U.S. FOOD AND DRUG ADMINISTRATION

Regulatory Fitness in Rare Disease Clinical Trials

Virtual Workshop

Day 2

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9:00 a.m. to 11:49 a.m.

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P R O C E E D I N G S

(9:00 a.m.)

Welcome – Kerry Jo Lee

DR. LEE: Hello again, and welcome to day 2 of our Regulatory Fitness in Rare Disease Clinical Trials. workshop, jointly presented by the Center for Drug Evaluation, or CDER, and the National Center for Advancing Translational Sciences, or NCATS, here at the NIH.

My name is Dr. Kerry Jo Lee. I am the associate director for rare diseases in the Division of Rare Diseases and Medical Genetics and the lead of the Rare Diseases Team at CDER. Yesterday was a wonderful and full day of information.

In the FDA Session 1, we talked about the approach to demonstrating substantial evidence of effectiveness for rare disease drug development products, as well as common challenges, potential solutions, the importance of adequate and well-controlled trials, confirmatory evidence, and biomarker development.

In the FDA Session 3, we learned about the fundamentals that were really critical to good trial design in rare disease. This includes the importance of dose finding and randomization, how the endpoint you choose can affect trial design, as well as strategies for primary endpoints and their interpretation, including global tests for multiple endpoints. We also heard about the potential and importance of adaptive and seamless designs.

Contributions from academia yesterday yielded very important examples and lessons learned, but also highlighted the tireless work that academics, physicians, and other healthcare providers do to advance rare disease drug development for patients.

Today's speakers from the FDA will explore topics such as the nuts and bolts of INDs and how to prepare for them. This will also include pharmacology and toxicology information, as well as special considerations when working with pediatric populations.

You'll also hear later today from speakers

that lead our programs in patient-focused drug development and critical path innovation meetings. These are two engagement opportunities with the FDA that can inform how you design your clinical trials.

Just a few reminders, CDER ensures that safe and effective drugs are available to improve the health of people in the United States and regulates over-the-counter and prescription drugs, including some biological therapeutics.

We do not regulate gene therapies or vaccines. Those are in the Center for Biologics, Evaluation, and Research, and also, this is not a forum to address specific questions about applications but rather a forum to promote general understanding of the fundamental principles necessary to develop safe and effective therapies.

Now, I will turn it over to Dr. Cynthia Welsh, an experienced medical officer and radiation oncologist on the Rare Diseases Team in CDER, to kick off our first section session.

Dr. Welsh?

Session 5

Cynthia Welsh - Moderator

DR. WELSH: Good morning. Welcome to Session 5 of our regulatory readiness workshop. My name is Cindy Welsh. I'm a medical officer on the Rare Diseases Team in the Division of Rare Diseases and Medical Genetics. This morning, our session will walk you through how to submit a package for an IND, and take into special considerations some pediatric issues and some preclinical packaging issues as well.

In the morning, our first speaker is a group presentation by Dr. Mari Suzuki, who's a medical officer in the Office of New Drugs at CDER, where she reviews and offers advice on investigational new drug and biologic applications for rare diseases. She received her medical degree from George Washington University and completed her internal medicine residency at New York Presbyterian Hospital before completing an interinstitute endocrinology fellowship at the National Institutes of Health. While at the NIH,

she was a rare disease investigator.

Mari will be joined by Margaret Kober, who's the chief project manager in the Office of Regulatory Operations within the Office of New Drugs at the Food and Drug Administration's CDER, Center for Drug Evaluation and Research. She provides supervisory leadership to project management staff.

Prior to that, she also worked in the Division of Marketing and Communications at CBER. Prior to joining the FDA, she had 15 years of experience in community pharmacy practice. She received her B.S. in pharmacy from the University of Rhode Island and her MPA with a concentration in health policy administration from George Mason University.

Welcome Mari and Margaret.

Presentation – Mari Suzuki

DR. SUZUKI: Thank you, and good morning. Welcome to Understanding the Investigational New Drug Application Process. I am Mari Suzuki, a physician and clinical reviewer in the Office of

New Drugs in FDA's Center for Drug Evaluation and Research, commonly referred to as CDER.

Presentation – Margaret Kober

MS. KOBER: Hi. I'm Margie Kober. I'm with the Office of Regulatory Operations in CDER.

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DR. SUZUKI: First, the disclosure statement. This talk reflects the views of the authors and is not intended to convey official U.S. government policy. The speakers have no conflicts of interest to disclose. In this talk, "drug" refers to both drugs and biologics regulated by the U.S. FDA's Center for Drug Evaluation and Research.

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MS. KOBER: What is a drug? Well, it's defined in the Food, Drug, and Cosmetic Act as "articles, other than food, intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."

What's an investigational new drug? That's defined as "a new drug or biologic drug that is used in a clinical investigation." INDs may also

be required for approved drugs being investigated for new uses, including a new indication or a new patient population. Other definitions, "a sponsor is a person or organization taking responsibility for a clinical investigation within the IND. An investigator is a person that actually conducts the investigation in the IND." An individual who does both is referred to as a sponsor investigator.

You'll find references to the federal regulation pertaining to this in the lower left-hand corner, and we'll continue this trend in future slides.

Next slide. The topics we're going to cover today: when to consider submitting an IND application and when exemption criteria would be met instead; considerations in preparing your IND; the IND application and submission process; responsibilities of sponsors and investigators; IND amendments; reporting requirements; and then inactivation, reactivation, withdrawal and termination of an IND; and finally, some tips for a successful IND application.

When is an IND required? An IND is required when there's a plan to experiment with a drug or research with administration to a human. Involving human administration is considered a clinical investigation. Clinical investigations are not exempt from the IND requirement unless they meet specific criteria. It's important to note that off-label use of a marketed product is not a clinical investigation.

Next slide, please.

DR. SUZUKI: A sponsor is exempt from filing an IND application when all exemption criteria are met. These are that the drug is marketed in the United States; there's no intention of reporting to the FDA a well-controlled study to support a new labeling indication or a significant change in drug advertising; there is no change in risk to the human subject such as through administration route, dose, or patient population, and the clinical investigation is compliable with an investigational review board with informed consent; finally, the investigation is not intended to promote or

commercialize the drug product.

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MS. KOBER: Common examples of IND exemptions include, bioequivalence or bioavailability studies; approved marketed products; and those BEBA studies, as long as the drug doesn't contain a new chemical entity, the drug doesn't exceed the maximum dose in approved labeling. Investigation is conducted under IRB requirements and with informed consent, and the sponsor meets all the requirements for retention of test articles, which we'll talk about later on.

Also, a carved-out exemption is radioactive isotopes. Research is permitted if it involves basic research not intended for immediate therapeutic diagnostic or similar purposes or to determine the safety and efficacy of the product. If you're uncertain about whether an IND is required or your IRB wants confirmation from FDA, submit your inquiry for our review.

Next slide.

DR. SUZUKI: There are two types of INDs,

commercial and research. A commercial IND is intended for later product marketing, or commercialization. A research IND is where the sponsor does not intend for commercialization, and drug administration will occur for research, perhaps with a publication in a peer-reviewed journal.

A research IND can be sponsored by an individual investigator, or an academic institution, or a nonprofit entity. The purpose may be for a clinical investigation or for clinical treatment, more commonly known as expanded access. A research IND can be converted to a commercial IND later if development progresses such as with plans for a phase 3 clinical trial.

Next slide.

Research INDs, typically for academic investigators, is a clinical investigation with an unapproved drug. A research IND may also involve expanded access, sometimes referred to also as compassionate use.

Expanded access, which also includes

single-patient IND requests, allows patients with either serious or immediately life-threatening diseases, without alternative treatment options, to be treated with an unapproved drug if the potential patient benefit justifies the potential risks of the treatment and potential risks are not unreasonable. Expanded access is separate from an emergency IND, which is often allowed to proceed urgently for patients in a critical state.

Next slide.

In some instances, a sponsor may consult the FDA prior to the IND application. Pre-IND consultations are a discussion with the therapeutic area review division, typically for FDA data requirements for the IND application; data needed to support rationale for testing the drug in humans usually with animal model studies; design of animal model studies for nonclinical pharmacology, toxicology, and drug activity studies; initial drug development plans; and regulatory requirements for safety and efficacy demonstration.

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MS. KOBER: So what are these therapeutic areas and review divisions? There's a chart there and a link because every once in a while that chart changes. Of note, it's important to remember that not all applications for rare diseases are reviewed by the rare disease division. So in these cases, your pre-IND consultation, and actually the entire development program, would be with the therapeutic area in CDER. This list is as up to date as today.

Next slide.

DR. SUZUKI: Some tips for pre-IND interactions are to provide relevant context for the investigational drug such as past use of drug in animal studies or humans with relevant brief summaries. Discuss the scope and design of your first-in-human study, then clearly state the intentions of your pre-IND meeting, posing specific, direct questions to the FDA, which may be answered in writing.

Next slide.

MS. KOBER: So how do you go about this? Well, if you want to talk to FDA in the pre-IND

phase, you could submit a meeting request. There's a guidance document, the link is there, and you would use that to determine how to go about requesting a meeting. Also in that guidance, it outlines several other opportunities that arise for meetings as development progresses.

Your meeting request will then be assigned to a regulatory project manager. He or she will serve as your point of contact for interacting with the review division as you navigate through the IND process. If you decide not to pursue a pre-IND meeting, your new IND, when it's submitted, will also be assigned to a specific project manager.

Next slide.

DR. SUZUKI: Now let's discuss the required components of an IND application. The following items should be compiled: a cover letter; Form FDA 1571 with contact information for the sponsor and sponsors authorized representative, if applicable; identification of the phase of clinical investigation; commitment not to begin the clinical investigation until 30 days after FDA receives the

IND application, or sooner if the FDA study may proceed communication as received; a commitment that an IRB will be responsible for the approval of the clinical investigation; and identification of IND investigators.

FDA Form 3674 certifies compliance with requirements of clinicaltrials.gov, the clinical trials data bank. The IND application should follow the structure outline found in Title 21, Code of Federal Regulations and will cover translational or animal studies with the drug chemistry; pharmacology and toxicology information; manufacturing and control information; clinical protocol; and previous human experience with the investigational drug.

A brief introductory statement about the unapproved drug; a brief summary of previous human experience with the drug; any safety or efficacy concerns in the past in any country where the drug was withdrawn; and a brief description of the overall plan for clinical investigation should be provided.

An investigator's brochure is required if there will be multiple investigators. It should provide information about the drug, pharmacologic and toxic effects, safety, and effectiveness in humans.

MS. KOBER: I wanted to add a few tips. When indicating the sponsor on the Form 1571, take into account that if the original 1571 lists an individual as the sponsor, that IND does not belong to the institution and the individual can continue to sponsor it even if he or she needs your institution.

Also, be sure to check that box on the Form 1571 that indicates your investigation involves a rare disease. Finally, if you've submitted an expanded access single-patient IND, you can use Form 2936 instead of Form 1571.

Next slide.

DR. SUZUKI: The nonclinical section of the IND application includes animal pharmacology and toxicology studies which form the basis of the sponsor's rationale for reasonable safety for a

clinical investigation and support dosage and duration of clinical investigation in humans. This is such an important component of the IND that there will be a separate talk later about this.

Next slide.

Chemistry, manufacturing, and control information includes the IND's composition, manufacturer, and controlled drug substance and drug product, focusing on the raw materials and new drug substance. There should be sufficient information to assure proper identification, quality, purity and strength, and sufficient information to assess whether batches can be adequately produced and consistently supplied.

Next slide.

A clinical protocol for each planned study should be submitted for the IND with determination of drug development phase. Supporting data from foreign studies may be included. An outline of the clinical investigation with number of patients; inclusion/exclusion criteria; dosing plan, dosing method, and duration; stopping criteria for both

the individual subjects and the study as a whole; and safety monitoring such as vital signs, clinical visits, and laboratory work, should be included.

