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FDA CBER OTP Town Hall:
Gene Therapy Manufacturing CMC and Facility Readiness for BLAs and Post-licensure Changes

October 22, 2025

Note: This document is not official FDA guidance.

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DR. KIM SCHULTZ: Good afternoon, everybody, and thanks for joining us for 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. Kim Schultz, and I'm the Director of the Division of Gene Therapy 2 in the Office of Gene Therapy in OTP. I will also be your moderator for today's event.

During today's town hall, we plan to answer questions regarding CMC and facility readiness for BLA submissions and post-licensure changes for gene therapy manufacturing facilities.

If you've been following our OTP virtual town hall series, you may know that we've hosted a number of town halls on gene therapy CMC, but today's event is the first time we've focused specifically on CMC and facility readiness, and we look forward to answering your questions. This is also the first time we've joined forces with our colleagues from CBER's Office of Compliance and Biologics Quality (OCBQ) to answer your questions. For those of you who may not be familiar, OCBQ leads our pre-licensed facility inspections and is an active participant in the review of BLA original submissions and supplements, among their many other responsibilities. So, we're grateful to have them here today to share that expertise.

We recognize that it's been a while since we've had an OTP virtual town hall, and we're excited to be back. It also seems like our audience is excited to be back too, because we quickly exceeded our registration capacity for this event. To accommodate those registration limitations and ensure all of our interested stakeholders are able to join today, we've set up a livestream on the FDA YouTube page for folks to tune in. So, whether you've joined us on Teams or YouTube, we welcome you and thank you for being a part of today's event.

Before we begin, I'd like to share some background about OTP's town hall series. OTP launched our virtual town hall series in 2022 to engage with product developers and researchers. These town halls have a question-and-answer (Q&A) format, and our goal is to answer your questions to support development of OTP-regulated products. I'm happy to share that today's event is the tenth town hall in our series. For those who are interested, you can revisit the recordings from our previous town halls on FDA.gov 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 recording will be posted on the FDA's website in the coming days, as well as on the FDA YouTube channel. Closed captioning for this event is available in Teams and on YouTube.

Thank you for the questions you submitted in advance, and we look forward to receiving more questions from you during today's event. We'll address as many as we can, but please note, we are not able to answer any questions about specific products, draft guidance documents, or guidance documents that are currently under development.

And for the live question portion of today's town hall, we're going to try something a little new and different to ensure that folks, whether they're joining us on Teams or YouTube, have a chance to submit questions. Please e-mail your questions directly to us at OTPPublicEventsandWorkshops@fda.hhs.gov. It's listed here on the slide and once again that e-mail address is OTPPublicEventsandWorkshops@fda.hhs.gov. And in case you don't have a chance to write that down right now, we will have the e-mail address posted on the upcoming slides for your reference. We do appreciate your questions, and as I mentioned, we'll do our best to answer as many as we can during today's event. You may also use that e-mail inbox to reach out to us if you're experiencing any technical difficulties or to submit feedback.

I'd like to take a moment to introduce our three experts who will answer your questions about gene therapy manufacturing and facility readiness for BLAs and post-licensure changes. Our first panelist is Dr. Jacob Bitterman, who is a CMC reviewer in the Office of Gene Therapy. Our next panelist is Dr. Jessica Chery, who is a senior CMC reviewer in the Office of Gene Therapy. And our final panelist is Dr. Christine Harman, who is a lead consumer safety officer in the Office of Compliance and Biologics Quality. Thank you to our panelists for your time and sharing your expertise today.

Today, we'll begin by answering questions submitted during registration and then we'll respond to some of the questions submitted to us via e-mail today. Again, that e-mail address is here on the screen and it is OTPPublicEventsandWorkshops@fda.hhs.gov. We'll try to answer as many questions as we can, but as I mentioned, we aren't able to answer any questions about specific products, draft guidance documents, or guidance documents that are currently under development. And just a reminder that this town hall is being recorded, so even if you can't stay for the entire event, you can revisit the full discussion after it's posted on our website.

Okay, so let's begin with our first question. For our first question, I'm going to ask Christine for a response.

Will all facilities listed in the BLA be inspected or only ones with major manufacturing activities? Is there a difference between U.S. and foreign facilities inspection goals?

DR. CHRISTINE HARMAN: Thank you, Kim. Good afternoon, everyone. I'm happy to start off with answering the first question.

Not necessarily all facilities listed in a BLA will be inspected. The agency uses a risk-based approach to determine which facilities require a pre-approval inspection. Typical considerations in determining if an inspection is needed includes several factors. First, the criticality of the manufacturing steps performed by the facility is considered. Facilities such as those performing drug substance manufacturing, drug product manufacturing, and sterile operations for biologics are at the highest risk and thus considered for inspection. Also, facilities using new or complex manufacturing processes, novel technologies, or are producing first in class biologics are likely to be inspected. The other consideration is the inspection history and compliance status of the facility. Upon receiving a submission, we immediately begin the process of evaluating the inspection history, if applicable, and compliance status of all manufacturing facilities and drug product testing facilities listed in the BLA to determine if a pre-license inspection is needed. In some cases, depending on our evaluation, we're able to waive the need for an inspection. If we cannot waive based on our evaluation, then we begin the process of scheduling inspections and aim to schedule the inspection at or around mid-cycle of the review timeframe.

Regarding inspections of U.S. versus foreign facilities, there is no difference with the inspection goals. We, FDA, apply the same cGMP standards to both domestic and foreign facilities with no difference in inspection goals or expectations in meeting the same quality standards for products intended for the U.S. market. However, with foreign inspections, there may be some logistical obstacles that would not be experienced with U.S. inspections. These could include scheduling challenges, travel restrictions, or coordination requirements with foreign regulatory authorities.

Also, I can mention for certain countries with Mutual Recognition Agreements, FDA may rely on inspections conducted by foreign regulatory partners, potentially reducing the need for FDA-conducted inspections. However, this typically has limited applicability to biologics due to the complexity of biological processes and associated regulations. Back to you, Kim.

DR. SCHULTZ: Thanks Christine. Our next question is for Jacob.

For cell and gene therapy (CGT) products, how does FDA assess risk when categorizing post-approval manufacturing changes, particularly those involving scale-up or automation of manual steps?

DR. JACOB BITTERMAN: Thanks for the question, Kim.

FDA's framework for assessing risk when categorizing a post-approval manufacturing change is described in the guidance document, "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products," published in June of 2021. Each post-approval change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the BLA must be reported. These changes can be reported into one of three categories depending on the potential of the change to have an adverse effect on the identity, strength, quality, purity, or potency of the product.

Changes that have a substantial potential to have an adverse effect on product quality should be reported as a prior approval supplement or PAS. A PAS must be approved by FDA prior to distribution of lots manufactured after the change.

Changes that have a moderate potential to have an adverse effect on the product quality may be reported as a Change is Being Effected (CBE) 30 or CBE 0. If the applicant does not receive communication from the FDA, they may begin distributing post-change slots after 30 days for a CBE 30 or immediately for a CBE 0.

Changes that have a minimal potential to have an adverse effect on product quality can be documented in an annual report after implementing the change. Upon receipt of a supplement, FDA performs an initial review and may communicate a change to the reporting category of the supplement. Specific examples of manufacturing changes and the associated reporting categories are described in the appendix of the 2021 guidance document that I mentioned earlier. Scale up generally requires a PAS while automation of an existing manufacturing step may generally be reported as a CBE 30, unless the product quality risk of the particular automation is high. If you are unsure about the appropriate reporting category for a manufacturing supplement, you may reach out to the regulatory project manager (RPM) for your file to obtain advice from FDA before submitting the supplement. Back to you, Kim.

