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FDA CBER OTP Town Hall:
Nonclinical Assessment of Cell and Gene Therapy Products

August 30, 2023

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DR. IWEN WU: Good morning, everyone. Thank you all for joining us for today's Office of Therapeutic Products virtual town hall. Today's event is hosted by the Office of Therapeutic Products — or OTP for short — within the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA). My name is Iwen Wu. I am the Director of the Office of Pharmacology and Toxicology within OTP, and I will also be your moderator for today's event.

As you all know, today's town hall is focused on the nonclinical assessment of cell and gene therapy (CGT) products. While we have hosted a number of town halls this year, this is the first time we've hosted a town hall on this particular topic, and we look forward to answering your questions.

Before we begin, I'd first like to welcome OTP's new director, Dr. Nicole Verdun, who's moved into this new role as of July 30. Dr. Verdun, thank you so much for joining us today. I will pass it over to you to say a few welcoming remarks.

DR. NICOLE VERDUN: Thank you. Thank you so much. I'm happy to be here. Hello everyone, it's great to be here at today's OTP virtual town hall event. As Dr. Wu mentioned, my name is Dr. Nicole Verdun, and I'm very pleased to be leading the Office of Therapeutic Products and all the exciting work happening within OTP. I've had the pleasure of working at FDA for more than a decade, starting my FDA career in the Center for Drug Evaluation and Research (CDER) and making the switch to CBER in 2016. I most recently served as the Director for the Office of Blood Research and Review within CBER before moving into my current role as OTP Director.

Just to share a little more information about myself. I am a board-certified pediatric hematologist-oncologist. After graduating from medical school, I completed a residency in pediatrics and a fellowship in pediatric hematology-oncology and then moved on to work on adeno-associated viral gene therapies while at the Children's Hospital of Philadelphia. Since then, I've had the pleasure of practicing medicine for about 12 years, including at the Children's National Health System here in Washington, DC. Being at CBER and OTP reaffirms the important work I've had the privilege to study and get to practice in many capacities.

As many of you are already aware, OTP became a super office within CBER just this year. This shift is already helping OTP respond to and navigate the expected growth in the coming years in the gene and cell therapy space. And we anticipate this restructuring will continue to enhance OTP's and CBER's capabilities to focus on our commitments to advance drug development and fulfill the FDA's mission of protecting and promoting public health.

Given the fast-paced and evolving landscape for gene and cell therapy development, it is vital that OTP keep an open line of communication with its many important stakeholders to inform the regulation of these biological products and do what we can, with our trusted stakeholders, to advance these products and get them to communities and patients that need

them. The virtual town hall series — as well as the many other events we host and participate in throughout the year — is just one way we at OTP are trying to keep those lines of communication open and talk with sponsors and stakeholders early and often about the multifaceted and nuanced aspects of gene and cell therapy product development.

Today's topic on nonclinical assessment of cell and gene therapy products is especially important, since nonclinical studies hold a large stake in informing regulatory decisions and deciding what happens next with many investigational products. And I'm excited to hear our subject matter experts and panelists share their experience and answer questions related to this important topic.

With that, I will pass the mic back to Dr. Wu and let the panelists do what they do best. I look forward to being a part of this town hall and many more to come. Thank you again for being here.

DR. WU: Thank you so much, Dr. Verdun. Before we begin, I first want to share some background about the OTP Town Hall series. OTP launched its virtual town hall series back in 2022 to engage with product development stakeholders and researchers. These town halls have a question-and-answer format, with the goal of providing regulatory information to stakeholders to help advance the development of OTP-regulated products. All of the recordings from previous town halls are on FDA.gov, and we encourage you to watch them for additional information.

Please note that this town hall is being recorded. The recording and event materials will be posted on FDA's website in the coming weeks. Closed captioning for this event is available directly in Zoom. If you do have a question today, please type it directly into the Q&A box in Zoom. You can find that Q&A box at the bottom of your Zoom window. We appreciate all of the questions that have been submitted in advance, and we look forward to seeing the questions from the audience during today's event. We will do our best to address as many as we can today, but please note that FDA is not able to answer questions regarding specific investigational products or drug applications (INDs). Also, we will not address any questions that are considered out of scope for this event. Lastly, please use the chat box if you are experiencing any technical difficulties. Great, I think we're ready for today's event.

As many of you are aware, nonclinical studies are an important part of medical product development and regulatory decisions. The data from these nonclinical studies provide information on the safety and activity profile of an investigational product and guide the design of early-phase clinical trials. During today's town hall, subject matter experts from OTP's Office of Pharmacology and Toxicology will answer questions related to nonclinical assessment of cell and gene therapy products.

I'd now like to take a moment to introduce today's panelists. We have Dr. Abby Shearin, Branch Chief for Pharmacology/Toxicology Branch 1; Dr. Sandhya Sanduja, Branch Chief for Pharmacology/Toxicology Branch 2; and Dr. Alyssa Galaro, Branch Chief for Pharmacology/Toxicology Branch 4. I'd also like to thank all of our panelists for their time today.

We will now move on to the Q&A portion of today's town hall. We will begin by answering the questions that were submitted during the registration process, followed by responding to questions that were submitted during today's event. As a reminder, you can

submit questions for our panelists in the Zoom Q&A box at any time during the event, and again, you can find that at the bottom of your screen in Zoom. We will try to address as many questions as we can get to today, but again, please remember we are not going to be able to discuss questions regarding specific products or applications. We will also not be able to discuss questions related to draft guidance documents that are under public comment or under revision prior to final guidance document publication.

We really hope that you can stay on with us for the entire time today. We would also like to reiterate that this town hall is being recorded, so you can also visit the full discussion after it is posted on our website. Let's begin with our first question. This first question will be for Abby.

In how many animal species should testing occur at phase 1?

DR. ABBY SHEARIN: Hi, good morning. To answer this question, we do not have requirements for the number of animal species needed to support a phase 1 clinical trial for cell and gene therapy products. The animal model or species selection for the conduct of safety studies should be guided by the knowledge of your cell or gene therapy product and the planned clinical trial, including the selection of a species that is biologically relevant based on factors such as the anatomy related to the feasibility of the intended route of administration, the progression of the disease phenotype in the disease model species, and pharmacological activity of the investigational product, including a species' sensitivity to product-specific toxicities. Sponsors should discuss their animal model species selection with us in INTERACT or pre-IND meetings and provide the rationale for their species selection. Thank you.

DR. WU: Thank you. Our next question will be for Sandhya.

How do the targeted patient demographics drive Good Laboratory Practice (GLP) toxicology species selection?

