UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FDA CBER OTP Town Hall:
CMC Readiness for Gene Therapy BLAs

June 4, 2024

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DR. ANDREW BYRNES: Good morning, everybody. Thanks for joining today's virtual town hall. My name is Andrew Byrnes, and I'm the Director of the Division of Gene Therapy 1 in the Office of Gene Therapy. Today's town hall will focus on chemistry, manufacturing, and controls (CMC) readiness for gene therapy biologics license applications (BLAs). We've had two previous town halls on gene therapy products, but this is the first time we've hosted a town hall on this gene therapy BLA readiness topic, and we look forward to answering your questions.

Before we begin, I'd like to share some background about the Office of Therapeutic Products (OTP) 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 about regulation and to support development of these biologics regulated by OTP. I'd also like to note that recordings from previous town halls are available at FDA.gov, so we'd encourage you to watch those previous recordings for additional information.

Today's town hall is being recorded, and the recording and event materials will be posted on the FDA website in a few weeks. Closed captioning for this event is available directly in Zoom. If you have a question, please type it directly into the Q&A box in Zoom. This is at the bottom of your Zoom window. Please don't use the chat box for questions. Thank you for the questions you submitted in advance, and we look forward to receiving additional questions from you during today's event. We'll address as many as we can today. Finally, please use the chat box if you're experiencing technical difficulties. So again, the Q&A box is just for any questions that you may want to submit to our panel of CMC experts, and the chat box is for technical issues. We appear to be having some difficulties advancing the slides, but I'll just go ahead and continue.

During today's town hall, we'll have three CMC experts from the Office of Gene Therapy who will answer your questions about CMC information needed to support pre-BLA meetings and original BLA submissions. I'd like to take a moment to introduce today's panelists. We have Tiffany Lucas, who is a senior biologist reviewer in Gene Therapy Branch 4; Anurag Sharma, Chief of Gene Therapy Branch 2; and Brian Stultz, Chief of Gene Therapy Branch 3.

Today we will begin by answering questions submitted during registration, and then we will be responding to some of the questions that you'll be submitting in 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 won't be answering 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 again that this town hall is being recorded. So even if you can't stay on for the full town hall, you can revisit the full discussion after it is posted on our website.

Let's begin with our first question, which is for Brian.

What are the basic BLA submission requirements for CMC information?

MR. BRIAN STULTZ: Thank you, Andrew, for the question. My name is Brian Stultz, and I'm happy to provide some information on this topic. A BLA submission is required to be

submitted in the electronic common technical document format, commonly referred to as eCTD. The International Council for Harmonisation (ICH) guideline *M4Q(R1) The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality* (ICH M4Q) contains guidance on the Quality section of the eCTD format and provides a harmonized structure and format for presenting CMC information in a regulatory dossier.

As outlined in ICH M4Q, for sections within Module 3, applicants should include centralized descriptions and/or narratives which summarize the information relevant to each specific section. These centralized narratives may consolidate data from numerous reports, documents, or justifications generated during product development. While protocols and reports may also be included in these sections, the sections should not be populated solely with collections of reports and documents, as this will impede a cohesive review of the material.

Please note that all reference documents, reports, protocols, and standard operating procedures (SOPs) should be included in the BLA submission. These documents should all be accessible through hyperlinks in the narrative summary and can be provided either in the appropriate section of Module 3 or in the reference section, 3.2.R.

That's all I have on this topic. Andrew, back to you.

DR. BYRNES: Thanks, Brian. Our next question is for Tiffany.

What are FDA's expectations for assay validation in the BLA, and how is this different from IND assay qualification?

DR. TIFFANY LUCAS: Thanks for the question, Andrew. Let me set the stage. For this question, I'll be discussing noncompendial analytical assays such as those used in drug substance and drug product release, like viral titers, potency, impurities, cell populations, or identity assays. The key difference between assay qualification and validation is the rigor by which the assay itself is tested. Qualification and validation both require that the assay be suitable for intended use. However, assay validation shows that your assay performed in a predictable way and that performance is consistent across a wide range of conditions that will be experienced when executing the assay for a commercial product.

A validation study requires that you establish acceptance criteria based on your assay knowledge to date and prior to initiation of the actual validation studies. It's important to note here that the type of analytical assay impacts how the assay is validated. There are generally three types of tests: identity tests, quantitative tests for product attributes, and limit tests for product impurities. Each one of these types of tests will have different validation parameters, and not all validation parameters will apply to each test. If this sounds like a lot already, don't worry, because there are excellent references available to everyone: first, the 2015 FDA guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics,* and second, the 2024 updated ICH guidance *Q2(R2) Validation of Analytical Procedures* (ICH Q2).

Development of your assay validation plan is an important time to ask yourself critical questions. In general, validation may include accuracy, precision—both repeatability and intermediate precision—, specificity, detection limit, quantitation limit, linearity, range, and importantly, it should investigate robustness. I will discuss expectations for robustness testing in a later question.

If you need help determining which parameters are relevant to different assay types, again,

I'll refer you to the 2024 updated guidance on validation of analytical procedures, ICH Q2, which has some nice tables showing when different parameters are used for specific test types. Having appropriately validated analytical assays is a large component of having control over your commercial drug product, and it will reduce the potential risk of analytical assay failures and out-of-specification release issues in the commercial space.

I'll turn it over now to our moderator, Andrew.

DR. BYRNES: Thanks, Tiffany. Our next question is for Anurag.

What is the most important aspect that FDA looks at while evaluating analytical assay qualification or validation?

DR. ANURAG SHARMA: Thank you, Andrew, and good morning. As Tiffany described in the previous response, we carefully review all the assay performance parameters, such as assay accuracy, precision, specificity, sensitivity, linearity, range, and you should ensure that the assay is robust. However, we pay close attention to precision of your assays. In particular, we closely assess how you have measured intermediate precision of your assay under the conditions that will be routinely encountered when running the assay, and where random errors can be introduced by factors like specific equipment, analysts, days, etc., which can lead to variable results.

For determining intermediate precision, you run the assay multiple times independently using a single lot—typically by varying the days, analysts, equipment, etc.—and measure the closeness of the results obtained and calculate percent CV, or coefficient of variation. The acceptable percent CV will vary by the type of assay and the attributed measures. For example, with an AAV (adeno-associated virus) vector genome strength assay, we recommend the percent CV to be less than 15%. For a different assay or attribute, a different percent CV—which can be lesser or higher—may be acceptable.

Overall, the goal is to measure the attribute precisely. If your assay is not sufficiently precise, we have some recommendations that you may consider to improve precision of your assay. For example, you can add additional replicates or dilutions during routine sample testing, or you can perform the assay multiple times and report the mean result on the certificate of analysis. You can consider adding a well-controlled reference material for normalization and report the results relative to a reference. This way, both the test article and the reference material are subjected to the same variations, which can cancel out some of the variation. Or you can simply switch to a different type of assay that has better precision—for example, using an ELISA (enzyme-linked immunosorbent assay) instead of a Western blot assay.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. This next question is for Brian.