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Additionally, clinical investigator qualifications with FDA Form 1572 [sic - 1571) and a curriculum vitae; disclosure of financial interests; plan for IRB review; and the informed consent form should be submitted.

Next slide.

MS. KOBER: Here are some of the ways to submit your IND. Electronically, it may be submitted in the common technical document format. For research INDs, the NextGen portal on the internet may be used, and for expanded access INDs, they may be submitted through the Reagan-Udall Foundation on the internet, and this is, again, only for expanded access. Lastly, it is possible to still submit paper copies, and the address is there. There's also a link to some additional submission resources.

Next slide.

After we receive your IND submission, we assemble a multidisciplinary team. This team includes experts in clinical; regulatory; nonclinical pharmacology/toxicology; chemistry; clinical pharmacology; biostatistics; and appropriate consultants as needed for, say, devices, botanicals, or ethics consults.

Next slide.

DR. SUZUKI: In the first 30 days from IND application receipt by the FDA, the therapeutic area review division will make a determination of whether the clinical study is reasonably safe to proceed or will be placed on clinical hold. It is important to keep in mind that INDs are not approved. The determination is safe to proceed. If FDA determines that an IND application meets exemption criteria during this time, it will be exempted.

Next slide.

In the first 30 days, the safety review will be multidisciplinary and include many aspects, including safety monitoring in the protocol.

Important to include are the type and frequency of laboratory testing; EKGs; clinical monitoring; monitoring for known safety signals with the drug; criteria for drug dose titration or discontinuation; and drug stopping criteria, including parameters to stop for lack of efficacy.

Product information on the drug doses and formulation and route of administration and frequency will be evaluated for acceptability, based on precedent nonclinical studies and relevant past experience of use in humans.

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MS. KOBER: Within the first 30 days, FDA may send information requests to the sponsor or authorized representative that further information or clarification is needed. IR responses should be submitted through established methods such as the NextGen portal or eCTD gateway. After 30 days from IND receipt by FDA, unless placed on clinical hold, the study is safe to proceed and permits investigational drug administration, and drug manufacturer may then ship the investigational drug

to the investigator once the IND is in effect.

Next slide, please.

If FDA determines the study is not reasonably safe to proceed, they will issue a clinical hold. This is an order to delay a proposed clinical investigation or suspend an ongoing clinical investigation.

There are two different types. First is the full clinical hold, where all clinical studies under the IND are not permitted. Examples are if we see toxicity in animals that precludes dosing in humans. Sometimes this can be remedied with further study in the animals, and eventually the studies may be allowed to proceed, but sometimes the drug is just too toxic to ever be used in humans.

The other type of a clinical hold is partial clinical hold, where only part or some of the clinical studies under the IND are allowed to proceed. This includes narrowing the patient population or perhaps you start with low doses and submit data for our review and clearance before you

proceed to the higher dose.

Next slide.

DR. SUZUKI: Grounds for clinical hold for phase 1 trials are if human subjects would be exposed to unreasonable and significant risk of illness or injury; clinical investigators are not qualified; the investigator brochure is misleading, erroneous, or materially incomplete; there is insufficient information to assess risks to subjects; or if there is exclusion by gender for a life-threatening disease or condition unless justified by special circumstances.

Next slide.

Grounds for a clinical hold for phase 2 and 3 studies are for any of the reasons listed for phase 1 trials or if the protocol is deficient in design to meet its stated objectives.

Next slide.

If a deficiency is identified that may be grounds for imposing a clinical hold, the review division may send an information request and/or request changes to the proposed protocol. Many

potential holds may be resolved through such communication such as in instances of inadequate patient safety monitoring. If unresolved, a letter is sent to the sponsor for the clinical hold.

Next slide.

MS. KOBER: If you do receive a clinical hold letter, you are free to respond, and in your response it should be complete and otherwise addressing all of the deficiencies. If you only address some of the deficiencies, we will not review your response.

If your response is complete, we will communicate within 30 days that either the clinical hold is removed, continued, or modified. Modification generally is to convert from a full hold to a partial hold, but sometimes it's to convert a partial hold to a full hold.

Next slide.

Now we're going to talk about some of the sponsor responsibilities going forward after your IND is an effect; in other words, after that 30 days or you've gotten your safe-to-proceed

letter.

Sponsor investigators [sic – responsibilities] include record-keeping and retention. You must keep records of receipt, shipment, and disposition of investigational drug and any financial interest paid clinical investigators. Records must be retained for two years after a marketing application is approved, or if no application is approved two years after shipment and delivery of the drug, the investigational use is discontinued, and we are notified.

Next slide, please.

Also, you must permit FDA to inspect your records and reports related to the clinical investigation upon request and provide copies and reports upon written request. You must properly dispose of all unused drug by assuring the return of unused supplies of the investigational drug and ensuring safe disposition.

Next slide.

Now we'll take a look at investigator

responsibilities. The investigator must ensure that the investigation is conducted according to the protocol and applicable regulations, and the investigator must protect the rights, safety, and welfare of subjects, which includes getting informed consent.

Investigators are also responsible for controlling investigation by administering it only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. A drug must not be supplied to any person not authorized to receive it.

Next slide.

Additional investigator responsibilities include retention and record keeping. Records include case histories, such as the case report forms and supporting data; the signed and dated consent forms and medical records. Records must also include the disposition of the investigational drug, including dates, quantity, and use by subjects.

Any unused drug must be returned to the sponsor, and you must keep and retain these records for two years after a marketing application is approved for the drug for that indication or if no application is approved two years after the investigation has been discontinued and we've been notified.

Investigators are also responsible for reporting to the sponsor the following: progress reports regarding the results of the study; safety reports or reports of adverse events reasonably regarded as caused by or probably caused by investigational drug, and you must do this promptly; final reports after completion of the investigator's participation in this study; and financial disclosure reports. These include things like compensation; patents; trademarks; copyright or licensing agreements; stock options; et cetera.

In the NDA submission, applicants must either certify that there were no financial arrangements with investigators, or if there were, they must disclose them. FDA then evaluates the

impact of these financial arrangements on the reliability of the study, taking into account designs that minimize bias such as multiple investigators, blinding, and objective endpoints. Studies can be audited, and we may request further analysis, discount the study, or we may ask for an additional confirmatory study.

Investigators must also allow FDA inspection of records and reports plausible for complying with the requirements surrounding controlled substances such as ensuring that the drug is securely stored and that access is limited only to authorized persons.

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Finally, investigator responsibilities include assurance of IRB review. They are responsible for review and approval of the protocol. Investigators must also report any unanticipated problems involving risk to patients and not make any changes without IRB approval, except to eliminate immediate hazards to subjects.

Next slide.

Now, we'll look at two types of amendments that sponsors must submit, protocol amendments and information amendments. Coming up, we'll discuss each type and subtype.

Next slide.

DR. SUZUKI: First, let's talk about new protocols. How is submitting a new protocol different from submitting a new IND? The answer is that there is no 30-day waiting or safety period. The new study may begin provided it has been submitted to the IND for FDA's review and it has been approved by the IRB.

A new protocol to an IND is submitted as a protocol amendment and must include a copy of the protocol; prominent identification such as protocol amendment; new protocol on the cover letter; and check box on FDA Form 1571. You may wish to wait for FDA comments before starting the study. In that case, the new protocol amendment must contain request for comment and the specific questions FDA should address.

Next slide.

If you make changes to an existing protocol, the changes may be implemented provided they are submitted to the IND for FDA's review and the changes have been approved by the IRB. An exception is a change to eliminate an immediate hazard to subjects. This can be implemented immediately providing a change in protocol amendment is submitted to the IND and the IRB is notified.

Next slide.

In your submission for a protocol amendment, reference relevant information in the IND to support any significant change, such as pharmacology/toxicology information to support longer duration of drug dose or a drug dose increase. Differences from past protocol versions should be identified such as with a summary of changes and submission of a track changes protocol version. Again, a request for FDA comment may be made.

Next slide.

MS. KOBER: I'm going to switch topics to

information amendments, and that just means something that's an amendment and it's not a protocol amendment. This is required for submitting essential information not within the scope of a protocol amendment or report such as a safety report or an annual report, and we'll discuss both of those later.

Examples of the kinds of information requiring submission of an information amendment include new information regarding clinical; clinical pharmacology; nonclinical pharm-tox; chemistry; and study reports. We code these as different types of information amendments so we can track what kind of information is in the submissions and also be able to tell who should look at it. A report is also required if you discontinue clinical investigations, and this report is required within 5 days of deciding to discontinue if the decision was based on safety concerns.

Next slide, please.

Now, we'll talk about in-depth IND reporting

requirements. There are two required reports, safety reports for adverse events and annual reports.

Next slide.

DR. SUZUKI: Let's go over definitions for the key component of safety reports. A serious adverse event or serious adverse reaction is a medical occurrence that in the view of the investigator or sponsor results in death; life-threatening adverse event; inpatient hospitalization or prolonged hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; congenital anomaly or birth defect; and medical or surgical intervention to prevent one of these outcomes.

Next slide.

An unexpected adverse event or unexpected suspected adverse reaction is one that is not listed in the investigator brochure or is not listed at the specificity or severity observed. If there is no investigator's brochure, an unexpected

adverse event is one that is inconsistent with the risk information described in the general investigational plan.

Next slide.

MS. KOBER: The other type of required reporting in addition to safety reports is the annual report. An annual report is a synopsis of the progress of the investigation and includes such things as the individual study information, including title, purpose, patient population, and the study status, in other words, whether it's been completed or it's ongoing or perhaps not even started yet; the total number of subjects planned; the total number of subjects entered to date by age, gender, and race; the number of subjects completed as planned and the number of dropouts; and a brief description of any study results.

Next slide.

The annual report should also include summary information obtained from the previous year's clinical and nonclinical investigations, including narrative or tabular summary of the most

frequent and most serious AEs by body system; summary of all IND safety reports submitted during the past year; a list of dropouts due to AEs; a list of all deaths and causes of those deaths; new information about the drug's action, in other words, dose-response, bioavailability; a list of nonclinical studies completed or in progress during the past year and a summary of the major nonclinical findings; and finally, a summary of any significant manufacturing or microbiological changes made during the year.

Next slide.

There are other activities that occur with INDs, and we'll go through each of them. FDA may inactivate an IND, either on its own initiative or your request, if no subjects have been entered into study for two years or more, as seen in the annual report, or all investigations are in clinical hold for one year or more.

If FDA initiates inactivation, we will notify you via a pre-inactivation letter. You'll then have 30 days to respond as to why the IND

should remain active before the status is changed to inactive. Of note, annual reports are not required for inactive INDs.

To reactivate a previously inactivated IND, you would submit a new protocol amendment. There is a 30-day waiting period before you may begin that study. You may also choose to withdraw an IND if no further studies are planned. If you decide later that studies should be resumed, you must submit a new IND application.

Finally, INDs may be terminated by FDA, and this generally occurs when there have been no activity and no response to our request for overdue annual reports.

Next slide.

DR. SUZUKI: This slide is a reminder about IND application components to include because we sometimes encounter applications that fail to include them, leading to delays and reaching a safe-to-proceed decision. In your IND application, it is important to include adequate safety monitoring plans such as laboratory studies and

EKGs; provide a drug dosage titration; administration plan with food and treatment duration; and include drug stopping criteria such as life-threatening adverse events or reactions, serious adverse events, or if the patient discontinues for single-patient INDs.

Next slide.

For INDs with intent to develop a clinical indication in rare disease, it may be prudent to think ahead of a phase 1 trial for PK/PD and safety. An adaptive trial design would allow for rollover of phase 1 patients into a phase 2/3 trial, which may be a dose-dependent randomized trial as discussed yesterday. This is particularly useful if there are few candidates for trial enrollment due to rarity of the disease condition. As is depicted in the figure, an adaptive trial design would allow for seamless transition from a dose-finding phase 2 trial to efficacy evaluation in a phase 3 trial.

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For INDs with the intention to develop a new

clinical investigation, although the phase 1 study may assess pharmacokinetics and safety, for phase 2/3 trials, endpoints and duration should reflect clinically meaningful change, defined as how a patient feels, functions, or survives.