DR. SANDHYA SANDUJA: Hi, thanks for that question. Welcome, everybody. As we just heard from Abby, the animal species selection for a nonclinical study — and that includes toxicology studies — should be biologically relevant and appropriate for evaluation of potential toxicities that can happen following CGT product administration. Factors like patient age and sex may help inform specific design aspects of the safety study. For example, if the clinical indication affects only males, you may choose to conduct toxicology studies in male animals and exclude female animals in these studies. Similarly, if the intended patient population is pediatric and there are specific safety concerns related to their age, juvenile animal studies may be helpful for the evaluation of the safety profile of the CGT product in that patient population. Back to you, Iwen.

DR. WU: Thank you. The next question we have will be for Alyssa.

Can you provide guidance on different approaches to address the absence of adequate animal models of disease for gene therapy?

DR. ALYSSA GALARO: Hi, thank you for that question, Iwen. Nonclinical studies using animal models of disease or injury are encouraged to better define the benefit/risk ratio associated with an investigational gene therapy product. However, each model has inherent strengths and weaknesses. Thus, no single model will predict, with complete accuracy, the

efficacy and safety outcome of the investigational gene product in the human patient population.

In cases where the intended product for clinical administration in animal models of disease may not be informative, testing of an analogous product might be a suitable alternative. Additionally, replacement of selected animal studies with in vitro or in silico studies, if such alternatives exist or can be developed, may also be considered.

In these situations, the design of the nonclinical development program is considered on a case-by-case basis. The suitability of any unique approach should be considered with respect to its ability to provide necessary data regarding the safety and activity of the gene therapy product.

DR. WU: Okay. Great. The next question that we have will be for Abby.

Given the nonhuman primate (NHP) shortage, coupled with their increasing use in nonclinical cell and gene therapy studies, can OTP discuss acceptable approaches to eliminate or reduce the use of nonhuman primates for nonclinical assessment of cell and gene therapy products?

DR. SHEARIN: Hi, thank you for that question. We certainly appreciate the challenges with the NHP shortage and support efforts to reduce the use of NHPs in these studies. There's no default requirement for the use of NHPs, and conduct of studies with NHPs should be scientifically justified. In many cases, there are other alternative species that may be appropriate for the toxicology studies. And as mentioned before, the species selection should be based on the biological relevance, sensitivity for detecting product-specific toxicities, and technical feasibility for the route of administration. Even when a specific route of administration may necessitate the use of larger animal species, there is flexibility in large animal species selection.

Publicly available data and/or cross-referenced data from an existing IND may be leveraged to aid in the reduction of the number of animals needed. However, leveraging of existing data may be product-specific, and sponsors should discuss their plans to do so to support their clinical trial at a pre-IND meeting, as supplemental safety or bridging studies may be needed. We have a case-by-case approach to evaluating such proposals. Thank you. Back to you, Iwen.

DR. WU: Thank you. The next question we have, I will direct to Sandhya.

What are the expectations for nonclinical studies to support entry into pediatric cohorts?

DR. SANDUJA: Thanks for that question, that's a great question. I'll start by saying that nonclinical safety studies to support any first-in-human trials in pediatric subjects must demonstrate safety and activity of the cell and gene therapy product. Based on the regulation, prior to initiating a study in children, you must provide evidence that administration of the investigational CGT product provides a prospect of direct benefit. Such evidence can come from clinical and/or nonclinical studies.

For a first-in-human trial in pediatric subjects, of course, such evidence would only come from prospectively designed, well-controlled nonclinical studies that are conducted in an appropriate model of disease showing that there is an improvement in the disease-relevant

parameter following administration of the product using the clinical route of administration. Following an appropriate extrapolation of dose to humans, these studies should support activity of the product at the intended clinical dose level.

Nonclinical studies demonstrating safety of the CGT product are required to support administration, and that can be conducted in healthy animals, although we also recommend that sponsors gather safety information from studies that are conducted in disease models as feasible. If differences are expected in the safety profile based on the age of patients, then conduct of safety studies in healthy juvenile animals may be needed.

I would also like to note here that in cases where nonclinical studies may not be feasible in an appropriate disease model, however an adult patient population exists, then we encourage that the first-in-human trial is conducted in adult patients and a prospect of direct benefit is established in adult patients in the first-in-human trial. Thank you. Back to you, Iwen.

DR. WU: Great. Thank you. The next question that we have is for Alyssa.

Can non-GLP studies alone be used to support first-in-human studies?

DR. GALARO: Thank you, Iwen. Ideally, all safety studies should be carried out in compliance with Good Laboratory Practice, or GLP, as per 21 CFR part 58. However, if technical limitations don't allow for this, it is acceptable to perform the study in a non-GLP testing facility. In this case, the studies should be conducted according to a prospectively written protocol to be performed in as non-biased a manner as possible, have appropriate record keeping and documentation of all data, and include quality assurance measures such that we can be confident that the resulting data are of sufficient quality and integrity to support the proposed clinical trial.

In addition, as directed by the regulations, the final study report should state why the study was not conducted in compliance with GLP, as well as specify any areas that deviate from the prospectively written protocol and the potential impact of these deviations on study integrity. We strongly recommend oversight of the conduct of all non-GLP toxicology studies and each resulting final study report by a quality assurance unit or person that is independent of the personnel responsible for conducting the study. The quality assurance oversight is important to assure study conduct according to sound procedures and to ensure the quality and the integrity of the results and data. Back to you, Iwen.

DR. WU: Great. Thank you. The next question we have is for Abby.

In cases where expression of a human protein causes an immune response or the clinical product is not compatible with animal models, is it required to evaluate a surrogate product? Or can the sponsor choose to not conduct in vivo studies?

DR. SHEARIN: Thank you for that question. These situations can be very challenging. The need for the development of an analogous product is evaluated on a case-by-case basis and depends on several factors, such as the experience with the product type, the safety concerns inherent to the product or administration procedure, the ability of in vitro studies to evaluate those safety concerns, the degree of unmet medical need for the indication, the clinical population, and the additional information that may be gained from the use of an analogous product. These factors should be weighed by the sponsor and a justification with

supporting data provided at an INTERACT or pre-IND meeting. FDA will provide product-specific feedback at that time. Thank you. Back to you, Iwen.

DR. WU: Great. Thank you. The next question we have I would direct to Sandhya.

Can FDA provide any insight into how it evaluates differences between the nonclinical and clinical delivery device or procedures in cases where it may not be possible to use the clinical delivery device or procedure in the available animal models of disease?

DR. SANDUJA: Thanks for that question, Iwen. We recommend that sponsors mimic the clinical delivery procedure and use the clinical delivery device in all nonclinical studies to the extent possible. In cases where it may not be possible, we recommend that sponsors provide details for all the modifications that are made to accommodate anatomical differences for administration of the CGT product in the selected animal model or species. This will particularly apply more often for small animal species, including rodents.

