FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Virtual Meeting

Day 1

Wednesday, May 11, 2022

10:00 a.m. to 3:14 p.m.

Meeting Roster

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Division of Advisory Committee and

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. PAPPO: It's hard to believe that it's been a year since we last met. I hope that all of you are doing well and are happy and healthy, and we're going to get this meeting going.

Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai, and her email and phone number are currently displayed.

My name is Alberto Pappo, and I will be chairing today's meeting. I will now call the May 11, 2022 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee to order. Dr. Joyce Yu is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Subcommittee

DR. YU: Thank you. Good morning. My name

is Joyce Yu, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

We'll start with Mr. Mitchell.

MR. MITCHELL: I'm David Mitchell. I am the consumer representative to the ODAC. I am president of Patients for Affordable Drugs, and I am a multiple myeloma patient.

DR. YU: Dr. Pappo?

DR. PAPPO: Good morning. My name is Alberto Pappo. I'm a pediatric oncologist at St. Jude Children's Research Hospital, and I am the chairperson for the Pediatric ODAC.

DR. YU: Thank you.

Dr. Bagatell?

DR. BAGATELL: Hi. My name is Ro Bagatell. I'm a pediatric oncologist at the Children's Hospital of Philadelphia, and I have just joined the ODAC.

DR. YU: Dr. DuBois?

DR. DuBOIS: Hi. I'm Steve DuBois. I'm a

pediatric oncologist at Dana-Farber Boston Children's.

DR. YU: Thank you.

Dr. Dunkel?

DR. DUNKEL: Good morning. My name is Ira Dunkel. I'm a pediatric neuro-oncologist at Memorial Sloan Kettering.

DR. YU: Dr. Glade Bender.

DR. GLADE BENDER: Good morning. I'm Julia Glade Bender. I am also a pediatric oncologist at Memorial Sloan Kettering, and the vice chair of clinical research.

DR. YU: Dr. Gorlick?

DR. GORLICK: Good morning, everybody. I'm Richard Gorlick. I'm a pediatric oncologist at MD Anderson Cancer Center.

DR. YU: Dr. Kim?

DR. KIM: Good morning. My name is AeRang Kim, and I am a pediatric oncologist at Children's National in Washington, DC.

DR. YU: Thank you.

Dr. Kolb?

(No response.)

DR. YU: Dr. Kolb, you may need to go to the top of your screen. I see you are muted in Adobe Connect.

DR. KOLB: Thank you. Sorry about that. My name is Andy Kolb. I'm a pediatric hematologist/oncologist at Nemours Children's Health.

DR. YU: Thanks.

Dr. Laetsch?

DR. LAETSCH: Hi. I'm Ted Laetsch. I'm a pediatric oncologist at the Children's Hospital of Philadelphia and University of Pennsylvania.

DR. YU: Ms. Ludwinski?

MS. LUDWINSKI: Hi. I'm Donna Ludwinski. I'm a patient representative and work for Solving Kids' Cancer in New York.

DR. YU: Dr. Parsons?

DR. PARSONS: Hi. Good morning. I'm Will Parsons. I'm a pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. YU: Dr. Kraus?

DR. KRAUS: Yes. Good morning, everyone. I'm Albert Kraus. I work in research and development, currently for Pfizer Corporation in oncological therapeutics.

DR. YU: Now we'll go ahead and introduce our FDA participants for today, starting with Dr. Reaman.

DR. REAMAN: Good morning. I'm Greg Reaman. I'm the associate director for pediatrics in the Oncology Center of Excellence at the FDA.

DR. YU: Thank you, Dr. Reaman.

Dr. Donoghue?

DR. DONOGHUE: Hi. Good morning. My name is Martha Donoghue. I'm a deputy division director of the Division of Oncology 2 at the FDA.

DR. YU: Dr. Saber?

DR. SABER: Good morning. I'm Haleh Saber, deputy director in the Division of Hematology Oncology Toxicology at CDER FDA.

DR. YU: Dr. Shord?

DR. SHORD: Good morning. My name is Stacy

Shord, and I am the deputy division director in the Division of Cancer Pharmacology II.

DR. YU: Dr. Duke?

DR. DUKE: Good morning. I'm Elizabeth Duke. I'm a pediatric neuro-oncologist and clinical reviewer in the Division of Oncology 2 at FDA.

DR. YU: Dr. Merino?

DR. MERINO: Good morning. My name is Margret Merino. I'm a pediatric hematologist/oncologist and a clinical reviewer in the Division of Hematologic Malignancies 2 at the FDA.

DR. PAPPO: Thank you, Joyce.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will

be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting in the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during the break. Thank you.

Now Dr. Joyce Yu will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. YU: The Food and Drug Administration, FDA, is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs

Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all ODAC members and temporary members of the subcommittee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this subcommittee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that ODAC members and temporary members of this subcommittee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a

special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, ODAC members and temporary members of this subcommittee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the development of a conceptual framework that will inform the decision making of the FDA on sponsor plans and requests for waivers of early pediatric investigations of molecularly targeted cancer drugs

and biologics when multiple same-in-class products are approved and/or in development, recognizing that the rarity of pediatric cancers may preclude the feasibility of investigations of multiple products.

Investigation of more than one product may be appropriate when specific product characteristics predict an improved benefit-risk assessment that warrants clinical investigation. The European Medicines Agency has also been invited to present.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the ODAC members and temporary members of the subcommittee, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all ODAC members and temporary members of the subcommittee to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following guest speakers have reported interests which are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Dominik Karres has acknowledged that he is employed by the European Medicines Agency, EMA. Dr. Scott Diede has acknowledged that he's employed by Merck and Company, and he has stock in the company. As guest speakers, Dr. Karres, Diede, Wang, and Ms. van Malderen will not participate in subcommittee deliberations, nor will they vote.

We would like to remind ODAC members and

temporary members of the subcommittee that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the subcommittee's discussions. Thank you.

DR. PAPPO: Thank you very much, Joyce.

We will now proceed with our first presentation from the FDA, from Dr. Gregory Reaman.

Greg?

FDA Introductory Remarks – Gregory Reaman

DR. REAMAN: Thank you, Dr. Pappo.

Good morning. I'd like to welcome and thank you for your participation in today's discussion of a conceptual framework for decision making relating to planned requests for waivers of pediatric investigations of targeted drugs and

biologic products directed at molecular targets relevant to the growth of progression of one or more pediatric cancers when multiple same-in-class products are in development or have been approved, and already subjected to the amended PREA requirements for a molecularly targeted pediatric cancer investigation.

I'd especially like to acknowledge and welcome our colleagues from the Paediatric Medicines Office at the European Medicines Agency and members of its pediatric committee.

As most of you know, the RACE for Children Act, Research Acceleration for Cure and Equity, was incorporated as Title V Section 504 of the FDA Reauthorization Act in 2017, amending the Pediatric Research Equity Act, or PREA, in Section 505(b) of the Food, Drug, and Cosmetic Act, and effective August 18, 2020 to require -- for all initial applications of a new drug or biologic product intended to treat an adult cancer that is directed at a target substantially relevant to the growth of progression of a pediatric cancer -- early

investigation of that drug in the pediatric population to provide clinically meaningful study data using appropriate formulations to hopefully inform product labeling on dosing, safety tolerability, and preliminary effectiveness.

Description of the proposed study, or studies, and timelines for protocol submission to FDA for review, study initiation, study completion, and submission of complete study reports are to be included in the initial pediatric study plan, which is expected to be submitted within 60 days following the end of phase 2 meeting with a division or at least 210 days prior to the submission of an application for review.

Agreement by the FDA to these initial pediatric study plans is required to be in place before a new drug or biologics licensing application is submitted; otherwise, FDA can refuse to file the application.