Are there any guidelines and resources for setting commercial specification acceptance criteria?

MR. STULTZ: We generally recommend that commercial lot release acceptance criteria should be based on lots shown to be safe and effective during the clinical study. This approach allows you to ensure that the commercial acceptance criteria will be aligned with the attributes of the lots used in the clinical study. To support this, we recommend that you use multiple lots during your clinical study, and if possible, in some cases it may be

feasible to conduct the PPQ (process performance qualification) runs and use the PPQ lots during the pivotal study. These data should be used to determine the commercial release criteria to ensure product consistency and quality.

Now that I've described the ideal situation, we realize that this may not be feasible for all products, especially those being made for rare diseases. This is where the conversation becomes much more product-specific. Applicants may consider leveraging data from other available lots of the product and setting the acceptance criteria based on manufacturing experience. Applicants may also consider designing the manufacturing process to allow more drug product lots to be used during the clinical study. Lastly, if applicants believe that the amount of data available to set commercial lot release acceptance criteria will be a problem for their product, we encourage them to initiate discussions with the review team early.

That's all from me. Andrew, back to you.

DR. BYRNES: Thanks, Brian. This next question is for Tiffany.

What assay validation documents should be submitted to the BLA, how does FDA evaluate these materials, and what are risks that applicants experience with poorly or inadequately validated assays?

DR. LUCAS: We often see two common mistakes made by BLA applicants: first, not submitting all documents necessary to support review of analytical assay validations, and second, inadequately validated assays.

First, I'll discuss what documents are necessary to review each assay's validation. Assay validation should include a complete, thorough description of the method used to perform the validation study. For example, an analytical assay summary, along with a detailed SOP, could include an appropriate level of detail. However, a summary alone is not adequate to support your validation. The test articles, materials, equipment, or methods used in the validation study should be clearly described in the information provided to the Agency.

Second, let's discuss inadequately or inappropriately validated studies. Validation of your assay is an opportunity to demonstrate a firm grasp of your assay now and reduce potential future risks and assay failures during commercial use. Assay failures can lead to out-of-specification products, lengthy investigation, delays in patient treatment, and drug product shortages. It may sound obvious, but your assay validation should follow your assay's standard procedures. If changes are necessary for the standard assay, the modification should be justified and fully described in your submission. The changes should also be part of the validation.

Part of designing an appropriate validation study is your honest assessment of assay performance to date. This means you will use your experience to date to set appropriate acceptance criteria for your validation study. For example, setting an acceptance criteria for a validation's parameter coefficient of variation as 30%, when the actual variability observed in the assay is under 5% CV, is inappropriate. While it may seem like a good idea to set a wide acceptance criterion to increase your chances of passing validation, it may cause significant issues in the commercial space.

One other issue we see is inadequate robustness testing, which is often overlooked during rapid clinical development. We recommend that you investigate robustness during your assay development and that you review the FDA 2024 guidance for industry *Q14 Analytical*

Procedure Development (ICH Q14). Here's an important point: If you've adequately investigated robustness during assay development, you may include this information in your BLA, and it does not need to be repeated during assay validation. For example, it makes sense to determine variability between, say, flow cytometry antibody lots or ELISA kit lots prior to performing final assay validation.

Robustness testing is your opportunity to derisk your assay by testing specific and variable components that are likely to be encountered when using the assay. For example, if you're using healthy donor cells in an assay, you may want to investigate the contribution of donor variability. You should also consider how temperature, time, and lot variability, as applicable across reagents and consumables, could impact assay performance and include these in your robustness testing.

Robustness testing offers you the opportunity to become aware of factors that are major variables in your assay's success. This knowledge will help you maintain control over your analytical assays through the BLA well into commercial production and may more rapidly help you troubleshoot problems when they arrive.

I'll turn it back over to you, Andrew.

DR. BYRNES: Thank you, Tiffany. This next question is for Anurag.

What are the FDA expectations on the selection, qualification, maintenance, and bridging of reference materials used in analytical assays?

DR. SHARMA: Thanks, Andrew. Reference materials are commonly used in analytical assays and are critical to accurate and precise measurements of product quality attributes. We encourage sponsors to use reference materials as controls for routine use in your analytical assays to enable better assay control and higher-quality measurements. However, the availability of certified or consensus reference materials for cell and gene therapy products is limited, and most manufacturers develop their own product-specific internal reference materials for product development and commercialization.

Use of reference materials is especially helpful when used with potency assays. When appropriate, we recommend that you report the potency of each product lot relative to a thoroughly characterized, product-specific reference product lot that will be included in each assay run. In our experience, assessing relative potency helps to improve assay control and reduces inter-assay variability of potency assays, such as cell-based assays. Because the potency of a product is determined by relative comparison to potency of the reference material, determination of reference material potency throughout the product's lifecycle, from development to commercialization, must be accurate, precise, reliable, and consistent across time and across multiple batches of reference materials.

If the potency of the reference material drifts over time, you may lose the ability to monitor the manufacturing process, and the potency of the product received by patients could unintentionally change. So it is critical that new lots of the reference material are properly bridged to the existing lot of reference material.

The typical procedure for bridging is to measure the new reference material against old reference material in many independent assay runs. The number of assay runs should be informed by power calculation using the assay's intermediate precision. Following the assay runs, evaluate—using equivalence testing—whether the new reference material is statistically similar to the old reference material. In that case, new reference material can

be assigned the same value as old reference material. If the value of new reference material is statistically different than old reference material, assign the measured value to the new reference material and subsequently use a conversion factor in your calculations to determine potency values of test samples. In both cases, it is critical to determine the value of new reference material with high confidence using an appropriate statistical approach.

All these procedures regarding qualification or bridging of reference materials should be well documented and included in your BLA. In addition to product-specific reference material, your BLA should include all other reference materials used in analytical procedures—including any reference materials sourced from third parties as components of assay kits—and describe your procedures for ensuring the quality and stability of each reference material.

Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. Our next question is for Brian.

If compendial-grade raw materials are not available, is a risk assessment sufficient to justify the use of noncompendial-grade raw materials?

MR. STULTZ: Key concerns with reagents and raw materials are that they are what they say they are and that they are free of contaminants that could be carried forward in the manufacturing process and pose a risk to patients. Many suppliers manufacture more than one material, and it is vital that there is no cross-contamination between them.

We recommend the use of the highest-quality reagents available at all stages of product manufacture. If a suitable quality reagent is not available, applicants should provide information regarding the source of the material, how it was manufactured, and how it was tested and found suitable for use in the manufacturing process. In some cases, testing of each lot of material to ensure it meets all necessary quality attributes for use in the manufacturing prior to releasing for manufacturing use may be required.