In situations where a clinical device can only be used in large animals, safety studies in healthy animals would be acceptable to evaluate or demonstrate safety of the procedure as well as the device. In nonclinical studies evaluating the devices or different versions of the devices, we also recommend that you conduct bench testing of compatibility of the device with the investigational product, and that can be performed separately in vitro. The point of this is basically to ensure that the product and the device that has been used to deliver the product are compatible. What goes in is what's going out, and there is no significant loss of product, cell viability, or vector titer during loading of the device and the delivery procedure. Thanks. Back to you, Iwen.

DR. WU: Okay. Great. Thanks, Sandhya. The next question we have is for Alyssa.

Do you think it is possible to move the nonclinical studies from in vivo to in vitro application?

DR. GALARO: Thanks for that question. Yes, we encourage sponsors to explore opportunities where in vitro studies may replace in vivo studies to support the safety and activity of cell and gene therapy products. In our 2013 guidance for industry on the preclinical assessment of investigational cellular and gene therapy products, we support efforts for reducing, refining, and replacing animal use in your nonclinical program. For example, it may be appropriate to use in vitro or in silico testing to complement or replace animal studies.

We encourage sponsors to submit proposals and justify any potential alternative approaches. The suitability of these efforts should be considered with respect to their ability to provide necessary data regarding the safety and activity of the investigational product. Data should be provided to clearly demonstrate aspects in which a particular in silico or in vitro assessment can act as a replacement for an in vivo study. In many cases, this requires substantial effort to establish the new method before the benefits of saved animals, time, and resources can be realized. But we do believe that it is a worthwhile and valuable effort. Back to you, Iwen.

DR. WU: Okay. Great. Thank you. The next question we have will be for Abby.

Can biodistribution studies be completed in rodents?

DR. SHEARIN: Thank you for that question. There is no requirement for the selection of a large animal model or species for a biodistribution study. However, the appropriateness of a rodent species may depend on if the delivery device or route of administration that will be used clinically is adaptable to a rodent species and whether the rodent species is permissive to the vector. If not, conducting biodistribution studies in a rodent species may be less informative than selecting a large animal model or species.

Sponsors should provide their plans for biodistribution studies, including their justification for the species selection, at the time of pre-IND. We also refer sponsors to the ICH S12 document for additional considerations for biodistribution assessment. Thank you. Back to you, Iwen.

DR. WU: Great. Thanks, Abby. The next question we have will be for Sandhya.

Lipid nanoparticles such as those used for mRNA delivery consist of a variety of lipid excipients. Can the FDA comment on the expectations for biodistribution and metabolite identification for these excipients?

DR. SANDUJA: Thanks for that question, Iwen. Biodistribution (BD) or pharmacokinetic (PK) analysis of each lipid component that is present in a lipid nanoparticle-based gene therapy product should include assessment of metabolism distribution as well as elimination of the component at several time points following administration of the product. This characterization is important for the overall safety profile of the product. We expect that you assess biodistribution, to be conducted for each novel lipid excipient.

For lipid excipients that may be present in cell and gene therapy products that are either approved or under existing clinical trials, if your position is to not conduct extensive PK analyses and repeat these assessments, we recommend that sponsors provide supporting data and your position that BD and PK of the lipid is not significantly impacted due to the change in the gene therapy cargo or other components that may be present in the lipid nanoparticle. Your position, as well as these supporting data, can be reviewed and discussed at a pre-IND meeting. Thank you. Back to you, Iwen.

DR. WU: Okay. Thanks, Sandhya. The next question we have will be for Alyssa.

Are biodistribution or cell distribution studies required for T cell therapies?

DR. GALARO: Generally, cell distribution studies are not required for T cell therapies, in accordance with ICH S12. However, cell distribution studies may be helpful in certain situations depending on the specific product, the route of the administration, and the potential for the expression product or gene modification event to affect the expected distribution of the cells within it. We recommend communication with OTP staff early in the development of novel T cell therapies for specific advice regarding the need for these studies. Back to you, Iwen.

DR. WU: Great. Thanks, Alyssa. The next question we have is for Abby.

Can the Agency provide their approach to toxicology studies for human stem cell therapies where there is a significant xenogeneic immune response in animal models?

DR. SHEARIN: Xenogeneic response is a common nonclinical challenge with human cell therapy products. We recommend consideration of immunodeficient animals, such as mice and rats, when feasible. If an immunodeficient model is not appropriate, the sponsor should consider the use of immunosuppression for the development of an analogous product. The sponsor should provide us with a justification for the approach that they choose. Plans can be discussed at early stages of product development, including through INTERACT and pre-IND meetings. Thank you.

DR. WU: Great. Thank you. The next question we have is for Sandhya.

For shedding, this information may be obtained either in the literature or from samples that are taken from patients during the clinical trial. Does the FDA expect that shedding be investigated nonclinically too?

DR. SANDUJA: Thanks for that question, Iwen. We generally do not expect shedding data to be collected in — for example — urine, feces, or saliva to be assessed in nonclinical studies unless a novel replication-competent vector is being investigated and we don't have any prior nonclinical or clinical experience on potential transmission of that novel vector. In case of a novel vector, shedding studies may then be conducted as part of toxicology studies in an animal species that is permissive to infection with that novel vector. We would also like to refer you to our 2015 CBER guidance on shedding studies for virus- or bacteria-based gene therapy products and oncolytic products. You may discuss the need to assess shedding of your product at a pre-IND meeting. Back to you, Iwen.

DR. WU: Great. Thanks, Sandhya. The next question we have is for Alyssa.

Does the FDA feel that publicly available, published data on biodistribution in rodents, along with additional information from physiologically based pharmacokinetic (PBPK) models, is sufficient to remove the need for biodistribution studies of engineered or targeted cell and gene therapy products?

DR. GALARO: Thanks for that question. FDA would consider publicly available, peer-reviewed, published data on cell distribution or biodistribution in animals, along with information from physiologically based pharmacokinetic modeling, as part of the overall safety and activity assessment of a novel cell and gene therapy product. However, the sufficiency of such data would depend on factors including the specific context, the relevance of the data, data quality, and model validity. The need for any additional studies will depend on the totality of the data submitted, the specific products, the indications, and previous experience with similar products. We encourage you to submit proposals and justify any potential approaches to satisfy the data needed for biodistribution of your product. Back to you, Iwen.

DR. WU: Great. Thanks, Alyssa. The next question we have is for Abby.