DR. SCHULTZ: Thanks Jacob. Our next question is for Jessica.

What does the FDA require when adding a new GMP facility to increase product manufacturing capacity post-licensure?

DR. JESSICA CHERY: Thank you for this question, Kim.

Adding a new manufacturing facility to increase capacity post-licensure is a substantial change that requires FDA approval via a prior approval supplement or PAS, as was referred to before, and this PAS needs to be approved before distributing product from the new site. The PAS should include comprehensive documentation starting with a risk assessment that follows the June 2006 ICH Q9 guidelines. The PAS should also include technology transfer documentation with a rationale for the manufacturing increase. The risk assessment should evaluate impacts on manufacturing steps, in-process parameters, method equivalence, critical process parameters, and product quality to help inform a statistical approach for comparability studies. For multi-product facilities, this risk assessment should also consider the potential for cross-contamination and impacts on other products manufactured at the site.

The findings from the risk assessment should be used to inform the comparability studies between the manufacturing facilities. Comparability studies represent a critical part of adding a new manufacturing facility and should evaluate effects on product critical quality attributes such as identity, purity, potency, strength, as well as stability and equivalence of analytical methods at the new facility. Comparability studies should use full-scale lots and demonstrate that the change does not adversely impact the quality of the licensed product. We really recommend applicants submit a detailed comparability protocol, also called a post-approval change management protocol, for FDA feedback before conducting any studies to introduce a new manufacturing facility.

Once the comparability studies have been completed, the results from the comparability studies should be submitted as a PAS. The validation section in the PAS should include process performance qualification (or PPQ) results and analytical method comparability data covering identity, potency, purity, safety testing, and stability from the new facility. You may consider designing your studies so that the same lots can be used for the comparability study and the PPQ study. For additional guidance, I recommend you refer to the June 2021 FDA document titled "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products," as well as the July 2023 draft guidance titled "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products." Now I'd like to hand this question over to Christine who can provide some insights on inspections and cGMP status when introducing a new facility.

DR. HARMAN: Thank you, Jessica.

So, for a new facility, detailed information regarding the facility should be included in the PAS in section 3.2.A.1. This information should include an overall description of the facility and design, including diagrams outlining facility flows for personnel, equipment, materials, waste and product. Also, the classifications of the manufacturing areas and air pressurization maps detailing the air flows & pressure differentials. Additionally, a description and qualification summary of the HVAC system used for the manufacturing areas, in addition to the details of the routine environmental monitoring program and summary of the environmental monitoring performance qualification should be included.

If a multi-product facility, a description of the types of products manufactured in the facility should be detailed in your PAS submission. Also, we recommend that you provide a detailed cross-contamination control strategy that is based on a risk assessment for the introduction of new products into your facility. This risk assessment should be comprehensive in evaluating all aspects of your manufacturing process that would be at highest risk of cross-contamination, with considerations in the facility design, such as the use of positive pressure bubbles, negative air sinks for containment and protection strategies; manufacturing process controls, such as closed system processing, using dedicated equipment vs. shared equipment, or single use disposable equipment; environmental controls, such as disinfectant efficacy, cleaning and sanitization; and procedural controls, such as waste handling, gowning, and change-over procedures.

Other details that should be included in the PAS are a description of product contact materials, such as single use disposable equipment, and other major equipment, and the qualification summaries in addition to cleaning validations if applicable. Also, summaries of relevant validations related to sterilization processes and disinfectant efficacy information for the cleaning and disinfecting agents that are used in the facility should also be provided.

Regarding inspections, more than likely if the new facility does not have an inspection history, we will be performing a pre-approval inspection. However, we evaluate the facility at the time we receive the PAS to determine if an inspection is needed. We expect facility qualifications to be completed at the time of the PAS submission. Additionally, the facility should also be inspection ready, which means that the inspection of the facility could reasonably be conducted, and post-inspection activities completed within the timeframe of the review cycle to meet the action due date. This is very important; if we are unable to finish our review activities including the post-inspectional activities by the action due date, this could negatively impact the regulatory action on the supplement. I would also like to note that it is our expectation that the facility be in production, as to allow the inspectors during the inspection to observe active manufacturing. We do understand that with some products, production of the drug substance or drug product may not be a frequent occurrence. For those cases, we accept observing a mock run of the production process. We recommend in these

cases, to discuss with us ahead of time, preferably prior to submitting a PAS or when submitting the PAS. Back to you, Kim.

DR. SCHULTZ: Thanks to both of you for that comprehensive answer. The next two questions are going to be about inspections, and I'm going ask Christine to answer them.

For a company preparing its first BLA for a cell or gene therapy product, where the manufacturing site has not previously been inspected by FDA, what guidance can FDA provide on expectations for inspection readiness and the logistics around planning and scheduling the facility inspection?

DR. HARMAN: Thanks again, Kim, for this question.

As I mentioned previously, our expectation for inspection readiness is that the facility is ready for inspection at the time of the BLA submission. If the facility is not ready at the time of the inspection, the 356h form should indicate when the facility will be ready for inspection. Our scheduling of the inspection is very dependent on the production schedule of the facility; thus, it is important for the facility to be in active production particularly during mid-cycle of the review timeline. We aim to schedule our inspections at mid-cycle as this allows us time to understand the information on the process, the facility design, and critical equipment that is submitted prior to the inspection. Additionally, this allows us time to complete all post-inspection activities within the timeframe of the review cycle to meet the action due date. If we end up performing the inspection late in the review cycle due to delays related to inspection readiness of the facility, this could negatively impact the regulatory action on the BLA submission, thus it is very important for the facility to be inspection ready at the time of the submission or at very least early in the review cycle. Back to you, Kim.

DR. SCHULTZ: Christine, can you also give us a little bit more information on inspections?

Specifically, do you provide a detailed checklist of what is needed for an institution to prepare for inspections?

DR. HARMAN: Thanks again, Kim.

We do not have a document that includes a specific checklist to reference for preparing for an inspection; however, to understand our approach to conducting inspections, which may be helpful for preparation, you can reference the Compliance Program Guidance Manual Chapter – 45 Biological Drug Products. This document can be found on our website, FDA.gov. This outlines our approach to conducting inspections as related to biologics. In a nutshell, it’s a systems-based, risk management approach, which breaks down the facility into

key systems that include quality system, facilities and equipment system, materials system, production system, packaging and labeling system, and laboratory control system and focuses on three critical elements within each system that include standard operating procedures, affectionately known as SOPs, training, and records. Also, we recommend that you reference cGMP regulations in 21 CFR 211 and any applicable regulations, such as 21 CFR Parts 600-680 for biologics, 1271 for human cells and tissues, and 21 CFR 820 if it's a combination product, which includes purchasing controls, design controls, management responsibilities, and corrective and preventive actions as related to the device component of the combination product. Understanding the applicable regulations will ensure that your facility is operating in compliance with all applicable regulations as related to the product that is being manufactured in your facility.

DR. SCHULTZ: Thanks for that helpful information to prepare for inspections. We're going to switch gears a little bit more and now talk about some changes to your application. So, the next question is for Jacob.

Given the high frequency of manufacturing changes in gene therapy products, how can manufacturers use comparability protocols to streamline post-approval changes?

