collection, the storage, and the shipment of the material, particularly if collection is taking place at multiple sites. And that's particularly to improve the consistency of the starting material and the resulting drug product.

And of course, I think it's been mentioned previously: The requirement for adherence to GMPs will start at the manufacturing sites. And so this includes the qualification testing that's performed on the starting material upon receipt of it at the GMP mean or at the drug product manufacturing site. Thanks, Steven.

**DR. OH:** Okay. Thanks, Anna. There is a follow-up question, actually. It's about the allogeneic donor cells.

***The question is, can donors for allogeneic cell therapy products be from outside the United States?***

**DR. KWILAS:** Thanks, Steven. Yes, donors for allogeneic cell therapy products that are genetically modified can be outside the U.S.A. However, you will still need to adhere to the donor screening and testing requirements outlined in 21 CFR 1271 Subpart C and, of course, the applicable FDA guidance documents for adventitious agent testing.

In the event that you're unable to adhere to any of these requirements, under 1271.155A, you may request an exemption from or an alternative to any requirement in Subpart C of 21 CFR 1271. This exemption request must contain either (1) information identifying the requested exemption from the specific requirement or (2) a description of the proposed alternative testing to meeting that requirement. This includes supporting documentation, relevant scientific data, as well as the strategies implemented to mitigate the risk of communicable disease transmission associated with that lack of screening or testing.

For more information on requesting exemptions, you can also refer to the exemptions and alternatives section of the guidance document, *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*.

We also strongly recommend that you submit an exemption request at the pre-IND stage or at least 90 days prior to submitting your IND in order to ensure adequate time for us to review your exemption request if that is something that you need to do. Thank you.

**DR. OH:** Thanks, Anna. We're going to shift gears a little bit and discuss a little bit about potency. The first question in this topic is for Denise.

***Has the agency shifted away from the potential to utilize a potency matrix that can be used as a surrogate for function to a firm stance that a quantitative functional assay is required? If not, how could a sponsor leverage a potency matrix in place of a quantitative functional assay? Would this approach be acceptable for BLA submission?***

**DR. GAVIN:** Thanks. That's a good question. We had several questions on potency, so I'll try to give a general — and then maybe we'll address one more specific question that Kim might suggest — I'm going to do.

General recommendations for potency testing and requirements are outlined in detail in the 211 potency guidance that we published. The guidance outlines phase-appropriate flexible approaches, but it tries not to be too prescriptive, so we couldn't give too many examples about specific potency testing because of the diversity of cell and gene therapy products.

One thing to keep in mind is that potency is required at all phases of product development, according to the Food, Drug, and Cosmetic Act. We generally accept quantitative measure of gene expression for first-in-human studies — early-phase studies. As your product advances in clinical development, the expectations are that the potency tests should be refined to measure a biological activity of the product per the regulations. The test should demonstrate that the product is capable of affecting a given result, and for this, we interpret that to mean that the product is functional and based on what you expect it to do.

We understand that some sponsors may have difficulties establishing a single suitable test for products with very complex mechanism action or number of activities in the product, which is why we recommend that you begin thinking about product characterization and potency assay development during your early clinical development. Ideally, during your preclinical development when you're designing your proof-of-concept studies, you really need to start thinking about this from the beginning.

A quantitative test that measures the biological function of the product is expected prior to the initiation of clinical studies meant to support efficacy for a marketing application. And the validation data should be submitted with your BLA. How this test is implemented, whether it's a single test or a product function or a matrix, as outlined in the question, is very product-specific and should be discussed with your review team early in development.

The suitability of a surrogate? Well, we don't absolutely require only functional tests. We do think that that's the ideal, and that is actually what's expected. If you want to use a surrogate approach to support your phase 3 studies or licensure, you have to comply with a number of product-specific considerations. Some of these include whether — that you should think about whether the tests and the matrix measure meaningful CQAs. How relevant is the functional test that you're using? If this is a semi-quantitative test, does it measure meaningful data that contributes to the overall potency assessment? It's important that this actually be a real measurement of the function. Whether your tests are quantitative, whether they're precise and specific to the product — these are all put into the consideration. How well the tests are correlated to the expected functional activity of the product — and what kind of data are you planning to submit for the statistical analysis that would be used to support correlation studies? If you're not planning to submit a quantitative functional test in your BLA, you need to have very strong correlation studies to support any other matrix approach.

These questions should all be considered when you're designing your matrix approach for potency testing. If there's insufficient supporting data, if the assays in the matrix are not controlled or have exceptionally wide acceptance criteria that provide no meaningful measure of activity, we're much less likely to accept this approach.

