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

FDA CBER OTP Town Hall:
Cell Therapy CMC Readiness for Late-Stage INDs

September 5, 2024

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DR. HEATHER LOMBARDI: Good morning, everyone, and thanks so much for joining today's virtual town hall. Today's event is hosted by the Office of Therapeutic Products, or OTP for short, within the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA). My name is Dr. Heather Lombardi, and I am the Director of the Office of Cellular Therapy and Human Tissues within OTP. I will also be your moderator for today's event.

During today's town hall, we plan to answer questions regarding development and readiness of chemistry, manufacturing, and controls (CMC) data and information for late-stage investigational new drug applications (INDs) intended to collect primary evidence of effectiveness to support a marketing application for both cell therapy and tissue-engineered products. If you've been following our OTP virtual town hall series, you may know that we've had two previous town halls on cell therapy CMC. But this is the first time we've hosted a town hall on late-stage IND readiness for cell therapy and tissue-engineered products, and we really look forward to answering your questions today.

Before we begin, I'd like to share some background about our town hall series. OTP launched the virtual town hall series in 2022 to engage with product developers and researchers. These town halls have a question-and-answer (Q&A) format, with the goal of providing information to help advance the development of OTP-regulated products. To date, we've hosted eight town hall events, including this one. All the recordings from our previous town halls are available on our website, FDA.gov, so we'd encourage you to watch those previous recordings for additional information.

There are just a few reminders I'd like to share before we get started. Today's town hall is being recorded, and the event materials will be posted on the FDA website in a few weeks, including a recording and a transcript. Closed captioning for this event is available directly in Zoom. If you have a question for our subject matter experts, please type it directly into the Q&A box in Zoom. This is at the bottom of your Zoom window. We ask that you please use the chat box only to report technical difficulties.

During today's town hall, we have three experts from the Office of Cellular Therapy and Human Tissues who will answer your questions. I'd like to take a moment to introduce each of them. Our first panelist is Dr. Alyssa Kitchel, who is Chief of Tissue Engineering Branch 2. Our next panelist is Dr. Karin Knudson, who is a biological reviewer in Cell Therapy Branch 2. And our final panelist is Dr. Kyung Sung, who is Chief of the Cellular and Tissue Therapy Branch.

Today we'll begin by answering questions submitted during registration. Then, we'll switch over to respond to some of your live questions submitted via the Q&A box at the bottom of your screen in Zoom. We'll try to answer as many questions as we can, but please remember that we aren't able to answer any questions about specific products. We also can't answer questions about draft guidance documents or guidance documents that are currently under development. And just to note it again, this town hall is being recorded. So even if you can't stay for the full event today, you can revisit the full recording once it's posted on our website.

Let's begin with our first question. And this first question is for Alyssa.

What are the most common CMC challenges that sponsors encounter when starting late-stage studies?

DR. ALYSSA KITCHEL: One common challenge is implementing manufacturing changes and demonstrating comparability. Ideally, all major manufacturing changes should be implemented prior to the pivotal study, to avoid comparability issues. However, we realize this is not always the case, as product development evolves, improves, and/or product demand increases over time. Thus, there are several challenges that come to mind based on our experience.

As INDs transition into late phase, sponsors are faced with challenges to manufacture larger lots to meet the demand of a phase 3 clinical trial. In trying to meet this increased need, there are several types of manufacturing changes that typically arise: (1) scale-up; (2) scale-out; and (3) reagent modifications. To increase the drug product lot size, manufacturers may initiate a scaled-up manufacturing process within their current site, or they may consider a new manufacturing site or unit to scale out. As for reagent modifications, sponsors may initiate a reagent change due to a number of reasons, such as upgrading the quality of reagent, or a change in reagent manufacturer due to the increased volume of reagent needed.

In any of these scenarios, comparability studies are needed to demonstrate that the product manufactured post-change is equivalent to the originally manufactured drug product. And it is especially important to demonstrate comparability for such changes in late-stage INDs, as the phase 1/2 clinical studies were conducted with pre-change drug product. Thus, ensuring that the drug product for the phase 3 study is the same as the drug product for the phase 1/2 is critical.

Another challenge IND sponsors encounter with late-stage INDs is ensuring that an adequate potency strategy is in place. We recommend that sponsors consider evaluating potential potency assays early in their IND. For example, early on in an IND, the acceptance criteria range can be set wide, and as sponsors progress through the phases of their IND and they gain additional manufacturing and clinical experience, the acceptance criteria can be more targeted or narrowed.

Many times we encounter issues with the timing of the potency assay, that the test sample is taken during the manufacturing process and not from the final drug product. Adjusting the timing of samples taken from the potency assay late in the IND can be problematic, as new acceptance criteria may need to be established due to the sample being obtained at a later stage of manufacturing.

And lastly, with regard to potency, sponsors sometimes have difficulty choosing a potency assay that is related to the mechanism of action, so many sponsors ask us what a good potency assay for their product would be. We always advise that they develop an assay based on their product, understanding, and experience.

Overall, we've seen sponsors struggle to keep up the pace of their CMC development when compared with their clinical development. Thus, we always recommend that sponsors come in to discuss anticipated challenges as they approach the late-stage IND phase.

Back to you, Heather.

DR. LOMBARDI: Thanks, Alyssa. Our next question is for Karin.

What is the expected progression of assay qualification/validation from early stage to biologics license application (BLA) submission?

DR. KARIN KNUDSON: Thank you for this question, and good morning, everyone. We sometimes see confusion about the difference between assay qualification and assay validation, so I first want to briefly address this.

The key difference between assay qualification and assay validation is the rigor by which the assay itself is tested. Qualification and validation both require the assay to be suitable for the intended use. However, assay validation takes this a step further and shows that your assay performs in a predictable way and that the performance is consistent across a wide range of conditions that would be experienced when you execute the assay.

For example, for assay validation, you will need to demonstrate that your assay is consistent when different operators, equipment, or reagent lots are used to perform the assay. A validation study also requires that you establish acceptance criteria based on your assay knowledge prior to initiation of the actual validation studies.

So overall, the use of the assay determines the level of qualification or validation needed for a specific stage of clinical investigation. For example, safety assays and dose-determining assays should be qualified for early stages of development, but there may be flexibility on how thoroughly developed or qualified other assays should be for early-phase studies.