There should be adequate trial duration to show clinically meaningful change, especially in slowly progressive diseases. Bioanalytical assays may need further data on reproducibility and FDA validation with the Center for Devices and Radiologic health.

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Some tips for informed consent, inadequate consent should be avoided. Include adequate consent for any genetic testing, including specific genes that will be sequenced and a clause on genetic study exclusions, such as "no other information about your DNA will be determined." Patient privacy expectations should be described such as your records will be kept as private as possible under law and personal identification will be encoded.

Next slide.

MS. KOBER:

I want to consider some takeaway points from this talk. First, understand what type of IND your clinical investigation is. Here we provide the internet link to the FDA forms, understanding interacting with FDA such as formal meetings, and here we provided the guidance on requesting a formal meeting, and remember your investigator responsibilities with an IND.

Next slide.

Finally, some additional links, although as we hope you've seen through this presentation, FDA has many resources to guide you through the IND process. But if your institution has an office or department staffed by regulatory affairs professionals, you should definitely avail yourselves of their expertise.

Finally, here's the link to the forms and instructions. I highly recommend that you read the instructions so there aren't any unnecessary delays in processing and reviewing your submission, and

again, that link to the therapeutic areas' division list.

This concludes our presentation. Thank you for your interest and attention, and we'll be happy to take your questions during the panel portion of this session. Thank you.

DR. WELSH: Thank you, Margie and Mari, for that very useful information. We've received quite a few questions during your presentation.

Next up, we're turning to Dr. Shamir Tuchman, who's a medical officer in the Division of Pediatrics and Maternal Health at the FDA. He works providing consultation to review divisions for varied topics relating to drug products and device development for pediatric patients.

Prior to joining the FDA, he was an academic pediatric nephrologist in the Division of Pediatric Nephrology at Children's National Hospital and an associate professor of pediatrics at the George Washington University School of Medicine. His research and clinical focus areas during his career in academic medicine were on bone and mineral

metabolism abnormalities in pediatric patients with chronic kidney disease. He was also a pediatric nephrology fellowship program director at Children's National Hospital.

Welcome, Dr. Tuchman.

Presentation – Shamir Tuchman

DR. TUCHMAN: Thank you for that introduction, and hello and good morning. As stated, my name is Shamir Tuchman. I'm a medical officer within DPMH in the Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine within the Office of New Drugs in CDER at the FDA.

Over the next 20 minutes, I would like to discuss the pediatric perspective in rare disease drug development. As a reminder, the views expressed in this presentation are my own and do not constitute an official position of the FDA. I have no conflicts of interest to disclose.

Next slide, please.

Here is an outline of my presentation. I'll begin by discussing the background of pediatric drug development at the FDA and how it has evolved

over the recent decades. I'll discuss the regulatory framework that promotes the studies in pediatric patients and the unique challenges and opportunities that come with these regulations. I will also discuss the unique regulatory, ethical, and study design considerations and challenges that occur with drug development in pediatric patients. And finally, I will review potential strategies that are used to overcome some of these unique challenges.

Several of the topics and content have been touched upon previously in this workshop, but remains a discussion of rare pediatric disease drug development.

Next slide, please.

Acronyms are commonly used at the FDA to describe many of the regulations and laws that underpin them. The acronyms you'll be hearing in this presentation are shown here.

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The past history of pediatric drug development was one of reluctance to study drug

products in pediatric patients. This reluctance was rooted in the presence of multiple perceived roadblocks, including ethical concerns with enrolling and exposing a vulnerable population to investigational drugs; the financial constraints of studying drug products in a patient population for which marketing opportunities may be limited; and trial design challenges with studying a population for which disease manifestations may differ from adults with what very well may be a further limited population from which to enroll. In addition to the above challenges, the past was characterized by the lack of incentives or requirements to conduct pediatric trials.

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As a result of these potential roadblocks and lack of requirements or incentives, pediatric drug development was characterized by a general lack of useful pediatric information in drug labeling in more than 80 percent of approved adult drugs. This posed a difficult dilemma for pediatric prescribers, including either not treat

pediatric patients with a drug that could provide a potential clinical benefit but which are not approved or studied in that population, or use the drug off label based on results of adult trials, which may not be applicable to pediatric patients or from limited anecdotal experience gleaned from published literature.

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So where are we now? We have evolved from a view that pediatric patients as a potential vulnerable study population must be protected from research to a view that they must be protected through research. As a result, we encourage sponsors to include pediatric patients in their drug development programs when possible, and especially when pediatric use of a drug product is anticipated.

The overriding principle is to provide prescribers with useful information for safe use of drug products in pediatric patients and to spurn approvals of marketed drug products in populations for whom the drug provides a real prospect of

direct clinical benefit. Ideally, this would discourage off-label use and focus on obtaining interpretable data in pediatric patients that can inform use or alternatively discourage use when safety data warrant.

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There are two programs that alternatively require and incentivize studying pediatric patients for drug products submitted for marketing approval. The more recent of these two is the Pediatric Research Equity Act, also known as PREA. PREA was signed into law in 2003 and requires an assessment to support labeling in all relevant pediatric age groups for the same indication, or indications, being sought in adults, unless the requirement is waived or deferred.

PREA's triggered when drug products are submitted for marketing approval for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration. There are specific criteria for which PREA postmarketing requirements may be waived by the

agency, and applicants may also request a deferral of PREA studies often when the drug product is ready for adult approval. Waiver requests for studies in part or all of the pediatric population must be justified by applicants.

PREA requires sponsors develop age-appropriate formulations that will facilitate dosing in all pediatric age groups required in the assessment. Applicants are not required to market these formulations, but it is not uncommon for them to do so if the results of pediatric studies confirm the efficacy and safety of the drug product for the studied indication of pediatric patients.

PREA does not apply to drug products who are granted orphan designation, which represents an important limitation of this law for pediatric drug development in the rare disease space. The exception to this is drugs or biologics developed to treat adult cancers who have molecular targets relevant to the growth or progression of pediatric cancers.

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In terms of incentivizing this study and development of potential beneficial drug products in pediatric patients, the 1997 Food and Drug Administration Modernization Act allowed the FDA to issue a written request. The Best Pharmaceuticals for Children's Act, also known as BPCA, was enacted in 2002 and codified as Section 505A of the FD&C Act.

BPCA provides for financial incentives to companies that voluntarily conduct FDA requested pediatric studies through a written request of an active moiety for indications which could provide health benefit to pediatric patients. The written request can, and ideally should, include the study of all potential pediatric indications for which the active ingredient in the drug product could provide use and benefit, which distinguishes it from PREA postmarketing requirements, which are indication-specific. FDAMA allows the FDA to grant an additional 6 months of marketing exclusivity to sponsors who complete these studies.

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Ultimately, the goal of PREA and BPCA was to provide useful pediatric information and labeling to prescribers and spurn drug product development and approvals in pediatric patients.

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PREA and BPCA do not specifically promote development of drug products in rare pediatric diseases. To encourage this, the Orphan Drug Act promotes the development and evaluation of new treatments for rare diseases and provides sponsors and companies with incentives to conduct trials in rare disease. The incentives include tax credits for up to half of qualified clinical trial costs; waiver of the prescription drug user filing fee; and the potential for seven years of market exclusivity after approval.

A rare disease or condition, as you have heard before, is defined as one affecting less than 200,000 persons in the U.S. or affecting more than 200,000 persons and for which there's no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or

condition will be recovered from sales.

The definition of rare disease or condition for purposes of orphan designation differs in other regions such as Europe, where the European Medicines Agency defines a rare disease as having a prevalence of less than 6 per 10,000 persons in countries regulated under the EMA. Orphan drug designation for pediatric subsets of diseases or conditions, which affect more than 200,000 persons in the U.S., are no longer typically considered when determining orphan drug designation, except for rare exceptions.

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Developing drug products for use in pediatric populations with rare diseases presents unique challenges, as well as opportunities, for innovative approaches to obtain efficacy and safety data to support approval. Some of the practical challenges for rare pediatric disease drug development fall into regulatory, ethical, and study design categories.

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From a regulatory standpoint, orphan drug designation in many ways is two sides of a coin. Orphan drug designation, while providing incentives for sponsors to conduct studies for rare pediatric disease, does not allow the FDA to require pediatric studies under PREA. Studies for orphan designated drugs may be limited to adult diseases and is not specific for rare pediatric disease.

As a result, there is another incentive program designed to specifically promote development of drug products for rare pediatric diseases, the Rare Pediatric Disease Priority Review Voucher Program provides an applicant who receives marketing approval for a drug or biologic for a rare pediatric disease the opportunity to qualify for a voucher that can be redeemed to receive a priority 6-month review of a subsequent marketing application for a different drug product. This is only applicable for drug products that do not contain a previously approved active ingredient.

Draft guidance for this program was posted

for industry in July 2019. The definition of a rare pediatric disease for this program is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals age birth to 18 years, and the disease is a rare disease and is defined in Section 526 of the FD&C Act.

The Rare Pediatric Disease Priority Review Voucher Program was due to sunset on September 30, 2022, but was renewed as part of the coronavirus response and relief supplementation, Supplemental Consolidated Appropriations Act on December 27, 2020, and is now due to sunset pending further renewals on September 30, 2024.

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Enrolling pediatric patients in trials of drug products requires careful consideration of ethical principles surrounding this vulnerable patient population who cannot legally provide informed consent. In general, including pediatric patients in drug product trials requires a determination that the scientific information

supporting efficacy and safety cannot be provided for patients who can consent for study participation.

Pediatric patients enrolled in FDA-regulated clinical trials must be afforded the additional safeguards found at 21 CFR 50 Subpart D that were established because children are unable to provide informed consent to treatment or procedures involved in clinical investigations. The administration of an investigational drug to pediatric patients must offer the prospect of direct clinical benefit to each individual patient, the risk must be justified by the anticipated benefit, and the anticipated benefit-risk profile must be at least as favorable as that presented by accepted alternative treatments.

Low-risk implies no more than a minor increase over minimal risk, which is often not the case for many investigational drugs. Protocol submission should include evidence to support the pediatric subjects enrollment in the trial that offers the prospect of direct clinical benefit to

each individually enrolled child. Obtaining generalizable knowledge to be able to treat other patients is not considered a direct benefit to a pediatric patient.

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Knowledge of the natural history of a rare pediatric disease is critical to successful drug development. This is important to defined disease populations and identified key disease subtypes. Examples of disease aspects that may be unique or substantially different than a pediatric population include the timing of diagnosis; stage of disease at diagnosis; nature and severity of symptoms; and the rate of disease progression.

Natural history studies that will inform the design of clinical trials or may be used as historical controls should be prospective, longitudinal, and well-designed. The duration of observation should be long enough to adequately track the disease symptoms and document variability, heterogeneity, severity, and potential prognostic factors in pediatric patients with the

disease.

A systemic evaluation of biomarkers, including laboratory, imaging, and histologic markers relevant to the disease, may identify useful diagnostic, prognostic, or monitoring biomarkers, which can be helpful in clinical trials. Sponsors should incorporate biomarker development when applicable into early phases of drug development.

Factors impacting the severity or trajectory of symptoms should be systematically captured. Examples may include genotype and its potential impact on phenotype and monogenetic diseases or the impact of a residual enzyme activity, diseases characterized by single enzyme defects.

Assessment of signs and symptoms in a natural history study that will inform clinical trial design and endpoints should utilize fit-for-purpose clinical outcome assessments that evaluate how pediatric patients with a rare disease feel, function, or survive. Ideally, natural history study results are made publicly available

to facilitate drug development for the same rare disease across development programs.

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The design of natural history studies in rare pediatric disease are often designed around a few critical principles. The study should have broad inclusion criteria to capture the spectrum of phenotypes and severity of disease. The study should be of sufficient duration to capture clinically meaningful outcomes and the variability in these outcomes, which may differ in adult versus pediatric patients.