As this is a very important topic, we recommend that you discuss this with your review team early in development. Don't wait until you're ready to come in for your registration study and then find out you don't have an adequate potency test. It's so important to product development that you'll see potency comments in INTERACT meetings and pre-IND meetings. Think in advance and work hard on getting the data you need to support whatever potency test you submit. Thank you.

**DR. OH:** Thank you, Denise. Next question is for Kim.

***Could CBER elaborate on the current expectations for potency tests for viral vectors used for ex vivo modified gene therapy products? Specifically, when***

***during clinical development does CBER expect that potency should be included as a part of lot release testing rather than as characterization?***

**DR. SCHULTZ:** Thanks, Steven. We do believe that transgene vectors used for ex vivo modified gene therapy products are critical to the activity of the drug product. And we do consider them critical components because of this, and this has really described in the gene therapy CMC guidance — that without the vector, the resulting product would not have the same pharmacological activity. And therefore, the activity of the vectors should be demonstrated as part of the vector lot release testing.

As Denise just talked about, we do have some flexibility in when you would introduce a biological potency assay for these factors. And so for early phase studies, you may use a transgene expression assay in lieu of the biological potency assay. However, similar to the drug product expectations, potency assays should be established and qualified prior to initiating the pivotal studies. And really, for the timing of implementing your potency assay for the transgene vector, we really would recommend that you implement it as early as possible so you can gain experience with it and gain information in order to inform lot release testing or specifications for the commercial setting. And so that could mean that you could implement your potency assay earlier on in development and during those early-stage studies, have it as report results, and then refine that acceptance criteria as you move on to the later-phase studies. Thanks.

**DR. OH:** Thank you, Kim. We're now going to discuss a little bit about manufacturing changes and comparability. The next question is for Denise.

***Which manufacturing changes will make a product be classified as “new product”?***

**DR. GAVIN:** Thanks, Steven. Generally speaking, manufacturing changes — they do require risk assessment and associated comparability studies if they're appropriate, but as outlined in our draft guidance, *Studying Multiple Versions of a Cellular or Gene Therapy Product*, unless you make a design change, we don't really consider manufacturing changes to be a new product. Design changes are outlined in the multiple-versions guidance, and that's draft now but will be finalized hopefully soon. If you make manufacturing changes, you may need to do a comparability study, and the results of that study could affect how a clinical data is reviewed. And I think the next question will cover this in more detail. Thank you.

**DR. OH:** Yes, thanks, Denise. Let's go to the next question, which is for Kim.

***What is the FDA's expectations for comparability assessment — for example, when there is a change from an adherent to suspension manufacturing process for viral vectors or a change to a new vector manufacturing facility or contract manufacturing organization?***

**DR. SCHULTZ:** Thanks. We did get a lot of questions that were about comparability studies, and we have found that most development programs do include changes in the manufacturing process during development or in a change in the manufacturing facility, such as moving from an academic facility to a more commercial manufacturing facility. And so we wanted to try and address this as best as possible here.

First and foremost, I want to say that we do acknowledge that this is a hot topic and that we are developing a guidance that pertains to comparability assessments. It's announced on the CBER Guidance Agenda. And so we hope to have that sometime in the near future in order to help our stakeholders.

At this time, we recommend that you apply the basic principles described in ICH Q5E when you're assessing comparability, and specifically, this means that you should start with a risk assessment. And this should be conducted to identify the impact of the proposed change or changes, and it should also inform the level of studies that are needed in order to support that change.

I think it's important that we remember that the goal of a comparability study is to demonstrate that there's a lack of an adverse effect on product quality. And the comparability study is needed in order to be able to combine the clinical data that's generated with the pre-change and the post-change product. And so with that in mind, the level of risk for introducing changes increases as you move further into the clinical study timeline, because it's going to affect how much data was generated — how much clinical data was generated with the pre-change product. And so our major recommendation to you is that you implement changes in your product manufacturing as early as possible to reduce the risk to your development program.

We consider both of the examples that were given here — a change from an adherent to a suspension cell production system or a change in the manufacturing facility — to usually be substantial changes. And we would generally expect comparability assessments to be conducted, in addition to developmental studies that should be conducted in order to support that change. And so from the developmental studies and the risk assessment, you should be able to rank the different product characteristics and

risks associated with them and determine the level of evaluation that's needed for each characteristic in the comparability assessment.