DR. BITTERMAN: Thank you for this question and the opportunity to clear up some potential confusion. First, I would like to point out that FDA has a guidance document titled "Comparability Protocols for Post-approval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA." The term comparability protocol when used in FDA guidance documents and applications is synonymous with what is referred to as a "post-approval change management protocol" in ICH guidance documents and other international regulations. A comparability protocol is a comprehensive, prospectively written plan for assessing the effect of a proposed post-approval CMC change on product quality. Submission of a comparability protocol should include a description of the proposed changes, a risk assessment of the potential effects of the change on product quality, and a description of the specific tests and acceptance criteria to be achieved to demonstrate the lack of adverse effect on product quality.

The protocol can be submitted with an original BLA, or as a prior approval supplement. When submitting a protocol in an original BLA, please keep in mind that the proposed manufacturing changes should be well understood to facilitate our review of the protocol during the review cycle. Review of comparability protocols may take significant back and forth during the review cycle and could potentially delay a review decision or require removal from the application, therefore you might find it easier to submit comparability protocols as prior approval supplements after your BLA is approved.

In the post-approval setting, a comparability protocol can be submitted once a manufacturing change and the potential risks to the product are well understood. Submitting protocols for FDA's approval well in advance of the need to implement the change can facilitate a more efficient and predictable implementation process for the manufacturer and a more efficient FDA review.

As part of the comparability protocol, manufacturers may request a reduced reporting requirement for the manufacturing change if the protocol is executed as specified and the predefined acceptance criteria are met. This could mean a change that would normally require a PAS could be reported as a CBE submission after agreement. However, a reduced reporting requirement is not guaranteed. For example, a comparability protocol involving a change of manufacturing site or addition of manufacturing site will likely require a PAS even with agreement to a comparability protocol. This is due to the potential need for inspection of the manufacturing facility. For more information on requirements for comparability protocols, please refer to the guidance document I mentioned earlier. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. And before I get to the next question, I'd just like to remind everybody that if you have a question for our panelists about the topic of today's town hall, please submit those to the e-mail inbox you see here on the screen, which is OTPPublicEventsandWorkshops@fda.hhs.gov. Now the next question is for Jessica.

What are the best practices for post-approval capacity study design for manufacturing expansion, capacity protocol submission, and demonstrating adequate capacity?

DR. CHERY: Thank you for this question, Kim. There are a few different ways that a product's manufacturing can be changed to increase capacity or to increase the amount of product that is available. For example, a manufacturing process scale can be increased by moving from a 50L bioreactor to a 200L bioreactor. This is usually referred to as scaling up. Or the number of parallel manufacturing lines can be increased, usually called scaling out. I am going to answer this question from the perspective of scaling out an ex vivo modified cell manufacturing process.

Some issues that might occur with increased capacity are challenges with process consistency and reproducibility, longer processing times, cross-contamination, or increased human error due to insufficient operators. Therefore, as part of your capacity increase, you should use a risk assessment to identify potential areas of greatest risk to product quality and safety under expanded capacity conditions. The capacity study should comprehensively evaluate how capacity increases affect product identity, strength, quality, purity, and potency to demonstrate that increased throughput does not adversely impact safety or effectiveness of the licensed product. The study design should assess whether the product manufactured at

expanded capacity meets established acceptance criteria for lot release, in-process parameters, critical process parameters, and normal operating ranges. There should be specific tests and acceptance criteria to demonstrate continued ability to produce product that meets historical quality standards. For products with limited starting material, such as autologous products, you may include lots with healthy donor material for the increased capacity lots. However, you would need to justify how the healthy donor material adequately represents manufacturing challenges and processing parameters you would normally encounter with patient material.

Manufacturing methods, facilities, and controls used for production, processing, packaging, packing, holding, testing, and quality control must continue to comply with current good manufacturing practice or cGMPs at the increased capacity, and you should demonstrate that all activities have been adequately scaled to not delay product production. Because capacity expansion is a substantial change with the potential for adverse effects on product quality, the study should be submitted as a PAS and requires FDA approval before distributing product manufactured at the higher capacity. We recommend that applicants submit a capacity protocol as a PAS seeking FDA feedback before performing their capacity studies. Once a capacity protocol is approved by FDA, the capacity study reports may be submitted as a CBE if all the acceptance criteria are met. Back to you, Kim.

DR. SCHULTZ: Thanks, Jessica. The next group of questions have to do with quality control testing. So, let's begin with Christine.

In the BLA, should the comprehensive description of the QC laboratories include details on the QC GMP laboratories for QC reagent qualification although patient material would not enter that area?

DR. HARMAN: Thanks for this question. There is no requirement to include a description of the QC laboratories in the BLA submission. I'd like to refer you to the several product-specific FDA guidances for industry regarding the chemistry, manufacturing, and controls information and establishment description information that is expected to be submitted in the BLA application. However, it should be noted, that QC laboratories are subject to pre-license inspections, specifically, QC labs that perform critical release testing of the product, and therefore, are expected to follow applicable cGMP requirements. Back to you, Kim.

DR. SCHULTZ: Thanks, Christine. The next question is for Jacob.

Do you have any guidance on analytical method lifecycle management post approval?

DR. BITTERMAN: Yes, we do have some advice for analytical method lifecycle management. Changes to analytical methods after approval can range from relatively minor reagent changes to changing an analytical method entirely for a specific critical quality attribute. A risk-based approach to analytical method lifecycle management is described in the guidance document Q14 Analytical Procedure Development. Most changes to an analytical method will require an appropriately designed bridging strategy based on risk. This may involve limited verification of the procedure's performance after the change, validation of the procedure after the change, or a full-scale comparative analysis of representative samples. The reporting category for a supplement for these changes will also be determined based on risk, as described in the guidance for industry "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products" published in June of 2021. Specific examples are given in the appendix of that guidance. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. We'll stay with you for the next question as well.

If an analytical method testing site changes, how should equivalence be demonstrated?

DR. BITTERMAN: When an analytical testing site changes, data should be provided to show that the methods at the new site are performing equivalently to those at the original site. This typically involves partial or full validation of the procedure at the new site followed by a bridging study. In the bridging study, representative samples should be analyzed at both sites, and the results compared using pre-defined acceptance criteria. For additional guidance on analytical method transfers, please refer to USP chapter 1224. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. The next question is for Jessica.

When can replication-competent lentivirus (RCL) testing be removed from the ex vivo modified cell drug product commercial release panel?

DR. CHERY: This is a great safety question. If an applicant has accumulated manufacturing and clinical experience demonstrating the transduced cell product is consistently RCL-(replication-competent lentivirus) negative, this data may be submitted as a PAS to support reduction or elimination of RCL testing for ex vivo genetically modified cells. We recommend including patient monitoring data for the product in the submission. FDA will make a final determination on removing the RCL the testing from the commercial release panel based on sufficiency of the data. For additional details, please refer to the FDA January 2020 guidance titled "Testing of Retroviral Vector-Based Human Gene Therapy Products for

Replication Competent Retrovirus During Product Manufacture and Patient Follow-up." Back to you, Kim.

DR. SCHULTZ: Thanks, Jessica. Once again, before I move on to the next questions, I just want to remind everybody that you are able to submit live questions to the e-mail address listed below: OTPPublicEventsandWorkshops@fda.hhs.gov. The next question is for Christine.

If the manufacturing process for a sterile parenteral drug is performed in a completely closed system, can the manufacturing equipment be located outside a cleanroom, or is a controlled environment still required?

DR. HARMAN: This is a great question, and this topic actually comes up a lot, particularly in Type C meetings. So, for cell and gene therapy products, we typically expect manufacturing in controlled environments that ensure sterility assurance and product quality. The specific ISO classification depends on the nature of the product, manufacturing process, and risk assessment. Our guidances, such as those for human cells, tissues, and cellular and tissue-based products emphasize appropriate environmental controls as opposed to mandating specific ISO classifications. Our focus will be on the demonstration that the manufacturing environment is suitable for maintaining microbial control of the product, either sterile or bioburden controlled.