Along the same rationale, natural history studies in pediatric patients should identify when specific manifestations develop and whether they are likely to persist. All of these aspects of the natural history of a rare pediatric disease require careful standardization of methods to collect this clinical data.

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In general, a single, adequate, and well-controlled clinical investigation supported by

additional confirmatory evidence of effectiveness may support drug approval in a rare pediatric disease. With that said, studies must be conducted with the same scientific rigor used to support efficacy and safety in non-rare diseases.

Extrapolation and the degree to which it is employed from adult or other pediatric trial populations has the potential to improve the efficiency and reduce the required sample size for rare pediatric disease trials. Extrapolation relies on key assumptions that the extrapolated pediatric population has a similar disease course and expected response to therapy as the reference population. However, it is important to note that a relatively lower prevalence and/or incidence of a disease in pediatric versus adult populations does not alone justify use of extrapolation.

Similar principles underlying efficacy extrapolation can also apply to safety extrapolation to determine if pediatric-specific safety data will be required, such as the potential for new safety signals and/or increased

susceptibility to observe safety signals in adults.

It is easy to think that an adolescent study population can be included with adult trials due to their age, maturity, and similar body size. However, the consideration of including pediatric patients should focus on safety, dosing, and appropriate efficacy endpoints that are understood and are in line with what is known in adult patients. PK studies may be needed to identify dosing regimen in pediatric patients less than 12 years of age, resulting in exposure range or distribution comparable to those observed in the reference population.

Modeling and simulation can explore a variety of pediatric dosing strategies to achieve a target range of exposures that may need to be confirmed in a pediatric trial. This approach potentially allows the conduct of pediatric trials in parallel with adult phase 3 trials, employing strategies such as bridging biomarkers or Bayesian statistical approaches to improve trial efficiency.

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The appropriateness of extrapolation of efficacy from adult or other reference populations to pediatric patients is not a binary decision, but rather a continuum on which the degree of a permissible extrapolations depends on multiple factors. As a result, this type of study design is governed by the degree of similarity between the natural history of disease, its manifestations, and exposure-response relationships for the drug products under consideration.

The type of study required to provide sufficient evidence of efficacy can therefore vary from a fully controlled efficacy trial to a trial relying on exposure matching to the reference population. In between these two ends of the spectrum exists a range of trial design options, using innovative trial designs, statistical approaches, and biomarkers to inform efficacy in the rare pediatric disease space.

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Trials designed with no reasonable expectation of producing interpretable efficacy

data such as single arm, uncontrolled trials assessing a subjective and/or bias prone efficacy endpoint potentially expose pediatric patients to unnecessary risks. Such trial proposals now raise important ethical concerns for the enrollment of pediatric patients and should be supported by strong scientific justification and evidence. Other study design strategies that can improve the successful completion and interpretability of drug product trials in rare pediatric disease include use of non-concurrent controls, innovative trial designs, and multiple endpoint strategies.

When objective measures of clinical benefit such as survival are used for demonstration of effectiveness, the use of non-concurrent controls, otherwise known as historical controls, may be reasonable or scientifically justified. Seamless trial designs such as employing an initial dose exploration phase, followed by an efficiency demonstration phase, can make the most efficient use of the small pediatric patient pool and fulfill ethical requirements by continuing pediatric

patients on treatment once an initial dose-finding phase is complete.

Incorporating one or more interim analyses to adapt the trial duration based on emerging data may also be useful in the appropriate duration of observation in a rare pediatric disease trial as unknown due to the limited knowledge of the natural history. Given the often heterogeneous and multisystemic manifestations of rare diseases in the pediatric population, the use of a multiple endpoint strategy such as multiple primary endpoints, multicomponent endpoints, or composite endpoints is encouraged to capture a series of distinct clinical outcomes that impact patients' daily lives.

In pediatric patients, a clinically meaningful endpoint relied upon for adult approval may not be applicable or directly measurable in a younger population. In this situation, considering the use of a biomarker or an intermediate clinical endpoint as a surrogate endpoint for an accelerated or traditional approval, sponsors should provide

quantifiable evidence of the relationship between the biomarker or their intermediate endpoint and the clinical outcome assessed in adults. This often requires advanced preparation and thought when designing phase 3 adult trials to establish these relationships.

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Trials studying a rare pediatric disease are often global in scope to ensure recruitment of sufficient patients to give interpretable efficacy and safety information. As such, collaboration across global regulatory agencies is critical to achieve a harmonized study design. There exists multiple initiatives that facilitate communication between the FDA and its international counterparts. The common commentary was developed jointly by the FDA and European Medicines Agency to provide comments to sponsors when pediatric development plans submitted to both agencies are under review and have been discussed at the Pediatric Cluster.

The Pediatric Cluster, established in 2007, is a monthly teleconference between staff from the

FDA and EMA, and serves as a forum to discuss product-specific pediatric development and topics related to product classes under the terms of confidentiality agreement. Japan's PMDA, Health Canada, and Australia's therapeutic goods administrations have since joined the teleconference as active participants.

The international rare disease cluster provides a forum that allows for enhanced interactions between different regulatory agencies for scientific exchange and specific issues related to drugs, drug classes, or pertinent issues and policies relative to the scientific evaluation of drug products for rare diseases.

The Parallel Scientific Advice program, which is a collaborative initiative by the EMA and FDA, provides a mechanism for experts in the field to engage in discussions with sponsors on critical scientific issues during the development phase of new medicinal products, including drugs, biologics, and vaccines.

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In conclusion, the development of drug products to treat rare pediatric diseases and conditions is vitally important. Regulatory, ethical, and trial design considerations represent unique challenges and opportunities in the pediatric rare disease drug development. Strategies to facilitate the successful completion of trials that yield interpretable efficacy and safety data continue to evolve.

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Here are some publicly available resources that can help inform rare pediatric disease drug development.

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I thank you for your attention and participation. Thank you very much.

DR. WELSH: Thank you, Shamir, for your presentation on the pediatric issues.

I just wanted to mention to people that a resource document has been put together by the Rare Diseases Team for you all to reference, and you can click on the I in the lower right-hand corner of

the webcast to find the link.

Next up, I would like to introduce Dr. Arianne Motter, who's a board certified senior toxicologist in the Division of Pharmacology and Toxicology for Infective Diseases at the FDA, where she reviews nonclinical studies for anti-viral drug products. She's also an adjunct assistant professor in the Department of Pharmacology and Physiology at Georgetown University.

Dr. Motter's been with the FDA for eight years and actively works on investigational new drug applications, as well as emergency use authorization and new drug applications. Prior to the FDA, she was a toxicologist with the Armed Forces Medical Examiner. She received her PhD in Pharmacology from Georgetown.

Good morning and welcome, Dr. Motter.

Presentation – Arianne Motter

DR. MOTTER: Thank you very much for that nice introduction.

Good morning, everyone. Today I will be speaking on the nonclinical perspective for drug

development for rare diseases.

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Just to go over what I will cover, first I'll go through the objectives of the nonclinical studies; as well as the types of nonclinical studies that are used to support drug development; as well as a number of items that we have to consider during the drug development program as they refer to nonclinical studies; as well as the timing for conducting the nonclinical studies; and lastly, I will cover specific issues concerning rare diseases.

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The main objective of nonclinical studies is safety. These studies are intended to assess the safety profile of a pharmacological agent based on all the available in vitro and in vivo studies submitted to the agency. They're intended to predict how exposure and toxicity in animal models may correlate to humans.

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There are several different types of

nonclinical studies that may be submitted to the agency in order to support a clinical program, and these consist of pharmacology studies, they may be primary or secondary pharmacodynamic studies, and safety pharmacology studies. You may submit pharmacokinetic and toxicokinetic evaluations. These studies aim to assess the absorption, distribution, metabolism, and excretion of the pharmacological agent.

Then lastly, there's a whole host of different toxicology studies. These consist of single-dose toxicity studies; repeat-dose toxicity studies; and genotoxicity evaluations and carcinogenicity assessments. Some studies will look at the effects on reproductive and developmental toxicity. You may need to conduct studies looking at local tolerance, phototoxicity, immunotoxicity, and even the potential for abuse.

Next to some of these, I've listed some guidances that you can reference, and next I will go into a few more of the details for the different types of studies.

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Pharmacodynamic studies are intended to evaluate the physiological effects of the drug, so that is what the drug is doing to the body. These are preliminary studies that are intended to demonstrate proof of concept, as well as determine a mechanism of action. They consist of in vitro studies that may look at receptor binding; that is the receptor that is the intended target, as well as any off-target effects. They may also attempt to evaluate changes in functional activity in the tissue itself. It may also conduct in vivo studies. These are conducted in specific animal models in an attempt to determine nonclinical efficacy. Now, you don't always need to show definitive efficacy in an animal model in order to proceed; after all, efficacy will be determined in a clinical trial.

These studies are conducted more for candidate election or prioritization. They also aid in understanding how the pharmacology may impact and interpret findings from the toxicology

studies.

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First up here, we have safety pharmacology studies. These studies are intended to identify any potential adverse effects on normal physiological function. The core battery consists of evaluations of cardiovascular, respiratory, and central nervous system function.

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Pharmacokinetic studies are intended to determine what the body does to the drug. So these studies will assess how the drug gets absorbed, distributed, metabolized, and then finally excreted from the body. They're generally conducted in animals using a single pharmacologically relevant dose. Oftentimes, they may utilize a radioactive labeled form of the drug. These studies are generally used to support dosing in nonclinical toxicology studies, and they can be used to help predict human PK parameters.

Toxicokinetics are pharmacokinetic parameters that are measured at toxicologically

relevant doses in the animal studies. These endpoints are integrated in the repeat-dose toxicology studies, and this data is used to correlate drug exposure with any toxic endpoints.

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Repeat-dose studies are our bread-and-butter studies. They're used to determine adverse effects of the drug in animal models. They are needed to support the initiation of clinical trials, and if longer clinical protocols are necessary, then there may be a need for longer repeat-dose studies.

They are pivotal in determining whether or not a post-clinical trial is considered safe to proceed, and this is because these studies are designed to identify any toxicities of concern, as well as determine if additional clinical monitoring may be needed.

They're also intended to define a no-observed effect level. This is a dose at which no toxicity is observed in the animal model, as well as using this dose, this NOAEL dose, to determine safety markets for the clinic.

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The duration of nonclinical studies is dependent on the duration of the clinical trial or the marketing authorization. This table comes from the ICH M3(R2) guidance. The table 1 at the top here shows the recommended duration of repeated-dose toxicity studies that are needed to support a clinical trial. So if your clinical trial is intended to be only up to about 2 weeks duration, then you would need a 2-week study in rodents and non-rodents. This would also apply to only a single-dose study.

Anything between 2 weeks and 6 months, you would need to conduct a nonclinical trial in both species that is of equal duration as the clinical trial. Any clinical trial lasting more than 6 months would require a 6-month rodent study and a 9-month non-rodent study.

When you are planning out, though, your nonclinical drug development program, you want to keep in mind table number 2, and these are the requirements of the recommended duration of

repeat-dose toxicity studies to support marketing, and as you can see here, there are some slight differences.

If you intend to treat in the clinic for up to 2 weeks, you'll need a 1- month study in both species; anywhere from 2 weeks to 1 month would be 3 months in each species; between 1 month and 3 months, it would be 6 months; and anything over 6 months would be a 6-month study in rodents and a 9-month study in rodents. These are just some important things to keep in mind, again, as you're designing the studies.

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There are several parameters that are evaluated during the repeat-dose toxicity study. These include mortality as well as clinical signs, and the body weight and food consumption of the animals throughout the entire duration. Clinical pathology parameters will be measured at specific time points. These will look at changes in hematology and clotting parameters. A general clinical chemistry panel will also be collected, as

well as standard urinalysis.

Ophthalmology examinations are also often conducted in order to determine any adverse effects on the eye, and pathology that looks at gross pathology of major organ systems that measures organ weights, as well as any sort of microscopic changes and histopathology for all organ systems. Depending on the route of administration, you may also have to look at local tolerance, and that should be drug administered either intramuscularly, IV, subcutaneous, and toxicokinetic parameters will also be evaluated in studies.