An important point to consider is that the current good manufacturing practice (CGMP) regulations require each lot of incoming material to be quarantined until tested for conformity with specifications for purity, strength, and quality before being either released or rejected, as described in 21 CFR part 211, subpart E. In specific cases for materials from a qualified and trusted vendor, material can be minimally tested for identity, along with a review of the certificate of analysis for release into manufacturing. We note that many BLA applicants do not provide information about the quality assurance testing of all incoming materials, which results in information requests to resolve the issue during BLA review.

Ultimately, when sourcing reagents, it is the applicant's responsibility to establish procedures confirming that each reagent is of suitable quality for use in their manufacturing process, and to provide this information in the BLA.

That's all for this topic. Andrew, back to you.

DR. BYRNES: Thanks, Brian. This next question is for Tiffany.

Can generic analytical assays performed at contract testing organizations—meaning assays that are not specifically developed for a specific drug substance or drug product—be used to support my BLA? And if so, how do I do this in my BLA submission?

DR. LUCAS: The short answer is yes, you can use analytical assays, such as those

developed and performed at contract testing organizations, or CTOs, in your BLA. One example of a generic assay could be an ELISA used to detect residual manufacturing cytokines. Another example might be a PCR (polymerase chain reaction) used to quantify residual plasmid copy numbers. However, there are some really important things you should keep in mind to ensure you have a complete BLA submission. Generic assays require the same level of detail in your submission as assays developed specifically for your product. This means that all of these require all assays, validation studies, and raw data results from validation studies—they must be made available in your BLA for the Agency's review. That means summaries of methods, validations, or data won't be adequate.

Additionally, you will need to provide data to support that your specific drug substance or product performs as expected with a generic analytical assay. Therefore, you'll provide product-specific qualification test results for each of the lots tested.

So how do you get this information into your BLA? It's important to point out that, per 21 CFR 601.2(g), BLAs are not permitted to incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file. This includes information to support release testing. Therefore, a BLA should incorporate all analytical assay information directly. This means you will submit detailed analytical assay SOPs and validation material directly to your BLA. Just to reiterate the expectation: The validation materials mean complete results from your validation and a description of how the validation is performed. Please note that, while you may submit summaries of assays or validations, a summary alone of any of these documents is not adequate.

In the case of CTOs, this is dependent on your CTO providing you with all detailed information. We recommend engaging with your testing organizations early and establishing strong communication between the BLA applicant and the CTO to ensure that all expectations are well outlined and understood between the two parties.

There are additional considerations we'd like you to be aware of. When an assay is used in an approved BLA, any changes made to that assay must be submitted to the BLA, and the applicant is responsible for submitting a supplement to the BLA for review, which is done prior to implementing the change for a modified assay. Also, please be aware that a master file that is suitable to support clinical studies may not be adequate to support a BLA. Misunderstandings between CTOs and BLA applicants can lead to your BLA containing insufficient information to support your analytical assays and a delay of your BLA review, so try to work out these expectations far in advance of your BLA submission.

I'll turn it back to Andrew. Thank you.

DR. BYRNES: Thank you, Tiffany. This next question is for Anurag.

What are the studies that can be performed with a buffer instead of utilizing the drug product?

DR. SHARMA: Thanks. We acknowledge that product material is often limited and can be precious, especially for rare disease indications, so there are situations where surrogates such as formulation buffer can be used in place of drug product. For example, container closure integrity testing, or CCIT, and extractable and leachable studies may be performed using formulation buffer.

Similarly, shipping validation studies that are intended to assess the impact of shipping

conditions on drug product critical quality attributes (CQAs) must be performed using the drug product in this case, but you can use drug product surrogate for certain simulated shipping studies that are intended to assess temperature control and the integrity of 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 with us and justify your plan.

Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. This next question is for Brian.

What are the expectations for extractable and leachable studies to be conducted for a BLA?

MR. STULTZ: For a BLA submission, we require assessment of the full profile of leachables accumulated in the product through the manufacturing process, product shelf life, and in-use conditions. Such assessment should be performed in a real-time study with validated analytical methods. Considering the complexity of the analytical matrix, it can be performed on a simulated drug product—by that I mean one without an active ingredient—in a simulated process, starting from the step where high-risk leachables are likely to appear and continue downstream with minimal/maximal hold times and temperatures at respective process steps, storage, and in-use conditions specified for the product.

I want to note that there are three common issues with extractable and leachable studies we have encountered during our BLA reviews. One issue is applicants relying solely on extractable or leachable studies conducted by a container closure vendor that do not adequately simulate the drug substance or drug product matrix, and so are not applicable. A second issue is only conducting extractable studies but not performing the follow-up leachable study. Finally, a third common issue in extractable and leachable studies is that they do not include the in-process manufacturing exposure and are only conducted on the final drug substance or drug product container.

That's all the information I have on this topic. Andrew, back to you.

DR. BYRNES: Thank you, Brian. Our next question is for Tiffany.

What are FDA's expectations for demonstrating successful analytical method transfer between sites?

DR. LUCAS: That's a great question. We recognize that analytical method transfer between sites is common in the transition from clinical to commercial phase. Common examples that we see of assay transfer are between a single company's sites—for example, from an R&D site to a commercial manufacturing site—or between a CTO and your in-house testing site. Either way, the expectations are generally the same.

Even when transferring an identical SOP and using identical equipment and consumables, it is not unusual to identify differences in assay performance between sites. This can cause issues such as delaying your assay transfer or increasing the likelihood of out-of-specification failures at your new site.

So how can you avoid potential problems in analytical method transfer? You should have a transfer protocol in place prior to the transfer of the assay, and you should provide a risk

assessment for the transfer of the assay. The transfer protocol is designed to demonstrate acceptable assay equivalence between the two sites. The acceptance criteria should be based on your experience to date with your drug substance or drug product and its performance in that assay. Depending upon the assay type, you may need to include samples that demonstrate the new site can perform the assay in a way that supports the assay's necessary range limits, such as an upper and lower limit that will be required for testing your commercial drug substance or product.

A reduced validation approach may be appropriate in your transfer protocol, but your approach should be justified by the risk assessment. In designing your studies, we recommend that you perform equivalency testing by using identical samples at each site. We recommend that you avoid making changes to the assay during transfer and try to keep as many variables as constant as possible between the two sites.

Related to analytical assay transfer, I'd like to caution you to be aware of trends in your analytical assays. Having robust trend monitoring of your analytical assays can help identify subtle shifts that may occur in your assays over time. Sometimes these shifts become apparent when an analytical assay is transferred to a new test site after initial validation at a primary or legacy site. If the assay will be performed at multiple locations, we recommend that you select a single reference site for all future assay transfers. This helps to ensure control of the assay and prevent assay drift. Keeping a close eye on trend results long before they are out of specification can save you significant time later.