The data from the pediatric studies are expected to be included as part of the initial application, but more likely planned requests for

deferrals are proposed and the study included in the pediatric study plan actually becomes a postmarketing requirement, as approval of the application for the adult indication is generally imminent, and there's certainly no intent on the part of the FDA to delay approval of and access to an effective adult cancer therapy.

Effectively, the requirement for early pediatric investigation, due to the amendments to PREA, has changed from the adult clinical indication for which a drug is being developed to the molecular mechanism of action of the drug. Importantly, the exemption from pediatric studies of drugs for which orphan designation has been granted has now been eliminated for targeted oncology products. Thus, RACE for Children Act finally brings equity to children with cancer.

RACE has clearly altered the regulatory landscape for cancer drug development for children by beginning to address the inexcusable gap in the timeline from first-in-human studies to first-in-children studies currently greater than

six years on average, with the expectation that the timeline from approval of an appropriate drug in adults, through its demonstration of safe and effective use and children, can and will also be shortened.

The RACE for Children Act has had a major impact globally given the global nature of cancer drug development in general, but particularly in children, and the expanding requirement in the U.S. and EU for pediatric investigations based on mechanism of action of drug products rather than the clinical indication in adults for which drugs are being developed.

As well, increasing acceptance of tissue agnostic drug development paradigms across not only clinical cancer diagnoses but across age groups, including children; the challenge to clinical trial conduct in small patient populations and increasing requirements for international clinical trial collaboration; increasing alignment of regulatory requirements for pediatric study plans in the U.S. and pediatric investigation plans in the EU, have

contributed to the global impact of the RACE for Children Act.

Since full implementation of the RACE for Children Act, the FDA has agreed to the planned or ongoing pediatric investigations described in the initial pediatric study plan, submitted to the agency in advance of the initial applications for new molecular entities or new active ingredients, relevant to the growth of one or more cancers that occur in children in 70 percent of submissions.

Just to give some idea of where or how the RACE for Children Act has impacted pediatric drug development, in 2021, 86 percent of approved new molecular entities for cancer, directed at relevant molecular targets, are being studied in children or have plans included in postmarketing requirements for pediatric studies. This contrasts with experience in 2020, wherein 44 percent of NMEs directed at relevant targets included plans for pediatric development, and only 14 percent the year before that.

The fact that a new drug is directed at a

molecular target relevant to a pediatric cancer, considerations for planned requests for waivers of pediatric investigations exist and are detailed in FDA's FDARA implementation and guidance, and include both full or age-associated partial waivers for drug products and biologics known or highly anticipated to be associated with significant developmental toxicities; as well as in situations where the development of age-appropriate formulations of drug products is not possible, thereby precluding some age groups, particularly among young children who aren't able to safely and effectively be dosed using available formulations, specifically solid tablet or capsule dosage forms.

However, the immediately evident and anticipated, yet totally unintended, problem for which waiver considerations are critical relates to the conundrum of too many drugs, specifically same-in-class drugs, for required testing, when there are too few patients in which to test them. The issue clearly begs the question of the utility, practicality and feasibility, and most importantly,

the clinical and scientific justification for required early pediatric investigations of multiple same-in-class products.

I don't believe that the immensity of the problem was contemplated. At the time, we were developing the guidance for industry on the implementation of the RACE for Children Act, but the extent to which the development of targeted TKIs to the same genomic aberrations or pathways; the redundancy of antibody drug conjugate development; and the supersaturated efforts in the immuno-oncology space, particularly in immune checkpoint inhibitors, has created an unprecedented number of overlapping and competitive development plans for many adult cancers, and clearly a potential challenge to realizing and sustaining the benefit to pediatric patients with cancer of the amended PREA provisions afforded by Section 504 of FDARA.

The importance of this piece of legislation has formed the overarching philosophy that has guided its patient-centric implementation, and

considerations of patient benefit remain the essential factor in decision making as to plans for waiver requests for early pediatric investigations.

The timelines for submission of initial pediatric study plans, and for which decisions must be made in advance of a planned new drug or biologic license in the application, make it difficult to recognize or fully appreciate what may be perceived by some as an undue burden on the company or applicant who leads development with a first-in-class targeted agent.

We feel that there's no reason to suggest that the company who leads the development in the field of multiple same-in-class agents is being penalized intentionally because of the requirement to conduct a limited pediatric investigation of what could be an effective new drug for children with cancer. It has clearly limited potential benefit to patients in merely duplicating a study of new drugs with the same mechanism of action to determine dosing tolerability and single activity unless there is a scientifically sound reason for

doing so.

The extent to which companies developing same-in-class products might discuss and compare the relative attributes of their products in a non-competitive space to reach agreement about which of their products might be most appropriate for early and limited pediatric investigation could be considered.

An industry-initiated platform in the outcome of its deliberations with the decision and commitment to which of their products might be the most appropriate for early pediatric studies could inform FDA decision making at the time of our review of initial pediatric study plans regarding considerations for planned waivers of pediatric studies of multiple same-in-class products.

Clearly, any strategies to delay development of a novel agent so as to not represent the first-in-class product, simply to avoid the requirement for a limited early pediatric investigation, would not constitute a preferred practice, and clearly would not best serve the best

interests of cancer patients, both adult and children.

Since August 2020, FDA has agreed to plans for full waivers of pediatric investigations of same-in-class products, despite the fact that these products are directed at relevant molecular targets. The agency's guidance for industry on implementation of FDARA Section 504 and the amendments to 505(b) of the FD&C Act has attempted to address this problem, citing waiver consideration, specifically for same-in-class agents and those with identical mechanisms of action, when competing studies in the pediatric population are being or have been conducted, and when there's no convincing evidence that the new active ingredient would provide a superior pharmacologic toxicity or activity profile when compared to products with the same molecular mechanism of action already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation; or when a drug or drugs

with the same mechanism of action, directed at the same molecular target, expressed in the same cancers in children, have already failed to demonstrate evidence of activity.

The agency's guidance, as I mentioned, has provided some information, but we would therefore like to discuss with the committee an approach to be more consistent or develop a more consistent framework for decision making, based on a set of critical variables and their individual and collective importance, and consider how available information on such variables of same-in-class products can best be included by sponsors in their initial pediatric study plans to enable a more objective approach to decisions regarding planned waiver requests.

As I mentioned previously, we have included in this discussion colleagues from the European Medicines Agency and the pediatric committee to align, to the extent possible, the criteria used to reach decisions regarding planned waivers of same-in-class products included in pediatric

investigation plans and in pediatric study plans, recognizing that the timelines for which information is to be included and the timelines for which decisions are made with respect to acceptance of PIPs and pediatric study plans are very different.

Variables that we've selected to consider -- and there's no suggestion that this is a complete list -- include any evidence of differences in clinical activity in adults, recognizing that data may be limited, and possibly in children, where data may be expected to even be more limited, and the specific cancer types in which any differences may have been demonstrated.

Equally important to efficacy is the relative difference in toxicity profiles of same-in-class agents or the demonstration in a specific product of specific toxicities in adults that may portend exaggerated risks for children. Relative differences in nonclinical activity, as far as effectiveness, as well as toxicity, of different same-in-class agents might also help

inform decisions related to which, if any, of multiple same-in-class drugs warrant investigation.

Important differences in pharmacologic parameters, including absorption, bioavailability, age-dependent metabolism, and clearance differences, as well as specific product attributes, including dosage forms, route, and schedule of administration, may prove useful in decisions about the need to investigate more than one product and same in class.

I would like to clarify that our objective today is not to focus on prioritization of same-in-class products for definitive pediatric development within the context of a single or multiple specific cancer diagnosis. Other processes and platforms exist for this purpose.