However, we do generally recommend that you evaluate assay performance at all stages of development, even if qualification of the assay is not required. This is because assays that don't measure what they're intended to measure or assays with high variability or little robustness will provide little to no information regarding the meaningful control of your product. So moving from early phase studies, by the time you start pivotal studies, most or all of your assays—including your potency assay—should at least be qualified so that the attributes of the product used and evaluated in your pivotal study are measured reliably.

I will reemphasize here that your potency assay should be qualified prior to your pivotal study. So before submitting a BLA, all assays should be fully validated and demonstrated to be suitable for their intended purpose.

In general, assay validation will include evaluation of accuracy, precision—both repeatability and intermediate precision—specificity, detection limit, quantitation limit, linearity, range, and, importantly, robustness. Robustness is something that our sponsors tend to miss or not fully investigate during assay validation. Even though validation is not required until the latest stages of development, we recommend that you think about how you will validate your assay when you are designing it, because limiting the sources of variability in your assay at the time of design could make it easier to validate your assay later.

So if you do need additional information on assay validation, we have references available, including two guidance documents. The first is the 2015 guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics.* The second is the 2024 International Council for Harmonisation (ICH) guidance for industry *Q2(R2) Validation of Analytical Procedures.* We also recommend that you request a meeting with us to discuss any predicted issues with your assay qualification or validation prior to initiating those studies.

Back to you, Heather.

DR. LOMBARDI: Thank you. The next question is for Alyssa.

Does FDA have recommendations on how to identify and establish product critical quality attributes (CQAs) during product development and for commercial manufacturing?

DR. KITCHEL: In general, a list of potential drug product CQAs are derived from the quality target product profile and/or prior knowledge of the product development. You need to acquire an appropriate understanding of the biological properties of your product to develop relevant and meaningful CQAs. As part of product development, we recommend that you measure a wide range of product attributes in addition to the tests used for routine lot release. While some of the assays you evaluate may not be practical for lot release, they may provide you with helpful information about product attributes related to biological activity or clinical effectiveness, or both.

As you progress through the product development and gain more manufacturing experience, you can modify the list of potential CQAs. Quality risk management can then be used to prioritize the list of potential CQAs for subsequent evaluation to identify relevant CQAs.

For recommendations in identifying and establishing product CQAs, we encourage you to look at ICH guidance for industry *Q8(R2) Pharmaceutical Development.*

Back to you, Heather.

DR. LOMBARDI: The next question is for Kyung.

The draft guidance for industry* Potency Assurance for Cellular and Gene Therapy Products *highlights the importance of using formal risk assessment tools to comprehensively assess risks to potency. Could FDA elaborate further on how to effectively conduct risk assessments?

DR. KYUNG SUNG: We emphasize using comprehensive risk assessment tools as a key part of quality risk management to evaluate risks to potency.

Risk assessment begins with identifying what might go wrong. It starts with identifying factors that could impact potency at various stages, such as during manufacturing, lot release, and post-release, which includes storage and shipping. To effectively identify these risks, it's important that you have a good understanding of the product's mechanism of action and potency-related CQAs.

We also recommend looking beyond just the manufacturing and release phases. For example, it is important to consider whether the container closure, shipping conditions, or even preparation and thawing procedures before product administration could affect the product's viability and functionality.

Risk assessments are not static. They should evolve as the understanding of the product and its manufacturing process grows. The risks should be reassessed regularly—especially before implementing any manufacturing changes or material substitutions—to ensure that the product potency remains consistently controlled.

Back to you, Heather.

DR. LOMBARDI: Thanks, Kyung. And you also have the next question.

What types of readouts are suitable for potency assays? And does FDA recommend using multiple potency assays or specifications for release testing?

DR. SUNG: When considering suitable readouts for potency assays, it is important to start with a broader risk-based potency assurance strategy. This strategy ensures that CQAs related to potency are consistently controlled throughout the product's life cycle, and it is guided by risk assessment. This means it is important to identify and prioritize potency-related CQAs—especially those that are high-risk—and to ensure that they are accurately quantified using appropriate assays.

Potency assays should use quantitative readouts that directly measure these high-risk CQAs. These assays should include clear acceptance criteria with well-defined lower and upper limits. The lower limit ensures that each lot of the product maintains the necessary potency to deliver its intended therapeutic effect, while the upper limit helps prevent overly high potency, which could potentially pose safety risks. These lower and upper limits should be based on data collected during clinical trials and refined as more is learned about the product. As Alyssa mentioned earlier, the range can be tightened as more data become available.

Regarding the use of multiple potency assays or specifications, we generally recommend this approach—especially for complex products like cell therapies. This approach allows for a more comprehensive evaluation of potency, by assessing different CQAs that contribute to the overall therapeutic effect. Utilizing multiple assays supports a broader control strategy, ensuring consistent product performance across its shelf life. As the understanding of the product and its performance in various conditions improves, new potency-related CQAs might be identified and incorporated over time.

In summary, suitable potency assay readouts should be quantitative and focused on high-risk CQAs, among others. We support using multiple potency assays to capture the complexity of cell therapies, ensuring consistent potency across the product life cycle.

Back to you, Heather.

DR. LOMBARDI: Thanks, Kyung. Our next question is for Alyssa.

How does FDA recommend assessing the potency of complex tissue-engineered products in late-stage development, especially when the product's therapeutic effect is influenced by multiple cell types or scaffold materials?

DR. KITCHEL: The potency of tissue-engineered products often depends on a combination of physical, structural, and biological attributes. The product's mechanism of action may involve a complex interplay between the cells, the scaffold, and how these components interact when combined to achieve the intended therapeutic outcome.

When developing potency assays, it is important to conduct a broad assessment that considers characteristics from all stages of the product, including the cells, scaffold, cell-scaffold intermediate, and the final cell-scaffold drug product, which Kyung previously described. This comprehensive approach ensures that the potency assay effectively captures the CQAs that are most relevant to the product's therapeutic function.

We recommend collecting detailed characterization data using a combination of non-

destructive and destructive assays. These assays should evaluate key attributes, like biomolecular markers, biochemical properties, immunological responses, biomechanical strengths, and other relevant factors that are mechanistically linked to the product's biological activity.

In addition, when cells are seeded into or onto a scaffold, it's crucial to assess the integrity of the final construct and the distribution of cells within the scaffold. Ensuring uniform cell distribution and proper structural integrity is essential for the product's overall potency and functionality.

For late-stage development, these potency-related CQAs should be rigorously assessed and incorporated into your release specifications if they are determined to be at risk.

Thanks. Back to you, Heather.