And I really like to emphasize that release testing alone is not generally sufficient to assess comparability. And we would expect that there's additional characterization testing, or in-process testing is going to be conducted. And that's really where you need those and what that additional testing needs to be — should come out from your risk assessment and your developmental studies. And so that comprehensive package together is going to support the determination of whether or not the products are comparable, whether or not there was an adverse effect on the product quality.

And so, for example, a vector that's made from an adherent cell line is likely to incorporate different cellular proteins than vector particles that were produced from a suspension cell line. And this is really due, if you think about it, to the inherent differences in the production cells, allowing them to have the inherent or suspension properties. What you need to think about — how that may affect your vector itself, including if it affects the infectivity characteristics of the viral vector. And so, to support the assessment of these manufacturing changes, we recommend that you include characterization testing during early-phase studies that so many — or so oftentimes, those early-phase studies are going to be needed to support the comparability assessment.

You also should keep retains from early lots for side-by-side testing of the pre- and post-change product if needed. And this is particularly important if there's changes in the analytical methods during development as well.

Additionally, I just want to point out that if the changes are in vector manufacturing for a transgene vector that's used for ex vivo modification of a cell-based gene therapy, then in most cases, the comparability study should also assess the effect on the final cellular drug product as well. Thanks.

**DR. OH:** Okay. I have a follow-up question for you, Kim.

***Please discuss acceptable comparability approach for CMC manufacturing changes during clinical development, specifically to statistical rationale used to assess comparability.***

**DR. SCHULTZ:** There are a few different ways that you can design your comparability study, and you should really think about the rest of your product when you're

determining the proper design. And so in all cases, though, the statistical power of this assessment is going to be driven by the number of lots that you have data for. And we recognize that this can be challenging, particularly when you only need a few lots in order to conduct your clinical study or when it's early on in development. And so you need to think about that as you're moving into your comparability study.

Additionally, there can be complications in your statistical analysis if the attributes are variable or if the results are not normally distributed. And so I'm going to offer some general advice, but first and foremost, we recommend that you think about if you have any of these limitations — that as you're starting to design your comparability study — and that you consult with a statistician to help determine the best approach for your particular situation.

And so specifically we recommend a couple different designs be used. And one of these is that you may do a comparison of historical pre-change testing to newer data from post-change lots. And we just want to point out that this can only really be used if the analytical methods have not changed. And if there are changes to the analytical methods, then you should conduct testing of the pre-change and the post-change lots using the same method, really to reduce variability in your comparability study. It's ideal if that testing is performed side by side.

For products that are made from donor- or patient-derived starting material, we recognize that the drug product attributes may vary from lot to lot due to the inherent differences in the starting material. And so we recommend that your comparability study isolates the differences in the manufacturing process. And so to do this, you should use a split cellular starting material design. And this will allow you to use a paired difference analysis for the comparability assessment. And so this will take out the variability that's associated with the starting material.

It's often appropriate to use an equivalence approach to evaluate the comparability. When you're really getting into the statistical approach and for this, it is important to have normally distributed data. And this is where talking to a statistician would be helpful if you don't have normally distributed data. And so for an equivalence approach, you can establish a range for the allowable difference in the population means, and in this case, exceeding that range would have an adverse effect on product quality.

Alternatively, you may use a quality range approach where you evaluate post-change results fall within a defined range. And this quality range approach is generally more acceptable for lower-risk attributes, as it's not as robust of an assessment.

In both cases, the equivalence acceptance criteria should be predefined before you start your study, and it should be based on your product knowledge. Once again, we do understand that this is a challenge for the field, and I've said a lot of technical things in that response related to some of the statistical approaches that we do recommend, and so we are developing that guidance. And we oftentimes do discuss these approaches with sponsors in the context of the IND, since there are a lot of product-specific considerations that you need to think about as you're designing your comparability study. Thanks.

**DR. OH:** Thanks, Kim. Thank you to all who submitted the questions during the registration process. We will now spend the remainder of today's event answering your live questions. I believe the first question is for Denise. Let me pull up the questions here.

***The first question is, does OTAT feel the gene therapy field need to start thinking about issuing method recommendations for assessing full, partial, and empty capsid ratio percentages?***

**DR. GAVIN:** Thank you, Steven. We don't routinely recommend product specific methods for non-compendial tests. However, we encourage sponsors of regulatory submissions and manufacturers to use appropriate voluntary consensus standards on developing methods. If a voluntary consensus standard-developing organization wants to develop a standard, they can submit that to CBER for recognition and consideration. Additional information for a CBER program on voluntary consensus standards, see the draft guidance on voluntary consensus standards. For regenerative medicine, we released that guidance in June 2022. And for additional information, there's also a 2019 guidance on standards development for regulatory submissions that you can also access to get more information about the development of such standards for methods regarding empty capsids. Thanks.

