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FDA CBER OTP Town Hall:
Best Practices for Regulatory Interactions With OTP

December 12, 2024

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DR. RAMANI SISTA: Good morning, everybody, and thanks for joining us for today's virtual town hall. Today's event is hosted by the Office of Therapeutic Products (OTP) within the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA). My name is Ramani Sista, and I'm the Director for the Office of Review Management and Regulatory Review (ORMRR) within OTP. I will also be a moderator for today's event.

The topic of today's town hall is best practices for regulatory interactions with OTP. If you've been following our OTP virtual town hall series, you'll know that this is our first town hall on this particular topic. As many of you joining today's town hall are already aware, there are many opportunities for sponsors to interact with OTP during product development of advanced therapies, including cell and gene therapy products. Today, we look forward to answering some of your questions on how to help sponsors facilitate productive interactions with OTP through the various formal meeting mechanisms that FDA offers.

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

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

During today's town hall, we have three experts from OTP's ORMRR, who will answer your questions. I'd like to take a moment to introduce them. Our first panelist is Jessica Boehmer, who is the Associate Director for Regulatory Policy within ORMRR. Our next panelist is Beatrice Kallungal, who is the Director of Division of Review Management and Regulatory Review 1. Our final panelist is Mara Miller, who's the Director of Division of Review Management and Regulatory Review 2.

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

Let's begin with our first question. This question is for Jessica.

How do I determine which FDA center will review my proposed biologic/device combination product if I'm unsure?

MS. JESSICA BOEHMER: If you are unsure which FDA center will review your proposed product, you may submit a Request for Designation (RFD) to FDA's Office of Combination Products (OCP). OCP assigns review responsibility for combination products to a lead center: CBER, the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH). OCP assigns review responsibility for combination products based on the product's primary mode of action. Refer to FDA's webpage titled "RFD Process" for information on how to submit an RFD.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Beatrice, the next question is for you.

Where can I find a consolidated table with the most updated information on where and how to submit a request for each meeting type?

MS. BEATRICE KALLUNGAL: Thank you for that question. There are multiple resources available, and some of the most succinct references may be found under the set of FDA webpages titled "Interactions with Office of Therapeutic Products." You may also refer to SOPP 8101.1, Appendix C, for examples and additional information on each meeting type, and to the FDA webpage titled "Regulatory Submission in Electronic Format for CBER-Regulated Products," which provides additional links to instructions on electronic submissions.

Back to you, Ramani.

DR. SISTA: Thanks, Beatrice. There is a follow-up.

How many questions are allowed in a meeting request?

MS. KALLUNGAL: Good question. Per the guidance for industry on formal meetings with FDA, there should be no more than 10 total questions, including subquestions. Also, new questions should not be added to the meeting package after your meeting request has been granted, and the current questions should not be significantly changed at the time of meeting package submission. Remember that the meeting was granted and the review team was established based on the questions posed in the meeting request.

Back to you.

DR. SISTA: Thanks, Beatrice. Mara, the next question is for you.

What is the appropriate timing to request an INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meeting?

MS. MARA MILLER: Thanks. INTERACT meetings should be requested early in product development. But you don't want to submit a request too early, and you also don't want to submit too late. The time to request an INTERACT meeting is when a sponsor has identified the investigational product to be evaluated in a clinical study and has conducted some preliminary preclinical proof-of-concept studies with the product but has not yet designed and conducted definitive toxicology studies.

Back to you, Ramani. Thanks.

DR. SISTA: Thanks, Mara. There's a follow-up.

What are the common reasons that INTERACT meetings are denied?

MS. MILLER: We will likely deny an INTERACT meeting if another INTERACT meeting was previously held for that product. We'll also deny if the package was not submitted with the meeting request, because this is a requirement. If we do receive that package but it's deficient and will limit our ability to provide any constructive feedback, we will deny the meeting.

Also, the stage of product development is a common reason for denial. It can be premature or too advanced for an INTERACT meeting. We would consider a meeting request for INTERACT to be premature if the sponsor does not specify the investigational product, does not provide preclinical proof-of-concept or other pilot data, or has not conducted any preclinical studies with the product.

A request may be too advanced for an INTERACT meeting—and more appropriate for a pre-investigational new drug application (pre-IND) meeting—if the sponsor has completed proof-of-concept and some safety studies and is at the point of design and conduct of the definitive toxicology studies. Another reason a request would be considered too advanced for INTERACT is if the manufacturing process to be used for the clinical studies has been defined and you've developed assays and preliminary lot release criteria. Also, the program's considered to be at an advanced stage if the preclinical testing and manufacturing process for the product uses the same platform as or a similar platform to other products submitted to OTP by the same sponsor. And we would also consider the existence of clinical data from previous studies for the same product and clinical indication as a more advanced development stage.

Thank you. Back to you.

DR. SISTA: Thanks, Mara. Jessica, the next question is for you.

If OTP suggests converting an INTERACT meeting to a pre-IND meeting, can the sponsor withdraw the meeting request and resubmit it as a formal pre-IND meeting request?

MS. BOEHMER: The answer is yes. If we suggest converting a meeting, the sponsor does have the option to withdraw the meeting and submit the request at a later date as a pre-IND meeting request. Before we officially convert the meeting, we would ask you if you are ready for a pre-IND meeting, since we will grant only one pre-IND meeting. And that meeting should be multidisciplinary to include questions for chemistry, manufacturing, and controls (CMC); pharmacology/ toxicology; and clinical.