DR. LOMBARDI: Thank you. This question is for Karin.

Does FDA have recommendations on how to establish release specifications for inherently variable cell therapy products?

DR. KNUDSON: Yes, we do have recommendations. Please be aware that, for all stages of clinical studies, your IND should provide your product specifications and clear justification for why you chose them, and they should be based on relevant data.

As Alyssa previously said, for cell therapy products, release acceptance criteria can be set to be permissive during the early-phase studies, since you're still gathering product characterization data and learning more about your product. However, as you progress through clinical development, you should use your manufacturing experience to tighten your acceptance criteria to ensure consistency and quality of your product.

If you intend to submit a BLA, your commercial specifications should be based on lots shown to be safe and effective during the clinical studies. However, as we are all aware, some cell therapy products—especially those derived from donor- or patient-specific cellular material—may be highly variable, and product attributes may not correlate with the expected or proposed mechanism of action. In this case, the release acceptance criteria may be based on clinical manufacturing experience to ensure product consistency and similar quality to the clinical lots used in your pivotal studies.

Regardless of the strategy used to set your release acceptance criteria and your release specifications, we highly recommend that you carefully consider the release specifications for your pivotal study, to ensure that you have collected sufficient data to support your proposed commercial specifications when you submit a BLA.

If you predict that establishing release specifications is going to be a problem for your product, we encourage you to submit your proposed product specifications under an amendment to the IND prior to implementation or request a meeting with us. Important times to engage with us about your product specifications are before you initiate a new clinical study—especially before your pivotal studies—, when you intend to make a significant manufacturing change, and prior to submission of your BLA, ideally during the pre-BLA meeting.

Back to you, Heather.

DR. LOMBARDI: Thanks, Karin. You also have the next question.

What are FDA's expectations for batch release testing when batch sizes are small or available material is limited?

DR. KNUDSON: This is a great question. For many of our cell therapy products, there is going to be a limited amount of final drug product to use for testing. Generally, all products should undergo release testing to ensure product safety, identity, quality, purity, and potency. We recommend that you optimize your release assays throughout product development to ensure that you can perform all of the necessary release testing with the product you have available and, importantly, the time you have available prior to product release.

But if that is not possible, here are a couple of strategies you can implement when there is limited material.

In certain cases, there may be the option to use a surrogate sample from manufacturing instead of the final drug product for some release testing. However, to use a surrogate sample, you will need to provide detailed scientific justification for this alternative sampling strategy and demonstrate that the surrogate sample is representative of your final drug product.

Alternatively, you may be able to qualify or validate your assay to use a smaller sample size. For example, we often see this as an option for sterility release testing. Use of a less than conventional sample size may be acceptable for your sterility testing, but you will need to demonstrate the sensitivity and reliability of your assay through qualification and eventually validation studies.

As we've said previously, we recommend that you talk to us—especially about alternative approaches—during both product and assay development and provide adequate justification for your approach in the IND and the BLA submission.

Back to you, Heather.

DR. LOMBARDI: The next question is for Kyung.

For tissue-engineered medical products that are not amenable to destructive sampling, what alternative approaches does FDA recommend for conducting product release testing?

DR. SUNG: When tissue-engineered medical products are not suitable for destructive sampling, alternative approaches for release testing can be considered. One common strategy is to manufacture an additional unit in the same batch specifically for testing, allowing assays to be conducted without affecting the final product.

If producing an extra unit is not feasible due to limited batch size or high cost, alternatives include using byproducts, such as the residual product pieces from processing, or producing a smaller size of the product.

It is important to verify that these alternatives accurately represent the CQAs of the final product. Additionally, we strongly recommend consulting us before implementing these strategies to ensure they meet regulatory expectations.

Back to you, Heather.

DR. LOMBARDI: Thank you. The next question is for Alyssa.

Do late-stage INDs have different requirements for raw materials or reagents than early-stage INDs? Does raw material identity testing need to be implemented prior to the initiation of a pivotal study?

DR. KITCHEL: Thanks for the question, Heather.

There are no differences in requirements, as safety and performance of raw materials should be established prior to the initiation of an early-stage IND to ensure consistency of drug manufacturing and safety of drug substance and drug products. The amount of information to support the safety and performance of the raw material depends on the nature of the material and the needs of the manufacturer.

For more information, we recommend that you check out the 2008 guidance *Content and Review of CMC Information for Human Somatic Cell Therapy INDs.*

Raw material identity testing is not required prior to initiation of a pivotal study. However, we recommend that you start looking into raw material identity tests during your pivotal studies, because at the point of licensure, you should have at least one validated identity test in place to confirm material identity for each incoming material that is introduced into the drug product manufacturing.

Back to you, Heather.

DR. LOMBARDI: Alyssa, you also have the next question.

Can master files be referenced for late-stage INDs and in BLA submissions?

DR. KITCHEL: Master files can be referenced for late-stage INDs. However, depending on the type of information that's in the master file, that may not be the case for a BLA. FDA generally does not permit applicants to include information about drug substance, drug substance intermediate, or drug product manufacturing in BLA submissions by reference to a master file.

This is because a BLA applicant is generally expected to have knowledge of and control over the manufacturing process for the biological product. Therefore, complete manufacturing information about drug substance, drug substance intermediate, or drug product that are in master files will need to be included in the BLA.

For more information, you can refer to the 2019 FDA draft guidance for industry *Drug Master Files*.

Thanks, Heather. Back to you.

DR. LOMBARDI: Thanks, Alyssa. Next question is for Karin.

What are FDA's expectations regarding the use of surrogate materials—for example, healthy donor material—for the process performance qualification (PPQ) runs?

DR. KNUDSON: We recognize that obtaining patient material for use in PPQ runs can sometimes be challenging—especially when working with autologous products or therapies used for rare diseases or in pediatric populations. So under these circumstances, healthy donor material can be acceptable for performing your PPQ runs. However, you should provide validation of the healthy donor model system, which includes data and discussion to support why healthy donor material is appropriate to use in your PPQ studies.

It's also critical to note that healthy donor material may not reflect the behavior of cells from your patient population during manufacturing and final release. So if you intend to use healthy donor material, we recommend you discuss this with us during your clinical studies and prior to initiation of your PPQ studies.

Back to you, Heather.

DR. LOMBARDI: Next question is for Alyssa.

Does FDA have recommendations for how to perform stability studies for products with limited material or shelf life?