Now, there are a number of factors that we at the FDA take into consideration when we are reviewing these studies. These will consist of whether or not the study was conducted according to GLP requirements. Not all studies can be or are conducted to these standards, however, if your study is not GLP compliant, you should submit an explanation as to why it wasn't conducted to GLP standards and specifically what portions of the study are not GLP compliant.

We want to look at any of the toxicities and try to determine if they are sex or species specific, as species-specific toxicities may or may not actually be human relevant. Are the toxicities dose-dependent and are they reversible? Oftentimes, these studies will include a recovery period. This is so that you can determine if there are any adverse findings and do they recover once the drug is withdrawn. We'll also look at whether or not these toxicities would be expected in the clinic and can they be monitored easily in the clinic.

We want to define a NOAEL, and that is that dose at which no toxicity occurs in the animal, and then finally ultimately determines whether or not this trial is safe to proceed; and if there are any unique findings, we'll have to determine and discuss with the applicant the need for additional studies.

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Genotoxicity and carcinogenicity toxicities are conducted to determine if there's any potential

for genetic damage or carcinogenic outcomes. The genotoxicity studies consist of short-term in vitro and in vivo studies to determine if the drug can induce genetic damage, and this genetic damage can be in the form of either causing mutations or clastogenetic effects.

Carcinogenicity studies are much longer in duration, and they are done in animals, usually a rodent species, mice or rats. They're generally required for approval if the drug is intended to be administered for at least 6 months per year, and that can either be continuous use or intermittent use throughout the year.

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Reproductive toxicology studies are intended to evaluate the ability of a drug to adversely affect either fertility, pregnancy, embryo, fetal, or neonatal development. There are three different specific types of tests that are conducted. First we'll conduct a fertility and embryonic development study. The second study is an embryo-fetal development study, and lastly, a pre- and postnatal

development study is conducted.

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In certain circumstances, special toxicology studies may be needed if there's a specific concern, and this can be based on the mechanism of action of the drug, the drug class -- so sometimes we see class effects -- or if there was a specific toxicity that was identified in the repeat-dose study that needs to be addressed further.

When these studies are designed, they're not always intended to be GLP compliant, and that is because the endpoints and the design of the study are necessary to address the specific concern. Some examples of special toxicology studies can include phototoxicity or T-dependent antigens response assay, or studies intended to look at mitochondrial toxicity.

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The nonclinical review is not conducted in a vacuum. We work in a multidisciplinary team, so therefore there are a number of different things that we must consider specifically when it comes to

the clinical portion of the application.

We want to look at the clinical protocol and determine if the findings and the conduct of the nonclinical studies are adequate to support the starting does, as well as any other dose escalation; the duration and the frequency of dosing; and do the studies support the route of administration, as well as the patient population.

We also want to look at the clinical portions of the application to determine if there was any previous clinical experience with this compound. If there is, then we can look at any of the findings that have been identified in those studies and compare them to the findings that were observed in nonclinical studies. And lastly, we always want to advise if there's any special monitoring or additional monitoring that should be conducted in the clinic.

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So when it comes to clinical pharmacology, there are a number of considerations that we must look at; specifically how the pharmacokinetic and

toxicokinetic parameters in the animals relate to humans. In doing so, this can help us better identify which species is more relevant. We also can look at how exposure relates to toxicity. Is the toxicity occurring at the Cmax, or what will be the peak plasma concentration, or is toxicity associated with the total amount of drug that is circulating in the body?

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Lastly, there are a number of chemistry or manufacturing considerations that we have to address. For example, are there any structure alerts or reactive groups of concern on the drug product? We also want to look at the formulation and make sure that the excipients, impurities, and leachables, as well as extractables, are all appropriate and they have been appropriately evaluated.

Lastly, we want to look at any differences in the drug substance profiles that were used in the nonclinical studies and how they relate to the clinical substance. They don't always have to be

the same, but they should be representative of one another.

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This is a lot of different types of studies and a lot of evaluations that are done in order to support all drug development. They do not need to be done all at the same time in order to initiate a first-in-human clinical trial. Therefore, what exactly is needed in order to open an IND for a first-in-human trial?

You'll want to conduct some pharmacodynamic and pharmacokinetic studies. You're also going to want to conduct a core battery of safety pharmacology studies. We'll also need to look at general toxicology, and this is either through single- or repeat-dose studies in rodent and non-rodent species. And remember, your duration should be reflective of what you're proposing in your clinical trial protocol, and depending on the type of drug, you may have to conduct a genotoxicity analysis, as well as look at local tolerance, depending on the route of

administration.

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As the clinical development progresses, and you go from your phase 1, to phase 2, to phase 3 clinical trials, you may need to conduct nonclinical studies of a longer duration in order to support longer duration clinical trials for your marketing approval. You may also need to continue on and complete all the genotoxicity studies, as well as conduct reproductive toxicity evaluations.

The fertility and embryo-fetal development studies are usually conducted prior to phase 3 in order to support individuals of reproductive potential. The pre- and postnatal development studies are usually conducted during the phase 3 trial in order to support marketing approval.

Carcinogenicity studies and/or other additional special toxicology studies may be recommended, depending on either the drug, as well as the treatment duration, the patient population, and any other findings.

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What I've have discussed so far are the general requirements that cover pretty much all clinical or nonclinical drug development programs. However, there are a number of special considerations that are made for rare diseases in which the FDA may consider additional flexibility for drugs that are intended to treat serious and life-threatening diseases. I want to specifically refer you to the rare disease, the common issues in drug development, as well as the investigational enzyme replacement therapy products for nonclinical assessment guidances.

It is intended that the timing and design of the nonclinical studies can vary depending on the type of drug or product that is being studied, as well as the type of disparity of indication. For example, some toxicity studies such as the reproductive and development studies may be deferred as postmarketing requirements. However, in order to get this flexibility, you need agreement with the agency.

So we encourage you to seek feedback very

early in the drug development process, specifically through the pre-IND meetings. Should any situations arrive after you've opened your IND, you can always request a Type C meeting. Whenever you are seeking flexibility, make sure that you include a written justification, and just be cognizant that flexibility is granted on a case-by-case basis, and it's largely driven by the patient population.

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Some other considerations are made when nonclinical pharmacology studies are used to inform a potential benefit of the drug on disease pathology. For example, when there's a lack of extensive natural history for the disease, these nonclinical studies may be used to show a direct benefit of that therapy. When this is done, the animal model should resemble the clinical disease phenotype as closely as possible, and that is because endpoints such as animal survival, functional improvement, and biochemical improvement can be used to relate the treatment in the animal model to how the patient may survive and function.

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Lastly, compelling mechanistic evidence from these pharmacology studies may also be used to support evidence for marketing applications. If this is your intention, we encourage you to seek agreement with the FDA early on, as this will be needed, and you'll also have to include this in the form of a written justification.

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So lastly here, I will wrap up with a case study that uses the weight of evidence approach for determining the necessity of a carcinogenicity study. Avalgulcosidase alfa-ngpt was approved last year. It is an enzyme replacement therapy for Pompe disease.

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The sponsor at some point in time was trying to determine whether or not carcinogenicity studies were going to be needed, as this drug, a biological agent, would be administered chronically. According to the ICH S6 (R1) guidance, which provides guidance on preclinical safety evaluations

for biotechnology derived pharmaceuticals, states that, "Genotoxicity studies are non-applicable, and therefore they are not needed." It also goes on to say that "standard carcinogenicity bioassays are generally not appropriate and should only be conducted depending on the duration of use, the patient population, or the biological activity of that product."

Further supporting this is the enzyme replacement therapy guidance, which was finalized in October of 2019, which also states that carcinogenicity studies are generally not needed for marketing unless the drug product is conjugated with a chemical linker; then in that situation, an assessment may be warranted.

Based on this --

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-- the sponsor did conduct a non-GLP in vivo micronucleus assay using a GAA knockout mouse, dosing it with up to 150 milligrams per kilogram IV. The results from this study showed that the drug was negative for genotoxicity.

They also submitted a carcinogenicity risk assessment, which included an evaluation of all the nonclinical toxicity findings, so for the 26-week repeat-dose study in monkeys, there were no histopathological findings, suggesting that there could be damage that could lead to a carcinogenic outcome.

They also conducted a review of the currently marketed drugs for Pompe disease. They also conducted a review of the impurity based on the available literature, as well as conducted a 13-week, repeat-dose toxicity study with the impurity. In this study, they spiked the drug product with higher levels of the drug impurity, and then administered it to the animals.

They also conducted in vitro genotoxicity studies, and they found that there was no additional or new toxicities in the monkeys when they added on the extra impurity, and both the Ames assay and the chromosomal aberration assay were negative for genotoxicity. And lastly, they conducted an evaluation for the potential of the

impurity to be released from the drug product.

So based on all of this data, the agency determined that there was no need for a carcinogenicity study to be conducted as a postmarket requirement.

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Lastly here, I have listed a number of guidances for reference, which will also be included in the materials that will be sent out at the end of the meeting.

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That concludes my talk. I thank you for your time and attention.

Session 5 – Questions and Answers

DR. WELSH: Thank you, Arianne, for your presentation. You showed a wealth of useful information.

Today's morning presentations were quite interesting and elicited quite a number of questions from our viewing audience.

Let's start with Mari and Margie. There were a number of questions about submitting an IND,

and it would go to the appropriate review division, but the questioners would like to know how would they request that the Rare Diseases Team be involved in their meetings?

DR. SUZUKI: I'd like to start by saying that many of the review divisions do have experience with rare disease trials, so it would probably be based on their level of comfort whether or not to have an interdisciplinary discussion with other regulators who are experienced with rare disease trials.

Margie?

MS. KOBER: In terms of the process, you can certainly include that request in your meeting request. It's very handy for us to know who you'd like at the table, but be mindful of the fact that, ultimately, the individual review division will decide who to bring to the table. We're not shy about consulting our expert colleagues in rare diseases, though.

DR. WELSH: Okay. Next, let's move to a question for Shamir on PREA.

Do you still, or would one still need to file a waiver if you're conducting a study in the pediatric population for a pediatric rare disease?

DR. TUCHMAN: Thank you for that question.

PREA postmarketing requirements are issued at the time of potential approval of the drug that is submitted for indication. If that drug product was studied in the entire pediatric population, then PREA requirements may apply, but the agency has, at times, found that the drug product has been fully assessed if the entire pediatric population was studied and the results were submitted for approval.

If however, the drug product was studied or proposed for indication in a subset of the pediatric population, then PREA requirements may still be issued for the remaining pediatric populations that were not submitted or not included in the indication; at which time what's usually done at the time of submission of the marketing application is what's called an agreed initial pediatric study plan that is submitted.

This is negotiated with the agency during drug development so it is clear what studies still need to be conducted to fulfill PREA at the time of approval if the approval does not include the entire pediatric population from birth to less than 17, is how we typically define it.

DR. WELSH: Thank you.

Let's move on to a question for Arianne.

Arianne, there were a number of questions about the duration of the toxicology studies. One in particular; how do you determine the most appropriate duration of nonclinical studies if you typically conduct these studies prior to clinical introduction and may not know how long the clinical study would be?

DR. MOTTER: An excellent question. I understand how it can be a little complicated.

For one, in general, you may know whether or not the disease is chronic or if it would only require perhaps a short-term study; you may or you may not know. It may be necessary to treat chronically or in some diseases, by it being

chronic, short-term duration of treatment may put it in remission.

In these cases, you want to start out usually with a 1-month study, and then go to maybe 3 months, and then go up to 6 months. We often see that. So as you are planning your clinical development, then that starts to inform you what your nonclinical program will need to be in order to determine that. Alternatively, you can always just err on the side of a longer dose study because you know that that will definitely support a shorter clinical trial.

DR. WELSH: Thank you.