With completely closed systems, our expectation is a minimum classification of ISO 8, however, closed systems may allow for flexibility regarding environmental requirements depending on risk and provided that the system has been demonstrated to be closed. This would include performing aseptic process simulation, or APS, that covers all the process steps within the defined aseptic boundary. If the entire process is considered aseptic, then all process steps, including worst-case, closed process steps should be demonstrated in the APS. If there is a final sterile filtration step, then only process steps occurring after the final sterile filtration require demonstration in the APS. For example, in the case of viral vectors which can be sterile filtered, only the process steps after sterile filtration would need to be included in the APS.

I do want to clarify though that for open aseptic processing steps, these steps should be performed in an ISO 5 environment with an ISO 7 background.

One consideration I would like to leave you with regarding this question is the emphasis on demonstration that the manufacturing environment is suitable. If you are not routinely monitoring the environment, as would be the case if performing manufacturing outside a cleanroom, how would you know if the environment is suitable and in control. This should be

considered in your risk assessment and the environment in which you intend to perform closed system processing should be scientifically justified. Back to you, Kim.

DR. SCHULTZ: Thanks, Christine. And we'll stay with you for the next question as well.

What are the common findings found during an inspection of cell and gene therapy facilities?

DR. HARMAN: This is also a great question, so I am going to spend some time on this one. The most common deficiencies we encounter usually revolve around sterility assurance, which from our perspective is the highest risk and what we focus on the most during an inspection, particularly with facilities that are performing aseptic processing. A prime example of observations in sterility assurance includes deficiencies with the APS and the validation of the aseptic process in general. In some cases, the aseptic boundary is not clearly defined, which leads to deficiencies in the risk assessment in determining which steps should be covered in the APS. These deficiencies become more apparent when we are on inspection, as we're able to carefully review all the procedures and the intricate details of the preparation and the process. One of the most common and significant deficiencies is in relation to the preparation of the various components, the medias and the buffers, that are introduced into the aseptic boundary of the overall process, and in most cases with cell and gene therapy products, the entire manufacturing process is considered aseptic, as there is really no final sterile filtration step for the drug product.

Anything and everything going into the process needs to sterile. The preparation, including the sterilization of the components used in the aseptic process, is often overlooked with respect to APS and the aseptic process in general. One example, which we have seen very frequently is that the sterile filters used for sterilization of the components are not validated. These filters tend to be used for custom medias and buffers that have small working volumes, and they are more bottle top filters or syringe top filters are used to sterilize the components. These filters, which are the primary mode to sterilize components, are often overlooked with respect to validation. There have been many instances of this type of deficiency observed on inspections that have resulted in 483 observations.

I strongly recommend that you evaluate the entire aseptic process and consider all the components, the medias, the buffers, that are required to be sterile and that are introduced into the aseptic boundary and include the preparation of these components in your APS risk assessment and ensure also that all the sterilization processes that are performed, including sterile filtration of the components, are validated to maintain the sterility assurance of the process. This validation could either be validation of the sterile filters or using purchased

sterile components that are then combined aseptically. If aseptically combining the sterile components, these process steps should be included in the APS.

However, if I am to choose the most common and most significant deficiencies that I have seen on inspection, these are related to quality system failures and inadequate quality assurance oversight. Quality System Deficiencies are commonly found in three areas:

Insufficient CAPAs and failure to implement corrective and preventive actions addressing all identified root causes, despite thorough investigations that identify multiple contributing factors.

Inadequate CAPA effectiveness verification; that includes lack of proper follow-up to confirm CAPA effectiveness, often evidenced by deficient documentation and repeated deviations.

And delayed closure timelines, referring to untimely closure of deviations and CAPAs.

The impact of these deficiencies create a "snowball effect," where improperly handled deviations lead to repeated occurrences, typically stemming from insufficient quality oversight. Timely deviation management—regardless of the severity—is critical for preventing additional quality issues. The failure of closing deviations and CAPAs in a timely manner to prevent repeated occurrences, I would say, is the most frustrating issue to encounter on inspection and usually signals major issues in the quality system and quality oversight. Back to you, Kim.

DR. SCHULTZ: Thanks, Christine, for that very informative answer. Our next question is for Jacob.

Does FDA have any advice on out of specification investigations? How should retesting be performed? Can retest results be averaged with the original result?

DR. BITTERMAN: Thanks for this question, as issues with out of specification (OOS) investigations have sometimes been observed by FDA during inspections of cell and gene therapy manufacturers. First, I would like to point out that OOS investigations are discussed in the FDA guidance document titled “Investigating OOS Test Results for Pharmaceutical Production.”

It is important that a manufacturer have SOPs that cover the procedures for OOS investigations. These SOPs should describe how investigations are performed, as well as how any retesting or other experimental protocols will be designed, approved, and executed.

The guidance discusses a two-phased approach to investigations of OOS results. In Phase 1, termed the laboratory investigation, the manufacturer should investigate the performance of the assay that produced the OOS result. This investigation is to determine if there was an obvious laboratory error, such as an incorrect dilution, a system suitability failure, an instrument error, or any other identifiable error. When clear evidence of a laboratory error exists, the original testing result can be invalidated at the end of the investigation. In this case, the results of a new assay can be used to replace the invalidated result.

When there is not clear evidence of a laboratory error, the investigation should move to Phase 2. The Phase 2 investigation should include a review of the production of the batch in question. The records and documentation of the manufacturing process should be reviewed to determine a possible cause of the OOS. If this production investigation confirms the OOS and identifies a root cause, the OOS investigation can be ended and the product rejected. If no cause is identified from the production review, additional laboratory testing may be performed. Some firms have been found to perform a single or limited number of retests until the results are no longer OOS, a process we call "testing into compliance." This process is not an acceptable retesting practice. Any retesting should be performed using a pre-approved protocol that indicates the maximum number of retests. The SOP should specify how the number of retests is determined, and this number should be based on scientifically sound principles, including a consideration of the variability of the analytical method.

Following a retesting procedure, the results should be provided to the quality unit. The quality unit is ultimately responsible for interpreting the results of the investigation and making the batch disposition decision. The guidance document I referred to earlier discusses considerations for the quality unit in batch disposition decisions. Please keep in mind that all aspects of an OOS investigation should be documented within the quality system. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. The next question is for Jessica.

What are FDA's requirements for incoming materials, including: (a) testing (b) qualification approaches for raw materials not available in GMP grade; and (c) timing requirements for implementing incoming raw material testing?

DR. CHERY: Thank you, Kim. This is a really good question to help applicants prepare for a BLA submission.

According to 21 CFR 312.23(a)(7)(iv)(b), the sponsor of an IND must provide a list of all materials used in manufacturing and a description of the quality or grade of these materials.

In 21 CFR 610.15, which deals with constituent materials used in manufacturing of licensed biologics, under which gene therapy products are classified, all ingredients used in a licensed product should meet generally accepted standards of purity and quality. Finally, 21 CFR 211.84 explains cGMP expectation for incoming material control, including identity testing.

Regardless of the purported grade of the material, you should perform a risk assessment to evaluate the quality of the raw material and its potential impact on product quality. The risk assessment should consider identity, strength, quality, purity and stability of the raw material. Qualification studies should be designed based on the risk assessment findings and include robust testing to ensure that the starting materials meet predetermined specifications. This includes identity testing to confirm the material, purity testing for absence of contaminants, functional testing if applicable, and safety testing such as sterility, endotoxin, and mycoplasma, depending on what is the raw material.