Back to you, Ramani.

DR. SISTA: Thanks, Jessica. The next question is for Beatrice.

What is the purpose of a pre-IND meeting?

MS. KALLUNGAL: The purpose of the pre-IND meeting is to provide information that will assist the sponsors in preparing to submit a complete IND. The primary purpose of a pre-IND meeting is to obtain FDA's feedback on the proposed design of the preclinical studies, design of the initial IND study, and product manufacturing and quality control needed to initiate human studies.

The meeting may also provide an opportunity to discuss plans for studying the product in pediatric populations, the target product profiles, the design and results of the natural history studies, and the best approach for presentation and formatting of the data in the IND.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Mara, the next question is for you.

When is the best time to request a pre-IND meeting?

MS. MILLER: We suggest submitting a pre-IND meeting request once you have defined the manufacturing process to be used for the clinical studies and you've developed assays and preliminary lot release criteria. We would also expect the sponsor to have completed proof-of-concept and possibly some preliminary preclinical safety and toxicology studies and be ready to move on to your definitive toxicology studies. We would also expect that the proposed questions in your meeting package will involve IND-enabling CMC, pharmacology/toxicology, and clinical trial design issues.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. The next question is for Jessica.

Can a sponsor request multiple meetings in the pre-IND phase?

MS. BOEHMER: Thank you for this question. Yes, sponsors can request both an INTERACT meeting and a pre-IND meeting prior to IND submission. Pre-IND meetings are expected to be multidisciplinary, and we will not grant multiple pre-IND meetings. There may also be an opportunity to hold a Type D or a Type C meeting in the pre-IND phase, but these requests are assessed on a case-by-case basis and must meet the requirements for each specific meeting type. Generally, all IND-enabling questions should be addressed in the pre-IND meeting.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Beatrice, the next question is for you.

Can a Type D meeting request be made and occur before a pre-IND meeting?

MS. KALLUNGAL: Great question. A Type D meeting may be considered at this point in time as long as the criteria for a Type D meeting request are met, which would be assessed upon receipt. As a reminder, the Type D meeting is meant for discussion of issues at key decision points when timely feedback is critical to move a program forward. As stated in response to the previous question, we expect that most IND-enabling questions should be able to be addressed in the pre-IND meeting.

Back to you.

DR. SISTA: Thanks, Beatrice. We now shift to another milestone meeting. This is for Mara.

What are the standard topics expected to be discussed at pre-biologics license application (pre-BLA) meetings?

MS. MILLER: First, I want to mention that, while the pre-BLA meeting is not required, we do strongly recommend requesting one with OTP to ensure that you're ready to submit your marketing application and prevent any delays during our initial review.

This meeting is an opportunity to identify any major unresolved issues from the development program and identify the studies that the sponsor is relying on as adequate and well-controlled to establish effectiveness. This meeting also allows our FDA review team to get acquainted with the general information to be submitted in the BLA. At this meeting, you may also discuss methods for statistical analysis, the best approach for presenting the data, and inspection- and facility-related information.

Thank you.

DR. SISTA: Thank you, Mara. Jessica, the next question is for you.

When should a pre-BLA meeting be requested in relation to the planned BLA submission date?

MS. BOEHMER: In general, the pre-BLA meetings should be requested at least 4 months in advance of the planned submission of the marketing application, so that the meeting can be scheduled to be held no more than 2 months prior to the planned marketing application submission. We expect that the top-line study results and technical information will be included in the briefing package for the pre-BLA meeting, so please consider this when deciding when to submit your request.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. We continue with pre-BLA. Beatrice, the next question is for you. It's a two-part question.

When is it appropriate to request a rolling review for a BLA? And when is the BLA considered received if under rolling review?

MS. KALLUNGAL: Thank you for that question. Only products and indications with a breakthrough designation, regenerative medicine advanced therapy (RMAT) designation, or fast track designation can be considered for rolling review. If a product is granted rolling review, then the applicant should not submit portions of the BLA prior to a pre-BLA meeting.

In the pre-BLA meeting package, sponsors should propose a timeline for the planned rolling review for discussion at their pre-BLA meeting. Following the pre-BLA meeting, the sponsors should submit a formal request for rolling review to the IND, and FDA will provide the grant/deny decision within 60 days of receipt.

While a pre-BLA meeting is highly recommended, it is not required. If you choose not to hold a pre-BLA meeting, you can still request a rolling review through a submission to the IND. The complete pre-BLA module can then be submitted according to the agreed-upon timeline, and the BLA will be considered received when the final module is submitted and received.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Mara, we come back to you. This is a different topic.

What are some of the best practices to help ensure an efficient new IND review?

MS. MILLER: Thanks for that question. I don't think we'd have time to go through everything, but we'll list a few.

First, we highly recommend that sponsors request a pre-IND meeting with us and, in that meeting request, propose very thoughtful questions related to your IND-enabling studies. It's also really important to carefully consider the specific advice that we have provided in a held pre-IND meeting when you are preparing the IND submission.

Also, make sure your IND is complete and includes the required information, which may vary depending on the phase of the clinical study. Take a look at all the appropriate FDA guidance documents for recommendations as you prepare your IND.

The timing of your submission can also be important. When we receive INDs on Fridays or Saturdays, we lose valuable review time, and this also impacts the amount of time you have to respond to our information requests if we send any. So, if it is possible, we recommend submitting INDs as early in the week as possible.