Although the principles to be considered may be generally similar, the timelines by which decisions are required to be made, dictated by the agreement with an initial pediatric study plan, and whether an application for a new drug for a specific adult indication is suitable for filing,

preclude decisions that may impact later stage or definitive pediatric development. It should be pointed out, however, that initial pediatric study plans with commitments through required early investigations can be amended should emerging science suggests that a potentially superior alternate or next-generation molecular entity is available.

We emphasize the importance of providing guidance to industry and clinical investigators, as well as to patients and advocates, but that doing so requires consistency and transparency and is better codified when feasible to avoid purely subjective or less than well-informed decisions.

I want to stress again that the fact that we are undertaking this effort is with a primary focus on patients, and to assure that FDA fairly and optimally exercises the important authorities that have been provided by the amended PREA provisions to benefit children with cancer. Again, we appreciate your time, your wisdom, and judgment as we create this framework, which will be codified

in a guidance and will work towards creating guidance for industry. Thank you.

DR. PAPPO: Thank you very much, Dr. Reaman.

We will now proceed to our next presentation from the FDA, from Dr. Margret Merino.

FDA Presentation – Margret Merino

DR. MERINO: Thank you, Dr. Pappo.

Good morning. This is Margret Merino, and I'm a pediatric hematologist/oncologist and clinical reviewer in the Division of Hematologic Malignancies 2 at the FDA. Our division reviews products in development for hematologic malignancies such as Hodgkin's lymphoma, indolent and aggressive non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and multiple myeloma.

To highlight the scope of the issue regarding single-class waivers and to provide some context for discussion, I'll first highlight some of the key topics just covered, and then review our division's experience with same-in-class waiver considerations for products in development for

hematologic malignancies.

As was previously mentioned, in an effort to address the inadequate early evaluation of anti-cancer agents for pediatric diseases, the Pediatric Research Equity Act, or PREA, amended by the FDA Reauthorization Act of 2017, or FDARA, requires that pediatric assessments are submitted for the original NDA or BLA, unless the requirement is waived or deferred, if the drug is intended for the treatment of an adult cancer and directed at a molecular target substantially relevant to the growth or progression to a pediatric cancer.

Importantly and relevant to the discussion of same-in-class waivers, the submission of the initial pediatric study plan, or IPST, outlining the plan for pediatric assessments should occur early in development, generally no later than 60 days after the end of phase 2 meeting. In a rapidly developing treatment landscape with multiple same-in-class agents and similar stages of development, same-in-class waiver plans and considerations are common.

It's important to highlight, again, that the requirement of the IPST is to provide data on the safety, dosing, and preliminary efficacy in pediatrics and does not require an exhaustive exploration of the agent in all potentially relevant diseases and settings.

Over the last several years, there has been rapid development of targeted agents in hematologic malignancies generally with a pattern of a first-in-class targeted agent demonstrating activity for an adult disease, with a number of next-in-class agents with the same or similar mechanism of action following shortly, often within a short time span.

While the situation of having a number of potential agents with the same or very similar mechanism of action, for the small number of pediatric patients that we typically see in pediatric diseases, can be considered a positive development, this obviously introduces challenges regarding prioritization of agents and trial feasibility considerations for pediatric studies.

To address this anticipated issue of the feasibility and appropriateness of requiring multiple pediatric studies and diseases with a limited number of patients, as outlined in the FDA guidance for industry, Section G, the Basis for Planned Waiver and Deferrals, circumstances where a waiver or deferral for pediatric studies may be appropriate for a later generation agent with an identical mechanism of action include when there are competing studies that are ongoing or have been conducted and there is no convincing evidence that the new active ingredient provides an advantage, and when a drug with the same mechanism of action directed at the same target, expressed in the same cancer and children, have failed to demonstrate evidence of activity. Some additional considerations include the assessment of an advantage, which can be due to superior pharmacologic activity with regards to efficacy and safety, and particularly important for pediatric formulation and ease of administration, as well as unique PK characteristics such as central nervous

system penetration.

Regarding whether a plan for a deferral of pediatric studies versus a plan for a waiver of pediatric studies is justified, evolving data from ongoing studies, either in adults or other pediatric studies, in same-in-class agents should be considered. This may include data regarding subpopulations such as a biomarker-positive population or new evolving data regarding safety or dosing.

Lastly, another consideration, given the importance of collaboration and cooperative group trials in pediatrics, is prioritization of same-in-class agents by cooperative groups can also be considered. Having covered that background, I'll now move on to discuss some of these considerations for some of the agents with initial pediatric study plans, including a plan to request for a same-in-class waiver or a deferral. While these examples are in the context of hematologic malignancies within our division, the concepts are applicable broadly.

I'll specifically review three classes of agents for which there are multiple products in development for hematologic malignancies: the Bruton tyrosine kinase, or BTK inhibitors, for which there are at least seven agents in development; the phosphatidylinositol 3 kinase, or PI3K inhibitors; and the anti-CD20-CD3 bispecific antibodies, or CD20 T-cell bispecifics, which there are at least four in development.

Bruton tyrosine kinase inhibitors have changed the treatment landscape significantly for adult hematologic malignancies. The first agent, ibrutinib, was initially approved in 2013, and there are currently two additional agents, acalabrutinib and zanubrutinib, approved for various hematologic indications.

Initial approvals of these agents occurred prior to the implementation of FDARA, and based on the adult indications and/or orphan designation, there were no required pediatric studies, although one agent, ibrutinib, was evaluated in a randomized study in pediatric patients with

relapsed/refractory aggressive B-cell lymphoma. The study which evaluated ibrutinib in combination with intensive chemotherapy was terminated early due to futility.

Since Bruton tyrosine kinase, which plays a key role in B-cell signaling, is considered a relevant target for pediatric B-cell lymphomas, for new agents in development post-FDARA, pediatric studies are required unless a waiver or deferral is granted.

As displayed on the table, there are four additional agents with the same or similar mechanism of action as the first-in-class agent that are in late clinical development and for which initial pediatric study plans, which have included a plan to request a waiver, have been reviewed. In general, there has been agency agreement on plans to request waivers based primarily on the previously mentioned prior study of an agent with the same mechanism of action that failed to demonstrate activity and no convincing evidence of an advantage of the next-generation agents under

consideration.

Additional considerations include the remaining uncertainty of the role in BTKis for aggressive lymphomas in adults, as these studies are ongoing, as well as the feasibility of conducting a study for this class, which is not currently prioritized by pediatric cooperative groups. And as indicated in the last column of the slide, for agents that may have potential increased CNS penetration, sponsors were required to address the relevance to pediatric CNS lymphomas in the pediatric study plan.

As mentioned earlier, there are at least nine PI3K inhibitors generally directed at the delta isoform in development for adult hematologic malignancies, with the first agent, idelalisib, initially approved in 2014, and with four same-in-class agents subsequently approved. Similar to the BTKis, the four agents that received approval did so prior to FDARA, and therefore pediatric studies were not required based on the adult indications and/or the orphan designation.

Also similar to the situation with the BTKis, one agent, copanlisib, which is an IV form, is under evaluation in a cooperative group study for pediatric patients with relapsed or refractory solid tumors and lymphomas.

It's important to mention that with regards to the PI3K inhibitors in hematologic malignancies, some of the original approval statuses have changed recently. For this presentation, I'm focusing on the considerations with regards to the initial pediatric study plans when they were submitted. Since PI3K is considered a relevant target for pediatric B-cell lymphomas and some solid tumors, for new agents in development with NDA submissions post-FDARA, pediatric studies are required once a waiver or deferral is granted.

As displayed in table 3, there are three additional agents with the same or similar mechanism of action as the first in class that are in late clinical development and in which initial pediatric study plans included a plan to request a waiver for pediatric studies. For the first agent,

the agency did not agree with a plan for a full waiver. One consideration was that this was the first post-FDARA agent, and there were no ongoing mandated pediatric studies, and the other was an oral formulation, which was considered a potential advantage in an important consideration for pediatric patients.