The ICH Q5A(R2) guidance discusses some viral testing studies needed for a BLA for a cellular product, so I refer you to that guidance as a useful resource. FDA's January 2020 Guidance titled "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" provides some clear examples of starting materials typically used in gene therapy products. Therefore, I would also recommend you check out that guidance for more details on the level of testing that FDA expects for starting materials used in gene therapy product manufacturing.

Now in terms of the timing for material testing, a complete incoming raw material testing plan, along with necessary supplier quality agreements, should be developed at the start of pivotal studies. These need to be in place at the time of BLA submission. An incomplete testing plan may delay approval if FDA determines that the missing data could significantly impact product quality, safety, and effectiveness, and if there is insufficient time during the review clock to resolve the testing gaps. Back to you, Kim.

DR. SCHULTZ: Thanks, Jessica. We'll stay with you for the next related question that's on the specifics about control of cellular starting material.

What are FDA's expectations for cellular starting material, including: (a) incoming specifications for cell counts, and (b) qualification requirements such as process characterization and process performance qualification (PPQ) in the BLA package?

DR. CHERY: Thank you for that question. Incoming starting material specification, regardless of the type of material, should be determined using a risk-based approach. For cellular products, the cell count specifications should ensure adequate material for successful manufacturing while considering patient variability and disease state impacts. In advanced

disease states, apheresis material may contain low cell counts that limit the ability to establish high acceptance criteria for incoming material. Regardless of these constraints, the acceptance criteria for incoming cell counts should be informed by product manufacturing experience during the clinical study. Cell count specifications supported by engineering runs or process development data and successful manufacturing from IND studies can be used to justify the specifications used in the BLA package, including the PPQ studies. The applicant should determine the attributes that must be controlled for acceptance of the cellular starting material into the manufacturing process and provide justification in the BLA. The PPQ runs should ideally include cellular material across the range that has been demonstrated to be adequate for successful manufacturing. Thanks, and back to you, Kim.

DR. SCHULTZ: Thanks, Jessica, for that information on incoming material control. Our next question is for Christine.

Will a novel excipient manufacturer be subject to a pre-license inspection (PLI)? What information is needed for the facility section of the BLA? What supportive information is required as part of the BLA submission?

DR. HARMAN: Thanks, Kim. These are great questions, and we've actually encountered these questions before in pre-BLA meetings. The answer to these questions regarding the PLI and facility information is dependent on how the excipient is manufactured and used with the drug product. For example, if the novel excipient is separately filled into a sterile final container and administered separately with the drug product, this raises the level of risk regarding sterility assurance, thus the manufacturing facility is subject to evaluation, and we expect that information regarding the facility and equipment be provided in the BLA.

Additionally, with this scenario, an inspection of the facility may be necessary after we evaluate the risk in association with the manufacturing process, if it is aseptically processed, in addition to an evaluation of the inspection history and manufacturing experience of the facility.

However, if the novel excipient is incorporated into the drug product during manufacturing, there would not be any separate evaluation of the facility that manufactures the excipient as it would be evaluated under the quality system of the manufacturer that is using the excipient in the manufacturing process. In this case, facility information of the novel excipient would not be required to be included in the BLA. Now I'm going to pass it over to Jacob to answer the question regarding supportive information to provide with the BLA.

DR. BITTERMAN: Thanks, Christine. Some novel excipients such as novel lipid components of a lipid nanoparticle drug product can affect the quality and performance of the

drug product. The level of information included for the novel excipient in the BLA submission should be comparable to that for a drug substance. Please keep in mind that this information needs to be included in your BLA and cannot be cross-referenced to a master file. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob and Christine, for that information on excipients. We did receive a number of questions in the pre-registration questions that are related to CBER lot release, and so the next three questions are for Jacob and will hopefully clear up the CBER lot release process.

What are the criteria that determine if CBER lot release will be necessary for a licensed recombinant AAV vector? And how does CBER lot release work?

DR. BITTERMAN: Thanks, Kim. According to the regulations at 21 CFR 610.2(a), manufacturers may be required to submit samples from all lots of a licensed biological product together with protocols showing results of applicable tests. We recognize that most AAV products are limited in batch size, and we generally do not require submission of samples of AAV products to CBER for lot release testing on a routine basis. However, we do require that manufacturers submit a lot release protocol showing results of drug substance and drug product tests for each lot intended for commercial distribution. The lots must not be distributed until CBER communicates that the lot is released.

To facilitate this process, applicants should submit a lot release protocol, or LRP, template in module 3 of the BLA. The LRP template is a document that is drafted by the applicant. It should include the name of the firm, the name of the product, the license number, lot number, date of manufacture, and signature of person who reviewed and approved the information in the LRP. The template should include the name of each assay, test date, acceptance criteria, and space for each test result. The LRP template should include all release tests for the drug product lot as well as release test results for the drug substance lots used to formulate the drug product. During review of the BLA, CBER may request changes to the LRP template, or may request other information to be added to the LRP template.

After approval, applicants can submit the completed LRP for each lot through an electronic system. CBER makes an effort to review all lot release protocols within 30 days of receipt. If there are urgent circumstances, applicants may request an expedited review of the lot release protocol.

For further information on CBER lot release, please refer to the FDA guidance document "Providing Lot Release Protocol Submissions to the Center for Biologics Evaluation and

Research (CBER) in Electronic Format" published in February 2019, and the CBER SOPP 8408.3. Back to you, Kim.

DR. SCHULTZ: Thanks. The second question on CBER lot release:

Does every single lot have to go through the CBER lot release process or can you propose to remove the CBER lot release requirement after a certain amount of time or lots manufactured?

DR. BITTERMAN: After the initial BLA approval, all drug product (DP) lots must go through the CBER lot release process. Manufacturers may, after significant post-approval manufacturing data is available, submit a supplement to request the product be moved from lot release and be put onto surveillance. If the supplement is approved, then a limited number of lots are submitted periodically to CBER, but a final release from CBER is not necessary prior to distribution of the product.

DR. SCHULTZ: And then for the last question on the CBER lot release process.

If your launch lot is included in your original BLA, do you need to submit the launch lot for CBER lot release after BLA approval and wait for CBER lot release prior to launch?

DR. BITTERMAN: As I just discussed, we ask that applicants include a draft lot release protocol template in their initial BLA. During the review cycle, FDA may propose changes to the protocol. Once the protocol has been finalized, an applicant should work with CBER's Product Release Branch to gain access to the electronic gateway used to submit lot release protocols. A limited number of launch lots can be submitted for CBER lot release before the BLA review is completed. However, no lots may be released until after the BLA is approved and CBER communicates the lot release decision. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob, for your answer to that question and all the questions that related to CBER lot release. We'll go to Christine for the next question.

Are there any considerations to be aware of regarding container closure integrity testing for cell and gene therapy products?

DR. HARMAN: Thanks, Kim. This is a very good question, and perfect timing for this, as we have recently been dealing with deficiencies related to Container Closure Integrity Testing (CCIT) for cell and gene therapy products. A majority of the deficiencies revolve around the positive controls, or lack thereof, particularly with the probabilistic methods that

are used such as dye ingress and microbial ingress. With these probabilistic methods, an appropriate positive control is critical for establishing the sensitivity of the method and should be representative of the detection limit, which is the smallest leakage rate/size that can be reliably detected. A common deficiency with the CCIT performed for the container closures of cell and gene therapy products is establishment of the sensitivity of the method and correlating the sensitivity, i.e., the positive control used to a minimum leak defect size. We recommend aligning with USP <1207.2> regarding the use of positive controls for establishing the sensitivity in the CCIT methods used.