For gene therapy development, when using nonclinical disease models for combined pharmacology/toxicology assessment, are there specific safety endpoints that would be considered minimally necessary for the study results to add weight to the safety assessment?

DR. SHEARIN: Thank you for that question. The conduct of a hybrid proof-of-concept and toxicology study may be appropriate for some indications; for example, if there are concerns that safety findings may be disease-specific and healthy animals may not be as informative as the disease model. In these cases, if the study cannot be conducted as a GLP-compliant study because of the proof-of-concept endpoints or the selection of a disease model, the study should be conducted in a manner as close as possible to a GLP-compliant study per 21 CFR part 58.

Therefore, the toxicology endpoints should be as consistent as feasible to a GLP toxicology study, including in-life safety assessments, comprehensive growth and histopathology, et cetera. As Alyssa stated previously, studies should include a prospectively designed protocol, be performed in as non-biased a manner as possible, have appropriate record keeping and documentation of all data, and quality assurance should be conducted per 21 CFR 58.35. Thank you. Back to you, Iwen.

DR. WU: Great. Thanks, Abby. The next question we have is for Sandhya.

Can FDA comment on the need for nonclinical toxicology studies for personalized medicines?

DR. SANDUJA: Thanks for that question, Iwen. This really depends on the specific product. Sponsors should be thinking about the specific risk for their product and how they can best evaluate and characterize those risks, which should then guide potential ways that can be used to mitigate those risks in subjects, including specific exclusion and inclusion criteria for patient selection and adequate clinical monitoring during the trial.

For certain personalized medicines, a toxicology study can also sometimes be useful to evaluate the safety of that particular platform or delivery modality or a specific adjuvant that may be used. It's also important to discuss the specific approaches with us if such a testing of a representative product can be performed to establish proof of concept and safety of an individualized product, and it doesn't have to be repeated for every single version of the product.

If it's not feasible to evaluate the individual products in nonclinical studies, we encourage that sponsors provide their positions in early communications — in their pre-IND interactions, for example —for further feedback on this topic. Thank you. Back to you, Iwen.

DR. WU: Great. Thanks, Sandhya. The next question we have is for Alyssa.

Will the FDA accept an in vitro tumorigenicity assay for cell therapies in replacement of an in vivo tumorigenicity assessment?

DR. GALARO: The potential for tumorigenicity, dysplasia, or hyperplasia to occur should be considered and addressed as appropriate based on the specific biological properties of each investigational product. We encourage you to submit proposals and justify any

potential alternative approaches. The suitability of these efforts should be considered with respect to their ability to provide necessary data regarding tumorigenicity assessment of your product in the context of the proposed clinical trial. Data should be provided to clearly demonstrate that a particular in vitro tumorigenicity assay can act as a replacement for the in vivo application. As mentioned previously, this can require substantial effort to establish the new method before the benefits of saved animals, time, and resources can be realized. Back to you, Iwen.

DR. WU: Great. Thanks, Alyssa. The next question we have is for Abby.

What types of studies would the Agency like to see to assess the risk of germline transmission with genome editing products?

DR. SHEARIN: Thank you for this question. The need to evaluate germline transmission risk for genome editing products depends on the product, the likelihood of exposure to editing components in the reproductive organs, and specific risks for the targeted patient population. The risk of germline transmission for in vivo genome editing products should be evaluated in a stepwise manner. First, biodistribution to the gonads should be determined. Then, the presence of editing within gonadal tissue should be evaluated. If this is established and editing is observed, the sponsor should proceed with more comprehensive assessment of the risk and provide scientific justification for their specific approach.

In some cases, this can involve more targeted studies to determine the specific cell types where editing is observed or more comprehensive assessment of the potential for germline transmission and developmental and reproductive toxicities. As these therapies are highly novel and the potential effects of gene editing in gonadal tissues is not yet well understood, FDA will evaluate each sponsor proposal on a case-by-case basis. For this class of products, having early discussions regarding the risks of developmental and reproductive toxicities can be very helpful and may be best included in a pre-IND meeting package. Thank you.

DR. WU: Great. Thanks, Abby. The next question we have is for Sandhya.

Is there a standard duration for single-dose GLP toxicology studies to enable IND and registration?

DR. SANDUJA: Thanks for that question, Iwen, and that's a very good question. The answer is no. We don't default to a standard study duration for GLP or non-GLP safety studies. What we recommend is that the duration of your safety study should be of appropriate length to evaluate all of the potential acute as well as late-onset adverse events that may happen following administration of your product, the procedure, and the use of the delivery device. I believe there should be an early and a late sacrifice time point that are based on persistence profiles or transgene expression of the CGT products. Having said that, for certain safety studies depending on what specific aspect of safety they are meant to assess — for example, tumorgenicity — the study duration may be much longer. But again, we don't default to a standard study duration. It should be an appropriate length to capture all potential toxicities following administration of the product. Thanks. Back to you, Iwen.

DR. WU: Thank you. The next question we have is for Alyssa.

What is the Agency's position regarding studies measuring the impact of pre-existing humoral immunogenicity on the gene therapy effectiveness?

DR. GALARO: Thanks for that question. Generally, for definitive studies assessing the activity of a gene therapy product, we recommend that sponsors include assessment of pre-existing neutralizing antibodies for the gene therapy product to assess any gross impact on product activity. Back to you, Iwen.

DR. WU: Great. Thank you. The next question we have is for Abby.

Can you discuss safety margins and expectations when extrapolating from animal studies to clinical dose levels?

DR. SHEARIN: Thank you for that question. Ideally, there is an adequate safety margin from the toxicology study to ensure the safety of study subjects in a clinical trial for cell and gene therapy products. We recognize that safety margins can frequently depend on product manufacturing issues, such as the product's concentrations and/or the maximum feasible dose able to be delivered in an animal model or species for a specific route of administration. Sponsors should justify their proposed dose levels for their toxicology studies based on their proposed clinical dose levels, the maximum feasible dose, manufacturing capabilities, et cetera.

The minimal effective dose level is the lowest dose level where in vivo activity of a product is observed. The method of extrapolation from both the highest safe dose level and the minimal effective dose level is dependent on many factors, including the route of administration — such as IV administration or into a space, such as the intraventricular space or intraparenchymal into a specific brain structure — or even potentially the surface area of gas exchange in the lung for inhaled products. Those are just a few examples.

The sponsor should justify their method of dose level extrapolation with supporting data. In regard to establishing a safety margin, it can be informative to provide more than one method of extrapolation and determine the safety margin for each, such as comparing the viable genomes for the volume of a specific brain structure that's injected versus comparing the viable genomes per gram of brain bleed. Ideally, the final starting clinical dose level will be one above the minimal effective dose level, where therapeutic activity is anticipated and where there is some margin of safety based on the toxicology studies. Thank you. Back to you, Iwen.