For subsequent agents, there has been general agreement with a plan for a waiver with ongoing negotiations. Importantly, other considerations for this class included isoform activity considerations for each agent, as this has relevance to safety and efficacy, and the important evolving safety data from adult studies and the need to consider this evolving data regarding the feasibility and interest of conducting studies in children given the safety and dose optimization concern.

Lastly, I'll discuss the CD20-CD3 T cell by specific agents, which are being developed in indolent and aggressive B-cell non-Hodgkin's lymphoma in adults. There are no currently

approved agents, however, there are at least four agents that are in late phases of development with activity demonstrated in adult studies in patients with relapsed and refractory CD20 positive lymphomas.

As these initial pediatric study plans are all being considered post-FDARA, pediatric studies are required unless a waiver or deferral is granted since CD20 is considered a relevant target for pediatric B-cell lymphomas. Importantly, this class of agents has been prioritized by the pediatric ACCELERATE group for inclusion in a future platform study in pediatric patients with relapsed or refractory B-cell lymphoma.

An important safety concern identified early in the adult studies the cytokine release syndrome with initial dosing, and this has required dose optimization to assure safety and mitigate potentially severe and life-threatening cytokine release syndrome. Initial proposals for pediatric study plans included plans to request a deferral for pediatric studies pending selection of an agent

for the platform study, as well as plans for deferrals, pending additional safety data in adults.

The agency did not agree with the plan to request a deferral pending the platform study, as the study was outside of the sponsor's control, was not a mandated study, and the timeline was uncertain. Therefore, the initial pediatric study plan should include a plan for studies in pediatric patients with relapsed or refractory B-cell lymphomas. For some products, the agency did agree with the plan for a deferral until additional safety data was obtained in adults to obtain dosing.

Considerations for these products included the platform study, which I'll cover in the next slide, as well as the safety considerations, and were individually evaluated for each product, considering the available data and the need to further optimize the dosing strategies. Another consideration with this class was the need to obtain monotherapy data on dosing and safety in

pediatrics either prior to or parallel to combination study evaluation. For this class, discussions that included the FDA, as well as other regulatory authorities, conducted through several formats to facilitate alignment in the required pediatric studies when feasible, were conducted.

Finally, I'd like to briefly review further some considerations regarding platform studies or cooperative group studies as related to initial pediatric study plans, given the importance of these studies in pediatric oncology.

A platform or cooperative group study may be included in an initial pediatric study plan and collaboration with cooperative groups is encouraged early in the developmental process. However, potential inclusion of an agent, or another same-in-class agent in a future planned cooperative group study, may not be sufficient to justify a plan for a waiver or deferral, as the responsibility for submitting the pediatric assessments, unless a waiver or deferral is granted, lies with the sponsor. In cases where a

cooperative or platform study is ongoing, and the agent has been selected and is in evaluation, this scenario could be considered as meeting the requirement for pediatric assessments or justification for a plan for a waiver or deferral.

In summary, based on the development landscape for hematologic malignancies and our division's experience to date, plans to request waivers for same-in-class products are common and are likely to continue. Early coordination and cooperative group considerations are key, but they cannot be relied upon solely, as ultimately it is the sponsor's responsibility to conduct pediatric studies unless a waiver or deferral is granted. Regulatory body alignment, when feasible, should be pursued, and prioritization of same-in-class agents will be an ongoing challenge and should be guided by science, but will be influenced by timing.

Although there will be circumstances where plans for waivers for same-in-class agents are appropriate, for agents that are early in development, given the rapidly developing treatment

landscape and evolving data, a deferral versus a waiver may be a preferred approach.

Thank you for your attention, and I will now turn it back over to Dr. Pappo.

DR. PAPPO: Thank you very much, Dr. Merino, for an excellent presentation.

We will not proceed with our guest speaker presentation by Dr. Dominik Karres.

Dominik?

Guest Speaker Presentation – Dominik Karres

DR. KARRES: Thank you very much, Dr. Pappo, and thank you very much to the FDA for the kind invitation to present EMA/PDCO's general considerations on waiving requirements for pediatric investigation plans for same-in-class products.

My name is Dominik Karres, and I'm a scientific officer in the Paediatric Medicines Office, and my clinical background is in pediatric oncology. This is my usual disclaimer. I'll give you a short regulatory background introduction leading to the challenges we face and an outline of

our current approach, including practical considerations on this issue before concluding.

The objective of the EU pediatric regulations is to stimulate timely development of better medicines for children based on ethical research of high quality and to ultimately increase the availability of appropriately authorized medicines through pediatric investigation plans, so-called PIPs agreed by the European Medicines Agency's pediatric community, the PDCO.

PIPs summarized the agreed quality nonclinical and clinical measures considered necessary to generate the data to allow conclusion on benefit-risk in the intended target population. The scope of the PIPs is framed by an overarching condition wording, which needs to cover the adult and pediatric target indication with tools like deferrals, modifications, and waivers available to ensure timely evidence generation while allowing refocus of development efforts based on emerging evidence and potential changing needs over time.

It is clearly acknowledged from our site

that rarity of pediatric cancer types make it challenging to complete a pediatric program in a setting with multiple same-in-class products. The two key challenges are, first, how to foster development approaches globally able to best and timely address high unmet medical needs based on robust evidence; and secondly, how to identify the most promising agent for timely initiation of a development effort in the most appropriate target population without discarding, actually, valuable candidates prematurely, but to ensure data generation to support developments for the most promising product or products able to offer significant therapeutic benefit to patients in need.

To achieve this objective to ultimately increasing the availability of pediatric medicines, the current regulatory strategy from the EMA's PDCO is to ensure they are using all available regulatory tools -- deferrals, modifications, waivers -- as I've mentioned, and taking into account for progress of science such that

scientific evidence generation leads to evolving insights and prompts modifications of hypotheses and expectations; and that means to acknowledge that optimal development efforts based on scientific data may lead to same-in-class products being initially subject to equal obligations.

Having said that, having several PIPs for same-in-class products agreed, there's no expectation that all agreed PIPs will necessarily start at the same time or be all completed.

So our regulate-free strategy is allowing for additional evidence generation as needed to support decision making, allowing for involving repeated cycles of evidence considerations as necessary to really be revisited in collaboration with stakeholders, and also empowering patients, parents, and investigators, including corporate groups, to lead and participate the discussions on evidence considerations among multiple, sometimes initially competing, requests for development efforts, acknowledging, again, that the extra responsibility is with the marketing authorization

holder.

To be very clear, this does not mean delaying the agreement of regulatory development obligations until supporting evidence becomes available to allow final decision making. To the contrary, it means to engage early to really fulfill the objective of the pediatric regulation, which is to ensure timely access to novel agents for patients with high unmet medical needs, but also providing predictability in terms of necessary global development requirements in that regard.

Coming to practical considerations, agreeing that product-specific waivers needs to be based on one of the three existing legal grounds: disease not occurring, which I will not touch on today; lack of safety or efficacy and lack of significant therapeutic benefit. If no strong supportive evidence is available at state of initial submission, a full waiver averse approach is usually taken, with additional evidence requested to be generated as part of an agreed PIP; for example, by means of additional nonclinical

data to further support decision making on a product's ability to address high unmet medical needs.

I would now like to go through some examples. Some have already been mentioned or will further be discussed in subsequent presentations. So I will not spend much time on it. But to exemplify, PDCO granted full waivers for individual products within certain classes for dedicated conditions such as PI3 kinase inhibitors for mature B-cell malignancies, sonic hedgehog inhibitors for AML, or kinase inhibitors for benign soft-tissue neoplasms based on safety considerations through generated nonclinical and/or clinical data, including data from adults.