**DR. OH:** Okay. Thanks, Denise. The next question is for Kim.

***Can the panel comment on the office's preferred pathway for sponsors to ask focused questions on CMC development topics — for example, via a form of type B or C meetings or submit directly to the IND?***

**DR. SCHULTZ:** This is a really good question. And I think that it does really depend on specifically what you're asking in the phase of development of the product itself. For

instance, since I'm thinking about comparability from the last question, if you're going to introduce changes into your manufacturing process, and you've conducted a risk assessment, and you've designed a comparability study, and you would like to understand if we agree with your assessment, or perhaps you don't think you need a comparability study, and you want to know if we agree with that, those types of questions, I think, generally could be answered as an amendment to an IND with a request for information.

And so what's important to think about is that — what are you going to get out of the meeting with the FDA? And so really, from our perspective, meetings are important when there's specific questions or challenges that are coming up in your product development timeline, and a discussion with the FDA is needed in order to move forward on those, whereas looking over our protocol or agreeing with something that you're proposing — it's asking a general question and piece of advice from the FDA but not asking for specific questions that are going to need a more detailed conversation.

**DR. OH:** Thanks, Kim. The next question is for Denise.

***As we automate the closed-cell therapy operations, the continuous nature of these processes seems to make the definition of “drug substance” superfluous. Is it possible to only declare a drug product?***

**DR. GAVIN:** That's a good question. In the CMC guidance, we acknowledged that some drug products may have a continuous and not a continuous production — not necessarily have a drug substance section. We recommend that you determine what your drug substance is. If you don't have one, you can provide the information in the drug product as a drug product. The information should be defined by the sponsor, and we all evaluate that when it comes into the agency. Thanks.

**DR. OH:** Thanks, Denise. Next question is for Anna.

***For IND applications, where should genotoxicity studies such as lentivirus insertion site analysis or genomic DNA insertion site analysis be reported? Should they be submitted under M3 CMC or M2 non-clinical sections?***

**DR. KWILAS:** Thanks, Steven. Where you submit it is dependent on the purpose of the study that was performed. If these analyses, particularly some of the genotoxicity studies — if we're talking about, like, iPSC clones and things like that and the ISA analyses were performed as part of your product development, say, on your

engineering runs, then that information can be submitted in the M3 CMC section. If a complete non-clinical study was performed on multiple lots, as kind of a more thorough analysis was performed, then you can provide that whole entire study report and all of the associated documentation in M4 in the nonclinical section.

And then, as far as any studies that were performed on patient material — so, for example, insertion site analysis that were performed on biopsies that were taken from patients — that information can all be provided in M5, in the clinical section, as part of your clinical study reports. As I said, it depends on the material that was used for the analysis and how large or what the purpose of the study was.

**DR. OH:** Thank you, Anna. Oh, next question is for Kim.

***Many companies, websites, and literature indicate the FDA recommends controlling vector copy numbers for lentiviruses to less than five copies for transduced cells. However, a primary reference has never been located. Does the FDA still recommend sponsor limiting VCN to less than five copies for transduced cells? If not, what is the recommendation?***

**DR. SCHULTZ:** Thanks. This is a good question, as this has been a place that we've been evolving with our thinking. And so we do talk about this a bit in the draft guidance for considerations for CAR T-cell development. But I'll go into it a little bit here.

And so we do recommend that vector copy number is reported as copies per transduced cell. And we recommend that you set your release criteria based on the manufacturing experience that you have at the time. And this is supported for phase 1 INDs with information from preclinical studies, and from developmental lots, we really recommend that you do some process development in order to optimize the transduction efficiency to maximize that in most cases while keeping the vector copy number as low as possible for safety reasons. And then you should propose the release criteria based on that and give justification from that information. In most cases, there's not a lot of information to initiate phase 1 studies. And so we are generally comfortable with five copies per transduced cell. However, that is not a hard rule. And then as you continue to gain manufacturing experience and clinical experience through the clinical study, these release criteria along with all your release criteria can be refined to better reflect product safety and consistency.