DR. WU: Great. Thanks, Abby. The next question we have is for Sandhya.

What are some of the challenges observed in nonclinical studies that could later affect IND submissions?

DR. SANDUJA: Thanks for that question, Iwen. Challenges — I'm using another term — I'm taking it as deficiencies or issues that we encounter in nonclinical studies that can impact IND submissions. Some of the deficiencies or issues we encounter that can really limit interpretation of safety, I can go over some general examples. The first example that comes to my mind is that the product that is tested in nonclinical studies is significantly different from the intended clinical product. For example, if the vector or the transgene being used are different than what is intended clinically. Another example could be if the clinical formulation is significantly different than how the product was formulated for

nonclinical studies. In cases like these, the data that are collected from nonclinical studies may not be directly supportive of the safety of the intended clinical product.

Another scenario where we see issues could be if the nonclinical study design itself is inadequate. Some of the examples under that scenario are: if the animal species used to conduct nonclinical safety studies or the study to evaluate activity and/or safety is not really permissive to the vector or the product; if the route of administration that has been used for product administration in these studies is not really the intended clinical route of administration; if dose level factor administered do not really bracket the intended clinical dose level and that dose level rationale or extrapolation is missing from nonclinical programs; if the safety assessments that are part of these studies are inadequate to really inform what may happen clinically and what could be potential risks to the intended patient population. Such issues with study design can really limit interpretation of safety data for the product.

Another challenge that could affect initiation of a clinical trial is if the safety concerns or the toxicities or risks that are identified from nonclinical studies are not sufficiently characterized — and therefore the potential risks to patients remain relatively unknown — to adequately inform patient selection, clinical monitoring, and risk mitigation. One example is if product-related adverse findings are seen in nonclinical studies, but the animals were not followed long enough to actually see whether these adverse findings would resolve or would worsen over time. That really limits our ability to understand what sort of risks there can be to the enrolled patients in a clinical trial.

One more scenario that I would like to note is lack of nonclinical data to support prospect of direct benefit (PDB). As I have mentioned earlier, for first-in-human trials in pediatrics, if nonclinical studies supporting PDB are not there, that can be an issue for INDs that are for first-in-human trials in pediatric subjects.

For additional guidance or resources to aid in the nonclinical development program so that these issues can be avoided, we would refer sponsors to our 2013 guidance on preclinical assessment of investigational cellular and gene therapy products, as well as other resources that we have on the OTP website, with specific guidance for rare diseases, retinal disorders, and neurodegenerative diseases. Our OTP Learn webinar series is also available on the OTP website. Thanks. Back to you, Iwen.

DR. WU: Great. Thank you, Sandhya. The next question we have is for Alyssa.

How should a sponsor leverage GLP toxicology data for a platform gene therapy with the same AAV and different transgenes and disease targets?

DR. GALARO: Thanks for that question, Iwen. We encourage sponsors to leverage GLP toxicology data for platform gene therapy products to inform the scope of additional nonclinical assessments. For instance, these studies could be leveraged to inform additional targeted safety assessments, which focus on known target issues and have a modified duration or more refined scope based on previous platform data. Additionally, in accordance with ICH S12, in some cases biodistribution data may be leveraged if the changes to the product are not anticipated to impact product biodistribution. We encourage early communication with OTP regarding platform technology and how to best leverage data for future nonclinical assessment. Back to you, Iwen.

DR. WU: Thanks, Alyssa. Our next question will be for Abby; this is a process-related one.

Considering the new Type D format has been introduced recently, does the Agency foresee a situation granting all three meetings in the order of INTERACT, Type D, and pre-IND meetings, provided the question(s) fit the criteria?

DR. SHEARIN: Thank you. That's a very good question. A Type D meeting may be requested and potentially granted at any stage of product development. However, a Type D meeting should have a narrow focus, such as one or two specific questions as to one discipline, which may be: Chemistry, Manufacturing, and Controls (CMC); pharmacology/toxicology; or clinical. For more information, please refer to the PDUFA VII Commitment Letter for fiscal years 2023 through 2027. In their meeting request, sponsors should provide their justification for why a Type D meeting is needed. Typically, sponsors obtain feedback regarding their nonclinical testing programs for supporting their initial clinical trial in the context of a pre-IND meeting. Thank you. Back to you.

DR. WU: Great. Thanks, Abby. The next question we have is for Sandhya.

Can you contrast the data that FDA feels sponsors should have or studies that should be complete to discuss at an INTERACT meeting versus a pre-IND meeting?

DR. SANDUJA: Thanks for that question, Iwen. As sponsors may already be aware, INTERACT and pre-IND meetings both are opportunities for early interaction, early communication with FDA.

INTERACTs are typically at a stage where sponsors have generated preliminary nonclinical data, proof of concept (POC), and some safety information. But they're not quite yet ready to conduct definitive nonclinical safety studies. The meeting package for an INTERACT should be submitted with the meeting request and should have detailed summaries of all the preliminary nonclinical studies that have been conducted so far.

A pre-IND meeting is a little further. It should be requested further in product development, when sponsors have conducted POC and preliminary safety studies and are ready to conduct their definitive nonclinical study. The pre-IND package should include a comprehensive summary of each completed in vitro and in vivo nonclinical study, including pharmacology and toxicology, as well as detailed protocols for all proposed definitive studies, including safety and biodistribution. The package also should contain elements of your nonclinical programs as well as your rationale for the respective study design, including the species selection.

We also recommend sponsors visit the OTP webpage on INTERACT and pre-IND meetings for more detailed information on these meetings. We also recommend listening to our previous OTP town hall meetings so that you can get information on the CMC and clinical design information that should be included in your meeting packages or meeting request for these meetings. Thank you. Back to you.

DR. WU: Great. Thank you. We have one final pre-submitted question, and this one will be for Alyssa.

For combined pharmacology/toxicology studies in efficacy models where histopathology has been evaluated, are Standard for Exchange of Nonclinical Data (SEND) datasets required? And could you also please discuss how SEND requirements will be implemented within CBER?

DR. GALARO: For applicable nonclinical studies initiated after March 15, 2023, standardized datasets in the Standard for the Exchange of Nonclinical Data — or SEND — format will be required to be submitted to your CBER Investigational New Drug Application (IND) and Biologics License Application (BLA). Further details on this requirement, including the types of nonclinical studies and exceptions from this requirement, can be found at the web addresses provided under Additional Resources at the end of the slides. The website also has an email address where any questions can be directed. Back to you, Iwen.