Of note, it's here that the actual rate of grounds might not necessarily then be based on safety, but the safety considerations and context of the potential added benefit, and existing unmet medical needs essentially supporting the grounds of lack of significant therapeutic benefit.

Similarly, the PDCO grants its

product-specific labels for individual products of certain classes based on lack of efficacy such as checkpoint inhibitors for solid tumors, excluding melanoma; products targeting BCMA for treatment of mature B-cell malignancies; or Bruton tyrosine kinase inhibitors, again, for treatment of mature B-cell malignancies; similar to the previous examples, based on nonclinical or clinical data generated within a PIP, leading to the necessary evidence supporting final regulatory decision making in that regard.

As I mentioned, what are considerations which might constitute significant therapeutic benefit or lack thereof, that, for example, could be, in addition to the examples I've mentioned related to quality considerations -- and my colleague, Dr. Wang, will talk about that in her presentation later today -- but also, for example, improved activity over standard of care shown by either extrapolation of adult data, if biologically relevant, or relevant nonclinical data, and better target organ penetration; for example, the ability

of a product to be more suitable for combination developments. I would like to point out that this is a non-exhaustive list, but just being examples for consideration in that regard.

To finalize the series of examples with some general reflections, I would like to emphasize that regulation decision making is for each individual product on its own merits based on the robustness and the rigor of the available and contextualized evidence submitted, allowing for development to be initiated timely, generating evidence with prespecified decision points agreed to re-evaluate the cumulative evidence to support modifications of obligations, including the potential for agreed requirements to be lifted.

To conclude, very generally, the EMA's pediatric committee has taken a waiver averse approach, waiving PIP requirements early only when there is sound and convincing scientific evidence in support of one of the three waiver grounds, as I've outlined. The focus of the committee is the patients, with the objective to bring development

efforts together into one arena -- in a pre-competitive space, if you will -- to allow for timely and refocused collaborative evidence generation effort according to emerging needs.

I would like to emphasize that a PIP is not an isolated regulatory requirement, it's not a protocol, but it's a plan that can be modified in light of emerging science, which means it can also be closed, as I've indicated and show in my examples. Very clearly, early interactions with regulators are key in order to reach our common objective together.

Finally, and to close, I would like to thank the FDA once again for this very kind invitation, as I believe collaboration is key to support reaching our common goal, bringing the right drug to the right patient at the right time as early as possible, and from a PIP perspective, to generate the data necessary for a pediatric indication.

Discussing conceptual framework considerations potentially able to support waiving

regulatory requirements of same-in-class products at the right time is an important aspect of our common objective, while appreciating the different regulatory frameworks governing our decision making, so we really appreciate today's discussion. And with that, I would like to thank colleagues and close my presentation. Thank you.

DR. PAPPO: Thank you very much, Dr. Karres.

We will now proceed to our next FDA presentation from Dr. Haleh Saber.

FDA Presentation – Haleh Saber

DR. SABER: Good morning. I'm Haleh Saber, deputy director in the Division of Hematology Oncology Toxicology and the Office of Oncologic Diseases at the FDA. Our group reviews pharmacology and toxicology data submitted to INDs and marketing applications.

This presentation is on the use of nonclinical studies in making decisions about pediatric studies, and during my talk, I will use the term "drug" to refer to both small-molecule

drugs, as well as biologics.

Here is the outline of my presentation. I will go over nonclinical studies recommended in support of adult and pediatric cancers. I will then discuss nonclinical studies to guide and in decision making on pediatric studies when multiple drugs are available against the same target.

This slide shows an overview of nonclinical studies in support of first-in-human studies. Recommendations in nonclinical studies in oncology drug development are described in ICH S9 and ICH S9 Questions and Answers. Often when an IND is submitted, it's initially for an adult indication, or it's for both adult and pediatric populations, with pediatric studies being a few cohorts behind adult studies.

Nonclinical studies in the IND include pharmacology studies to evaluate the mechanism of action and binding in anti-tumor activities of a drug. The IND will also include results of general toxicology studies and pharmacokinetic data, such as systemic exposure and a half-life of a drug. PK

data are usually incorporated into the design of toxicology studies. General toxicology studies are conducted in animals to assist drug-induced toxicities and can assist in patient monitoring. They can also assist in selecting a first-in-human dose.

As mentioned earlier, pediatric studies often fall behind studies in adult patients, and nonclinical studies described in the previous slide have been conducted. Additional nonclinical studies in support of pediatric indications may include proof-of-concept pharmacology studies to show that the drug has activity in pediatric models of the disease and appropriate cell lines. Pharmacology studies can also evaluate schedule-dependent effects of the drug for an optimal trial design and could also contain arms of approved drugs such as drugs against the same target or for the same disease.

Safety of a drug in children is evaluated through an integrated risk assessment based on the totality of data. The risk assessment will include

safety data from adult patients, safety data from nonclinical studies conducted in support of studies in adult patients, and safety assessment based on the mode of action of the drug and the pathway that is being inhibited; and this latter can include information from published articles.

When multiple drugs are available against the same target, comparative pharmacology studies can assist in deciding whether study in pediatric patients is warranted. I will expand on this a little bit more in the next slide. Comparative binding studies are typically in vitro studies and comparative activity is usually in vitro and in vivo studies. Additional comparative data may be also needed as applicable, such as comparative pharmacokinetic data.

To better describe the importance of comparative studies, I'm providing two examples on this slide. Starting with the example on the left, an IND has been submitted for an investigational drug, which is an IgG4 antibody called mAb1. Nonclinical studies in support of adult indications

have been conducted, and data in adult patients are available with mAb1.

Two other IgG4 antibodies -- mAb2 and mAb3 -- against the same target were previously approved and their data in adults and children with mAb2 and mAb3. MAb2 and mAb3 had no activity in the pediatric cancer of interest. The sponsor has conducted comparative pharmacology studies comparing mAb1 to mAb2 and mAb3, which indicate the products are comparable. Using these data and other relevant data, the clinical team may decide that a study in that specific pediatric cancer is not warranted.

In the other example on the right, the investigational product, mAb1, is an IgG1 antibody, and comparative studies showed differences in the activities between mAb1 and the other two approved products, with mAb1 being more potent than mAb2 and mAb3. In this case, the clinical team may decide that the study in children is indeed warranted.

This concludes my presentation on nonclinical studies, and I will turn it over to

Dr. Pappo.

DR. PAPPO: Thank you very much for your excellent presentation, Dr. Saber.

We will now proceed to our next guest speaker presentation from Ms. Karen van Malderen.

Guest Speaker Presentation – Karen van Malderen

MS. VAN MALDEREN: Hello, and thank you for giving us the opportunity to present here today. I'm Karen van Malderen. I'm a nonclinical assessor at the Belgian Medicines Agency. I have a background in toxicology, and I'm also at the paediatric committee at EMA and at the nonclinical working party of the EMA.

As an introduction, the nonclinical data that we usually have in oncology PIPs or waiver requests, as has been partially covered by the previous speaker, are pharmacodynamic data, as said before, and safety pharmacology data; and those endpoints are usually included in the general toxicology studies.

We have pharmacokinetic data and data from repeat-dose toxicity studies in animals, which

allow us to have an idea of the target organs of the drug and the reversibility or irreversibility of the effect. Sometimes we have limited data from reproduction tox studies or genotox studies, as not all of these studies are considered essential to support trials for patients with advanced cancer.

Based on these data, the applicant, and we as a regulator as well, we make an assessment of what concerns there could potentially be for using this product in the pediatric population, and those can be different from concerns expected or known in the adult population.

As shown in the figure, you see the age-dependent development of the major human organ systems, and you can see that the younger you go in age, the more organ systems are still undergoing critical development, and that can be structural or functional. So the younger in age, the more likely that there may be a different sensitivity to the toxicity of the product or that novel toxicities could occur.