Thank you very much. I'll turn it back over to Andrew.

DR. BYRNES: Thank you, Tiffany. This next question is for Anurag.

For the products where a precise batch titer is not possible to achieve—for example, an oncolytic virus where the titer is based on infectivity assays—what is the FDA expectation regarding formulation of the drug product based on nominal titer?

DR. SHARMA: Thanks. During our previous town hall, we talked about formulating and labeling your drug product with nominal strength for AAV-based products. For other products, including oncolytic viral vectors, we expect commercial drug product to be labeled with a nominal strength—for example, infectivity units per milliliter—that has been measured with a suitable assay.

In general, we expect the drug product vector strength acceptance criteria to have as narrow a range as feasible—for example, nominal concentration plus/minus an acceptable range—to limit variability in dosing among subjects who receive different lots of drug product. However, we acknowledge that viral infectivity-based strength assays for oncolytic viral vectors can be variable. Therefore, a relatively wider range may be acceptable for such products.

In your BLA, you should provide the justification of the proposed range. The experience gained during the clinical study with dosing using nominal concentration will be important to support your commercial product labeling. In addition, dosing based on labeled nominal strength decreases the risk of pharmacy preparation mistakes and enables compliance with labeling regulations and the National Drug Code or NDC regulations for licensed products.

Therefore, we expect that your drug product manufacturing process will be designed to achieve a nominal target concentration, and nominal drug product concentration should be listed on the drug product label used in your pivotal study. So commercial labels will

require a defined strength.

Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. This next question is for Brian.

With a limited number of manufacturing batches, what are the expectations for comparability and statistical analysis?

MR. STULTZ: We have found that most developmental programs include changes in manufacturing during process development, such as changes in the production process or a change in the manufacturing facility. We recommend that applicants apply the basic principles described in the ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (ICH Q5E) and FDA's draft guidance for industry *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products.* Specifically, a risk assessment should be conducted to identify the impact of the proposed change and to inform the level of studies needed to support the change. It's important to remember that the goal of a comparability study is to demonstrate that the manufacturing change doesn't have an adverse effect on product quality.

There are a few different ways that applicants can design a comparability study, and it's important to determine the design that appropriately fits the product and risk assessment. In all cases, the statistical power of the assessment is going to be driven by the number of lots used in the assessment. This can be challenging when there are a limited number of lots, attributes are variable, or they are not normally distributed.

I will offer some general advice, but we recommend that you consult a statistician to help determine the best approach. It is often appropriate to use an equivalence approach to evaluate comparability where, for normally distributed data, you can establish a range for the allowable difference in the population means. In this case, exceeding the range would have an adverse effect on product quality. These equivalence acceptance criteria should be predefined and based on product knowledge.

Alternatively, you may use a quality range approach, where you evaluate if the post-change results fall within a defined range. The quality range approach is generally more appropriate for lower-risk attributes.

Back to you, Andrew.

DR. BYRNES: Thank you, Brian. The next question is for Tiffany.

How is process performance qualification performed to support a BLA, and what data should be submitted to the BLA for review?

DR. LUCAS: Thanks. For a broader perspective on process validation, please see FDA's 2011 guidance for industry *Process Validation: General Principles and Practices.* This guidance is a great reference for many of the critical regulations required for validation. In my response, I will be focusing on process performance qualification, which I'll also abbreviate as PPQ. This is the second element of Stage 2, process qualification. In this element, you're demonstrating that your process design for the commercial manufacturing process is capable of reproducible commercial manufacturing.

The validation of a commercial manufacturing process should be supported by data for

commercial-scale batches. The use of scaled-down models is not appropriate for PPQ. I'll talk more about the use of scaled-down models later.

Your PPQ approach should be outlined in a written protocol, and it should be guided by several types of knowledge, including clinical experience, commercial-scale batches, laboratory and pilot studies, and science. The PPQ will typically have a higher level of sampling than may be used in future commercial manufacturing, and—importantly—it should meaningfully capture manufacturing conditions such as, but not limited to, operating parameters, processing limits, and raw material inputs. It should describe the data that will be collected, tests performed, sampling plan, and an analytical approach for assessment of the data, in addition to other components described in the 2011 guidance document. Importantly, how you will manage any departures or excursions should be described in the PPQ protocol. Once the validation protocol is finalized, PPQ runs can then be executed. Please remember that documentation should meet CGMP standards.

Regarding the number of PPQ lots required for process validation, there's no one-size-fits-all number of lots. In justification of your manufacturing process validation, you should have an appropriate number of batches for data analysis based on process variability that demonstrates that the process is reproducible and can consistently deliver quality products. In general, the greater your understanding and knowledge of the product from process development, the better informed your PPQ approach will be.

As you're going through process validation, you must have a clear plan in place for PPQ run failures and investigations. This should include definitions for deviations, failures, early termination investigation, root cause analysis, and out-of-specification results and how you will handle them. For example, it would not be acceptable to fail PPQ runs without addressing the root cause of failure and then continue to perform runs until you've obtained sequential passing PPQ runs. That's just an example.

While we hope that all revisions are made during process characterization studies, it may be necessary for a manufacturer to return to the drawing board, further evaluate their process, and make adjustments and begin new PPQ runs. This is acceptable, and it can be communicated in your BLA submission to support your collective process validation approach. By sharing this information and including additional process revisions, you can help demonstrate that you've improved your understanding and control of the manufacturing process.

In your BLA submission, you should include your PPQ protocol, a summary of relevant PPQ batch record data (which can be included in formats such as an Excel file), and a clear written justification for the selection of parameters, operating ranges, quality attributes, and acceptance criteria. Please be aware that your BLA submission should address all three steps, which includes continuous process validation, as outlined in that 2011 process validation guidance document.

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

DR. BYRNES: Thank you, Tiffany. This next question will be for Anurag.

What are the FDA expectations regarding the stability data required to be submitted in the BLA?

DR. SHARMA: We recommend you follow the ICH Q1 guideline series for our expectations on the stability data to be submitted in your BLA. You should provide real-

time stability data from at least three lots in the proposed commercial container closure to support shelf life. We expect you to analyze the stability data using regression analysis and assign the shelf life based on the time point at which the lower 95% confidence limit intersects the lower acceptance criteria from the regression analysis. The shelf life for drug substance and any intermediate whole step should also be supported by real-time stability data.

The starting materials such as cell banks, viral banks, or plasmids used in the manufacture of your products usually have significant potential impact on the quality of the drug product. Therefore, the stability of starting materials should also be evaluated and the data submitted in the BLA. The in-use stability of a drug product should be assessed if the product or the diluted product is not administered immediately after preparation, and you should provide data demonstrating product stability when exposed to intended in-use conditions and holding time. You should also provide data supporting compatibility of the drug product with the delivery device, demonstrating that administering the drug product using the delivery device will not negatively affect the product's quality.