DR. KITCHEL: We do acknowledge that cell therapy product material can be limited, which can affect the generation of stability data. Design of stability study protocols in terms of the number of batches, frequency of data point collection, and test conditions is dependent on the unique nature of your product and expected product stability. So we ask that you provide clear justification on your stability study design plan.

For cases when you may have a limited amount of product available for stability studies, such as with autologous products, you can conduct your stability study with another lot, perhaps manufactured with the same process dedicated for stability testing. You can also use drug product surrogate for certain simulated shipping studies that are intended to assess the temperature control and the integrity of the primary and secondary packaging when subjected to simulated shocks and vibrations.

If you have alternate plans where surrogates can be used in place of drug product without compromising the safety and quality of the product, we encourage you to discuss your plans with us and justify them.

Back to you, Heather.

DR. LOMBARDI: Thanks, Alyssa. The next question is for Kyung.

What are FDA's expectations for stability testing of tissue-engineered products during late-stage IND development, given their unique storage and handling requirements?

DR. SUNG: For tissue-engineered products in late-stage IND development, stability testing involves special considerations due to their unique storage and handling needs. These products often involve living cells, scaffolds, or complex constructs. So the stability assessment should address factors that impact potency, safety, and integrity over time.

The storage conditions—like temperature, humidity, and light exposure—can significantly affect cell viability, scaffold degradation, and overall product performance. The stability testing should evaluate both the individual components—such as cells and scaffold—and the final drug product, under real-time and accelerated conditions, focusing on CQAs such as cell viability, functionality, and structural integrity.

For products where cells are seeded into or onto the scaffold, it is essential to assess the stability of the cell-scaffold construct—particularly in maintaining cell distribution and scaffold integrity over time.

For tissue-engineered products that are stored in specialized bioreactors or containers to maintain their function and characteristics, stability testing should also evaluate the effects of bioreactor or container conditions on product quality. Factors like flow dynamics,

nutrient supply, and oxygen levels play a critical role in product stability, and stability studies should ensure that CQAs remain consistent and that the final product maintains its intended potency and function.

Handling and shipping also require special consideration, as temperature fluctuations, vibration, and transit time can significantly impact stability. We generally expect stability studies to simulate real-world handling and shipping conditions and assess how these factors affect the product quality and potency.

Back to you, Heather.

DR. LOMBARDI: Next question is for Karin.

How should sponsors determine when a late-stage manufacturing change requires a comparability study?

DR. KNUDSON: This is a great question. The short answer is that we recommend you apply the basic principles described in ICH guidance documents *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* and *Q9(R1) Quality Risk Management* and in our 2023 draft guidance for industry *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* to determine when a late-stage manufacturing change requires a comparability study.

But to provide more information in a longer answer: Sponsors should perform a risk assessment to determine whether the manufacturing change has the potential to affect product quality. This risk assessment consists of the identification of potential hazards for implementing a manufacturing change, the likelihood that the hazard will occur, and the severity of the consequences of those hazards.

The output of the risk assessment will then inform whether there is a need to perform a comparability study to assess whether the manufacturing change will affect product quality or safety. As an example, changing a minor reagent may be a lower risk to product quality and safety if you compare that to changing from manual centrifugation and drug product formulation to an automated washing or formulation system like the Lovo system.

So not every change requires a comparability study. However, we do recommend that you consult with us after performing your risk assessment to confirm whether you will need to perform a comparability study.

It's important to remember that the goal of a comparability study is to demonstrate a lack of an adverse effect on product quality, which will allow you to combine the clinical data generated with the pre-change and the post-change products. Because of this, the level of risk for introducing changes during your product development increases as you move further into the clinical study timeline.

As Alyssa previously mentioned, we recommend that major manufacturing changes be implemented as early as possible—ideally before initiation of the pivotal study—so that post-change products are used in those clinical studies that will provide the primary evidence of effectiveness for a licensing application.

Back to you, Heather.

DR. LOMBARDI: The next question is for Kyung.

How do sponsors successfully demonstrate comparability when the number of batches manufactured or samples available for testing is limited?

DR. SUNG: This is a great question. As Karin previously mentioned, you should always start with a risk assessment to identify the impact of the proposed change and to inform the level of studies needed to support the change. In all cases, the statistical power of the assessment is driven by the number of lots you have data for. This can be very challenging when there are a limited number of lots or attributes are variable.

We generally recommend that sponsors use split starting material for their comparability assessment, as it removes the inherent variability of the cellular starting material observed with most donor-derived or patient-derived materials. It also avoids some of the issues that can occur when comparing historical pre-change testing data to newer data from post-change lots.

However, if performing split manufacturing is not feasible, the comparability study may be designed as a comparison of historical pre-change testing data to newer data from post-change lots. You should assess a statistically justified number of lots to maintain statistical power, so we highly recommend you consult with a statistician and consider the number of lots you intend to manufacture for clinical studies carefully. Ideally, the only differences between the historical pre-change lots and the post-change lots should be the manufacturing changes that are being evaluated in the comparability study, and this strategy can only be used if the analytical method has not changed. This strategy also requires retained samples from pre-change lots be available for testing.

If you're facing challenges with the design of your comparability plan due to small batch or sample sizes, we encourage you to discuss these issues with us. For example, for ultra-rare diseases, where it may be challenging to obtain statistically relevant data, working closely with us is really important.

Back to you, Heather.

DR. LOMBARDI: Thank you. The next question is for Alyssa.

What are the most common issues FDA sees when assessing a comparability package for a manufacturing process change?

DR. KITCHEL: One of the biggest challenges for our sponsors is insufficient identification or justification of product CQAs—which I talked about earlier—and when those CQAs are evaluated in a comparability exercise. Without data demonstrating that the CQAs affect product safety and quality, it can be very difficult to establish relevant equivalence acceptance criteria and determine if a change observed in a comparability study will affect clinical efficacy and safety.

So we recommend that you start product characterization early and continue it throughout product development, as this data is likely to help you identify more robust and reliable product attributes that can be used in a comparability study.

A common issue is that sponsors will use only routine in-process or release tests for the comparability analytical assessment. Release testing alone is generally insufficient to assess comparability, and additional testing at multiple stages of manufacturing should generally be conducted to demonstrate that there is no adverse effect on product quality.

Another issue that we observe is that the analytical assays are not adequately qualified. Interpretation of comparability test results depends on the suitability of the analytical methods used. So all release assays used to demonstrate comparability should be qualified, depending on the phase of the clinical study. Assays used for extra characterization do not necessarily need to be qualified, but they should be scientifically sound and fit for their intended use and sufficiently precise to detect meaningful differences in product quality.