The immaturity of organ systems during drug

treatment can also affect the pharmacokinetics or the pharmacodynamics, and also off-target effects of pharmaceuticals, which may potentially lead to differences in safety or efficacy profiles between the pediatric population when compared to adults.

I'm focusing here today on the safety aspect. When we assess product-specific waivers based on the grounds of lack of safety, this is, in fact, an integrated assessment based on the totality of the evidence, and that includes the clinical context together with the pharmacology, pharmacokinetics, and nonclinical and clinical safety data that are available that can be in adults or in children. But with respect to the nonclinical data in adult animals or in juvenile animals, data generated with the compound or with the same-class compounds.

Generally, we consider that a single factor should not be considered in isolation, and we also consider that with respect to nonclinical data, that also the translatability and the biological relevance of findings in nonclinical studies should

be considered; so what is the clinical relevance? In addition, we also have a look at the other specific factors such as risk mitigation.

If strong data are not available or lead to a conclusion that this would be sufficient to conclude that there is a lack of safety, then at EMA, we are likely to take a waiver averse approach, and we then request more evidence to be generated; for instance, an additional nonclinical study to support further decision making. But the outcome of this assessment with regard to waiver request can be reassessed if there are new safety signals in nonclinical or clinical studies, or changes in drug formulation or indication.

To illustrate this, I have collected some examples with respect to requests for safety-based waivers. The first example was a CSF 1 receptor inhibitor for the treatment of tenosynovial giant cell tumors. The applicant here requested a full waiver and received a full waiver with the population from birth to prepubertal children, having a waiver on the grounds of lack of safety.

The basis for that was the observation of adverse effects observed in rodent studies that were relevant to organs undergoing development in the target population.

The targeted receptor had a known role also during postnatal development. There was existing standard of care, and there was also a full waiver granted already for a same-in-class product, although in a different condition, but also based on safety concerns.

The second example concerns a multi-tyrosine kinase inhibitor which was proposed for the treatment of soft tissue sarcomas and Ewing sarcoma. The applicant requested a waiver below the age of 12 years for lack of safety, based mainly on the nonclinical profile of the drug and the mode of action, and concerns known for other TKI inhibitors. And indeed, based on the nonclinical data, effects on several developing organs were expected based on the mode of action and off-target effects.

However, tyrosine kinases inhibited by

different TKI inhibitors vary, and also their potency varies, so making the bridge to the other compounds was not so obvious in our view here. Also, waivers for some of these same-in-class products were granted, but only in the youngest age range, not up to 12 years, and these were specifically supported by lack of tolerability in juvenile animal tox studies.

Here, the outcome of the PDCO discussion was that, for now, no waiver would be granted, but a deferral and further nonclinical studies were requested to generate additional evidence supporting either development in the youngest or a waiver if further concerns would appear in the data that would still be generated.

The next example was the smoothened hedgehog inhibitor for a treatment of AML in children 2 to 18 years. The applicant here proposed development in this population, however, we rendered a full waiver on the grounds that this specific product was likely to be unsafe in children from birth to closure of the epiphysis,

and that was based on preclinical, irreversible adverse effects complemented with clinical data available for same products in this class.

The first example was a RET inhibitor, where the initial PIP proposed the development from 6 months onward in patients with RET-altered, locally advanced or metastatic solid tumors, or primary CNS tumors. When we approved the initial PIP, several nonclinical tox studies were still planned by the sponsor, and there was one clinical study planned in the whole age range from 6 months to less than 18 years.

At a later stage, however, a modification was submitted, and a staggered development was agreed below the age of 12 years based on no nonclinical data that indicated a lack of tolerability at clinically relevant exposure levels. These emerging nonclinical data showing lack of tolerability were different from the data we had seen at the initial PIP.

The final example was an NK1 receptor antagonist, where the initial PIP was proposed for

the prevention of chemotherapy-induced nausea and vomiting from 6 months to less than 18 years, and was also agreed. However, at a later stage, this plan was modified into a full waiver for all subsets on the grounds that the product is likely to be unsafe based on new nonclinical data, indicating irreversible adverse findings to organs under development and also in combination with the availability of other compounds in this class with a less severe tox profile.

In conclusion, when we make such regulatory decisions, it's based on the robustness in all the data of the available scientific evidence for each individual product, based on the old nonclinical data from the compound itself or from the same class of compounds, taking into account the maturation of the organ systems that can be literature-based, or also from actual data, and also to have an understanding of the overall clinical development plan and experience from same-class products. As clinical development progresses, adjustments to the plan can be made

based on the available data at that time, and the decision can be different for different applications of the same drug product, depending on the target population.

Data from compounds of the same class can certainly be useful and support waiver requests, however, some cautiousness is needed, especially if there may be differences between the receptors targeted or the potency to these receptors, such as multi-TKIs as shown in the example, and also for these products, unexpected toxicity. Toxicities not related to primary pharmacology have occurred, so some cautiousness is warranted for extrapolating safety data within the same class there.

Finally, waiving the PIP requirement early should only be based on sound scientific justifications, as shown by the examples. However, when serious safety concerns arise in nonclinical data, waivers are usually requested for the youngest patient population as a result. However, medical needs are often high there, so, ideally, more efforts should be undertaken to understand the

clinical relevance of such known clinical findings. For instance, when the reason for novel findings or an increased sensitivity and toxicity is not understood, additional mechanistic investigations could be useful to help interpret these differences and support the need, or not, for a waiver. Thank you.

DR. PAPPO: Thank you very much for your presentation, Ms. van Malderen.

We will now go on to the last FDA presentation of the morning from Dr. Stacy Shord, followed by Dr. Elizabeth Duke.

FDA Presentation – Stacy Shord

DR. SHORD: Good morning, and thank you for this opportunity. My name is Stacy Shord, and I'm a clinical oncology pharmacist in the Division of Cancer Pharmacology II. The Division of Cancer Pharmacology II reviews the clinical pharmacology information for products being developed for solid tumors.

This morning, I will be discussing some clinical pharmacology considerations for

same-in-class products. Briefly, I will discuss the following: what physiological differences are observed between adult and pediatric patients or between different pediatric age groups; what factors should be considered when selecting a dosage form for the relevant pediatric age groups; and how a dosing regimen for pediatric patients can be identified, with the aim of generating discussion on how the clinical pharmacology of a drug can form a pediatric development plan for same-in-class products.

Multiple physiological differences have been observed in pediatric patients that can cause observable differences in drug absorption, distribution, and elimination between adult and pediatric patients and across pediatric age groups, such as infants, children, and adolescents. As an example, gastric pH is initially higher in younger pediatric patients compared to that of adults, as noted by the red columns.

With higher gastric pH, the oral absorption of drugs, classified as wheat basis, with low

intrinsic solubility would likely decrease, which could negatively alter effectiveness. Wheat-based drugs that have both pediatric and adult indications include dasatinib for CML, crizotinib for non-small cell lung cancer in adults, and ALCL in pediatric patients. As another example, hepatic metabolism is typically less for younger pediatric patients compared to older pediatric patients as observed on the next slide.

This graphic shows the relative expression of human hepatic cytochrome P450 enzymes in pediatric patients to that of adults on the Y-axis, with age on the X-axis. CYP3A4 is the most abundant CYP subfamily, and it is responsible for metabolism in about 50 percent of currently marketed drugs.

This graphic suggests that CYP3A4 levels drawn as the black line, in pediatrics age 5 years and older, is similar in value to that of adults. Reduced metabolism in younger pediatric patients may have a clinically meaningful effect on safety, allowing the parent drug to accumulate for

effectiveness by minimizing the formation of active metabolites.