Let's move back to Mari and Margie. We did have a number of questions regarding protocol submission after a new IND had already been submitted and allowed to proceed.

If you have an existing IND and you want to submit a new indication to an existing IND, do you submit to the same IND? Do you need to wait 30 days again?

MS. KOBER: I can start with the concept

that a short answer is, it varies. It just depends on how closely aligned the two different indications are.

Again, the best way to get an answer for your particular circumstances is to reach out to your regulatory project manager. You can certainly send an information amendment to the existing IND posing that question so that we can respond and have that in the record as saying, yes, it needs a new IND, or no, it can be submitted as a protocol amendment to the existing IND.

In the case of requiring a new IND, there would be a 30-day waiting period. This is particularly important when perhaps the population is quite different, so the risk-benefit analysis would be perhaps different, and for that reason, you would want to wait the 30 days. In the case of a new IND, you actually have to wait that unless we waive it. If the determination is that it can be submitted as a protocol amendment to the existing IND, then there is no 30-day waiting period.

DR. WELSH: Thank you.

Let's go back to another question for Shamir.

There were a number of questions about coordination and collaboration between the FDA and the international agencies. One in particular was how often does the rare disease cluster meet, and does this meeting include applications under Project Orbis?

DR. TUCHMAN: Thank you for that question. The rare disease cluster meets approximately three to four times per year. My understanding of Project Orbis is that it's an oncology related collaborative. I'm not sure whether this is typically discussed in the rare disease cluster. I do know that the FDA and EMA also have an oncology-hematology teleconference, which occurs on a monthly basis, where this may be a forum where Project Orbis would be discussed. Thank you.

DR. WELSH: Thank you.

Let's go next to Arianne. One of the questions was about reproductive development.

Unlike in adults, children may go through

reproductive development during or after treatment with an investigational drug. Are these additional considerations for preclinical reproductive toxicity testing for drugs anticipated to be the only ones to be only used in children?

DR. MOTTER: I'm going to go with that they're asking -- I'm a little confused by the question -- about the need for reproductive toxicology studies, even if it's only a pediatric indication. In general, yes. Children's reproductive and developmental systems are developing as they are children, so you want to look at any effects, even though they are not currently reproducing, to determine whether or not there may be any effects later on in life.

Sometimes in certain situations -- and you can refer to the guidance on this one -- there may be a need for juvenile toxicology studies in order to determine if there could be any adverse effects on earlier development. Sometimes these are picked up in the nonclinical toxicology studies if the animals that are used are often a younger age when

they start dosing, and sometimes they can also be picked up on reproductive developmental toxicology studies because the pup is being exposed to the drug postnatally through the mother's milk and is being exposed to the drug in utero.

But if you ever have a concern again as to whether these are actually needed, we do recommend that you reach out to the nonclinical division in order to discuss the new clinical studies early on. Thank you.

DR. WELSH: Thank you, Arianne.

I just wanted to follow up on Shamir's question, that the rare disease cluster meets approximately monthly, and that Project Orbis is not under the international rare disease cluster.

So let's turn to Mari and Margie. There was a question about being on hold. If an IND is on clinical hold for greater than a year, are we still able to submit safety reports for subjects continuing to be followed based on prior communication with FDA?

MS. KOBER: Yes.

DR. WELSH: Thank you. That's a great answer.

MS. KOBER: Yes, when we can.

DR. WELSH: Let's go back to Shamir. For Shamir, there were questions about pediatric consideration and considering initiating peds trials as a lead indication.

What are the criteria that FDA uses to allow pediatric clinical trials to initiate prior to generating potential benefit in adults?

DR. TUCHMAN: Those criteria really focus on a few things. One is what we would maybe term proof of concept, so understanding the mechanistic and pathophysiology of the disease process in pediatric patients and how a potential drug product would be able to ameliorate symptoms or provide a clinical benefit based on those rationales.

The second is also trying to have a good handle, especially on the potential safety implications of treating patients before we have adult data for pediatric diseases, and that is often data from our nonclinical studies used

specifically in juvenile animals, representing the potential study population where we have a clear idea of what the potential adverse reactions or safety signals may occur with studying the drug in pediatric patients. Then finally, of course, having a good handle on what we suspect the dosing would be required to provide a clinical benefit from nonclinical or early-phase development trials.

DR. WELSH: Thank you.

Next, I'm going to go to Margie and Mari again. There was a question about cannabis.

With more states adopting laws supporting and taxing medical marijuana use, opportunities are emerging in clinical studies supported by state tax funds. What suggestions do you have for researchers seeking to prepare INDs for the use of cannabis in clinical studies for potential rare disease indications?

MS. KOBER: Well, I certainly agree that the interest in cannabis-derived products is blossoming. FDA has issued a number of documents around this. Specifically, the challenges involved

with cannabis-derived products in terms of the quality aspects is the chemistry, and how do you demonstrate that you can essentially produce the same product time after time, batch to batch. There is a guidance document about the special considerations for these types of products.

I will tell you that every review division in CDER has run into some questions around this, so again, I would think that it's particularly important to read all the guidances and documents that are out there.

In this case you would also, in most cases, consult the botanicals guidance. That also addresses things like alternative medicine and some of the Chinese medicines that have been around for a while, so therefore maybe you don't need the same type of data for those products that you would for a traditional small-molecule kind of made-it-in-the-lab sort of thing.

I would also in this case strongly encourage a pre-IND meeting because there are probably things you haven't even thought of. I will say that

there's been some progress in this in terms of who you can use as a supplier for your product. It used to be a single farm, and I believe it was Mississippi or Alabama, and now there are alternatives for that. So stay tuned; lots happening in this field.

DR. WELSH: Thank you.

Next, I wanted to turn to Arianna.

There was a question; is there any case that only in vitro and/or in silico toxicology studies are appropriate for a clinical trial?

DR. MOTTER: This is an excellent question. There is a huge movement, a push, in the toxicology field in order to reduce the use of animals in nonclinical assessments in drug development. At this time, I'm unaware of any cases or any drugs that have been approved, or even let into first clinical studies, without any in vivo data. However, if you are working on alternative approaches, I encourage you to reach out to the review division to make sure that you are undergoing the necessary steps to appropriately

validate these assays if you do intend to use them to support a clinical trial, but I don't know of any.

DR. WELSH: Thank you. I wanted to turn back to Mari and Margie again. There were a number of questions about how far in advance would you suggest a pre-IND meeting be held.

DR. SUZUKI: I would recommend coming in as soon as you do have questions for us. Oftentimes, after a discussion, it may become apparent that there are additional or longer term nonclinical studies that need to be conducted prior to initiating an IND, so I would recommend coming in sooner than later.

MS. KOBER: This is Margie. That being said, I do want to counsel people not to come in too soon. Don't come in, in a situation where, "Hey, I have an idea that this might work." You have to do at least some of the background gathering. The other thing I would caution you about doing is putting together a meeting request and a meeting package that essentially says, "Hey,

here's what we're going to submit. Is this enough?" We really need focused, specific questions to address.

Again, that being said, if you don't ask questions we think you should have asked, we're not shy about giving advice outside of the questions. There are oftentimes situations where we start our preliminary comments with just, in general, here's what you need to know, so hopefully that's helpful. There's a sweet spot; not too early, not too late.

DR. WELSH: We're out of time today. Thank you so much to all of our presenters this morning, Mari, Margie, Shamir, and Arianne. This was a very interesting topic as evidenced by the plethora of questions that were submitted, and we're sorry we couldn't get to all of them. There will be a 10-minute break, and according to the agenda, we will be back at 11 a.m. Thank you.

(Whereupon, at 10:53 a.m., a recess was taken.)

Session 6

Presentation - Chekesha Clingman-Henry

DR. CLINGMAN-HENRY: My name is Chekesha Clingman-Henry, and I am the associate director for Strategic Partnerships in the CDER Office of Translational Sciences. In this session, we will discuss some additional pathways to interact with CDER. We will focus on two meeting forums that stakeholders can use to engage CDER beyond formal regulatory meetings.

First, I will discuss the critical path innovation meetings. I will be followed by Captain Robyn Bent, who will discuss the patient-focused drug development program. After Captain Bent and I have given our presentations, we will have the question and answer session. Please submit your questions by clicking on the "Ask A Question" icon on the bottom-right of your screen.

Next slide, please.

Now, I will give an overview of the critical path innovation meetings or CPIM program.

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The CPIM program was launched in 2013 as one of FDA's efforts in response to the 2004 Innovation

or Stagnation report that identified several areas for needed improvement to advance medical product development and opportunities to create better tools and knowledge based on reliable insights into pathways for patients.

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The goal of the CPIM is to provide an opportunity for stakeholders to communicate directly with FDA subject matter experts and have an open scientific exchange of ideas about innovation and potential ways to improve efficiency in drug development.

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CPIM discussions are focused on the science, medicine, and regulatory aspects of innovation in drug development. These are non-binding, non-regulatory discussions, meaning they are not like a traditional regulatory meeting that a sponsor would have with a review division focused on the development of a specific product.

The CPIM does not address FDA policy or official regulatory guidance, nor is it a detailed

review of data. Instead, CPIMs provide an opportunity for stakeholders -- including individuals from industry, academia, patient advocacy groups, or other government agencies -- to have an open scientific discussion with FDA and hear the agency's perspective on the method, approach, or technology being presented.

There is a CPIM guidance document, which contains more detailed information on the procedural aspects of the program. The guidance can be found on the FDA website. In the following slides, I will highlight a few of the program logistics.

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Anyone with a role in drug development can request a CPIM by completing the one-page form on FDA's CPIM website. Once FDA receives the form, CPIM staff evaluate it to determine if CPIM is the appropriate venue for the discussion. Acceptance of a CPIM request is dependent on the relevance of the topic to drug development and availability of appropriate FDA expertise to engage in the

discussion.

Once the meeting is accepted, CPIM staff coordinates the meeting. We will identify subject matter experts in CDER's offices and review divisions to request participation in the area of interest. Depending on the topic, we may also invite subject matter experts from other FDA centers such as CBER and CDRH.

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We ask to receive slides and presentation materials at a minimum of two weeks prior to the scheduled CPIM. The FDA staff who are participating in the CPIM meet in advance to preview the scientific discussion and help participants avoid specific policy or regulatory issues that should not be a part of the CPIM.

At the CPIM, which last about 90 minutes, the meeting requester leads the scientific discussion, and facilitators help to guide the discussion to meaningful potential next steps as appropriate.

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CPIMs have focused on a variety of topics, including specific disease areas, including various rare diseases. For example, there have been discussions around progression studies or early discussions of potential biomarkers or clinical trial endpoints. CPIMs have also addressed cross-cutting topics such as tools and methods that could more generally apply to the conduct of clinical trials or the quality and evaluation of clinical trial registry and other data.

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Following the meeting, CPIM staff share a brief high-level summary of the meeting discussion with all of the participants. The topic for CPIM is also posted on the FDA's public website. A CPIM can help investigators connect with others in the scientific community exploring similar drug development challenges.

The FDA may facilitate subsequent discussions with review divisions or other FDA staff. Recommendations at the conclusion of the CPIM may include convening a public workshop or

collaborating with other groups like various consortia, or in some instances, meetings have fostered research collaborations between FDA and external researchers through, for example, a cooperative research and development agreement or CRADA. To date, we have held 102 CPIMs with approximately 30 percent of these on various rare disease topics.

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I would like to share some helpful tips for a successful CPIM. It is important to keep in mind that these meetings are not replacements for regulatory meetings such as a pre-IND or IND meeting. CPIMs are high-level discussions of science, technology, methods, and innovation. FDA will ask questions at these meetings, and we hope to gain insight into emergent science and innovation and understand the implications for drug development. Again, no policy discussion or discussion of specific products under review by the agency are held within the scope of the CPIM.

In the meeting request, please provide a

clear, brief description of the meeting purpose, background, and steps taken to advance the project. We advise that you provide up to four questions for the FDA and state the desired feedback you hope to gain from the meeting. A well-written request will help us determine if a CPIM is the right fit for the discussion or if another meeting format would be more appropriate.