Although not a requirement, we recommend that you test the product stability under accelerated or stress conditions. Such studies are important to evaluate stability-determining attributes. Additionally, they may be designed to inform in-use stability or to understand the effect of temperature excursions. Because the commercial shelf life is based on real-time stability data, in your pre-BLA meeting you may discuss a plan for submission of updated stability data during the BLA review and also consider if post-licensure stability studies will be needed to extend the product shelf life.

Also be aware that if you introduce any changes to product manufacturing late in product development, you may—based on the risk of change to product stability—be required to generate additional real-time stability data to support the product shelf life. You may be aware that the ICH stability guideline series is being revised to combine into a single guideline. The scope of the revised guideline will include cell and gene therapies, so please keep an eye out for that as well.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. The next question is for Brian.

Can process performance qualification be achieved post-BLA approval for rare diseases?

MR. STULTZ: Process validation should be completed before commercial distribution of a product. The PPQ protocol is designed to establish confidence that the manufacturing process is under a state of control and can consistently manufacture a quality product that meets the commercial specifications. Conclusions about the qualification of the manufacturing process can only be made after the PPQ protocol is completed. However, in rare circumstances it may be appropriate to release a batch prior to completion of the full protocol. Applicants who wish to request concurrent release will need to adequately address the following issues.

First, they should provide an adequate justification on the drug's limited use and how it fills an urgent medical need. Applicants should also provide sufficient evidence that the manufacturing process is under a state of control. This may include all testing performed on all lots manufactured to date with the commercial process, including any PPQ lots, release testing, in-process testing, and additional product or process characterization studies.

Finally, the risk to patients from an unsuccessful qualification study is greater after the product has been distributed—for example, negative findings from the second or third PPQ lot run following release of a successful first PPQ lot. To mitigate this risk, applicants will need to establish a system for careful oversight of distributed product, which may include a rapid response to customer feedback, evaluating lots in a stability program, and corrective actions if there are any negative PPQ findings.

In the event concurrent release of PPQ batches is granted, any lot released must comply with all CGMPs, regulatory approval requirements, and commercial release criteria. Since the release criteria will be defined during BLA review, concurrent commercial release of PPQ runs would only happen after BLA approval.

That's all the information I have on this topic. Andrew, back to you.

DR. BYRNES: Thanks, Brian. The next question is for Tiffany.

How can sponsors leverage multiple approaches—for example, scaled-down model systems or healthy donor material—when working toward manufacturing process validation?

DR. LUCAS: This is a common question, and we regularly see the use of multiple approaches. When we review your BLA, we're evaluating your control of your manufacturing process. Your control is largely based on your experience and your knowledge of the data you have or have not collected to date. I'm going to give you three examples of approaches you can use to support process development and inform the final manufacturing process validation study.

Scaled-down models can be used at the process design and characterization studies to determine process variability and further refine your approach. However, you should demonstrate the validity of your scaled-down model. This is very important. It means that you should provide validation of your scaled-down model and justify its use in your BLA submission. The scaled-down version should represent the intended commercial manufacturing process as closely as possible.

You may be able to leverage other development data from highly similar programs to the development of the manufacturing process validation plan. For example, your manufacturing data from a highly similar viral vector or cellular manufacturing process could be used to further justify establishment of the acceptance criteria, operating ranges, and/or selection of quality attributes that will be used in your process validation studies. If you would like feedback on your plans to leverage your other manufacturing data, you may engage with the Agency, and we would encourage you to do so early.

One common process validation challenge in ex vivo gene therapies is the use of patient cells. We recognize that many of you are working with rare diseases and pediatric populations, and there can be issues obtaining patient material for use in process validation runs. In these circumstances, sometimes healthy donor material is acceptable for process validation. 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 support your process validation studies.

We encourage you to pay special attention to how healthy donor material behaves in your system. It's critical to note that healthy donor material may not reflect the vigor or behavior of your patient population cells in manufacturing. For example, patients who have

undergone extensive chemotherapy or have genetic diseases may have cells that behave differently than healthy donor cells. Additionally, healthy donor material may vary significantly between your donors. If you intend to use healthy donor material, you may further discuss any concerns with the Agency during your clinical studies. These are some common suggestions for consideration and to help you set yourself up for success in the validation of your manufacturing process.

Thanks. I'm going to turn it back over to Andrew.

DR. BYRNES: Thank you, Tiffany. The next question is for Anurag.

In the context of the release of new draft guidance on potency assurance of gene and cell therapy products, what are the new expectations for the potency assays? Is the expectation from FDA that industry should move more exclusively to a functional release assay reflecting mechanism of action for potency?

DR. SHARMA: Yes, we recently released our draft guidance for industry *Potency Assurance for Cellular and Gene Therapy Products.* Thank you for submitting your comments to the docket for this guidance, which we are carefully reviewing and working toward finalizing the guidance. This draft guidance document when finalized will supersede and replace our 2011 potency guidance. The 2011 potency guidance focused on the development of potency tests. The main focus of the new guidance is the concept of potency assurance strategy that covers all aspects of potency, not just potency assays.

A potency assurance strategy is a comprehensive approach that reduces risks to the potency of a product through manufacturing process design, manufacturing process control, material control, in-process testing, and potency lot release assays with the goal of ensuring that every lot of a product released will have the potency necessary to achieve the intended therapeutic effect. While this new approach is certainly broader, it is also more flexible and provides more options without imposing new burdens on developers.

For example, if there are limitations in one aspect of your potency assurance strategy, other aspects of the strategy may be able to compensate for those limitations. Potency release assays and their acceptance criteria remain essential elements of a potency assurance strategy, but the release assays can take a variety of forms. Both physicochemical assays and bioassays can be considered potency tests as long as they measure a CQA of the product that is related to potency.

Although every potency-related attribute should be adequately controlled by your potency assurance strategy, it is not necessary to measure every potency-related CQA. Only the potency-related attributes that are considered to be at risk should be tested for a lot release. For cell and gene therapy products, it is usually not feasible to reduce risks to all potency-related CQAs to an acceptable level. So the potency assurance strategy should usually include multiple release assays and in most cases should include at least one assay that measures a product activity that is relevant to its intended therapeutic effect.

Let me also clarify that it is not essential for a potency bioassay to mimic the product's mechanism of action. Rather, your understanding of the mechanism of action should help to drive selection of the product's potency-related CQAs.

The new draft guidance continues to allow progressive implementation of potency assays during clinical development, and potency assurance strategies in early phases are not expected to be as comprehensive as those in place for late-stage studies.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. The next question is for Brian.

What is the guidance on the level of detail required for plasmid manufacturing and control in a BLA?