We strongly recommend that sponsors submit a detailed comparability study protocol and request our feedback on the study design and statistical approach prior to the initiation of the study. These discussions can be facilitated either by requesting FDA comment on relevant information submitted in an IND amendment or through a formal meeting request. The type of meeting used for such discussions depends on the stage of the product life cycle and the issues to be considered.

Thanks. Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Kyung.

What specific design controls and testing strategies should be implemented for combination products in late-stage INDs, particularly when introducing a new device or a new version of a device with a biologic?

DR. SUNG: This is a great question. In late-stage INDs, you may encounter the need to change a device component or upgrade to a new version of a device. When introducing a new device component or a new device or updated version, it is important to implement specific design controls and testing strategies to ensure product safety, effectiveness, and consistency.

We expect a comprehensive approach that integrates device design controls with biologic quality considerations. Design controls should begin with a clear understanding of the combination product, intended use, user needs, and essential performance requirements. For a new or updated device, risk assessments should identify potential failure modes, interactions with the biologic, and any new risks introduced by the integration. The goal is to anticipate issues that could impact performance, safety, or usability.

The verification should confirm that the device consistently meets its essential performance requirements when combined with a biologic. This includes assessing whether the device affects the biologic's stability, potency, or quality. Human factors and usability testing can be conducted, when needed, to ensure that the device is safe and user-friendly.

Establishing robust specifications and acceptance criteria is key. These criteria should set clear performance thresholds for both the device and biologic, ensuring that any variability introduced by the combination does not compromise overall product quality.

So, in summary, introducing a new or updated device in a combination product during late-stage IND development requires a well-coordinated approach. This includes a thorough risk assessment, verification of essential performance parameters, and human factor testing when necessary. The focus should be on ensuring that the combined product meets all safety, potency, and usability requirements as it moves toward commercialization.

Back to you, Heather.

DR. LOMBARDI: Thanks, Kyung. You also have the next question.

What are FDA's CMC expectations and key considerations when submitting late-stage INDs based on products manufactured and studied in foreign countries, particularly regarding alignment with U.S. regulatory requirements?

DR. SUNG: This is another great question. If a sponsor chooses to submit late-stage INDs for products manufactured and studied in foreign countries, from a CMC perspective, it is important to demonstrate that the manufacturing processes and controls align with U.S. regulations, particularly relevant parts in Title 21 of the Code of Federal Regulations (CFR), as well as our recommendations and expectations stated in various guidance documents. This ensures that the product is produced under the standards expected in the United States with all CQAs consistently controlled.

To meet these expectations, the CMC documentation should comprehensively address the manufacturing site, process controls, and product specifications to ensure alignment with our recommendations. Any differences between foreign regulatory requirements and U.S. regulations should be discussed with us. In some cases, bridging studies or additional data may be needed to demonstrate that U.S. regulatory requirements are met. The approach to addressing these differences can vary based on the specific circumstances.

Additionally, if there are differences in donor eligibility criteria, particularly for products manufactured outside the United States, sponsors may need to submit an exemption request. This is especially relevant if the foreign lab does not have appropriate Clinical Laboratory Improvement Amendments (CLIA) certification or does not use FDA-approved donor test kits, as required under 21 CFR part 1271.

We also recommend early communication to discuss your CMC approach. Proactively engaging with us—particularly if there are significant differences between foreign regulatory frameworks and our expectations—can help avoid the delays and ensure a smoother IND review process.

Back to you, Heather.

DR. LOMBARDI: Thanks. This will be the last of our pre-submitted questions, and this question is for Karin.

Are there any FDA resources or programs to further help sponsors with CMC development?

DR. KNUDSON: Yes, there are. We actually have a new program called the CMC Development and Readiness Pilot, or CDRP, which was launched April 1, 2023, as a part of PDUFA VII. The CDRP program should help facilitate expedited CMC development of cell and gene therapy products through increased communication with us. Overall, the program is intended to prioritize early CMC development to help the CMC keep pace with accelerated clinical development timelines.

So how do you qualify? CBER INDs with expedited programs—meaning Breakthrough Therapy or Regenerative Medicine Advanced Therapy (RMAT) designations—are eligible to apply, and there are some other eligibility requirements.

Participants can take advantage of two dedicated Type B CMC meetings, in addition to your existing meetings, to help reach mutual understanding of approaches needed to compete CMC activities to ensure CMC readiness for marketing application. 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 FDA website on this program, which can be found using a web search for the term "FDA CDRP." We do encourage you to apply for this program and to reach out to us if you have any questions on eligibility or about the program in general.

Back to you, Heather.

DR. LOMBARDI: Thanks so much, Karin. And thanks to everyone who submitted questions during our registration process.

We're now going to spend the remainder of today's event answering your live questions. Our first live question will be for Karin.

What are some of the common issues observed in late-stage INDs with container closure, extractable, and leachable testing?

DR. KNUDSON: This is a great question. I will say that extractable and leachable studies are something that our sponsors particularly struggle with. So I'm happy to answer it.

The testing for extractables and leachables is most critical when the product moves from late-phase studies that may lead to a BLA. For those of you unfamiliar with extractables and leachables testing, I'm going to provide a brief overview and then go over some common issues we see.

Extractable studies are conducted to evaluate the list of potential leachables in the drug product from the container closure system. The extractable study is performed under exaggerated conditions, including the use of solvents with high extracting propensity and a higher temperature and longer incubation time than would be normally seen in the clinical setting.

The extractable study is followed by a leachable study, which is performed using the actual drug product or a simulated matrix. So the samples are analyzed for compounds leaching into that matrix due to its direct contact with the container closure system. The leachable study is performed under real-time drug product storage conditions over the whole product shelf life, with multiple time points of analysis.

Then, after you complete these two studies, the toxicology risk assessment is used to evaluate whether the chemicals that are detected are within safety levels, depending on the proposed route of administration.

One common issue that we see with these studies is that sponsors only assess extractables and leachables from the container closure itself. However, please be aware that leachables start to accumulate in the product as early as the drug substance and during the subsequent processing steps from materials such as tubing, connectors, containers, and the container closure system itself. So, keep in mind that leachables from the container closure represent only a fraction of the cumulative leachables in the drug product, and cumulative leachables should be assessed as a part of these studies.