If the product is filled in a cryobag, CCIT may not be necessary if the bag is 510k cleared and the bag is used as intended under the 510k clearance. However, if the intended use or storage conditions are different, than CCIT may be needed. For all container closure configurations, we recommend performing a risk assessment with regards to when to perform a CCIT and if to perform CCIT after shipping. Particularly, if the product is stored under cryo conditions. We have seen instances in which cryo bags were found to have broken ports and were leaking after shipping due to a combination of the rigors of transport and the cryogenic storage conditions, which can make the vulnerable parts of the container closure system more susceptible to damage during shipping. Given this, it is important to consider the risks to container integrity after shipping to determine if performing CCIT would be needed. Additionally, depending on the container closures selected, such as the vials and elastomer combinations, and the sensitivity of the product to environmental conditions, such as exposure to gas ingress, a risk assessment may be beneficial in determining if CCIT should be performed under cryogenic storage conditions, to evaluate the impact on the container integrity during cryostorage. There are some studies that indicate the integrity of the container can be comprised during cryostorage due to the changes in the elastomer properties that could result in the ingress of gases and could potentially impact product quality.

And my last point to make on this topic, regarding sterile vectors that are used in further manufacturing such as with CAR-T products, there is an expectation to perform CCIT on the container closure given that the vector is purported to be sterile and will be used in the aseptic process; therefore, the container used for the vector should be demonstrated to be integral in maintaining the sterility of the vector that is used in aseptic manufacturing. Back to you, Kim.

DR. SCHULTZ: Thanks, Christine, for all that useful information. Our next question is for Jacob.

What is the minimum number of batches that can be used in stability studies to support the commercial shelf-life? Can it be any three batches, or does it need to be the first three PPQ batches? Can stability data be added during the BLA review cycle?

DR. BITTERMAN: Thanks, Kim. In general, a shelf-life is assigned based on real-time stability data from at least 3 primary stability lots manufactured using the proposed commercial manufacturing process and stored in the commercial container closure. The lots used to support the commercial shelf-life are not required to be the first three PPQ batches. I would like to let you know that FDA recently published the draft ICH Q1 Guidance on Stability Testing of Drug Substances and Drug Products. This draft guidance outlines stability data expectations for drug substances and drug products to support drug product marketing, including marketing authorization applications. The revision includes specific stability related guidance for cell and gene therapy products, which in ICH guidance documents are referred to as ATMPs, in Annex 3. The draft guidance goes into detail about how to leverage prior knowledge, data from similar products, or stability data from clinical batches manufactured using a different process. If you would like to use any of these alternative sources of supportive stability data in your application, we recommend you discuss your proposed approach at your pre-BLA meeting.

We understand that the manufacturing process is frequently finalized close to approval for many cell and gene therapy products, and limited stability data might be available at the time of BLA submission. FDA does generally allow submission of additional stability data during the BLA review cycle to support the commercial shelf-life. To discuss the specifics, we recommend that you discuss submission of stability data during the BLA review cycle at your pre-BLA meeting. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. And staying on the topic of stability, the next question is for Jessica.

What are FDA's expectations for stability data and functional analytical method qualification status for lentiviral vectors (LVV) used in CAR T cell products?

DR. CHERY: Thank you, Kim, for that question. Transgene vectors, including lentiviral vectors are essential for CAR T products. And lentiviral vectors used for ex-vivo cell transduction and that provide pharmacological activity for disease treatment are critical components that require comprehensive stability data to support their shelf-life. The stability data should support the proposed storage conditions and demonstrate maintenance of vector potency and safety characteristics. The stability studies should include testing for vector function, identity, purity, and safety parameters including sterility. The stability protocol should describe the storage container, formulation, storage conditions, testing frequency, specifications, test methodologies, and acceptance criteria.

The analytical methods for lentiviral vector testing should be demonstrated as fit-for-purpose at the initiation of the IND and qualified for later-phase studies, especially for studies

providing primary evidence of efficacy for licensure. For additional information, I recommend you reference the January 2020 FDA Guidance for "Chemistry, Manufacturing, and Controls (CMC) for Human Gene Therapy Investigational New Drug Applications (IND)," and the January 2024 FDA Guidance "Considerations for the Development of CAR T Cell Products." Back to you, Kim.

DR. SCHULTZ: Thanks, Jessica, and thanks to everyone who submitted questions during the registration process. We'll now spend the remainder of today's event answering questions that we received through our e-mail inbox. Please note, if you do have a question for our panelists, you can still submit that to our inbox at OTPPublicEventsandWorkshops@fda.hhs.gov. We'll go ahead and pull down our slides. I can see how that's been done. And our first question is for Christine.

Christine, can the future addition of new manufacturing sites be classified under a post-approval change management protocol – or a comparability protocol – as a Changes Being Effected in 30 days (CBE-30) submission instead of a prior approval supplement (PAS)?

DR. HARMAN: I think we did touch upon this in our pre-submitted questions, and I guess I'll just reiterate. A prior approval supplement would be needed because a new facility represents a significant change to the manufacturing process that could potentially affect the product quality, safety, and efficacy. So, unfortunately, it will have to be a PAS.

DR. SCHULTZ: Yeah, and I think that this is something that we see that comes up a lot, where we still get a comparability protocol to go over the PPQs, and, you know, any comparability studies that are needed. However, the PAS is still needed because of the inspection and the qualification the new facility. So, thanks for that.

Jessica, the next question is for you.

Does the FDA need to see SOPs (or SOP-level detail) for compendial analytical methods in the BLA, or is it enough to refer to the specific pharmacopeial chapter in the BLA?

DR. CHERY: Thank you, Kim, for that question. So, the methods used in the BLA need to be described and generally the SOPs for compendial methods are not required for the BLA if the methods are adequately described or described in sufficient detail in the BLA to allow FDA to comprehensively understand and evaluate how the method is performed, including all appropriate controls in the sampling plan. However, SOPs for compendial methods are often reviewed during the on-site inspections to help verify how the methods are being performed. Thanks, Kim.

DR. SCHULTZ: Thanks, Jessica. The next question is for Jacob.

If the Biologics License Application (BLA) includes a reference to a Drug Master File (DMF) for a novel excipient, is it necessary to include in the BLA the specifications, descriptions/validations of the analytical methods utilized by the drug product manufacturer to test the novel excipient?

DR. BITTERMAN: Hi. Cross-reference of manufacturing information to drug master files is generally not allowed for biologic license applications. The BLA should include manufacturing information for novel excipients and will require a similar level of manufacturing information as a drug substance. For the level of information required for a specific novel excipient, we recommend you discuss this with the FDA review team prior to your BLA submission. Back to you, Kim.

DR. SCHULTZ: Thanks for that clarification, Jacob. This next question is for Christine.

Besides manufacturing of the actual subject product of a BLA submission, what other activities and processes are acceptable as a demonstration of inspection readiness from an FDA regulatory perspective?

DR. HARMAN: From an FDA regulatory perspective, several activities and processes beyond actual subject product manufacturing can demonstrate inspection readiness for a BLA submission. Mock or surrogate product runs or simulation exercises that test the entire manufacturing workflow, documentation systems, and personnel training without using the actual product may be acceptable but should be discussed with the inspection team during the planning phase to ensure suitability.

DR. SCHULTZ: Thanks so much for that, Christine. The next question is for Jessica, and it's related to potency assays, a hot topic in cell and gene therapy.

Could the FDA provide guidance on setting potency assay specifications for a cell therapy product, particularly in the context of autologous therapies where donor-to-donor variability is expected? What are the minimum expectations for such specifications, particularly when setting the specifications from clinical experience is difficult? Any examples from approved or late-phase products would be greatly appreciated.