MR. STULTZ: This is a good question, Andrew. When the plasmid is part of the active pharmaceutical ingredient, or the API, all aspects of plasmid manufacturing and control should be submitted in the BLA, as would be expected for any drug substance or drug product. Plasmids are also critical materials in the manufacturing process for multiple types of gene therapy products, including some viral vectors, mRNA-based products, and some cell-based gene therapies. When the plasmid is part of the API, all aspects of plasmid manufacturing and control should be submitted in the BLA, as would be expected for any drug substance or drug product.

For plasmids that are critical materials for further manufacturing, U.S. regulations do not require the same level of detail for these materials as for a drug substance. For instance, plasmid starting material information can be added to the drug substance Module 3 under Control of Materials. Keep in mind that plasmid quality is critical to the drug product manufacturing, and individual manufacturers should set standards as needed on all materials brought into their CGMP facility to ensure they can reproducibly make their product.

Methods used at the vendor should be determined to be suitable for use to ensure that the quality of the plasmid meets predefined specifications with plasmid quality attributes in mind. Qualification of assays is often sufficient for critical materials, but individual manufacturers may have their own expectations for assay validation performed by the vendors, so we recommend these concerns be outlined in the quality agreements with the suppliers.

For plasmids used as critical materials, if a plasmid vendor has a master file, it may be cross-referenced in a BLA if the master file has sufficient information to support control of plasmid quality to manufacture a commercial licensed product. While plasmids used as a critical material do not need to be made in a CGMP environment, the downstream manufacturing process does. Therefore, the drug substance manufacturing site must comply with GMPs, and as such, starting materials coming into the GMP facility must be tested to verify identity and conformity to specifications for purity, strength, and quality.

The GMP facility may rely on vendor qualification, but the facility must verify identity. Responsibility lies with the GMP facility to ensure that only materials of specified quality are brought into their facility. The quality and testing of incoming materials will be verified at the inspection.

Andrew, back to you.

DR. BYRNES: Thanks, Brian. The next question is for Tiffany.

For ex vivo cellular gene therapies, what are FDA's expectations for control of starting cellular materials necessary to support a BLA (for example, apheresis centers, collection methods, logistics, shipping, or receipt at the manufacturing site)?

DR. LUCAS: Great. For this question, I'm going to focus on autologous apheresis, since

this is the most common collection procedure for ex vivo modified cells. For ex vivo cellular gene therapies, you're expected to be in control of the patient's cellular material from the time of apheresis through administration of the final drug product. This means you are responsible for ensuring that materials are collected in a consistent manner across clinical and commercial apheresis sites, which can be accomplished through quality agreements. For example, if a minimum number of cells is required in an apheresis center, this must be clearly defined in the instructions.

An apheresis center would have trained staff, protocols, and specific equipment cleared for apheresis use in adult or potentially pediatric populations. CGMPs start at the manufacturing facility. Therefore, the BLA should describe adequate control and receipt of the apheresis material to support manufacturing. In your BLA, you should describe how and when patient cellular material is collected, how it is labeled at each step, and how it is stored. This includes containers and any reagents or additives used in the cells. It would not typically include details of the apheresis process unless there were unique circumstances.

For a BLA submission, you would include a description of the starting material collection, labeling, transportation, and receipt; a description of responsibilities of each party at each site; shipping validation stability for the proposed range of conditions the starting material may encounter; receipt and control of the starting cellular material at the manufacturing site, including any testing at the manufacturing site; and all holding times and environmental conditions that the cellular material may incur.

Critically, you should have a robust description of the chain of identity and a detailed description of when and how unique patient and lot identifiers are used throughout this process. Collectively, this information provides assurance of control and consistency in the starting cellular materials, which then ensures consistent quality of the final product.

Thank you. Turning it back to you, Andrew.

DR. BYRNES: Thanks, Tiffany. The next question is for Anurag.

What are the expectations for pre-licensure inspections of the gene therapy manufacturing facility?

DR. SHARMA: The pre-license inspections, or PLIs, are performed as part of the BLA review process. A PLI is necessary for licensure under the Code of Federal Regulations, or CFR. There are circumstances when a PLI can be waived, but generally it is necessary to do one. If the BLA involves several sites at different locations, multiple PLIs may be necessary. FDA typically inspects the sites where drug substances and drug products are being produced and where tests are being performed.

We received quite a few questions regarding the timing of PLIs. You are supposed to be ready for an inspection at the time of BLA submission. In theory, FDA can go out immediately after application is received, but FDA generally coordinates with the firm regarding their production schedule, and inspections are timed appropriately so that the investigators can observe the pertinent operations at the facility. In general, the timing of inspections is always halfway through the review cycle. This allows FDA to review the submission before inspection and allows sufficient time to resolve any inspectional observation items prior to the BLA action due date.

For PLIs, the Division of Manufacturing and Product Quality (DMPQ) at CBER serves as

the lead of these inspections, and a product specialist also usually joins the inspection. An investigator from FDA's Office of Regulatory Affairs, or ORA, may also be invited. During the inspections, FDA will make a determination of compliance with the application and applicable standards, including GMP standards, in order to approve the BLA. We will also verify the authenticity and accuracy of data submitted in the BLA and focus on the specific product, including verifying that the process has been validated and observing the manufacturing of the product.

Now let me point out some of the commonly observed inspection issues. We commonly notice that the written procedures for the operations are absent, deficient, or not followed; that good documentation practices are not followed, or data are not adequately secured and managed; that some of the incoming raw materials are not tested for identity; or that deviations are not managed properly—either the root cause analysis is not adequate or implementation of corrective and preventive actions is not effective—or the deviations are not closed out in a timely manner. We also notice sometimes that the batch records are incomplete. For example, they do not document that all the critical in-process parameters are met, changes have been made to the commercial manufacturing process that were not evaluated during the PPQ study, or there's a lack of quality oversight over the facility operations. This is not an exhaustive list, only some of the common issues.

For any of the inspections, a documentation of observations known as FDA Form 483 could be issued. For BLA inspections, if the firm wants to get licensed, they will need to respond to the observations and resolve the concerns raised by the inspectors. These concerns need to be addressed before the application can be approved.

In addition to PLIs, there are also pre-approval inspections, or PAIs, performed for a prior approval supplement. A PAI is for changes to an approved application. For example, when there is an addition of a new manufacturing facility, or significant changes are made to the manufacturing process, that may require an inspection.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. We have one last pre-submitted question for Brian before we switch over to the live questions.

Overall, what are the most common and most significant deficiencies for gene therapy BLAs?

MR. STULTZ: This is also a very good question. We have encountered many common deficiencies during BLA review of gene therapy products. We have been trying to communicate to industry—at pre-BLA meetings and through avenues such as this town hall—some of the things that applicants should consider in their BLA application. I'm going to run through a list of common issues during BLA review, many of which we have actually already discussed in today's town hall in more detail.