DR. WU: Great, thanks, Alyssa.

Thank you to everyone who submitted questions during the registration process. We will now spend the remainder of today's event answering your live questions.

The first live question that we have, I will direct to Sandhya.

Is it acceptable to run safety studies in animal models of disease?

DR. SANDUJA: Thanks for that question, Iwen. And I think part of this question was also addressed before by Abby and I would like to reiterate that, yes, it's acceptable to run safety studies or what we call hybrid studies, which include proof-of-concept and toxicology assessments, in animal models of disease. And I'll go over a few points to elaborate on that further.

Hybrid studies in animal models of disease can be particularly beneficial. For example, the potential risk or toxicities may be impacted or exacerbated by an underlying disease status for certain indications, and in those cases, healthy animals may not be as informative as the disease model. Similarly, as Abby had pointed out earlier, these studies may not be conducted under GLP, and that's why we recommend that quality assurance (QA) and appropriate record keeping and documentation for all data and quality is included in such studies.

I would also like to point out that, if a special delivery procedure or device is to be used for the intended clinical trial and the use of such device is limited to studies conducted in the animal model, separate studies in healthy animals may be necessary in that situation.

Thanks. Back to you, Iwen.

DR. WU: Great. Thanks, Sandhya. The next question I will direct to Alyssa, and this is a long one.

According to FDA guidance, biodistribution studies should have a minimum of at least three animals per group per sex per time point. However, considering the principles of the three R's, can the Agency agree with pooling the biodistribution data from different time points? For example, in an NHP study, if we have two necropsy time points and each dose with three monkeys at each time point, can we pool the biodistribution data from these six animals together?

DR. GALARO: Thanks for that question, Iwen. I think that that is referring to the ICH S12 guidance that was published in May of this year on the nonclinical biodistribution considerations for gene therapy products. As it states in the guidance, biodistribution data can be pooled from multiple studies, but the pooling should be for the same evaluation time point. Time points should be selected to sufficiently characterize the time-related changes in gene therapy product levels over appropriate time points. And, of course, justification should be provided if there are unequal numbers of animals of each sex, or if a single sex is evaluated. Further guidance can be found in ICH S12. Back to you, Iwen.

DR. WU: Great. Thanks, Alyssa. The next question I have will be for Abby.

Is there a minimum number of animals to include for GLP toxicology studies?

DR. SHEARIN: Thank you for that question. No, we do not necessarily have a minimum number of animals that should be included for a GLP toxicology study. This is dependent on many factors. However, an adequate number of animals should be included that the study is able to yield interpretable data. It is not necessary to incorporate an equivalent number of animals of each sex in each group, unless sex-specific differences are anticipated.

The sponsor should also take into account any anticipated attrition due to the administration procedure or delivery procedure or any other factors related to the conduct of the GLP toxicology study. However, we do encourage judicious use of animals, as related to the three R's discussed in the preclinical assessment guidance. Thank you.

DR. WU: Great. Thanks, Abby. The next question we have will be for Sandhya.

Does the clinical product need to be used in the nonclinical studies?

DR. SANDUJA: Thanks for that question, Iwen. We recommend that the product that is administered in nonclinical studies be identical to the intended clinical product to the extent possible in terms of the manufacturing as well as key quality attributes, including identity and final formulation. Having said that, we acknowledge that there may be differences between nonclinical and clinical products — for example, situations where the use of a surrogate or a species-specific product may be needed. In those cases, we recommend that the sponsor provides a list of similarities and differences for the nonclinical and clinical products and how these differences can impact interpretation of data that are generated from nonclinical studies to support safety of administration of the product in their clinical trials. Thank you. Back to you, Iwen.

DR. WU: Thanks, Sandhya. The next question I have will be for Alyssa.

If a gene therapy is intended to be used in combination with an existing FDA-approved product, does the FDA require dedicated nonclinical combination toxicity studies to support registration of the combination product?

DR. GALARO: Thanks for that question, Iwen. I would say that that is to be determined on a case-by-case basis and that scientific justification should be provided for the nonclinical approach that's taken. Some factors to take in consideration would be if the approved product is being administered according to the product label, if there are expected to be synergistic activities between the combination products, or if the combination is expected to affect activity. And as we have mentioned previously, we recommend discussing with OTP staff early to justify and discuss your approach to the nonclinical program. Back to you, Iwen.

DR. WU: Thanks, Alyssa. The next question I have will be for Abby.

What is the current requirement or expectation for insertional mutagenesis evaluation for AAV-based gene therapy to support IND and marketing application?

DR. SHEARIN: Thank you. That's a great question. This is product-specific and is going to depend on the risk of insertional mutagenesis based on knowledge of the product and the sponsor's knowledge of the product. Therefore, some products may need these analyses prior to initiation of a first and clinical trial. However, there is no blanket requirement for evaluating AAV insertional mutagenesis in nonclinical studies prior to initiation of phase 1 clinical trials. We do request that comprehensive tissues be archived for potential analyses in the future, and this may include potential analysis of insertional mutagenesis. Thank you.

DR. WU: Great. Thanks, Abby. The next question I have will be for Sandhya.

When are additional nonclinical studies needed when manufacturing changes are introduced?

DR. SANDUJA: Thanks for that question, Iwen. That's a good question. It really depends on what those changes are. Once those changes are made, once you have decided that you are making manufacturing changes, if those changes are expected to impact the safety and activity of your product significantly, then we expect that studies are done to evaluate that.

You should provide your justification and your approach for the conduct of these additional studies during your product development, and we can provide further feedback on this. We also recommend incorporating in your thinking your product comparability plan. You may also consider doing bridging studies, depending on what those changes are in manufacturing, to support the safety of the changes that are made in your product manufacturing. Thank you. Back to you, Iwen.

DR. WU: Thanks, Sandhya. The next question I have is for Alyssa and it's another long one.

Cytokine-independent growth for CAR T cells is a long and highly variable assay with little published evidence of clinical relevance. Given this, what is the rationale or significance of the FDA asking some sponsors to assess cytokine-independent growth in the preclinical package? Will this study be required of all CAR T cell developers in the future?

DR. GALARO: Thanks, Iwen. As per FDA's guidance for industry on the considerations for the development of chimeric antigen receptor (CAR) T, cell products, addressing the potential for CAR T cells to undergo cytokine-independent growth and uncontrolled proliferation is an important aspect of the nonclinical evaluation of these products.

However, if a sponsor intends to address this concern using an alternative approach, scientific justification should be provided in the IND submission. These alternative approaches can also be discussed with OTP early on in the development program at pre-IND or INTERACT meetings. Back to you, Iwen.