Also, ensuring that you have provided more than one authorized regulatory contact can be extremely helpful for your regulatory project manager (RPM). This way, there's always someone available to receive information requests that we may send and able to provide a response to us within the timelines that we've asked. These response timelines are critical to ensure that our review staff do have the sufficient time to review the response, work with you to resolve any possible deficiencies, and then make a decision on the IND.

Thank you, Ramani. Back to you.

DR. SISTA: Thank you, Mara. Jessica, the next question is for you.

What are the best practices for responding to a clinical hold?

MS. BOEHMER: Though we strive to work with sponsors to resolve hold deficiencies during the 30-day review and allow the IND to proceed, that is not always possible. If your IND is put on hold, we recommend that you wait until you get the official hold letter that includes the list of hold deficiencies and the information required to resolve them.

You will receive this letter within 30 days of being placed on clinical hold. If, upon receipt of the letter, you need clarification on a hold deficiency, please reach out to your assigned RPM, who will discuss this with the team and will likely set up an informal teleconference with you.

When you respond to the hold, identify your response—in uppercase, bold letters—as a **CLINICAL HOLD COMPLETE RESPONSE** in the cover letter of the submission to ensure that the submission is easily identified. In the submission, address only the hold deficiencies. We recommend that you restate each deficiency and follow it with your explanation or clarification response.

Thank you, and back to you, Ramani.

DR. SISTA: Thank you, Jessica. The next question is for Beatrice.

How do I ensure that my submission gets to the appropriate review team within CBER for cell versus gene therapy and the proper therapeutic area?

MS. KALLUNGAL: Thank you for that question. Submissions are reviewed and triaged to the appropriate office upon FDA receipt, regardless of whom you address the submission to. Once OTP receives the submission, the regulatory project management staff assess the submission to determine the product type and ensure that the correct CMC review office is assigned. They also review the indication and assign it to the appropriate clinical review office and division. Even if you inadvertently address your submission to the wrong office or division within OTP, it will be assigned to the appropriate OTP review teams during the submission triage process.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Mara, the next question is for you.

Will OTP consider informal communications with sponsors even if they are not selected for pilot programs?

MS. MILLER: Our goal is always going to be to have good open communication with our sponsors. Even if you're not selected for a pilot program, you still have multiple opportunities to interact with us through our formal meeting process. But informal interactions are interactions that are typically for simple clarifications and are not intended to be in lieu of formal meetings. And we will consider these on a case-by-case basis.

OTP considers several factors when deciding if an informal interaction is appropriate, including the nature of the request and any previous interactions you've had with the office. You can just contact your RPM to discuss your need for an informal interaction, and then we will discuss with the review team and get back to you to determine next steps.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. Here's a question on amendments, and this is for Jessica.

How do I get feedback on an amendment to the IND (for example, a new protocol or a protocol amendment)?

MS. BOEHMER: If you have specific questions about a submission to your IND, such as a protocol, it is best to clearly state this in your cover letter for the submission, including your plan timeline for implementation. You can also send the RPM a courtesy copy of the submission and note this in your email. The RPM can then discuss the amendment with the review team and provide you with an estimated timeline for response.

We must prioritize review of submissions that have regulatory and Prescription Drug User Fee Act (PDUFA) goal dates. However, we are more than willing to work with you in order to get feedback from the review team on a submission that does not have a goal date.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. There are a few questions now about designations. We'll start with Beatrice.

What are some reasons that fast track designation requests are denied?

MS. KALLUNGAL: Great question. For fast track designation, requests have been denied by OTP if the product does not show potential to address an unmet medical need. The submitted data should demonstrate that the investigational product could address an unmet medical need—where available therapies exist, by demonstrating improved safety, efficacy, or other documented benefits. Another possible reason for denial of a fast track designation request is if the drug development plan is inadequate.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Mara, the next question is for you.

What are some reasons that breakthrough therapy designation requests are denied?

MS. MILLER: For breakthrough therapy designation, requests have been denied by OTP when the preliminary clinical evidence provided did not demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. This can be because trial results were challenging to interpret or data submitted were not persuasive, possibly due to a small sample size or short duration of follow-up. Another reason breakthrough designation requests have been denied is when the proposed indication does not meet the criteria for being a serious or life-threatening disease or condition.

Back to you, Ramani.

DR. SISTA: Thank you, Mara. The next question is for Jessica.

What are some reasons that RMAT designation requests are denied?

MS. BOEHMER: RMAT designation requests have been denied by OTP when the preliminary clinical evidence submitted does not indicate that the investigational product has the potential to address unmet medical need for the disease or condition. This could be because of uncertainty regarding the interpretability of the results, difficulty in reaching a conclusion regarding treatment effect, or concern about a potentially unfavorable benefit risk profile.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. And there's a follow-up regarding all three designations for you, Jessica.

When should I submit my RMAT, breakthrough, or fast track designation request?

MS. BOEHMER: Thank you for this question. Fast track, breakthrough, and RMAT are generally requested with an original IND submission or after, as an amendment, ideally before the end-of-phase 2 meeting with FDA. Because fast track, breakthrough, and RMAT designations are meant to facilitate development and support efficient review, FDA does not anticipate that these requests will be made after submission of a marketing application or supplement.