We ask that you provide your meeting package, including slides and agenda, at least two weeks before the meeting. This will give the FDA subject matter experts sufficient time to review the background information and prepare for the meeting. Be sure to prioritize your questions as well.

During the meeting, the requester leads the meeting, so please be mindful of your time. Ask clarifying questions. We want to make sure that you receive useful information to help advance your research efforts. The discussion can move fairly quickly. We recommend that you leave a few minutes to recap and discuss next steps with the agency.

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For more information, please visit the CPIM website and feel free to email us at the address provided.

This concludes my presentation. Now, I would like to introduce Captain Bent.

Captain Bent is the director of the Patient-Focused Drug Development program in the FDA Center for Drug Evaluation and Research. The title of her presentation is Patient-Focused Drug Development.

Captain Bent?

Presentation – Robyn Bent

CAPT BENT: Thank you so much, and thank you, everyone, for joining us. I am very excited to participate in this meeting today. I spent the majority of my career actually at NIH, both in the intramural and extramural worlds, and I love that NIH and FDA have come together to talk about ways to facilitate rare disease drug development because speaking just for myself, it's amazing how little I knew about how FDA worked

before I landed here a few years ago.

Today I'm going to talk to you a little bit about patient-focused drug development and about some select efforts that we have going on. Unlike the CPIM process that you heard about, patient-focused drug development doesn't completely fit under the umbrella of how to interact with FDA, but we still thought that it was important to talk about it because we wanted you to be aware of some of our efforts and potentially be able to leverage them in your important work. This morning, I'm going to talk a little bit about what we've done, what we've learned, and where we're going next.

Next slide, please.

Patient-focused drug development, or PFDD, is an approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. Today I'm going to talk about the following programs. There are five of them, so I'm going to touch on each one of them pretty briefly.

I'm going to provide you with information on our Patient-Focused Drug Development meeting program, the methodologic guidance series, our Standard Core Clinical Outcome Assessment Grant Program, the Rare Disease Cures Accelerator, and then I'm going to wrap up by just briefly mentioning one of our international efforts.

Next slide, please.

So let me start with patient-focused drug development meetings. These meetings were really the start of patient-focused drug development. We've been holding them since 2013 when we launched an effort to more systematically obtain the patient perspectives on specific diseases and their treatments, and to strengthen our understanding of disease and treatment burden.

These meetings provide an important opportunity for us to hear directly from patients, patient advocates, and caregivers about the symptoms that matter most to them, the impact their condition has on their daily life, and a patient's experience with currently available treatments.

Overall, FDA has held 30 of these PFDD meetings, and patient groups have held over 50 meetings that follow a very similar format, and we call those our externally-led PFDD meetings. The information gained from both of these meeting types was initially intended to provide FDA with information to inform our understanding of clinical context as part of our benefit-risk assessment framework that we use when making regulatory decisions, but they've really become a lot, lot more than that.

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On this slide, you can see the externally-led meetings that have been led or held by patient groups, and if you've had an opportunity to attend any of them, either virtually or in person, I'm sure that you'll agree that these groups do an amazing job in planning and conducting these meetings. On the FDA PFDD webpage, we host all of the meeting reports called the Voice of the Patient Reports from both the FDA meetings and the externally-led meetings.

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As I mentioned, we've learned a lot from PFDD meetings held so far. We've learned about the clinical context of a condition and what matters to patients and their loved ones. We've learned that patients really are experts and what it's like to live with their conditions, and they want to be involved in the medical product development process as much as possible.

We've heard about potential new targets for therapies, and we've learned that there are times when the endpoints being measured in clinical trials are not the endpoints that matter to patients. These learnings have really helped to motivate some of our newer initiatives that I'll talk about in just a few minutes.

But I think that one thing that is so important about the PFDD meeting program is that FDA isn't the only group that benefits from these meetings. On this slide, you can see the results of some interviews that were done by FDA's program evaluation staff, and you can see that stakeholders

really felt that these meetings had a great deal of value to them as well. And I'll tell you that I've been a nurse for over 20 years, and I still practice regularly, and I still never fail to learn a lot from these meetings no matter how much I thought I knew about the condition going in.

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Often I get questions from people about how PFDD meetings have informed FDA reviews. Here you can see two examples. In the first example, we received an application for a drug to treat hyperhidrosis, and some of the data from the co-primary endpoints was difficult to interpret and seemed to almost be telling two different stories, with the weekly, in-office gravimetric sweat test showing a great deal of variability.

Statistical reviewers looking at the data recalled hearing from patients during a PFDD meeting that their hyperhidrosis was not always constant and that many people experienced episodic hyperhidrosis. This information provided the context that was really needed to help understand

the variability of the data and ultimately support the approval of the product. Most often, however, for FDA, PFDD meetings informed the benefit-risk assessment by providing what we call the therapeutic context.

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You'll recall that a few slides back, I mentioned that as part of our meetings, we discovered that the endpoints being measured in clinical trials aren't always the endpoints that matter to patients.

Here you see a bit of the benefit-risk framework, and you can see that building on what we've learned from our PFDD meetings, we're working on other ways to include the patient perspective into regulatory decision making to enable stakeholders to go beyond just hearing the powerful narrative and actually collect data that can serve as study endpoints and be used as a basis for marketing decisions.

Our projects include the Standard Core Clinical Outcome Assessment Grant Program, which

I'll discuss in a moment, and we're also working on a methodologic guidance series that provides guidance in a stepwise manner of how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers.

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Before we take a deeper dive into each of the methodologic guidances, I wanted to show them all together really because they build on each other, starting at talking to patients, and going all the way through developing endpoints from clinical outcome assessments.

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This first guidance is a joint effort between the Center for Drugs and the Center for Biologics. It was published in draft in 2018 and was finalized in June of 2020. It discusses sampling methods that can be used when planning a study to collect patient input. It also provides a general overview of the relationship between potential research questions and methods when

deciding from whom to get input. This includes defining the target population and developing a sampling strategy.

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Guidance 2 is also a CBER and CDER guidance. It was finalized just recently in February and discusses methods for eliciting information from individuals identified in Guidance 1. It presents a range of methods and established best research practices to identify what's important to patients with respect to burden of disease, burden of treatment, and the benefits and risks in the management of the patient's disease.

In particular, the methods and best practices presented in the document can help elicit relevant information from patients and other stakeholders such as how their disease affects their daily lives, what they find most troublesome, and the challenges, problems, and burdens of existing treatments for the disease.

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We've also been really working hard to get

Guidance 3 published, and we think that it will be out soon. This guidance is a collaboration between the Center for Drugs, the Center for Biologics, and the Center for Devices, and we really hope that those who are waiting for it will find it worth the wait. It will address refining the concepts of interest important to patients for measurement.

We understand that not everything identified as important by patients, caregivers, and clinicians can be addressed by an investigational treatment or really even be measured in the context of a clinical trial. This guidance will address issues related to selecting what to measure in the medical product development program and identifying or developing fit-for-purpose clinical outcome assessments to assess the outcomes of importance to patients. We're working on internal and external training materials to go with this guidance, and we hope to be able to share those as soon as the guidance publishes

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Guidance 4, the fourth guidance in this

series, is also in progress. It will discuss topics related to incorporating clinical outcome assessments into endpoints for regulatory decision making. This includes the COA related endpoint development, defining meaningful within-patient core changes, and collection, analysis, interpretation, and submission of data to FDA.

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There's one more guidance that we're working on. It isn't part of the methodologic guidance series, but it is a PFDD guidance, and this one talks about how a person seeking to develop and submit proposed draft guidance related to patient experience data for consideration by FDA can submit that draft guidance.

Now I just want to move on to talk a little bit about the Standard Core Clinical Outcome Assessment Grant Program.

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In 2019, as part of the PFDD efforts, we launched this Pilot Grant Program to support the development of these publicly available core sets

of clinical outcome assessments and their related endpoints for specific disease indications. This grant program grew out of the patient-focused drug development and the things that we are hearing at those PFDD meetings that I talked about.

The purpose of the grant program is really to help make incorporating the patient perspective really more sustainable, so I'm just going to touch a little bit on the grants that we have in the program.

We have the Migraine Clinical Outcome Assessment System, or MiCOAS grant, which is working to develop and standardize a core set of endpoints and related COAs for use across migraine clinical trials. We also have the Clinical Outcome Assessments for Acute Pain Therapeutics in infants and young children, or COA-APTIC grant, which is working to identify COAs and endpoints for use when developing acute pain therapeutics for infants and young children, primarily those ages 0 to 2 years.

We have the Northwestern University Clinical Outcome Assessment Team, or NUCOAT grant, that will

develop and validate clinical outcome assessments with applicability across a range of chronic conditions that assess physical function using patient-reported and performance outcomes.

We have our newer grants that we funded about a year ago, maybe a little bit more now. The first one is entitled Preparing Clinical Outcome Assessment Set for Nephrotic Syndrome or Prepare-NS. This grant will develop and establish a core set of COAs for nephrotic syndrome with a primary focus on fluid overload.

We have a grant titled, Expanding the Observer-Reported Communication Ability Measure, or ORCA, that will expand the existing ORCA measure, which is a measurement tool created to assess caregiver observations of a child's ability for expressive communication in nonverbal patients with Angelman syndrome, and they're hoping to expand this grant to cover 13 other neurodevelopmental disorders.

These are UG3-UH3 cooperative grants, and they're meant to enable a close collaboration

between FDA and the grantees throughout the development process, and they certainly are doing that. Each of our grantees has a public website, which they are updating as the grants progress, and where they'll be publishing milestone documents such as literature reviews, qualitative study reports, and other documents so that others can be aware of the information that they have collected and analyzed. And as you would expect, grantees are also publishing some of this information in peer-reviewed journals.

This kind of brings me to the importance of data sharing, particularly the importance of sharing natural history data and clinical trial data in rare diseases. One way that we're working to kind of enhance the sharing of data is through the Rare Disease Cures Accelerator data analytics platform.

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The platform is being developed by the Critical Path Institute in collaboration with the National Organization for Rare Disorders, or NORD,

and is funded, again, by a cooperative agreement from FDA. The platform provides an integrative database and analytics hub designed to promote the secure sharing of existing patient-level data to encourage the standardization of new data collection.

The aim is to receive and protect data from a variety of sources that can inform rare disease characterization, clinical trial design, and other critical questions in rare disease drug development. This data analytics platform provides a resource through which authorized users, like disease researchers and drug developers, can access patient-level clinical data for a particular rare disease, which may be analyzed to better understand disease progression and the disease heterogeneity across the effective patient population. This in turn can inform trial design, selection of endpoints, and other important considerations.

Additionally, by pooling data from many different patients across many different rare diseases, researchers may be able to examine

similarities within and across these conditions and gain insight that would be impossible from just looking at individuals in isolation or in a small population.

You may find yourself kind of wondering how this relates to patient-focused drug development, but we really see this as a very complementary effort because we often hear from patient groups who are very involved in the development and the conduct of natural history studies, and we continuously hear that patients that are participating in research are doing so because they want to move science forward and that they would really prefer that their information continue to be useful after a study or trial is complete.

Obviously, they want this to happen in a way that protects and secures the data, so the RDCA platform uses a process similar to the one used by dbGaP [database of Genotypes and Phenotypes] to ensure that people who are requesting access to this patient-level data plan to use it to advance rare disease drug development.

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Finally, I'd just like to briefly touch on the International Council for Harmonization Patient-Focused Drug Development Reflection Paper. The goal of this paper was to take steps to harmonize approaches, methods, and standards to advance the incorporation of the patient perspective in drug development globally. The goal really is to build on existing work and not necessarily reinvent the wheel, and this reflection paper proposes the development of, really, two guidelines; the first to address how to measure things that are meaningful to patients in a clinical trial -- for example, through the use of clinical outcome assessments -- and the second is really geared towards looking at methods for elicitation or collection of information on patient preferences.