DR. WU: Great. Thank you. The next question I have will go to Abby.

Increasing numbers of clinical trials implement prophylactic immunosuppressive and/or immunomodulatory agents to address the potential safety issues. How should use of these agents and their potential impact on the safety and activity be addressed during the nonclinical stage of a developmental gene therapy?

DR. SHEARIN: Thank you for that great question. It may be informative to include a group of animals that receives immunosuppression and the high dose of your gene therapy product in your definitive toxicology study, especially if immune response-related toxicities are anticipated in your clinical trial and/or have been observed in pilot nonclinical studies.

The sponsor should provide the rationale for the immunosuppression regimen selected, which may be informed by the anticipated clinical immunosuppression regimen and the ability of the animal model to tolerate the immunosuppression regimen. The sponsor's approach can be discussed at a pre-IND meeting, and we will provide product-specific feedback at that time. Thank you.

DR. WU: Great. Thanks, Abby. The next question I have will be for Sandhya.

How do you determine the dosing regimen to use for the animal studies?

DR. SANDUJA: Thanks for that question, Iwen. Our general recommendation is that your nonclinical studies should mimic the clinical dosing regimen to the extent possible. If there are differences, then sponsors should discuss how those differences can impact interpretation of your findings and conclusion of safety from the nonclinical studies to support the intended regimen in the clinical trial. Thanks. Back to you, Iwen.

DR. WU: Great. Thanks, Sandhya. The next question I have will go to Alyssa.

Can you comment on the need for nonclinical toxicology studies for modifications of a lymphodepletion regimen for CAR T cell therapy? For example, addition of other small or large molecules that were previously approved for use in other contexts.

DR. GALARO: All right. Thanks for that question, Iwen. This would be considered again on a case-by-case basis. If modifications in the lymphodepletion regimen, for example, have been used in other clinical trials, a description of those clinical trial results could be supportive for the IND submission. Also, if there are relevant animal models that any modifications could be evaluated in, those in vivo studies should also be considered to support the changes in the regimen. Back to you, Iwen.

DR. WU: Great. Thanks, Alyssa. The next question I have is for Abby.
For local injections, such as intracerebroventricular for a central nervous system (CNS) disorder or intravitreal administration for ocular programs, is systemic toxicology study required for an IND?

DR. SHEARIN: Thank you for that question. For products with a targeted or local administration, we generally recommend some analysis of systemic toxicities and biodistribution be conducted. This may be to evaluate potential distribution outside of the targeted area and any toxicities that may be related to that distribution outside the targeted area. The sponsor can provide a justification for conducting a limited analysis, which is best provided at a pre-IND meeting stage, where we can provide specific feedback regarding the product and clinical development program that the sponsor is proposing. Thank you.

DR. WU: Great. Thanks, Abby. I have a question which is actually a follow-up for Sandhya.

Can you clarify the answer regarding data needed to request an INTERACT meeting? Noting the need for preliminary safety data but also preliminary safety data was needed for pre-IND, would an INTERACT meeting be granted without any preliminary safety data?

DR. SANDUJA: Thanks for that question. The point is that we do not really require you to have safety data at the time of an INTERACT package. If you have gathered any safety information from your preliminary studies, that's welcome to be included in the package, but you are not required to have safety data gathered by that stage. Thanks.

DR. WU: Great. The next question I have is for Abby.

Because DRG toxicity is a potential hazard for AAV-based gene therapies and nonhuman primates appear to be most susceptible, does the Agency expect that all AAV-based gene therapies will be tested in NHPs to capture this?

DR. SHEARIN: Yes, this is a very important question. We do not have a blanket requirement for the conduct of NHP studies for AAV-based gene therapies. However, we do consider factors such as our experience with a particular capsid, the route of administration, et cetera, that may influence the need to conduct toxicology studies in a species that is sensitive to potential CNS toxicities. Those are things that the sponsor should be considering as they design their preclinical development program, and that should be discussed at a pre-IND meeting with OTP. Thank you.

DR. WU: Great. Thank you. The next question I have, I will direct to Alyssa.

If the in vivo part of a toxicology study can only be conducted in a non-GLP environment, would you still recommend conducting certain assessments, like histopathology or bioanalysis, under GLP?

DR. GALARO: Thanks for that question, Iwen. I would say that as much of a study should be conducted per GLP as possible. As we mentioned earlier, sponsors should provide documentation showing that the study or parts of the study were conducted in compliance with GLP, or a brief statement regarding the reason for noncompliance. And if the study was not GLP-compliant, as we've mentioned previously, sponsors should report any areas that deviate from the prospectively written protocol and the potential impact of these deviations on study integrity.

Even if parts of studies are not conducted in compliance with GLP, they should still be conducted according to a prospectively written protocol, they should be performed in as non-biased a manner as possible and have appropriate record keeping and documentation of all data. And, again, we recommend oversight of all non-GLP toxicology studies by a quality assurance unit or person. Back to you, Iwen.

DR. WU: Great. Thank you, Alyssa. The next question I have will be for Sandhya.

For locally administered products where there's absence of systemic exposure, are local toxicity biodistribution studies only sufficient?

DR. SANDUJA: Thanks for that question. So, it depends. What we recommend is that, for the studies that you have done, you provide evidence of how the product is staying within the local administration site. And if there is absence of systemic exposure, we recommend that you provide supporting data. It is important to note that in certain cases, you may need to conduct safety studies that also capture worst-case scenarios.

For example, although the intended clinical administration is at a local site, errors during the delivery procedure can also cause inadvertent systemic exposure and potential risk to the patients. Those scenarios should also be taken into consideration for the design of your nonclinical safety study. Thanks. Back to you, Iwen.

DR. WU: Thanks, Sandhya. The next question we have will be for Abby.

Are GLP toxicology data in SEND format required for a first-in-human study? And as a second part to the question, what other data need to be submitted in SEND format?

DR. SHEARIN: Datasets for nonclinical studies that can be modeled in an FDA-supported SEND format and were initiated after March 15, 2023, are required to be submitted in SEND format. This currently includes single-dose, repeat-dose, general toxicology studies, carcinogenicity studies, and safety pharmacology studies. It is not limited to only GLP toxicology studies. We recommend that you see the resource slide with links for SEND for further information regarding the studies that need to be submitted in SEND format. Thank you.

DR. WU: Thanks, Abby. The next question I have will be for Alyssa.

For the starting clinical dose level, will FDA accept dose levels that are based on what was previously allowed for other similar products?

DR. GALARO: Thanks for that question, Iwen. For cell-based products, clinical data evaluating similar products can be supportive for selecting the starting clinical dose level for the investigational product. We often see this with T cell–based products where there are limitations to animal models and their use in extrapolating the dose levels to humans because of species-specific differences and the use of immunodeficient animal models, which may affect the safety and activity of the product in those studies.