First, potency assurance strategy is a difficult issue that applicants struggle with during development of the product, and that continues to be an issue for BLAs as well. Applicants often lack sufficient data to support the stability of intermediates, drug substance, or drug product shelf life. Another issue is that applicants may not include at least three lots with real-time stability data. Remember that the drug product evaluated in stability studies needs to be the commercial representative and in the commercial container closure system. We also see, as a common issue, assays that lack robustness data during assay validation, and insufficient extractable and leachable studies—I've covered two common issues earlier

in this town hall.

Approval of a BLA requires demonstrating that future lots of the product will be consistent and that the manufacturing process is fully established. Tentative plans or work in progress should not be part of a BLA application. Material acceptance testing of incoming material at the GMP facility is also an issue. Remember that every lot of material must minimally be tested for identity. We also see insufficient information for reference materials, including lack of bridging plans for future reference material lots.

Finally, common issues involve submitting all the appropriate documents, the correct version of the document, and all reference documents, written in English or legible. If documents are not in English, you should provide a translation. That concludes my list of common deficiencies during BLA review.

Andrew, back to you.

DR. BYRNES: Thank you, Brian. And thank you to everyone who submitted questions during the registration process. I'd now like to invite Brian, Tiffany, and Anurag to turn their cameras on, and we'll spend the remainder of today's event answering the live questions that you've submitted.

Our first question is for Brian.

Is there any CMC BLA package available that FDA can share with novice applicants?

MR. STULTZ: That is a good question. However, because BLAs are full of proprietary and special information, we certainly cannot release those to the public. I'm going to refer you back to my response to question one, which involves a reference to ICH M4Q, which contains guidance on the Quality section of the eCTD format and provides a harmonized structure for format for CMC information in Module 3 of your BLA.

I'd also like to refer to the question I just answered on common deficiencies. Hopefully you can use that list of deficiencies to further think about your BLA during preparation.

That's all I have on that topic. Andrew, back to you.

DR. BYRNES: Thanks, Brian. Tiffany, I have a question for you.

What are compendial assays?

DR. LUCAS: That's a great question. Compendial assays are standardized protocols, and what we typically see at FDA are going to be ones provided by U.S. Pharmacopeia, or USP. There are three that we typically see in the gene therapy space for products and drug substances. These compendial assays would be sterility testing, which is USP 71; mycoplasma testing, USP 63; and endotoxin testing, which is USP 85. During the clinical phase, gene therapy reviewers are typically going to provide you with some advice that you'll need to validate these assays by the time you come to your BLA submission.

Those compendial assays are generally accepted. We do not accept European or other international compendial assays. We do work with some of these USP ones. If you need specific advice prior to the BLA, we encourage you to reach out through the project manager and potentially request a meeting type that would be appropriate for your questions if you choose to use a noncompendial version of these assays. I want to say that we do see a lot of noncompendial versions for sterility, mycoplasma, and endotoxin testing.

We recognize that times change, and we do have resources available to address some of those questions if you're working with noncompendial assays where there is a compendial counterpart—for example, sterility, mycoplasma, and endotoxin testing.

If you use a noncompendial assay, you will be expected to demonstrate that your noncompendial version performs as well or better than the compendial version. We do have expertise in house, and that's provided through the Division of Biological Standards and Quality Control, our colleagues in DBSQC, who can provide additional advice that may be necessary to validate the noncompendial version of an available compendial version assay.

Thank you very much. I'll turn it back to Andrew.

DR. BYRNES: Thanks, Tiffany. Our next question will be for Anurag.

Can this panel speak to the recommendations on viral clearance requirements, including any differences between baculovirus and HEK293 cells? Is a risk-based approach to viral clearance, including viral clearance studies with data and rationale provided, sufficient? Or is a 4 log_{10} reduction via viral clearance step a requirement?

DR. SHARMA: Thanks, Andrew. That's a great question. In general, our recommendation is that you include viral clearance steps in your manufacturing process whenever possible. We understand that for some of the products, it is not feasible to introduce viral clearance steps, especially if the product itself is a virus or the product is a cell-based product. But we think viral clearance is quite crucial for AAV-based products, especially those utilizing helper viruses, such as adenoviruses or herpes viruses, and those that use baculovirus insect cell systems. This is necessary to remove these helper viruses.

At times, the insect cells that are commonly used for propagation of AAVs—that is, Sf9 cells—may harbor rhabdovirus. In general, you cannot completely guard against contamination, either against unintentional introduction of adventitious viruses or from the viruses that are manufactured at the same manufacturing facility.

If your process has these built-in robust virus clearance steps, then it gives us additional assurance regarding product safety. For AAVs, fortunately, there are manufacturing steps that are built into the process, such as detergent lysis or exposure to high pH, nanofiltration, and chromatography steps. These are known to be very effective to reduce the virus burden of these adventitious virus agents.

For the baculovirus system, it is essential that you have built-in virus clearance steps, and that you perform a virus clearance validation study by the time you submit the BLA. At the time of initial submission, demonstrating that you have built-in virus clearance steps and that you are performing some testing for these residual helper viruses would be sufficient.

Regarding the limit of a 4 log_{10} reduction, in general it is considered quite robust if your particular unit operation is able to achieve more than a 4 log_{10} reduction. But it is not something that is mandatory. Because at the end, the cumulative logarithmic reduction, which is achieved by multiple steps in your manufacturing process, is what is taken into account. Even if your particular unit step is not able to achieve this reduction, in your virus clearance validation studies you can calculate the cumulative logarithmic reductions and provide risk assessment and justification that, for example, 10 to 10 log reduction is sufficient for rhabdovirus and it does not pose a safety risk to the patients.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. The next question will be for Brian.

Is it possible to use clinical batches manufactured and used for pivotal studies as part of PPQ batches? If so, what are the assay validation requirements in that case prior to manufacturing those clinical batches?

MR. STULTZ: Thank you for the question, Andrew. I did touch on some of the aspects of this during my response to setting commercial specification acceptance criteria. The answer to the first part of the question is yes, you can use PPQ batches in your pivotal clinical trials. In fact, we recommend that for products that might manufacture very large batches that might be able to treat most or all of the patients in their proposed clinical study. Note that the PPQ batches after BLA approval could be released for commercial use, provided they meet all commercial release specifications.

To answer the second part of that question: As far as assay validation, again the answer is yes, assays would need to be validated for the PPQ lot manufacturing.

I believe that answers that question. Andrew, back to you.

DR. BYRNES: Thank you, Brian. The next question will be for Tiffany.

When bridging a new analytical method or performing tech transfer, is it necessary to test old lots in the new method or at the transferred site? And can historical data be leveraged if retains are not available to assess comparability?