The reflection paper has been endorsed by the ICH management committee and has been revised based on public comment. You can read about it on the ICH website. Because of the pandemic and,

really, the availability of subject matter experts, we've not begun working on these papers, but we do expect that they will move forward shortly.

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Thank you so much for your time. I hope that you can see that FDA considers patient input critical to any drug development effort. And finally, I did just want to mention again that the information on everything that I've spoken about today can be found on the CDER PFDD website, and you can find that website simply by typing FDA and PFDD into any search engine.

So thank you so much, and I look forward to your questions.

Session 6 – Questions and Answers

DR. CLINGMAN-HENRY: Great. Thank you, Captain Bent.

I see a few questions in the chat. One, it looks like it pertains to CPIM, and I can start with that one.

It says, do you have a case about which stage of drug development we can take advantage of

the CPIM program?

As mentioned before, the CPIM is really a non-binding and non-formal meeting forum for discussions. I don't have a specific case, however, for example, if you have a compound for example, that shows promise in in vitro, and maybe a limited animal study shows promise as a potential therapeutic for a disease, that's something that you can come into the CPIM program and have a discussion with the broader FDA subject matter experts to discuss that preliminary data at a very high level, and to perhaps obtain considerations for future research for future development so that you can advance your program to the stage where you can come in for a pre-IND and ultimately submit an IND application.

The next question is how far in advance should a CPIM be requested?

You can request a CPIM as early as possible. On average, from the time that we receive a request, it takes about two months or so for that meeting to be actually scheduled, so based on that,

I would encourage you to plan earlier. We can also consider specific dates that you may have in mind.

CAPT BENT: Thanks. I can maybe speak a little bit to some questions that we've received related to PFDD, if that works.

DR. CLINGMAN-HENRY: Yes.

CAPT BENT: Sure.

The first question that I see is, are PFDD public?

Yes, patient-focused drug development meetings are FDA public meetings. The externally-led meetings also are usually public. They do usually require some registration, but they usually are public.

FDA has another type of meeting program that's a little bit smaller. It's a little bit more informal called The Listening Sessions, and that is where a group of maybe six to eight patients come in and share experiences with FDA staff. Typically, those are not public, but the summaries from those meetings are available to the public on the patient engagement team's website.

Let me move on maybe to one other question, where I'm seeing a question about, for externally-led, patient-focused drug development meetings, is a consultant required?

I would say that certainly if you're a patient group and you're interested in hosting an externally-led, patient-focused drug development meeting, you submit a letter of intent. The information is all on our website. You submit a letter of intent, and our team will work with you to plan the meeting and try to help you navigate through the process.

Different organizations have found the use of a consultant to be very helpful, and they do put on beautiful meetings. But I think what's really important is that the use of a consultant or the need to use a consultant, that should not be a barrier to holding the meeting. What's really important to us and to the community is really that that information is being shared out there.

So while I think a consultant can be helpful, there's certainly not a requirement or

even a necessity, and we would really, really hate for that to be a barrier to hosting a meeting.

Let me see. Do you have another question for --

DR. CLINGMAN-HENRY: I don't see one at the moment.

CAPT BENT: Okay.

DR. CLINGMAN-HENRY: I see a question for patient-focused drug development. What are the benefits of a patient-focused drug development meeting versus an FDA listening session?

I touched on that a little bit. I think it's certainly faster, and it takes less time, and maybe a little bit less, from a logistics standpoint, to participate in an FDA listening session. So I think that that is a helpful way if the group that you're really trying to meet with and share information with is the FDA.

I think that the PFDD meetings, as I touched on earlier, are public, so that's a way to engage stakeholders beyond just FDA. I think that this is a really important point because FDA, as much as we

want to help to advance drug development, we don't develop drugs. So it really takes a village to move this forward, and I think that's why a lot of us are here today, is to really be part of that larger effort. So with the PFDD meetings, you're engaging a broader group of stakeholders. Hopefully that answered that question.

DR. CLINGMAN-HENRY: Thank you, Captain Bent.

While this is not a question, I do want to share. Where do we see a lot of utility with respect to the rare disease space with the CPIM program?

I would say the CPIM has been utilized primarily in the rare disease space for having very early conversations around potential biomarkers or potential clinical outcome assessments for utility and clinical trials for rare disease drug development. These are conversations that may not be right for, for example, the Biomarker Qualification Program, however, they are an opportunity for investigators to meet with the

agency in a non-binding, informal way, and really have a general discussion around the science and around what other opportunities or considerations may be appropriate for advancing that biomarker, so to speak, and that you are at the stage to come back into the agency under a discussion, a more specific discussion, with the Biomarker Qualification Program.

CAPT BENT: Great.

Let me take one more question, which is a question of, when is the best time to engage with patients?

I would say from an FDA perspective, we really think that it's important to engage with patients throughout the drug development process, really starting at that translational point, where you're really understanding what matters to patients and really starting to think about your clinical trial endpoints or your targets, and also making sure that you engage with them earlier, rather than later, because this is going to direct your path. This is going to direct the way that

you're conducting your entire drug development process.

So the last thing you want to find out as you're approaching your late-phase studies, if you start to engage patients there, is that you've been heading down the wrong pathway and now you have to back up. So we really would recommend the discussion and inclusion of patients throughout the drug development process.

Sometimes we hear from people that they're concerned that that's going to delay their work, and I would say that there may be a little bit of a short upfront delay, but you get a lot of efficiencies later. There's a lot of information in the literature that supports that by engaging patients early on, you actually can improve your recruitment, you can improve your retention, and you can decrease the number of protocol amendments that you need.

All of these things shorten the duration of the clinical study and can really build in some efficiencies. So a little bit of extra time that

it takes to engage with patients is really, really worth it in the big scheme of things.

I did just want to mention -- I don't think I mentioned it in my presentation -- that the Center for Devices just recently, in January of this year, published really useful guidance titled, Patient Engagement in the Design and Conduct of Medical Device Clinical Studies: Guidance for Industry, FDA Staff, and Other Stakeholders. That document really provides a lot of really critical information about how to engage with patients and FDA's, particularly the Center for Devices, current thinking on that.

DR. CLINGMAN-HENRY: I see a few more questions. One question we have is, is CPIM information made public?

We post a general title of the CPIM discussion on our public website. As I mentioned before, summaries of the discussion are issued to meeting participants, however, we do not make those summaries public. The reason being is that while these meetings are non-binding, requesters that

come into us may share confidential information with the agency that we are not at liberty to disclose.

With that said, however, we have been in a position where we have connected certain requesters with other requesters around similar topics for CPIM to advance a collaboration and so forth, so we are able to make those connections.

Captain Bent, do you see any questions that -- do you have a question?

CAPT BENT: Yes.

DR. CLINGMAN-HENRY: Okay.

CAPT BENT: Thanks. I see a question. Are the PFDD meetings available on demand for reviewing or listening after the event?

I would say yes, absolutely. In fact, we've just undertaken an effort to take all of the FDA-led PFDD meetings -- the information on them is available on all of the meeting websites. You can get the transcripts of the meeting, you can get the Voice of the Patient report that's developed after the meeting, as well as watching a recording of the

meeting. But those are sometimes in a format that people find difficult, so what we've done is we've converted all of those meetings to a format that allows them to be posted on YouTube, so they are all available on the FDA's YouTube channel.

For the externally-led patient-focused drug development meetings, most of those meetings are posted on the organization's website, the organization that sponsored that meeting. So if you go to the PFDD website, or if you just Google the condition and PFDD, you can usually find it. But on the PFDD website we do link to any available meeting reports, and that can bring you back to the recordings if they're available.

DR. CLINGMAN-HENRY: Thank you.

I see one final question on CPIM, and the question is, if programs are already in the clinic, is it too late to discuss, generally, drug development considerations for specific diseases, including biomarkers?

I would say the short answer is no, however, we will not be discussing the proprietary drug

development program that you may be referencing in the clinic. However, CPIMs are an opportunity to discuss considerations for biomarkers and other considerations for specific diseases.

With that, we will conclude this session, and thank you very much. Now we will turn the floor back over to Kerry Jo. Thank you.

Closing Remarks – Kerry Jo Lee and Alice Chen Grady

DR. LEE: Thanks so much, everyone. It's been a wonderful few days.

Hello again; Dr. Kerry Jo Lee, the associate director for rare diseases in the Division of Rare Diseases and Medical Genetics, and the lead of the Rare Diseases Team at CDER.

I want to start off by really thanking everyone who has worked so hard to put together this Regulatory Fitness and Rare Disease Clinical Trials Workshop, especially Audrey Thomas on the Rare Diseases Team, CDER, and Dr. Alice Chen on the NCATS NIH staff. I also want to thank all of our speakers and moderators for contributing their time and expertise to this very important endeavor.

Your lessons and experiences have been very valuable.

Finally, for the audience that attended and will watch this in the future, thank you so much for all of your questions and engagement during this event. We will take these questions and feedback and use it to inform future events and communications, so it is very important. This event has truly been a collaborative effort and a great example of what we can accomplish in rare diseases when we work together.

As I said yesterday, this workshop over the past few days is really an example of the types of engagement working with and for the rare disease community that we hope to achieve under CDER's new ARC program to really achieve our program's vision of speeding and increasing the development of effective and safe treatment options and addressing the unmet needs of patients with rare diseases.

Recordings are already available from day 1 and soon will be from today. For those who are looking for slides -- many of you have

asked -- they will also be posted on the website as soon as they become 508 compliant, so that's going to take a little more time, but they will be up there.

As was mentioned earlier, the FDA CDER Rare Diseases Team has also compiled a wealth of resources and guidances in one place to help investigators in rare disease drug development. You can find this link on the YourCast site at the registration site if you click on the information I button at the bottom of your screen and at the NIH and FDA sites for the workshop. This resource is entitled, FDA Drug Development Resources for the Rare Disease Community. I encourage you to find this list, and I hope that you find it useful.

In closing, I'm going to turn it over to Dr. Alice Chen Grady, a program officer in the Division of Rare Diseases and Research Innovation, NCATS NIH, where she works with the division team to advance diagnosis and treatment for rare diseases through research.

Dr. Chen?

DR. CHEN: Hi, everyone, and thank you, Kerry Jo, and thank you for everything that you did leading up to this workshop, as well as these past two days.

Again, I'm Alice Chen. I am in the Division of Rare Diseases Research Innovation -- we just changed our name -- at NIH NCATS. Many of you may be expecting P.J. Brooks, our acting director, to close us out, but he is actually receiving the Sonia Skarlatos Public Service Award today at the American Society for Gene and Cell Therapy, or ASGCT, annual meeting. We're all very proud of him for this recognition as a tireless gene therapy advocate. I know many of you have had discussions with him on that topic itself, so we just want to send him a virtual congratulations.

Just to reiterate again, we will be sending all registrants a post-event email for feedback, as well as to capture some of the many resources and links that Kerry Jo just went through. So if you have not yet registered and just joined via the webcast, please consider registering. That will

remain open, and if you register, you will be included in our communications.

Check back often to that registration page because you'll see an event materials link on the left. The resources PDF is included there, as well as any future event materials that will be posted on that table as well, so it's a good thing to bookmark.

Just as a reminder, the recording for both days will be posted. It's actually going to be the same link, so just refresh it until you see it being posted. The cool thing is that they'll be chapter marks there, so you can jump straight to a particular talk or topic that you really enjoyed.

From the NIH NCATS team, we just want to thank everybody again, especially the speakers and our moderators for all of the panel Q&As that were very insightful, and for our FDA studio staff for helping to make this virtual workshop possible.

All of the workshop organizers behind the scenes, thank you for your tireless work over the months. And as a special thank you to our hundreds

of viewers who joined us these past few days, thank you for making it so engaging, and we hope that future workshops can at least be a hybrid platform where we can see your faces in person.

Adjournment

DR. CHEN: So thank you again from both NIH NCATS and FDA CDER, and we hope to see you guys soon.

(Whereupon, at 11:49 a.m., the meeting was adjourned.)