**DR. OH:** Thank you, Kim. The next question is for Denise.

***For viral vector production, can cell lines such as HEK293 or 293T cells that are derived from tumors be employed as long as the proper testing is performed to assess the amount, size, and levels of the transforming gene products fall within the FDA guidance as being less than 10 nanograms per patient dose?***

**DR. GAVIN:** Thanks. That's a good question. Our thinking on this is also, like, evolving as we collect more data from sponsors that we've been asking for information about these cell lines.

In general, yes, you can use these cell lines to make vectors. We recommend that you do a risk assessment to make sure what you would need to test for those cells and then that you monitor for the amount of host cell DNA for the amount of specific oncogenes from the cell — say, if it's HeLa cells, that you would monitor E6 or E7; for these 293T cells, that you look for the T antigen and things like that.

We understand that you may not be able to meet the WHO standard for certain gene therapy products such as AAVs at 10 nanograms per dose, and we recommend that you measure the amount you have, you report it, and you determine levels that are shown to be safe in lots that have been administered, and we'll evaluate the data as you go through. Thanks. I think that's good. The answer is yes.

**DR. OH:** Thanks, Denise. Next question is for Anna.

***At ASGCT earlier this week, there was a confusion regarding FDA's expectations for off-target assessment during the development if the profile is found to be "clean" early in development. That is, how can a sponsor demonstrate, sufficiently to be done with off-target assessments, that an editing therapy in development has a sufficiently understood and acceptable editing profile?***

**DR. KWILAS:** Thanks, Steven. This is a really great question. First of all, I would say that the first thing we look at is to make sure that orthogonal assessments have been performed to assess the editing profile. We generally request that an in silico analysis be performed, as well as either a biochemical or a cellular assessment — be performed as well. And I'm going to assume by "clean," we mean that there haven't been any off-targets identified in any of those studies. We'll go off the idea that if no off-targets have been identified in either your in silico or your biochemical or cellular assessments, then the next thing that we will look at is whether we think that — based on the totality of the data provided, whether the potential for effect of genetic heterogeneity of the indicated patient population has been sufficiently addressed.

And that's something that we at FDA here are still currently trying to figure out: what's the best way to address the potential for heterogeneity in the population. And so we're currently working with sponsors to try to figure out the best way to address that. But that's the next thing — kind of hurdle that we'll look at. And definitely, whenever you provide your off-target analyses in your IND or in response to our IRs or anything like that, you can definitely provide justifications for why you think that the analyses that have been performed to date have addressed the concern of potential genetic heterogeneity in the patient population that you're targeting. And we'll definitely consider that. After the initial studies that have been performed, that's kind of the next hurdle to consider.

And then once all of that has been addressed satisfactorily, then we can kind of go forward with the idea that, potentially, you don't have any off-targets for your product. Thanks.

**DR. OH:** Thanks, Anna. I think we have time for one more question. And this is for you, Kim.

***In the interest of improving the quality of the submissions submitted, would OTAT consider publishing mock IND Module 3 sections for those sections where they may see common deficiencies — for example, 3.2.S.2.3: Control of Materials?***

**DR. SCHULTZ:** Thanks. This is a good suggestion, and then we'll take it into consideration. We're always looking for new ways to provide information to our stakeholders. We'll take this back and talk about it internally.

I would like to direct people to the gene therapy CMC guidance. Not to sound like a broken record, but that is set up to be comprehensive for all of the different gene therapy products. It's broken down into the CTD format. And it does, for example, for the control of materials, talk about the types of information that are needed: CFAs, quality information related to safety testing, for instance, of human or animal-derived materials, cell bank qualification — all the things that we would expect to have in the Control Materials section.

Another thing that's helpful — so this is talking about INDs. But when we're thinking about BLA submissions, it's important to have all of your ducks in a row. One thing that we might consider you to think about is to give us a more granular submission of the

table of contents for your submitted or expected BLA. Right now, oftentimes, we get the headings — the CTD headings — with no information on what's actually going to be provided in each of those different sections. It's good to know not only that you were going to include control of materials but exactly what different document headings will be included in there for us to be able to give you better feedback as you're preparing for a BLA submission. Thanks.

**DR. OH:** Thanks, Anna. This wraps up our Q&A discussion for today. Thank you for attending the first OTAT town hall, and thank you to 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 gene therapy CMC and find other OTAT and gene therapy resources.

We plan to host our next town hall meeting in December, and the topic will be cell therapy chemistry, manufacturing, and controls. This will also include tissue-engineered medical products regulated in OTAT. Please be on the lookout for more information about that town hall by signing up for our FDA email updates and following us on Twitter.

Thank you again for joining us. Have a great day.

###