Another issue that we see is that scale-up or scale-out and process improvements can change the container closure system and the product formulation. This makes it more critical to remember to conduct the extractables and leachables testing on the final drug product during late-phase studies, and ideally using your intended commercial

manufacturing process if you are moving toward a BLA.

I'm going to cover just a few more basic issues that we see, because this is an important topic. Some other basic issues we see are that the sponsor relies solely on extractable or leachable studies conducted by the container closure vendor that do not adequately simulate the drug substance or the drug product matrix. And we also see that sponsors are conducting only extractables testing but not performing the follow-up leachable study.

Back to you, Heather.

DR. LOMBARDI: Thanks, Karin. The next question from our live questions is for Alyssa.

What are FDA's expectations for demonstrating comparability of tissue-engineered medical products?

DR. KITCHEL: Thanks, Heather. Manufacturing changes to tissue-engineered medical products (or TEMPs) do pose additional unique challenges, as these changes may impact the cells, the scaffold, and/or the combined cell-scaffold product in ways that are not readily anticipated or detectable based on the current measurement technologies.

So as Kyung mentioned previously, we do recommend that sponsors conduct a thorough risk assessment that considers the potential effects of the change on each component—for example, the cells and the scaffold—and on the final cell-scaffold construct. The risk assessment should determine whether a comparability study is necessary to evaluate any potential impact of the change on product quality, and whether this comparability study should evaluate the cells, scaffold, cell-scaffold intermediate, and/or the cell-scaffold drug product.

Of note: As manufacturing changes introduced either before or after combining the cells and scaffold may have a significant impact on the overall biological activity and/or the performance of the TEMP, comparability studies should include an evaluation of the effect on drug product quality even when manufacturing changes are made only to the scaffold or only to the cells prior to combining these two components.

You should assess the potential impact of the change on product quality post administration, such as remodeling and degradation. And depending on the outcome of the risk assessment and the anticipated impact of the change to product quality, you may need to evaluate the performance of the TEMP in a physiologically relevant environment to demonstrate comparability.

There are practical challenges to the completion of comparability studies, including difficulty in acquiring the samples for testing and retention when the integrity and structure of the TEMP need to be maintained or when manufacturing occurs in a closed system. The lack of uniform cell growth on the scaffold may also make obtaining representative samples difficult.

Thus, it is important to consider these unique challenges in the context of comparability study design. And if relevant, surrogate TEMPs could be manufactured in parallel during clinical lot production or manufactured during specific production for a comparability study. Such surrogate TEMPs could be particularly useful when destructive sampling is used for testing additional CQAs that are not routinely evaluated for lot release. An alternate approach could include sampling of the incubation media instead of the product itself, when the incubation media can be considered a representative sample of the product

for the specific CQAs.

Thanks, Heather. Back to you.

DR. LOMBARDI: Thanks, Alyssa. The next question is for Kyung.

What are the recommendations for potency assay development for cell therapies when there's limited time between manufacturing and administration?

DR. SUNG: Thanks for the question. For a product with an extremely short shelf life, where there is not enough time to complete a potency bioassay before lot release, we recommend you use other rapid assays for lot release. These rapid assays can provide a rapid indication of potency. However, a potency assay, even if performed after release, could enhance potency assurance. In these cases, we recommend initiating one or more potency assays immediately after manufacturing the drug product, with the results evaluated when they become available post release.

For both investigational and licensed products, this post-release testing is important for verifying that the manufacturing process consistently produced potent lots. The appropriateness and the frequency of this post-release testing should be determined by a risk assessment.

Back to you, Heather.

DR. LOMBARDI: The next question is for Karin.

Are the requirements for process validation similar for all cell therapies?

DR. KNUDSON: Yes. In general, the principles are the same. To provide a little bit more information: Process validation should be performed to support a licensing application. Generally, process performance qualification, or PPQ, should include a justified number of full-scale manufacturing runs performed sequentially and should evaluate all steps, including in-process and release testing.

For a broader perspective on process validation, please see FDA's 2011 guidance for industry *Process Validation: General Principles and Practices.*

Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Kyung.

For a phase 3 study, do the potency assays require established acceptance criteria? And is it ever acceptable to collect release data during the phase 3 study to establish the potency assay acceptance criteria?

DR. SUNG: We really recommend that acceptance criteria should be established and justified before initiating phase 3 studies. Acceptance criteria can be initially broad and can be refined as you collect additional product manufacturing data during the phase 3 study. By the time of licensure, you should have well-established acceptance criteria for the potency assays.

Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Alyssa.

Does FDA have advice on how to set acceptance criteria for comparability studies?

DR. KITCHEL: Great question. Setting comparability acceptance criteria can certainly be difficult for complex cell therapy products. In general, comparability acceptance criteria should ideally be based on the understanding of the potential effect of the attribute on the safety and effectiveness of the product, and not only based on statistical analysis of historical data from the pre-change product.

If there is clinical or manufacturing experience supporting the differences in CQAs that negatively or positively impact product quality, you should use this information to select appropriate quality ranges or equivalence margins for your comparability study.

If instead you don't have the characterization data to set biologically relevant comparability acceptance criteria, you may use statistical analysis of historical data to define the comparability acceptance criteria. An equivalence approach is often appropriate for evaluating comparability of CQAs when it is important to directly compare the pre- and post-change values and determine whether they are sufficiently similar. However, you should justify how your statistical-based acceptance criteria are adequate to ensure the safety and effectiveness of the post-change product. As mentioned earlier, we recommend that sponsors check out our draft comparability guidance, posted in July 2023.

Thanks. Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Kyung.

Can one potency assay be used for multiple products and/or indications?

DR. SUNG: Yes. This is actually a two-part question, so I'll first address whether one potency assay can be used for multiple distinct products. Potency assays are designed to measure the specific biological activity that aligns with a product's unique mechanism of action. Because different products often have distinct mechanisms of action, it is challenging for a single potency assay to be applicable across multiple distinct products. Even within the same therapeutic category, products may have unique potency-related CQAs that need to be measured. So a single assay may not fully capture the critical attributes of distinct products, leading to potentially inaccurate potency assessment.

In some cases, related products with very similar mechanisms of action and CQAs might be able to share a common core assay. However, even in those situations, product-specific modifications and validations are typically required.

Now I'll address the second part of the question: Can we develop and use one potency assay when the product is used in different indications? If a product's mechanism of action remains consistent across different indications, it is possible to use a single potency assay for multiple indications. For example, when a product targets the same biological pathway across indications, the same assay can be used to measure potency in each case.