As an example, midazolam is a sensitive CYP3A4 substrate. It undergoes extensive metabolism to major active metabolites, and its oral clearance is markedly decreased in preterm infants as compared to that of other pediatric patients, probably due to immature CYP3A4 activity. Alternative dosage recommendations are available for the neonates.

These physiological changes that affect absorption, distribution, and elimination can alter the pharmacokinetics of the drug. This graphic shows a possible relationship between drug exposure and safety, the red curve, and efficacy, the blue curve. As noted by the dashed gray and black vertical lines on this graphic, changes in drug exposure can alter the safety or effectiveness of the drug. These physiological changes could also affect the impact of food, other drugs, and organ impairment on drug exposure.

This table compares five drugs that inhibit

the same target. Drug A was approved for the treatment of an oncologic diseases in pediatric patients. The remaining drugs were being developed in adult patients. These drugs showed marked differences in the proposed dosing interval, administration relative to food, and doses modifications for organ impairment and drug interactions.

Therefore, it is important to consider how food, other drugs, and organ impairment impacts drug exposure in the relevant pediatric age groups compared to that of adults, based on physiological differences. It is also important to consider how these differences affect administration of the drug product to the relevant pediatric age groups, as shown on the next slide.

When considering whether to develop these four remaining drugs in pediatrics, the following questions could be considered. Will pediatric patients prefer to take the drug once or twice daily? Will pediatric patients be able to take the drug with food? Will pediatric patients have

underlying renal or hepatic impairment? Will pediatric patients be taking other drugs that may interact with these drugs?

These drugs may be taken to manage comorbid illnesses, adverse reactions, and other items. By addressing these questions and considering the impact of the physiological differences on drug exposure, an assessment could be made whether one or more of these remaining drugs pose a potential advantage to pediatric patients compared to drug A.

When developing a drug for pediatric patients, it is also important to consider the dosage form. Multiple dosage forms are possible with some of the dosage forms calmly administered to pediatric patients listed here, however, the most appropriate dosage forms depends on the relevant pediatric age group. For example, for pediatric patients less than 5 years old, liquid dosage forms, rather than solid dosage forms, may be preferred for oral use, given younger pediatric patients typically cannot swallow an intact solid dosage form. Other factors such as taste and

appearance may also affect acceptability of dosage forms for relevant pediatric age groups.

The next two slides show two drugs with different approaches to evaluating a drug in pediatric patients. For this example, it is important to determine if the approved drug product can be administered to relevant pediatric age groups likely to be enrolled in the trial and if the dosage form and strength could accommodate the recommended dosage and doses modifications for adverse reactions, drug interactions, and organ impairment in the relevant pediatric age groups.

For this drug product, the labeling states that pediatric patients must be able to swallow intact capsules and that the dosage is not available for pediatrics with a body surface area less than 0.6 meter squared. Of note, a body surface area of 0.6 meter squared typically is associated with pediatrics weighing about 14 kilograms.

When developing a drug in pediatric patients with solid dosage forms, addressing these

questions can help inform the pediatric development plan.

Can the approved drug product be administered to pediatric age groups likely to be enrolled in a trial? Can the dosage form and strength accommodate the recommended dosage and dosage modification for adverse reactions, drug interactions, and organ impairment in pediatric patients? For this example, the pediatric patients to be evaluated in the clinical trials could not typically swallow an intact capsule. An investigational drug product was made to support the clinical trials.

This additional question can help inform the pediatric development plan. Is an alternative dosage form or route of administration that is appropriate for pediatric age groups likely to be enrolled in a trial if needed?

If a new dosage form, or alternative route or method of administration, will be used to support pediatric development, additional studies such as those listed here may be needed before the

new dosage forms, strength, or alternative administration is implemented in clinical trials.

The final two slides provide a summary of the pediatric study plan design and points to consider as detailed in the guidance for industry, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. The information detailed in this guidance could be considered when evaluating pediatric development plans for same-in-class products.

As example, selecting an appropriate dosage range to be studied is important to subsequently be able to provide rational dose recommendations for pediatric patients. In general, possible approaches to identify a dose in pediatric patients include separate studies in pediatric patients and relevant age groups, or PK studies in pediatrics to determine how the dosing regimen should be adjusted to achieve the same level of systemic exposure in adults.

When determining the most appropriate

approach to identifying the dosage for pediatric trials, factors that may be considered are listed here, including disease biology; exposure or dose-response relationships for safety and effectiveness; dosing based on body size; growth and developmental changes that affect pharmacokinetics; and adverse reactions specific to pediatric patients.

Possible approaches to pediatric studies include extrapolation or separate approaches. Extrapolation is appropriate when pediatric patients have similar disease progression, treatment response, and exposure response to that of adult patients, and that the drug exposure is measurable and predictive of response.

Comparatively, a separate approach is appropriate when disease progression or treatment response is unique to pediatric patients as compared to that of adults. For this approach, clinical studies are designed to provide substantial evidence of safety and effectiveness and characterize the PK and exposure-response

relationships in pediatric patients.

This table provides examples that show when the indication was extrapolated to pediatric patients from adults on the left-hand side of the table, and when the indication was based on results from studies that included pediatric patients on the right-hand side of the table.

This slide lists some questions that may be considered when determining whether an extrapolation or separate development plan may be warranted, including, is the disease biology anticipated to be the same in pediatrics and adults; is the response to the drug anticipated to be the same in pediatrics and adults; is the pharmacokinetics anticipated to be the same; and lastly, are additional adverse reactions anticipated in pediatrics compared to adults; as examples, bone, dental, or other effects on growth and development?

Whether extrapolation or a separate development would be an appropriate approach may be an important consideration when assessing the

pediatric development plan for a same-in-class product.

In conclusion, it may be appropriate to consider evaluating the following items: relevant pediatric age groups; possible physiological differences in the relevant age groups that may impact drug exposure and how food, organ impairment, and other drugs impact exposure; availability of an acceptable dosage form and strength that can be administered to the relevant pediatric age groups within an appropriate dose range; and lastly, the most appropriate approach for identifying the dosage to be studied, establishing the safety and effectiveness and characterizing the drug exposure and the relevant pediatric age groups. When assessing the pediatric drug development plan, some same-in-class products may have clinical pharmacology characteristics that support their development.

With that, I want to just acknowledge a few individuals who helped with their time and support. Thank you again.

DR. PAPPO: Dr. Duke, you're next.

FDA Presentation – Elizabeth Duke

DR. DUKE: Good morning. Thank you, Dr. Pappo.

My name is Elizabeth Duke. I'm a pediatric neuro-oncologist in the Division of Oncology 2, where we review brain tumors, pediatric solid tumors, and other rare tumor submissions. Today I'll be discussing central nervous system penetration and pediatric brain tumor considerations for same-in-class products.

Different drugs, even those within the same class, have varying levels of activity in the central nervous system, or CNS, which includes the brain and the spinal cord. This issue is multifactorial and important to consider in our discussion of the criteria to grant waivers of pediatric evaluation for same-in-class molecularly targeted agents.

Today, I'll discuss several aspects of pharmacokinetics as they relate to the CNS: the role of the blood-brain barrier and its

complexities, followed by a discussion of how CNS penetrance can be measured, and provide some conclusions.

There are several examples in oncology in which same-in-class products have different levels of activity within the central nervous system. This table was published in the Clinical Cancer Research journal. The four drugs listed in bold are different oral eGFR tyrosine kinase inhibitors or TKIs. The box in red highlights the ratio of the peak drug concentration observed in the brain compared to the blood, and this ratio is one of the tools we have to estimate the CNS pharmacokinetics of various drugs, with higher values suggesting higher CNS concentrations. As you can see, the ratio varies widely across the four drugs even though they're in the same class.