DR. LUCAS: I want to note that there may be some subtle differences between bridging a new analytical method and performing a tech transfer where there's not a new analytical method being put into place. What I want to start with is, you may not necessarily need to test old lots. It can be a great tool to leverage if you have old lots available to you. For example, it's not unusual for sponsors or applicants to have backup material or reference material that maybe wasn't suitable for clinical use that you may be able to leverage at two different sites.

Historical data may be very useful, obviously, because it's your foundation for understanding how the assay performs. If you have to switch from one lot release of a kit to another one and every kit lot has its own unique polyclonal antibody, it may be very useful if you have material that you can test with both an old and a new kit. That would be an example of a new analytical method. Historical data is very useful for establishing acceptance criteria and also for developing a comparability or an equivalence plan, depending on what you're comparing.

The important thing to know is that you should really be responsible for considering how you would be able to detect any problems at your new site or between the old and the new assay. In general, we expect our sponsors and applicants to have the most robust understanding of their assays and their products when they come to us with justification. Be honest with yourself, because this is not the time—when you're bringing on a new assay or transferring an assay—to not be honest with yourself about where you can run your boat ashore.

Part of that honest assessment is a risk evaluation, so you should provide a risk assessment, and that should include how you'd be able to detect any issues. That assay transfer protocol that you can use is going to bring all of these components together. It's probably going to have some historical data, as well as your new lots. Importantly, you should include

justification for all of these components in the documentation that you provide to the Agency.

Thank you very much. I'll turn it back to you, Andrew.

DR. BYRNES: Thank you, Tiffany. The next question is for Anurag.

Can I forgo process validation if I submit a BLA that is being reviewed under an accelerated approval pathway for a rare disease?

DR. SHARMA: That's a good question. Of late, we are seeing a lot of these requests about BLAs being submitted on an accelerated approval pathway where the surrogate point is used to predict clinical benefit, and then subsequently, a confirmatory study is needed post-approval.

Regarding the CMC expectations, there is no change from our standard CMC general expectation because of this accelerated approval pathway. And with regard to process validation, our expectations also remain the same.

What we can advise is that in such situations, if you are planning accelerated approval pathway, you plan ahead. From the very beginning, you invest in the process that you intend to be a commercial process, which is scalable. Invest a lot in the process design and try to plan process validation earlier. You can use some of the PPQ lots in your clinical studies, so that may help you to comply with the requirement of process validation by the time you submit the BLA.

In the earlier part, my colleague Brian talked about some of the real situations where there is an urgent unmet need. In that case, you may come and discuss with us if some sort of concurrent process validation is a possibility.

Thank you. Back to you, Andrew.

DR. BYRNES: Thanks, Anurag. For Brian, a question about plasmids.

If a plasmid is part of an API, an active pharmaceutical ingredient, can a sponsor reference a master file for that plasmid in the BLA instead of providing the information in the BLA itself?

MR. STULTZ: I want to be clear on the distinction between plasmids that are part of the API and plasmids that are a critical material for further manufacturing of another gene therapy product (and I did cover this briefly in my response earlier).

The answer to the question is no. If a plasmid is part of the API, part of the drug product, it cannot be cross-referenced to a master file. As I mentioned previously, all the information that would be expected for a drug substance or drug product would be required to be submitted in the BLA for that plasmid product.

For critical materials, that would be the only case where you might be able to cross-reference a master file. Again, that is provided that that master file has the appropriate quality information for the plasmid suitable for a commercial product.

I believe that answers the question. Andrew, back to you.

DR. BYRNES: Thank you, Brian. The next question is for Tiffany.

What can we do to release our fresh cellular product if our potency assay takes two weeks?

DR. LUCAS: First of all, let me acknowledge that this may be necessary in some cases. This is often something that we observe in the clinical phases. We'd invite you to consider a multilayered approach to ensuring and assuring that the product is sterile upon administration to the patient. Consider what you could do for a multilayered approach. For example, a Gram stain could be used at the time of the final product formulation. However, we know that a Gram stain is not a particularly sensitive assay.

You might consider implementing testing during manufacturing, where you pull a sample and put it under your sterility testing plan and monitor that through patient administration, and then for the full 14 days. If you're looking for an answer related to reduction in the number of days for sterility testing, you would need to validate that. So if you had some specific test that you're thinking of, you should reach out to us and discuss that further.

The reason why you need to have a multilayered approach is because it's necessary to have a clinical intervention plan. For example, if you administered a fresh product to a patient and three days later—let's say you're using a BacT/ALERT® system or some other microbial alert system—that were to come up positive, you would need a rapid system in place so that the patient could be treated by the clinician.

One thing I'd also like you to assess in addition to rapid release of these fresh products: When you're going into the commercial space and you're thinking about a BLA, you're going to need to have an honest assessment of whether an acceptable number of CQA results are available to you to effectively release that product in the commercial space. There can certainly be differences between the clinical space and the commercial space and those expectations for release. So those are definitely questions that you would want to come to the Agency with and discuss further prior to submitting a BLA.

Thank you. I'll turn it back to you, Andrew.

DR. BYRNES: Thanks, Tiffany. We're running low on time. We have one remaining question, and this will be for Anurag.

Can we qualify a primary reference material and set a new 100% relative potency after a thorough comparability study? This would mean no bridging with the previous reference material.

DR. SHARMA: We touched on this question earlier as well, and this is a good question because bridging of reference materials is very critical. Because when you start, you start with an original or primary reference material, and all your subsequent reference materials that will be generated link back to their original reference material. And if there is a gradual shift when you connect one reference material to your previous material, it may amplify and start to be reflected in the values of the product lots.

But essentially what you are asking in your question regarding thorough comparability to compare the two reference materials, that is essentially the bridging. If after comparability analysis your result is that the previous and the new reference material are statistically similar—after performing, say, equivalence testing—, then yes, you can assign 100% of value to that reference material.

But if after comparability assessment your results show that it is not equivalent or that new

reference material is, say, 1.3-fold higher than the previous one, then that reference material is still good. The only thing is that you will use that 1.3 conversion factor in your subsequent calculations when you are trying to calculate the absolute value of your samples. So in that case, you will be assigning 130% value to your new reference material.

Thank you, Andrew.

DR. BYRNES: Thanks, Anurag. And thank you to everyone for attending today's OTP town hall. Thank you to Anurag, Brian, and Tiffany for answering all of these questions. As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming weeks. We also wanted to remind everyone that we have three draft guidance documents that are open for public comment through July 29, including a cross-center draft guidance that was published last week outlining FDA's Platform Technology Designation Program. These guidance documents are listed here on the slide, and my colleague will also add a link to those in the chat.

OTP plans to hold the next town hall meeting this fall, along with some other events, and we hope to see you all there. You can find more information about all of our town halls and other OTP-hosted events on our new OTP meetings and workshops page.

Thank you again for joining and have a great day.