However, the different indications may require specific potency thresholds or functional activities to ensure that the assay detects levels appropriate for the distinct therapeutic needs, such as dosing requirements, disease severity, and clinical objectives. So while the core assay can stay the same, additional criteria or endpoints might need to be incorporated to address the specific needs of each indication.

Back to you, Heather.

DR. LOMBARDI: The next question is for Karin.

Can comparability after a major manufacturing change implemented during or after the pivotal study be established using an analytical comparability study alone?

DR. KNUDSON: I cannot provide a simple yes or no answer to this question, because whether an analytical comparability study alone will be sufficient to establish comparability between a pre- and post-change product depends on the type of change that you are making, your level of understanding of the product's CQAs, and the impact of the change on the safety and efficacy of your product.

I do want to reiterate that we recommend you discuss late-stage manufacturing changes with us prior to implementing them or to performing a comparability study, so that we can come to an agreement on the strategy needed to establish comparability.

I hope that was helpful. Thanks, Heather. Back to you.

DR. LOBARDI: The next question is for Alyssa.

What are FDA's expectations for use and qualification of reference standards for release assays?

DR. KITCHEL: It's a great question. Reference standards are commonly used in analytical assays to ensure accurate and precise measurements of product quality attributes. However, compared with other drugs and biologics, there is a limited availability of certified or consensus reference standards for cell therapy products. So as such, we don't typically see reference standards included in cell therapy INDs.

However, manufacturers may develop their own product-specific internal reference materials, and we typically see that those internal reference materials are based on a product lot.

Here are some general expectations on the use of qualification of reference materials. First, testing should be performed to qualify in-house primary reference materials and to establish the full identity, purity, and attribute being evaluated. Measurement of the intended product attribute should be accurate, precise, reliable, and consistent across time. Appropriate documentation for this testing should be submitted to your IND and maintained. In addition, we recommend that you have a sufficient amount of the material reserved for your clinical study, to avoid potential issues with the data analysis or interpretation that could occur if you run out of reference material mid-study.

So we do recognize that material may be limited and that you'll likely need to qualify a batch of reference material at some point. That new reference material should be appropriately prepared, identified, tested, approved, and stored, and the suitability of each batch of reference material should be determined prior to first use by comparing it against the existing lot.

All of these procedures regarding qualification, requalification, or bridging of the reference materials should be well documented in your IND and included in your IND.

Thanks. Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Kyung.

Can in vivo potency tests be used for lot release in late-stage INDs? And under what circumstances does FDA recommend replacing an in vivo potency test with an in vitro alternative?

DR. SUNG: Thanks for the question. In vivo potency tests can be used for late-stage INDs, but they are generally less recommended as products move closer to commercial approval. We encourage replacing in vivo potency assays with in vitro alternatives when it's possible to do so without compromising the reliability of potency assurance. This also aligns with the 3Rs principles—replacement, reduction, and refinement—which aim to minimize animal use in product testing.

While in vivo assays can provide valuable data, particularly in early development, they present several challenges in late-stage development. In vivo tests often have higher variability due to the biological differences between animals, making them less reliable for routine lot release. Additionally, in vivo tests are generally time-consuming, which can delay product release.

In vitro assays offer faster turnaround times, reduced variability, and lower cost, making them more practical for routine lot release as products move into late-stage development. In particular, if the product mechanism of action is well characterized and can be reliably measured through in vitro methods, transitioning from in vivo to in vitro is highly recommended.

However, in vivo potency assays may still be necessary if the product's mechanism of action involves complex biological interactions that cannot be fully captured by in vitro methods, or if no validated in vitro alternative is available that can measure the relevant potency-related CQAs with confidence.

Back to you, Heather.

DR. LOMBARDI: Thanks. Karin, next one is for you.

Does FDA have recommendations on low viability for cell therapy products, such as below the 70% viability specification?

DR. KNUDSON: Yes. We recognize that cell viability below 70% can be encountered, either at the time of release of the product or following product storage. If that is the case for your product, we ask that you provide scientific justification in support of this low viability acceptance criterion, including justification that the product is safe at that level.

Back to you, Heather.

DR. LOMBARDI: Great. Next question is for Kyung.

What are FDA's expectations for reference standards for potency assays?

DR. SUNG: Thank you for the question. For potency assays, particularly bioassays, it is acceptable to use reference materials that are calibrated relative to an assigned potency value, which is typically expressed as a percentage, like 100%. This assigned value is based on a defined reference standard, which helps ensure consistency of assay performance.

If no compendial or recognized standard exists, the development of an in-house reference material is necessary. The reference material should be thoroughly qualified and monitored

for stability and have a clear plan for replacement before exhausting the supply of the current lot of reference material. This involves running multiple independent assays to assign a potency value to the new reference material using statistical procedures.

For cell products where there may not be any suitable external standards, FDA recommends selecting a well-characterized representative lot of drug substance (DS) or drug product (DP) as the reference material. If using DS or DP is not feasible due to factors like limited batch size or short shelf life, alternative reference materials should be developed. These materials should still be relevant to the potency-related CQA and be available in sufficient quantities for ongoing use.

In addition to the reference material used for calibration in each assay run, we recommend including a separate control material to test the system's suitability. This additional control helps confirm that the assay is functioning properly. New lots of control material should be qualified through multiple potency assay runs, and an expected potency range should be assigned based on the data from these runs.

Thank you for the question. Back to you, Heather.

DR. LOMBARDI: Thanks. Alyssa, you have the next question.

What data is necessary to support a change in the container closure system during the phase 3 study?

DR. KITCHEL: Thanks for the question, Heather. At that point, sponsors should be providing a detailed description of the new container closure and a justification for the change. In addition to this information, sponsors should also provide information to demonstrate the compatibility of the container closure with the product, to show that the drug product quality is not impacted by the change.

Additional stability and shipping studies will need to be performed to evaluate the stability of the final product stored and shipped in the new container closure. And at the time of licensure, extractables and leachables studies, like Karin described earlier, will need to be performed using the new container closure system.

Thanks. Back to you, Heather.

DR. LOMBARDI: Thanks. The next question is for Karin.

During late-phase IND, can product lots that do not meet release specifications still be administered to subjects?

DR. KNUDSON: Yes. Product lots that do not meet release criteria are considered out of specification and should be rejected. However, it is possible to administer an out-of-specification product—for instance, when the patient has been preconditioned. So there are some situations under which you can administer an out-of-specification product lot.