DR. CHERY: Thank you, Kim, for that question. Potency assays for a cellular therapy product should measure a product attribute that is relevant to the product's intended therapeutic effect, regardless if the product is an allogeneic or autologous product. We recommend you use your clinical study experience, any available manufacturing data, such as

nonclinical data, and published scientific studies to identify potency Critical Quality Attributes (CQAs) that are relevant and appropriate to evaluate the potency of your product. Potency assays or potency specifications should be designed to be precise, accurate, specific, and robust. The potency CQAs should include quantitative acceptance criteria that help contribute to potency assurance by mitigating risks to potency related CQAs. The AC for a potency assay should have an appropriate quantitative lower limit to help confirm that each lot has an adequate ability or capacity to mediate the intended therapeutic effect. For cellular products with high inherent variability, as was mentioned in the question, the AC should ensure that the lots will be rejected if their potency is outside an expected range that is guided by the available manufacturing data, nonclinical studies, and/or clinical experience. If you have concerns about your potency assay and the ability to set specifications for it, we really recommend you discuss this as early as possible with the FDA or your review team, such as during the pre-BLA meeting. Thanks, Kim. Back to you.

DR. SCHULTZ: Thanks, Jessica. The next question is for Jacob.

For post-licensure changes to linearized DNA templates used in mRNA manufacturing, including plasmid-derived or synthetic templates, where backbone or non-coding regulatory elements are modified but the transcribed mRNA sequence remains unchanged, what analytical comparability would typically be expected to support such a change?

DR. BITTERMAN: Thanks, Kim. In this case, the manufacturer should perform a risk assessment to evaluate potential effects of the proposed changes on the drug substance or drug product critical quality attributes. A comparability study should be designed based on the outcome of the risk assessment to evaluate the at-risk CQAs. In many situations, changes to plasmids used for mRNA manufacturing, such as changes to the backbone, may be minor and low risk. If that is the case, a comparability study will not be needed. In other cases, such as changes to the transcribed regions, the change may be higher risk. In this case, an analytical comparability study evaluating pre-change and post-change drug substance lots of the mRNA may be appropriate. Thanks, Kim. Back to you.

DR. SCHULTZ: Thanks, Jacob. Our next question is for Christine.

During inspection, should a facility expect that the FDA inspectors will suit up and enter the active manufacturing suite to observe the manufacturing process? If cameras are available that allows viewing of operations in the suite, would the inspectors still need to go into the suite?

DR. HARMAN: This is a cool question. Yes, the inspectors – and to be honest with you, that's my least favorite thing to do is gown up and go in, so anything to avoid that, I'll do it –

but yes, the inspectors will. You can expect that they'll want to suit up and go in. We are mindful of the sensitive areas, the Grade B aseptic areas, and we do understand that there are certain restrictions and qualifications that have to be passed in order to enter those areas. So, we are definitely mindful of those, and we'll follow all the procedures that are required. So, you can expect that inspectors will want to do that.

However, if you do have alternative ways for us to view the room and view operations in the room, if you don't have nice observation windows that are in lower classification areas, we will look at those alternatives to avoid having to gown for aseptic – gowning and do the plating and all that – we don't want to do that.

Be mindful the cameras, if you do cameras, I use them when I'm on inspection. Just make sure the cameras can provide a nice view of the room itself, and also the operations that are going on. Some of the things that I run into if I'm viewing windows outside of the Grade B area and I'm watching operations in the bio safety cabinet, if you can position cameras that can view right into the bio safety cabinet, that would be great.

But yes, we do use cameras. If the cameras are available, we'll view those as opposed to trying to go through aseptic gowning qualifications. I hope that answers the question – it's off the cuff.

DR. SCHULTZ: Thanks, Christine. It's always nice when there's a big window that you can look in through the manufacturing suite. Our next question is for Jessica.

Is there a mechanism to discuss manufacturing changes with the FDA before implementation?

DR. CHERY: If you have a specific change, including a manufacturing change that you would like to discuss with the FDA, you can consider requesting a meeting with the FDA, such as a Type B or Type C meeting. If the manufacturing changes were agreed upon with FDA as a post-marketing commitment or something similar, then you can also request a post-marketing commitment meeting. Thanks Kim.

DR. SCHULTZ: Thanks, Jessica. Jacob, the next question is for you.

Can we consider testing of BET, sterility, and CCIT – container closure integrity testing – at the initial and end time points of shelf life? Or should we still need to consider middle time points to test for BET, stability, and CCIT?

DR. BITTERMAN: Thanks, Kim. We generally recommend that container closure integrity testing be performed in place of sterility testing as part of the stability program. These recommendations are described in the guidance document, "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products." That's a guidance document. We recommend that the CCIT be performed annually, as well as at the end of shelf life.

For frozen products, endotoxin is not a stability indicating attribute and does not need to be tested in the stability program. Back to you, Kim.

DR. SCHULTZ: Thanks, Jacob. The next question is for Christine.

With regard to the A1 Section of the BLA – the Appendix, Facility and Equipment section – what procedures, protocols, or reports must be included in the BLA application versus only summarizing their content in the application and not submitting the actual procedure, protocol, or reports? Or is there any requirement to submit procedures, qualification/validation protocols, or qualification/validation reports in the initial BLA?

DR. HARMAN: I don't think there's a requirement to submit the actual protocol or report, but we have accepted summaries. But, the problem is the summaries sometimes don't have enough detail in them, and then we end up asking for the report or the summary report.

So, if you provide enough detail as a summary that includes details of what you performed, the acceptance criteria, the results, and any deviations and kappas that were involved in in the process, that's pretty sufficient. As long as the summaries are complete, we probably wouldn't ask for the specific reports. Back to you, Kim.

DR. SCHULTZ: Thanks Christine. Jessica, the next question is for you, and it's another question about the stability program. This time for the incoming cellular material.

Does the FDA expect to see stability data for cellular starting material that has been treated with cryoprotectant, which have been shown in literature to be stable for very long periods of time?

DR. CHERY: Thank you, Kim, for that question. The answer is yes. While you can use literature or scientific studies to inform your stability protocol for the incoming starting material or the incoming cellular material, we do generally expect to see stability of the incoming cellular material in your BLA to support your specific product. So, the stability of the incoming cellular material is needed to support the whole time proposed in your BLA. Thanks.

DR. SCHULTZ: Thanks, Jessica. Jacob, the next question is for you.

Can you clarify for cell and gene therapy products the FDA expectations for GMP at various clinical phases?

DR. BITTERMAN: Thanks Kim. We expect GMP requirements to be addressed in a phase appropriate manner. Appropriate compliance with GMPs helps to ensure subject safety in the clinical trials. We understand that early in product development, it may be challenging to fully comply with GMP requirements for noncommercial manufacturers. Our specific expectations for Phase I manufacturing are described in a guidance document titled, "CGMP for Phase 1 Investigational Drugs." I recommend that you refer to that for a description of phase appropriate GMPs. By the time of BLA approval, the manufacturing process should be fully GMP compliant. Back to you, Kim.

DR. SCHULTZ: Thanks for that, Jacob. We'll go back to Christine for the next question.

What is FDA's expectation around sterility assurance for purchased raw materials, such as cell culture media that are used in an aseptic processes? Is the expectation that suppliers of these materials strictly adhere to aseptic processing guidelines?