Sponsors may apply for and receive more than one designation for a given product, but sponsors should apply for each designation separately. Information that supports more than one designation may be submitted in each separate designation request.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Beatrice, the next question is for you.

When should I request a priority review designation?

MS. KALLUNGAL: Thank you for that question. Sponsors should consider discussing with OTP whether their application may be eligible for priority review at the pre-BLA meeting, and they should request priority review designation with their marketing application or efficacy supplement submission. Priority review designation will be determined following submission, and the applicant will be notified in the filing communication.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. The next question is for Jessica.

When can we use the formal request-for-clarification process for meetings?

MS. BOEHMER: Thank you, we get a lot of questions about this. Formal requests for clarification are only applicable to clarify questions on final meeting documents. If you have a clarification question after receipt of a meeting summary or written response only (WRO) document, you have 20 days to submit the request. And if we determine it is appropriate for a formal request for clarification, we will respond within 20 days. This process does not apply to INDs or other submissions in general, only to meeting documents.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Mara, the next question is for you.

Can I request a WRO for any formal meeting?

MS. MILLER: Yes, you absolutely can request a WRO for any formal meeting. However, for meetings such as end-of-phase meetings, a pre-BLA meeting, a Type C surrogate endpoint meeting, or the RMAT or breakthrough initial multidisciplinary meeting, what we like to ask is that we hold a face-to-face meeting, either virtual or in person, because the discussions in those meetings are so critical that being able to do back-and-forth discussion would be really important and helpful for both parties involved.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. The next question is for Beatrice.

If a physician contacts my company to request expanded access use of our investigational gene therapy product for treatment of a single patient, what should I include in the letter of authorization (LOA) allowing them to cross-reference our IND with FDA?

MS. KALLUNGAL: For information on what to include in the LOA, we recommend that you refer to FDA's webpage titled "Example of Wording for Letter of Authorization (LOA) for Individual Patient Expanded Access IND." The webpage provides a template LOA with example wording. You can find the website at FDA.gov/news-events/expanded-access/example-wording-letter-authorization-loa-individual-patient-expanded-access-ind.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Jessica, next is an electronic common technical document (eCTD) question.

Section 3.1.9 of the eCTD Technical Conformance Guide, the section on the Field Copy Certification, indicates that there is a requirement to notify the FDA district office by letter that your BLA eCTD submission will be submitted to FDA. How do we contact that office, and is email contact available?

MS. BOEHMER: This is a great question. For BLAs reviewed by CBER, this notification is not required, since CBER acts as the home district for pre-licensure inspections of CBER-regulated products.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Mara, you have the next question.

What is considered a commercial IND?

MS. MILLER: Thanks for this question. We would consider an IND a commercial IND when the sponsor intends to commercialize the product and submit a marketing application in the future. Usually, this is a corporate entity. However, we may also consider an IND to be commercial from a research sponsor if it's clear that the sponsor intends for the product to be commercialized later. If you take a look at Form FDA 1571, you'll see that the instructions indicate that when a sponsor of a research IND submits either a phase 2 or phase 3 clinical protocol, they should select "Commercial" on the form.

However, if your plans are not to commercialize the product, then you can submit a justification with your phase 2 or phase 3 protocol stating why you're doing the studies in phase 2 and phase 3 and that you're doing this still solely for research, and then we wouldn't consider it a commercial IND. If we did consider it a commercial IND, then you would be required to submit via eCTD and meet any of the conditions that are required of commercial sponsors.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you. Mara. Beatrice, this question is for you.

One of the ways we identify our products is through the IND title. Can you explain IND titles in OTP?

MS. KALLUNGAL: Thank you for that question. OTP's IND titles are reflective of the investigational products and are standardized for searchability in CBER databases. Company-specific product names—such as TV-102 or LP 2025—do not provide enough detail on the product characteristics. We review the information on the product you provide in your original submission and create the title using that information.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Jessica, we often get this next question about inactive INDs.

Can an inactive IND file be cross-referenced?

MS. BOEHMER: Yes, this does come up from time to time. The answer is yes: Both active and inactive files may be cross-referenced, but sponsors must always cross-reference the original source of information.

This means that if a sponsor cross-references an IND that refers to another submission, the sponsor must also include an LOA from the cross-referenced IND and the other submission it referenced. An example of this is: If IND 123 cross-references IND 456, and IND 456 cross-references IND 789, an LOA from both cross-referenced INDs must be submitted to IND 123. As an additional note, withdrawn INDs cannot be cross-referenced for products reviewed by CBER.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Another common issue that we come across frequently is with pre-assigned tracking numbers. Mara, this next question is for you.

When is a sponsor required to request a pre-assigned tracking number for their submission?

MS. MILLER: You'll need to request a pre-assigned tracking number for any original submission that will be submitted via eCTD, so only those electronically submitted through the gateway. This would include your INTERACT meeting request, pre-IND meeting request, master files, INDs, and BLAs if you are submitting via eCTD. Obviously, we do expect our BLAs to be coming in that way. The tracking number should be requested no earlier than 4 weeks prior to the target submission date.

One thing I want to also state is that you will have different numbers for your INTERACT and pre-IND meetings versus what you will get for your INDs, whereas other centers use the same number for a pre-IND, for example, submitted under their IND. But in CBER, you will need to request what we call a pre-submission tracking number (or PTS number) that will be assigned to that. And when you submit your IND, you will then get your IND number, or you will have requested that prior. There is information on the FDA website (which I don't have handy right now) about how to request it, what information to include, and the email address for doing that.