In that case, we do recommend that sponsors reach out to the assigned regulatory project manager, or RPM, for their IND and provide a risk assessment and a request to release the out-of-specification product before administration to the patient.

Thank you, and back to you, Heather.

DR. LOMBARDI: Thanks, Karin. Alyssa, next question.

What are the expectations for late-stage shipping stability studies?

DR. KITCHEL: During the IND stage, we recommend that sponsors develop and initiate a stability protocol to collect adequate data to establish shelf life, storage conditions, and shipping conditions for timely submission in a license application. The shipping conditions need to be fully validated by the time of licensure.

We recommend that the shipping and storage conditions be qualified before initiating a phase 3 study or whatever study that is intended to support the marketing application. And the worst-case shipping conditions should be evaluated as part of the shipping studies, including environmental conditions and the duration.

Thanks for the question, Heather. Back to you.

DR. LOMBARDI: Karin, the next question is for you.

What is the best approach to obtain FDA feedback about comparability studies?

DR KNUDSON: We strongly, strongly recommend that sponsors submit the comparability protocol as an amendment to the IND with the request for feedback prior to performing a comparability study. Sponsors may also submit a meeting request to the RPM with the intention of discussing the comparability protocol and also asking specific questions that they request feedback with.

In the IND amendment or the meeting package, we recommend that you provide information and justification for your proposed manufacturing change, the risk assessment that you've already performed, and the comparability protocol for our review.

Back to you, Heather.

DR. LOMBARDI: The next question is for Kyung.

When human serum albumin (HSA) is used as an excipient, is it sufficient to indicate that it is a U.S.-licensed product?

DR. SUNG: Thank you for the question. We recommend that sponsors use the safest, highest-quality human serum albumin available, which in most cases would be a version licensed in the United States or United States Pharmacopeia (USP)-grade albumin. We ask that sponsors submit a package insert in their IND and ensure that none of the albumin lots have been withdrawn from the market.

If a U.S.-licensed HSA is not used, then sponsors should submit information documenting that the source and manufacturing of the unlicensed albumin conform to the requirements for U.S.-licensed product as described in 21 CFR part 640, subpart H, or specify if the human albumin is recombinant or isn't.

Thank you for the question. Back to you, Heather.

DR. LOMBARDI: Next question is for Alyssa.

Does FDA expect numerical criteria for all in-process controls and release specifications for pivotal studies?

DR. KITCHEL: That's a great question. In general, for pivotal studies, we do expect that all in-process and final product release specifications have numerical criteria as is

appropriate. As we previously mentioned, it is appropriate to set wide-range numerical acceptance criteria when initiating the phase 3 studies. We expect that sponsors will then refine the acceptance criteria ranges as they collect additional data. For example, quantitative criteria are helpful in assessing manufacturing control and comparability when manufacturing changes are made.

Thanks, Heather.

DR. LOMBARDI: Karin, the next question is for you.

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

DR. KNUDSON: This is a great question. Instead of just focusing on phase 3, I'm going to cover some earlier phases as well, because this is a question we get a lot.

Phase-specific CGMP (current good manufacturing practice) requirements are expected for all products under clinical study. In general, with regards to meeting CGMP requirements, you need to provide increasing information and meet these requirements more and more as product development progresses. We have an FDA guidance explaining the CGMP expectations for phase 1 studies that I highly recommend you take a look at.

Moving on to later phase studies, there should be proper control of the manufacturing process to ensure product safety and quality. This will include proper material control, environmental monitoring, segregation and tracking of your product—which is very important, especially for autologous products or patient-derived products—, deviation investigations, and quality control and quality assurance oversight. All of this should be documented within your IND and, if you're submitting a marketing application, within your BLA.

I do want to say that many sponsors and clinical studies use contract manufacturing organizations and contract testing organizations for their clinical studies. It's important to understand that the IND sponsor themselves is responsible for making sure that CGMPs are followed and that the necessary information is provided under your IND.

With regard to the question about inspections, FDA does generally conduct inspections during the BLA review period. And if we take this to after licensure, there are surveillance inspections and additional inspections if warranted. For example, an inspection may be needed for a supplement introducing a new manufacturing facility after licensure.

Back to you, Heather.

DR. LOMBARDI: Thanks, Karin. Kyung, the next question is for you.

Can multiple scientifically sound and fit-for-purpose potency assay methods be used at the start of a pivotal clinical study and then, as data is collected, only one single final potency assay be used and validated for the BLA submission?

DR. SUNG: Yes. Developing multiple potency assays for use in a pivotal clinical study and narrowing them down to a few or a single final potency assay would be acceptable. We recommend that you collect sufficient information during the IND stage to justify the selection of the final potency assays and their acceptance criteria.

Thank you for the question. Back to you, Heather.

DR. LOMBARDI: Thank you. The next question is for Alyssa.

Besides potency, what are some common challenges for late-stage studies?

DR. KITCHEL: In general, if there are manufacturing changes, comparability is certainly an issue that we come across a lot for sponsors due to either scale-up or scale-out, as well as the introduction of commercial manufacturing facilities when they're transitioning to commercialization readiness and changing those facilities.

We recommend that you move to your expected commercial configuration prior to conducting your pivotal study. This will help reduce the risk of your development process. We also recommend that you use the intended commercial manufacturing process at the intended manufacturing facility with the expected lot release testing strategy you plan to implement. This will position you to have maximal data at your disposal to use in your licensing application and reduce the complications related to comparability assessments that I previously mentioned during our BLA review.

Back to you, Heather.

DR. LOMBARDI: Thanks, everyone. I think that's all we have time for today in terms of our live questions. We appreciate all the questions that you submitted.

I'd like to thank you all for joining and for attending today's OTP town hall. I'd also like to extend a huge thank you to our panelists. I think you all did a great job today. Thank you so much. As a reminder, a recording of today's town hall will be posted on our website, FDA.gov, in the coming weeks.

We aim to host another town hall before the end of the year, as well as a number of other events this fall. One event in particular I'd like to mention is an upcoming patient listening meeting on patient and care partner perspectives on safety considerations for approved gene therapy treatments for rare diseases. This event is scheduled for Friday, September 20. It's fully virtual, and registration is still open for those who would like to attend. My colleague will add a link to that event in the chat box.

You can find more information about the upcoming listening meeting, town halls, and other OTP-hosted events on our OTP meetings and workshops page, which we'll share in the chat box as well.

We appreciate your attendance and your feedback. Once again, thank you for joining. I hope everyone has an awesome day.