DR. HARMAN: Thanks, Kim. Our general requirements, the FDA expects manufacturers to assess the sterility risk posed by each raw material based on its intended use, processing steps, and potential for contamination. The manufacturer is responsible to qualify the suppliers and establish appropriate quality agreements that define sterility requirements and testing responsibilities and vendor qualification as part of the raw material system.

Appropriate testing, inspection, and certification procedures must be in place to verify the materials meet specified sterility requirements before use. So, this can be done with incoming testing of your raw materials from your vendors and suppliers. And you also would undergo qualification of those suppliers of those critical raw materials. Back to you, Kim.

DR. SCHULTZ: Thanks, Christine. Sticking on control of raw materials, we'll go to Jessica for the next question. Jessica, earlier on you mentioned that raw materials must be tested for identity and strength.

If a critical manufacturing raw material has a proprietary formulation, such as something like a growth supplement, but has a drug master file deposited with the FDA, may we exempt that raw material from testing? For instance, is it possible to test it for sterility and

functionality, but not for identity and strength? What level of testing would FDA consider appropriate in that case?

DR. CHERY: Thanks, Kim, for that question. So, regardless if the material is proprietary, FDA does expect that all raw materials will be tested at minimum for identity because that is required in our regulations. So, specifically 21 CFR 211.84 explains the cGMP expectations for incoming raw material control, and this includes performing identity testing. So, if there are issues that a sponsor or an applicant is encountering in being able to test a material, we recommend that you work with a vendor or the supplier for that material to develop a testing plan to be able to perform sufficient testing for that material to confirm, as I said before, at minimum, identity and strength if needed, as well as purity and potency and functionality. Thank you.

DR. SCHULTZ: Thanks, Jessica. Jacob, we'll go back to you for a question on the CBER lot release protocol.

Is the FDA's lot release protocol review timeline 30 calendar days or 30 business days?

DR. BITTERMAN: Thanks, Kim. We make an effort to complete the review in 30 calendar days. As I discussed earlier, if there's an urgent situation, we can expedite our review if requested by the applicant, and we have the resources available. Back to you, Kim.

DR. SCHULTZ: Thanks for that clarification. Jessica, we'll go back to you for a BLA logistical question.

Can you please clarify that if a cross-reference in a module 3 document refers to another module 3 document, whether a hyperlink is necessary?

DR. CHERY: Thank you, Kim, for that question. So, we would highly prefer a functional hyperlink for ease of review given the volume of information that we have to review in a very limited amount of time. I think it is both in our interest and in your interest for efficiency of the review to submit functional hyperlinks across your submission. Thanks.

DR. SCHULTZ: I agree. Those hyperlinks really help to with our review processes, so we appreciate that.

Jacob, we'll go to you for the next question.

Is leachable testing required for commercial batches? What leachable information should be provided in the BLA?

DR. BITTERMAN: Thanks, Kim. There is no expectation for routine leachable testing on commercial batches of approved cell and gene therapy products. In the BLA submission, the applicant should include an assessment of the full profile of leachables accumulated in the product through the manufacturing process, product shelf-life, and in-use conditions. The cumulative leachables profile should be evaluated in a real-time study with validated analytical methods. Considering the complexity of the analytical matrix for many cell and gene therapies, the leachables study can be performed on a simulated drug product, for example without the active ingredient present, in a simulated process starting from the step where high-risk leachables are likely to appear and continuing downstream, with maximal hold-times and temperatures at respective process steps, storage, and in-use conditions specified for the product. If the leachables study is found to be acceptable, this study would only need to be performed once to support a license application. Back to you, Kim.

DR. SCHULTZ: Thanks Jacob. Jessica, the next question is for you.

For ex-vivo modified gene therapy products, at what points in the manufacturing process is adventitious agents testing required?

DR. CHERY: Thank you for this question, Kim. Adventitious agents testing is such a critical part of gene therapy manufacturing for ensuring patient safety. For ex-vivo modified gene therapy products, adventitious agent testing is required throughout the manufacturing process at multiple critical control points. FDA guidances recommend adventitious agent testing at critical in-process steps, particularly after the cell culture harvest and at key purification steps where contamination risk is highest.

There are a number of guidances that provide recommendations on adventitious agent testing, including the February 2010 FDA Guidance titled, "Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines." There is also the ICH Q5A(R2) Guidance that is titled “Viral Safety Evaluation of Biotechnology Products,” as well as the 2008 gene therapy CMC guidance. So, let me take a few minutes to give a quick overview of what’s pointed out in these guidances.

For both vectors and cellular products, in vivo and in vitro adventitious agent testing and species-specific testing should be performed for master cell banks, or MCBs as we often call them, while in vitro adventitious agent testing should be performed on the working cell banks, or WCBs as we also call them.

In addition to donor testing and screening, we recommend that cell banks generated from a single donor or tissue source be tested for adventitious agents in a similar fashion as cell

banks used for viral vector production. This testing includes, but is not limited to, testing for CMV, HIV-1 & 2, HTLV-1 &-2, HHV-6, -7& -8, etc. While this testing is not required for autologous cells, you should describe any precautions you have in place to prevent the spread of adventitious agents from people other than the autologous recipient.

Now for cell banks that have been exposed to bovine or porcine components, like serum and trypsin which are highly used in our gene therapy products, testing for bovine and porcine adventitious agents should be included. For other animal or insect cell lines, which are also occasionally used in our gene therapy products, we recommend tests for species-specific viruses, as appropriate. The same species-specific virus testing applies for cell banks that have been exposed to human derived components.

Now for vectors, unprocessed bulk harvest, and purified bulk drug substances testing should include in vitro adventitious agents testing. Now as a I mentioned earlier, we recommend that cell culture harvest material be used for mycoplasma and adventitious agents release testing, while sterility and endotoxin can generally be performed on the final container product.

Now one more point to consider is that animal-derived materials that are used during the manufacture of gene therapy products increase the risk of introducing adventitious agents. These materials can include recombinant proteins, such as cytokines that are purified by affinity chromatography using antibodies generated from mouse hybridomas. Given this, we recommend that you consider using non-animal-derived reagents if possible, to decrease the risks from adventitious agents. Back to you, Kim.

DR. SCHULTZ: Thanks for that, Jessica. And we'll finish today's town hall with just one more question with Jacob.

Could you please explain the expectations for device compatibility and in-use stability data in a BLA?

DR. BITTERMAN: Device compatibility and in-use stability data are important to ensure that the drug product maintains its quality during handling prior to administration. If the product is administered with a delivery device, device compatibility studies should be provided in Module 3.2.P.2.6 of the BLA submission. We recommend that device compatibility studies be designed to evaluate product quantity and potency after use of the commercial device. These studies should evaluate the maximum hold times and the holding temperatures described in the product labeling. For complex administration procedures, the compatibility and in-use stability studies should include robust data supporting that the administration procedures are consistent at different clinical sites by different operators under optimal and worst-case conditions. If the product is light sensitive, this should be taken into

consideration when designing the worst-case conditions. If the product is not a combination product and could be administered using a variety of different approved devices, applicants should include a variety of different devices in the in-use stability study. Back to you, Kim.

DR. SCHULTZ: Thanks so much for that answer.

And this concludes the OTP town hall, so thank you to everyone for attending today's OTP town hall and for your questions. I know we received many questions and we weren't able to get to all of them; we do hope you're able to use them for future town hall events.

I'd also like to extend a thank you to our panelists and our behind the scenes folks who helped make today's event a success.

As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming days. I'd also like to note that we have a few draft guidance documents that are open for public comment that are listed on the slide. If interested, please submit your comments to the docket by November 24th, 2025. All of the FDA guidance documents can be found on FDA.gov.

Once again, thank you for joining, and have a great day.

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