Thank you, and back to you, Ramani.

DR. SISTA: Thank you, Mara. We do sometimes have quite a few requests that get voided because of the time lapse from the time of request to the actual submission, so please be cognizant of the time when you request this number for use.

Beatrice, this next question is for you.

Does Form 1571 need to be submitted with amendments to the IND?

MS. KALLUNGAL: Good question. Yes: All submissions to the IND should include a signed copy of Form FDA 1571. Sponsors who do not reside or have a place of business in the United States must have an authorized official who resides or maintains a place of business in the United States. This person will need to countersign Form 1571.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. A frequent question we get is about acknowledging amendments. We get about 14,000 amendments a year, and it's physically impossible to acknowledge these. If you submit something and it's of significance, then your RPM is the best point of contact to reach to see the progress of review and where it stands. We technically don't acknowledge IND amendments. I just thought I'd add that, since this was a question related to IND amendments.

Jessica, the next question is for you.

Will I get an acknowledgement letter upon OTP receipt of a meeting request?

MS. BOEHMER: While we don't send a formal acknowledgement letter for meeting requests, you will likely get an email confirmation of receipt from one of the ORMRR staff. This will be followed by a meeting confirmation or denial letter within 14 to 21 days, depending on the type of meeting.

Back to you, Ramani.

DR. SISTA: Thank you, Jessica. The next question is for Mara.

Are there regulatory requirements for who can be considered a U.S. agent?

MS. MILLER: Thanks, Ramani. There are not any actual regulatory requirements for acting as a U.S. agent. A U.S. agent is needed for a company that does not have a place of business or reside in the United States. You will need to choose someone who can speak on your behalf, and you can choose anyone to be a U.S. agent, but it is up to you as the sponsor to determine whether you feel that the U.S. agent is qualified and how you're going to use them—whether that is just to send your documents back and forth or to actually answer questions on your behalf. It is completely up to the sponsor to determine the best fit and requirements for your company for a U.S. agent.

Thank you. Back to you, Ramani.

DR. SISTA: Thanks, Mara. And again, a reminder here to identify very clearly in your cover letter who are the authorized representatives we can contact on behalf of the sponsor.

The next question is for Beatrice.

When should I use the CBER Document Control Center (DCC) email address?

MS. KALLUNGAL: Thank you for that question. We often receive emails addressed to CBER DCC, but the CBER DCC address is to be used strictly for sending non-eCTD submissions. Don't send them questions related to your submissions. If you have questions, you can contact your RPM or the ORMRR immediate office. The email address for the ORMRR immediate office is OTPRPMS@fda.hhs.gov.

Back to you, Ramani.

DR. SISTA: Thanks, Beatrice. The CBER DCC email is used very frequently. All kinds of questions are forwarded to that email address, including questions that are pertinent to CDER! I guess this is one email that is very easily available on the Internet, so they get a lot of questions. Please be mindful that this is strictly for submitting amendments or INDs for research or sponsor-investigators. Commercial sponsors will, of course, use and submit through the eCTD.

Mara, the next question is for you.

How will I know if a submission to my IND is acceptable? Will I hear back in 30 days?

MS. MILLER: That's a really good question, and we get lots of questions about that as well. As Ramani had mentioned before, we cannot acknowledge every amendment that is received. That would probably take up our entire workday, based on the number of amendments that each RPM is getting.

We obviously do have certain IND amendments—such as meeting requests, your responses to clinical hold, or RMAT or breakthrough designation requests—that are required to be reviewed within a specific amount of time. Depending on the amendment type, for these more formal requests and submissions, you will get a letter sent that confirms your meeting, grants your designation, etc. And we have different time frames for each of those.

There are lots more amendments that are not under a review clock, including new protocols and protocol amendments. As soon as you have submitted those to FDA and gotten IRB approval as necessary, you can go ahead and implement them. You don't have to wait for FDA, because we may not review those within 30 days. I think Jessica mentioned that we have to meet regulatory and PDUFA timelines. Those are the top priority, and then we work on the other things, but we can't get to them quite as fast.

You can always ask your RPM about the status of a review as needed. And also, as mentioned in another question, if you absolutely need feedback and in a specific time critical to moving your program along, put that in the cover letter. You can also send that directly to your RPM with your official submission as well, so that they're aware. Then the RPM can discuss that with the review team and we can come to an agreement on a timeline for response, because we do understand that there are factors in your development program that require our feedback that are not under a more formal clock.

Thank you, and back to you, Ramani.

DR. SISTA: Thanks, Mara. I was going to emphasize that as well. If you are waiting for a critical piece of information or feedback from us, please make that clear in the cover letter. Most of the amendments that don't have a clock associated with them get reviewed on a more "as resources permit" time frame. So, if there is something urgent that you're waiting for, then it should absolutely be included in your cover letter that you're waiting for this piece of information, which will kind of alert the RPM to poke the review team. Also, feedback to the review team regarding the fact that you're waiting for some information from us is also helpful. So, include as much information as you can in your cover letter.

Mara, this last question is for you as well.

Is it a requirement to have a secure email to communicate with OTP?

MS. MILLER: I think this is probably the most important question that has been asked, actually. The answer is yes. To protect your proprietary and confidential information, CBER does require the use of secure email for all of the regulatory communications. This requirement was put into place starting October 1, 2018.