Sponsors should provide a clear discussion regarding the use of existing clinical data or in vivo animal studies in selecting their clinical dose levels in their IND submissions. Back to you, Iwen.

DR. WU: Thanks, Alyssa. I actually have a two-part question about tumorigenicity studies for Sandhya.

Should tumorigenicity studies be done under GLP conditions? And as a follow-up, should the clinical route of administration be used?

DR. SANDUJA: Thanks for that question, Iwen. We recommend that the safety studies, including those evaluating potential tumorigenicity of a product, be conducted under GLP if possible. If a study cannot be conducted under GLP, then we request that you provide your rationale for noncompliance to GLP. In situations like this, as my colleagues have mentioned before, all non-GLP studies should be conducted with proper oversight so that you can provide assurance that the study is conducted with data that is generated and is robust and reliable to support safety of the product.

For the second part of this question, whether the clinical administration route is to be followed, it depends on the product. We generally recommend that you use the intended clinical route of administration. However, we also recommend that you take into account that the maximum feasible dose of the product is delivered in your tumorigenicity study. Thanks. Back to you, Iwen.

DR. WU: Thanks, Sandhya. The next question I have is for Abby.

What are the general recommendations if safety studies cannot be performed in compliance with GLP?

DR. SHEARIN: Thanks. As discussed previously, studies should be conducted in as GLP-like a manner as possible per 21 CFR 58. This includes comprehensive toxicology endpoints, a prospectively designed protocol, documentation of any protocol deviations, et cetera. We also recommend that quality assurance be conducted for safety studies that are not conducted in compliance with GLP. Thank you.

DR. WU: Thanks. The next question I have, I will direct to Sandhya.

For autologous cell therapies, does FDA have a recommendation on the number of donors from which product is derived to be used for a GLP toxicology study?

DR. SANDUJA: Thanks for that question, Iwen. We usually are not prescriptive with how many donors to use in toxicology studies for autologous cell therapy. However, we do recommend that you provide data showing that you are able to manufacture the product consistently, and therefore, that the representative product that's being used in your GLP toxicity study is representative of your intended clinical product and there are no significant variations which can otherwise warrant testing of every autologous product that you will manufacture. Thank you. Back to you, Iwen.

DR. WU: Thanks, Sandhya. I'm going to go back to Abby with another question which I think will be good for you.

Does the Agency have recommendations regarding the need for reproductive toxicology evaluation of lipid nanoparticle (LNP) formulations?

DR. SHEARIN: As discussed in response to the question regarding gene editing, a stepwise approach is recommended for evaluating the need for developmental and reproductive toxicology studies. First, distribution of the LNP to the gonads should be assessed; then, evaluation of the LNP clearance or half-life should be determined. If this is established for the LNP product and for LNP products that will be administered repeatedly, the sponsor should propose a plan to address developmental and reproductive toxicities. This may be included in a pre-IND meeting or, for active files, can be included in an IND meeting. Thank you.

DR. WU: Great. Thanks, Abby. The next question I have will be for Alyssa.

Do multiple dose levels need to be explored to meet biodistribution requirements? If not, should the dose be above what is anticipated for human clinical dose levels, or should it be designed to mimic a human equivalent dose?

DR. GALARO: Thanks for that question, Iwen. For gene therapy products, sponsors should provide justification for the design of their nonclinical biodistribution studies. The selected dose levels of the administered gene therapy products should provide adequate characterization of the biodistribution profile to aid in interpretation of the pharmacology and toxicology assessments. The highest dose level evaluated should be the expected maximum dose level in the toxicology studies, which is usually limited by animal size rather than administration, anatomic target, or the concentration of the gene therapy product.

It's important that the dose level for biodistribution evaluation equate to or exceed the anticipated maximum clinical dose level. However, it should not exceed the highest dose level administered in the toxicology study. For further guidance, you can also refer to ICH S12, the Nonclinical Biodistribution Considerations for Gene Therapy Products guidance for industry. Back to you, Iwen.

DR. WU: Great. Thank you, Alyssa. The next question I have, I will direct to Sandhya.

A lot of the gene therapy companies are doing their first-in-human trials outside of the United States, without FDA oversight. What are the challenges and requirements for

such companies when they want to come back to the United States? Will they need to do a bridging study, or will the safety data generated abroad be considered?

DR. SANDUJA: Thanks for that question, Iwen. Clinical studies that are conducted within the United States under INDs follow the requirements of U.S. regulations. We definitely consider clinical experience and safety data that are gathered from foreign trials. The review of these data is done on a case-by-case basis. In scenarios where manufacturing changes may be happening from the foreign side versus the U.S. side, bridging studies may be needed. But, again, all these are determined on a case-by-case basis as to what those manufacturing changes are and how they impact safety of your proposed trial that is intended in the United States. Back to you, Iwen.

DR. WU: Great. Thanks, Sandhya. The next question I have will be for Abby.

For gene editing therapies, in the event that biodistribution and editing is observed in both NHPs and rodents, is it acceptable to understand germline transmission with only a rodent F1 progeny study, or will an F1 progeny–like study also be required?

DR. SHEARIN: The design of germline transmission studies is product-specific. The sponsors should provide their proposal with their justification and supporting data to assess the developmental and reproductive toxicities in a pre-IND meeting or, for files that are currently active, in an IND meeting format. We will provide product-specific feedback at that time. Thank you.

DR. WU: Great, thank you. I think we have time for one more question. This last question I will direct to Alyssa.

In what cases would nonclinical studies need to be conducted after completion of a phase 1 or phase 2 clinical trial to support either a phase 3 clinical trial or BLA submission?

DR. GALARO: Thanks for that question, Iwen. There are some cases that could warrant additional nonclinical studies regardless of the phase of the clinical trial. Some of these examples could be changes to the manufacturing of the product, significant changes to the dose level, or changes to the patient population or the route of administration. And then for some products, other types of nonclinical studies that may be performed in later-phase trials or prior to licensure could include developmental and reproductive toxicity studies, or DART studies, or carcinogenicity studies, depending on the product on a case-by-case basis. Back to you, Iwen.

DR. WU: Great. Thank you, Alyssa.

Thank you all for attending today's OTP town hall. I'd also like to extend a thank you to all of our panelists. As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming weeks. For more information, you can visit the FDA website to read the FDA guidance document on the nonclinical assessment of cell and gene therapy products, which you can see on the screen right now, and to find other relevant resources. We plan to host our next town hall meeting this fall, 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 all again for joining. Have a great day.