If you need to establish your secure email with FDA or for any related questions, you could submit your request to OTPRPMS@fda.hhs.gov. If we don't have secure email when we have to start sending you regulatory communications, we're going to have to put that into

snail mail, maybe fax if faxes are going through, maybe give you a call and read out what the information is that we need to give you… So, as soon as you know you want to do some communications with FDA, I suggest getting that secure email set up.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. And thanks to everyone who submitted questions during the registration process.

We will now spend the remainder of today's event answering your live questions. Our first live question is for Beatrice.

Will sponsors be required to submit responses to INTERACT meeting comments in future IND submissions, as is requested by FDA for pre-IND meeting comments?

MS. KALLUNGAL: Great question. Thank you. Sponsors are not required to submit an INTERACT meeting, although early and timely interaction with FDA during your product development is recommended. The timing of an INTERACT meeting request is important, keeping in mind that the sponsor has identified the investigational product to be evaluated in a clinical study and conducted some preliminary preclinical proof-of-concept studies with the intended investigational product but has not yet designed and conducted definitive toxicology studies.

Back to you, Ramani.

DR. SISTA: Thanks, Beatrice. The next question is for you as well.

As there are more development programs now in the cell and gene therapy space, we understand that the RPMs may have tremendous workloads. How can we, as sponsors, facilitate timely responses or email acknowledgements from RPMs for high-priority requests?

MS. KALLUNGAL: That is a great question. RPMs will acknowledge an email inquiry within 48 hours. Please provide as much information as possible to your RPM, noting any time-sensitive request.

The sponsor may also CC the email address OTPRPMS@fda.hhs.gov, which is an inbox for general inquiries, in case the RPM is not available to respond. By including this email, others in the group will see it and will be able to respond to your inquiry.

Back to you.

DR. SISTA: Thank you, Beatrice. And thank you so much for asking this question and for thinking of the RPMs. Jessica, the next question is for you.

Is eCTD format required for INTERACT and/or pre-IND first contact meetings?

MS. BOEHMER: No, eCTD format is not required for INTERACT meetings and pre-IND meetings. It is recommended that commercial sponsors submit in this format, but it is not required. For further information, we recommend referring to the 2024 guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

Thanks. Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Mara, the next question is for you.

If a pre-IND meeting was previously held for a specific product and a specific indication under an investigator-sponsored IND, can a commercial sponsor who has licensed that product request a new pre-IND meeting for the same product and indication?

MS. MILLER: Thanks, Ramani. Yes. Because it's a different sponsor—and especially if you're starting from an investigator-sponsored IND and you're now going to run this under a commercial IND, hopefully preparing for marketing later down the line—it is important for you to come in and have a discussion with FDA. So yes, please submit that. If we have any questions or concerns about that, we'd obviously let you know, but that sounds reasonable.

DR. SISTA: I'm thinking that at this point the product is still not licensed. Even though the question says "licensed," I'm thinking the product is still under development at this point and the sponsor changed from a sponsor-investigator to a commercial sponsor. We wouldn't be doing a pre-IND if the product was licensed already.

The next question is for you, Beatrice.

Is the same RPM triage process used to assign review responsibility following submission of an INTERACT meeting request?

MS. KALLUNGAL: The answer is yes. Once an RPM has been assigned to a file or meeting, subsequent submissions under that file will typically be assigned to the same RPM as resources allow.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. The next question is for you, Jessica.

Should a pre-IND number be obtained prior to submission of a meeting request?

MS. BOEHMER: A new submission tracking number (STN) must be obtained before submitting an eCTD submission via the Electronic Submissions Gateway. Please refer to SOPP 8119 for detailed guidance on this. If an INTERACT meeting was submitted and assigned an STN, a pre-IND meeting should be submitted to that same STN.

Thanks. Back to you, Ramani.

DR. SISTA: Thanks Jessica. Mara, the next question is for you.

Can an inactivated Drug Master File, DMF, also be cross-referenced?

MS. MILLER: Master files are considered either in active status or closed status, and we do expect them to remain up to date through annual reporting. It is recommended that files only reference those master files that are currently up to date. So, if you plan to cross-reference a master file, make sure that it's been kept up to date with us.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. Beatrice, the next question is for you.

Is Form 1571 needed for a pre-IND meeting request?

MS. KALLUNGAL: Good question. Form 1571 is not required for a pre-IND meeting request. However, a comprehensive cover letter is highly recommended, providing all the required information for a pre-IND meeting, as noted in the formal meeting guidance.

Please take a look at the 2023 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA products*. It provides a lot of information that you should pay close attention to and incorporate into the request so that we will be able to make an assessment of your request and make a determination of whether to grant or deny the request.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. Jessica, next question is for you. This is revisiting the question about cross-referencing an inactive IND.

Will CBER not allow a sponsor to cross-reference an inactive IND?

MS. BOEHMER: Thank you for this clarification question. The answer is that inactive INDs can be cross-referenced. The sponsor must submit an LOA for cross-reference. You cannot cross-reference a withdrawn IND for applications reviewed by CBER.

Thanks, and back to you, Ramani.

DR. SISTA: Thank you, Jessica. The next question is for Mara.

Is there a limit to how many individuals a sponsor can include in to bring to a formal meeting?

MS. MILLER: Thanks, Ramani. There is not a limit to how many people you can bring to a formal meeting. But you need to definitely let the RPM know how many are coming, because we need to be able to find a meeting room that is large enough to hold all of the participants.

Remember that it's not only sponsor participants. We also have the review team coming from the FDA side. We have multiple escorts, depending on the number of people that you're bringing in. We have a person who is managing the virtual aspect, so that you and FDA can have people calling in and listening and watching. We have somebody who monitors and makes sure there are no audio issues. We really need to make sure that we know how many people are coming so we're able to find a room that will fit them. If we have any problems finding a room, we'll let you know and see if we can work out cutting a few people, but we will try very hard not to have to do that.

Thank you. Back to you, Ramani.

DR. SISTA: Thank you, Mara. A lot of the arrangements for the in-person meetings are handled by our group. And usually, there are a significant number of RPMs involved to make sure the meeting runs smoothly from the time of receiving the sponsor attendees at security to the end.

One thing I will add here is that if you have foreign participants or other attendees on your team, we request that you strictly adhere to the timelines provided by the RPM for the required documentation. A last-minute addition of foreign participants is not possible,

because we have to submit all the names to FDA security, and it actually goes to the HHS level, so things are beyond the control of our Agency to ensure that a foreign participant added at the last minute can be accommodated. So, please plan your attendees in advance and strictly follow the timelines that the RPM provides for the required paperwork.

Beatrice, the next question is for you.

If an INTERACT meeting request is submitted to the CBER DCC email account, should we copy a different CBER email to ensure that we receive an acknowledgment of the submission?

MS. KALLUNGAL: Thank you for that question. When emailing a submission to CBER DCC, the only requirement is to use the email address CBERDCC_eMailSub@fda.hhs.gov. CBER DCC will not issue an acknowledgement. Once the RPM has been assigned, acknowledgement of the receipt will be issued in accordance with the applicable INTERACT timeline.

Back to you, Ramani.

DR. SISTA: Thank you, Beatrice. It's really hard to acknowledge the many meeting requests that we get. If you've not heard from us right away, within a week or so, absolutely feel free to poke us at OTPRPMS@fda.hhs.gov, and we'll try to investigate what happened to the request and get back to you. Sometimes there are jurisdictional issues, so it doesn't even come to us, and it gets transferred to a different center or office, so it definitely is helpful. If you meant to send a meeting request to OTP and you have not heard back in a week or two after you've submitted your request, please do write to us at the OTP RPMs email to investigate where your request is. Thank you.

Jessica, the next question is for you. This is, again, a cross-reference question.

If you have an LOA to cross-reference an IND for a pre-IND meeting with an established pre-IND tracking number, once the new IND is cleared, do you need a new LOA referring to the newly established IND number? Or will the original LOA in association with the pre-IND tracking number apply to the IND going forward?

MS. BOEHMER: Thanks for this question. The new IND submission should include an LOA for the cross-referenced IND.

Thanks, and back to you, Ramani.

DR. SISTA: Thanks, Jessica. Just to clarify, the pre-IND meeting and the IND meeting have different STN numbers associated, unlike other parts of the Agency—such as CDER—that provide just one pre-IND number that becomes the IND number for the future. That's not the case with CBER submissions, so each of them is pretty much a separate submission, if you will. So, it's helpful if you include your LOA in your IND as well. Thanks for that question.

Mara, the next question is for you.

For IND cover letters for eCTD submissions, is the CBER DCC mailing address appropriate? Or is there a boilerplate note that FDA would prefer at the top that indicates an eCTD submission?

MS. MILLER: I'm thinking that this is related to the technical aspect of making sure it gets to the right centers. The CBER DCC address is not required, but it would be good to have that information in the cover letter for our products that are managed in CBER. That way, it is clear that it is for CBER versus CDER or CDRH.

Thank you. Back to you, Ramani.

DR. SISTA: Thanks, Mara. The next question is for Beatrice.

How early can a sponsor submit an orphan drug designation request and/or a rare pediatric disease (RPD) designation request? If such a designation request is submitted before the IND submission, is a tracking number requested 4 weeks prior to submission of the orphan or RPD designation request?

MS. KALLUNGAL: Thank you for that question. Please note the orphan drug designation request or RPD designation request is reviewed outside of the OTP. The questions regarding the orphan drug designation request and/or RPD can be submitted to the Office of Orphan Products Development at orphan@fda.hhs.gov.

Back to you, Ramani.

DR. SISTA: Thanks, Beatrice. Jessica, the next question is for you.

When we submit amendments to our existing submissions, how do we know who our assigned RPM is?

MS. BOEHMER: Thank you for this question. When an original application like an IND or a BLA has been submitted to CBER, an RPM will be assigned, and they will remain assigned to the file for subsequent amendments. Occasionally, reassignments of applications may occur, and if the file is active, the sponsor may be notified of the new RPM. If you ever can't get in touch with your RPM for some reason, you can always reach out to our inbox, OTPRPMS@fda.hhs.gov, and one of us will put you in touch with your assigned RPM.

Thanks. Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Mara, this is a question for you.

Is OTP granting face-to-face pre-BLA meetings with sponsors, or is virtual encouraged?

MS. MILLER: Thanks, Ramani. Yes, we are granting and have had many, many face-to-face meetings recently and in the past. If you would like to have a face-to-face with us, please put that very specifically in your cover letter. I will say, as you can read on the FDA webpage about meetings, face-to-face is considered both in-person face-to-face and virtual face-to-face. So, you can make that clear if you would like one or the other. For example, for a pre-BLA meeting, that in-person face-to-face is very helpful.

If you want to come in, put that in your meeting request and we'll consider that, or you can say if you prefer virtual, and then we could have either one if we grant your meeting. Just make sure it's specified as either face-to-face in-person or face-to-face virtual in your

meeting request. Then when we determine if your meeting will be granted, we will put that information into the meeting confirmation.

Another thing I want to mention is that if you say you want to have a "teleconference," we may follow up with you to ask if you mean just a teleconference with no video or if you actually mean a virtual face-to-face meeting, because how people are using that terminology is not the same as what we would consider. If you say "teleconference," we assume you mean no video, but we'll want to confirm that. Just be very clear up front what exactly you're looking for, and that will help a lot.

Thank you. Back to you, Ramani.

DR. SISTA: Thanks, Mara. As Mara mentioned earlier in the conversation, some of the meetings where we encourage face-to-face in-person are pre-BLA meetings, Type C surrogate endpoint meetings, Type B RMAT initial comprehensive meetings, and even some Type A meetings. These were definitely strongly featured for an in-person meeting, for these meeting types.

Beatrice, the next question is for you.

Can you restate the OTP email that we should CC when emailing the RPM?

MS. KALLUNGAL: Thank you for that question. The email address is OTPRPMS@fda.hhs.gov. We have also added this to the chat so that you can copy that.

Back to you, Ramani.

DR. SISTA: Thanks, Beatrice. Jessica, this question is for you.

I understand that I don't have to wait 30 days for a protocol amendment as long as I have IRB approval, but how about with amendments with regard to manufacturing changes?

MS. BOEHMER: There is no mandatory requirement for FDA to formally respond to accept these revisions or changes. The sponsor will be accepting the risk with proceeding with the changes without advice from FDA. So, if you are waiting for feedback, it's good to reach out to your RPM and let them know, or to include that in the cover letter for your submission if you're awaiting feedback from FDA before proceeding. You could also submit a question in a formal meeting request if you require feedback within a certain time frame.

Thanks. Back to you, Ramani.

DR. SISTA: Thank you, Jessica. Mara, the next question is for you.

How do I request an INTERACT meeting number from FDA?

MS. MILLER: If you recall, you do not need to have a pre-assigned INTERACT meeting number if you are not submitting through the eCTD. However, if you are submitting your INTERACT meeting through the eCTD, then you will need that pre-assigned number. We do have an SOP that is available externally; it's SOPP 8117. I didn't have the information before right at hand, but I do now. You should request the pre-assigned number by sending a request to CBERRIB@fda.hhs.gov. You should include in that request the name and address of the sponsor or applicant, and your primary point of contact's name and phone

number, as well as the biologic product name, indication, and your anticipated submission date.

Thank you. Back to you, Ramani.

DR. SISTA: Thanks, Mara. I do want to add that this pre-assignment is specific for submissions coming through the gateway. If you request a pre-assigned number and send it through the CBER DCC email, it does cause some problems for the DCC. So, please be sure that you request this number only if you plan to submit through the gateway.

The next question is for Jessica.

I'm not getting a response from the RPM on a time-critical issue that is not associated with the PDUFA timelines. How should I proceed?

MS. BOEHMER: If you're not receiving a timely response to an urgent question, please feel free to contact our OTP RPMs inbox, and we will ensure that you get an update. Again, that inbox is in the chat, but it's OTPRPMS@fda.hhs.gov. You can reach out to us, and we'll make sure that you get an update if it's an urgent issue that you're awaiting response on.

Thanks. Back to you, Ramani.

DR. SISTA: Thank you, Jessica. I hope this is not a frequent occurrence. All our RPMs are diligent and very quick to respond unless they are out of the office. But absolutely feel free to respond to or write to OTP RPMs, and someone will get back to you with a response.

Mara, this next question is for you.

As a follow-up to the response for not requiring Form 1571 for a meeting request, is this still true for an eCTD submission as well?

MS. MILLER: Yes, actually, that is true. You are not required to submit Form 1571, even with eCTD format. When you get to the IND stage, though, you will need to submit that Form 1571 with every submission, but not when you're still under INTERACT or pre-IND. Just make sure that you are including the authorized contacts information and any backup person for contact in your cover letter and your address. We have had a few submissions—or at least one I can remember—where we didn't have any way to contact anybody. If we got a Form 1571 it would have been there, but because you were not required, there was no contact information.

Just make sure the information that we need in order to contact you and get the submission through is provided in your cover letter. But Form 1571 is specific for the IND.

Thank you.

DR. SISTA: Thank you, Mara. And I cannot emphasize enough how critical it is for you to include the contact information. We do occasionally run into challenges where there is absolutely no way to contact the person. There's no email or phone number, and it becomes really challenging, because if it is an original IND, the clock is ticking, and we have no way of contacting the person.

I think that's about it for the live questions. Thank you so much for attending today's OTP town hall. I'd like to extend a big thank-you to our panelists and also our behind-the-scenes technical crew that made this webinar possible.

As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming weeks. You can find more information about the town hall series and other OTP-hosted events on our OTP meetings and workshops page, which we'll share in the chat box. We've also included links to a few other helpful resources on the slide for your awareness.

Once again, thank you all for joining. Wishing everyone the season's best for the upcoming holiday season and a very happy New Year.

Thanks for joining. Have a fantastic day. Thank you.