Why is this an important issue to discuss today? There's a significant unmet medical need for children with malignant brain and spinal tumors, and new safe and effective therapies are needed for this population. Waiving the study of a

same-in-class drug that has improved activity in the CNS may be a missed opportunity for those patients.

To date, the efficacy of anti-cancer agents at the site of the CNS has been limited by challenges with drug delivery, adequate exposure, and dosing requirements needed to achieve efficacy. These parameters may differ from other sites in the body. So to better understand what we really mean by CNS penetrance, I'll focus on pharmacokinetics as it relates to the CNS.

Pharmacokinetics in general is the branch of pharmacology dedicated to the understanding of what the body does to a drug as it passes through four phases. First is absorption, the rate and extent of drug appearance at a target site; in this case, the brain. This is highly dependent on the route of administration such as intravenous, oral, intraventricular, intrathecal, as well as aspects of the drug substance itself. In general, to enter the CNS, drugs must be small, highly lipid soluble, and positively charged.

Second is distribution. The volume of distribution is the amount of the drug in a certain area of the body, and we consider the concentration of the drug in the brain compared to that observed in the blood. There are limitations to the accuracy and precision of bioanalytical methods, and often the cerebrospinal fluid, or CSF, is used as an alternative site to measure the concentration of a given drug.

Third is metabolism, the chemical modification of a drug molecule in the body. This process can lead to formation of active or inactive metabolites which have varying levels of activity in the brain. There can also be interactions with other drugs that complicate this process.

Finally excretion, the process of the drug and its metabolites leaving the body, and a drug's accumulation may lead to adverse side effects, which can potentially be life-threatening in the enclosed space of the skull.

So really, all aspects of pharmacokinetics are impacted by the blood-brain barrier and other

protective mechanisms that shield the CNS from toxic substances in the blood, also supply nutrients to the brain, and then filter compounds back into the bloodstream.

The blood-brain barrier is much more than just a structural barrier. There are cellular components, enzymes, transport systems, reflex mechanisms, and immune cells that have complex interactions and vary by location in the brain. As a brain tumor grows and disrupts the surrounding environment, there are even more additional factors, the interactions between the tumor, the blood, the surrounding CSF, as well as the normal brain and tumor. Recent research has shown that tumors can actually make functional synapses with normal neurons to facilitate tumor growth. All of these aspects are important to consider to understand the ability of drugs to have efficacy for tumors of the central nervous system.

There are data to suggest that some brain tumors, particularly high-grade tumors, release factors that cause swelling, leading to breakdown

of the blood-brain barrier. This can be observed at a high level on MRI as areas of contrast enhancement, as you can see in the MRI scan here for patient A. Many low-grade tumors do not have contrast enhancement, as you can see for patient B, although there are exceptions to this general rule.

So while the breakdown of the blood-brain barrier might suggest that drugs could potentially act at the tumor site despite their inability to penetrate the blood-brain barrier, several studies have shown that even though we don't see that contrast enhancement on an MRI, there are still areas of tumor that remain inside the blood-brain barrier. Thus, effective therapy cannot be delivered with adequate exposure to the entire population of targeted cells.

I'll also briefly mention there are an increasing number of methods to directly deliver drugs to the CNS, intrathecal delivery into the spinal fluid via a needle in the lower back or intraventricular delivery via an injection into the fluid-filled spaces around the brain.

Convection-enhanced delivery is a method of local drug delivery whereby a pressure gradient is created at the tip of an infusion catheter to deliver drug directly to the tumor microenvironment.

In addition, several devices are under development to transiently open the blood-brain barrier such as focused ultrasound or microbubbles as depicted in this figure. These methods highlight the importance of preclinical models to help understand whether giving a drug could be effective in brain tissue regardless of how it gets there.

There are several ways to assess the potential of a drug to be efficacious in the CNS. Both in vitro and in vivo models can be used. Measurements include the rate of transport into the brain, which is a measure of permeability; the efflux ratio or potential of a drug to be actively pumped out by transporters; the quantitative concentrations of the drug in the brain, or CSS, compared to the plasma, and ideally those would be

the unbound or free brain concentrations of the drug; and then the ratio of the brain-to-plasma or CSF-to-plasma concentrations.

The appropriate parameters to affect potential CNS activity will really depend on the drug being investigated, its mechanism of action, and chemical and pharmacological properties. The appropriate parameters will also depend on the disease or diseases being targeted. We recommend meeting with FDA early in clinical development to discuss the potential of a drug to penetrate the CNS and potentially show efficacy for CNS cancers.

In summary, there's an unmet need for children with brain and spinal tumors. The blood-brain barrier and CNS penetrance are complex but important to measure. Ultimately, same-in-class molecularly targeted agents may have different activity in the CNS, and this may be important to consider in our discussion of the criteria to grant waivers of pediatric evaluation for same-in-class products.

Thanks to my colleagues at FDA, and thank

you for your attention.

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Shord and Duke for your excellent presentation. We will now take clarifying questions for our presenters thus far. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We will now proceed with questions, and Joyce is going to help me prioritize the questions. I'm going to start with a question while you all start figuring out to raise your hand in this Adobe

application.

This is a question for Greg and for Dominik.

Since the implementation of the RACE Act, do you have an idea of how often you get a combined PSP and PIP submission by a sponsor? And when that is not the case, when a specific drug application goes either to the EMA or the FDA, is there some kind of mechanism for crosstalk between those two agencies to be sure that there are not duplicative efforts, and to ensure that the same-in-class drugs are not being developed separately; and again, there's no duplicative efforts?

DR. REAMAN: This is Greg Reaman, Alberto, and I can take a first stab.

I would say that the minority of applications, or the minority of initial pediatric study plans that we see are associated with P-I-Ps, or PIPs, being submitted to the EMA at the same time.

As you may know, we, from a regulatory agency perspective, have actually recommended

simultaneous submission of pediatric investigation plans to the EMA and pediatric study plans to the FDA to accomplish exactly what you're asking. More recently, we have seen there are concomitant submission of these documents.

But again, I would just remind you that as much as we think it is important to align our thinking and decision making, there are very significant timeline differences by which agreement decisions must be made, and there are also important differences in the impact of those agreements with respect to initial versus more definitive development.

But there are opportunities for us to discuss jointly. We have regular meetings monthly, pediatric cluster calls, which originated with discussions between the EMA and the FDA, and now include participants from other regulatory agencies, including Health Canada, the PMDA in Japan, and the TGA in Australia, where we have sometimes general issue discussions, but more importantly product-specific discussions related to

either initial investigations that come in as part of pediatric study plans, or even more definitive development plans that we see as components of proposed pediatric study requests for written requests.

So there definitely are opportunities for us to have these discussions and to align to the best of our abilities in the advice we provide to sponsors. But again, I just want to point out that there are timeline differences that sort of preclude making this something that is always available and immediately of use to all sponsors.

I'll let Dominik provide any additional info that he might share.

DR. KARRES: Thank you very much. Thank you very much for the question, and not much to add.

Indeed, we're seeing only a minority of publications being submitted simultaneously. While similar to what Greg has mentioned, this is something we would generally encourage to do in order to use the interaction frameworks through the

clusters we have in place.

While at the same time, there is now increasing reference in our PIP applications of how sponsors intend to fulfill FDA requirements in view of the RACE Act, something we also highly recommend sponsors doing in their PIP publication so that we have an understanding in terms of what are the plans with regard to the global regulatory requirement plans in that regard. And I'll stop here. Thank you.

DR. PAPPO: Thank you very much. No further questions.

The next person on queue is Steve DuBois.

DR. DuBOIS: Thank you, Alberto. Steve DuBois from Dana-Farber. I really enjoyed Dr. Duke's presentation and have a couple of follow-up questions.

The first is, what is the agency's view on the role of phase zero trials, which I often see proposed in pediatric neuro-oncology in which patients receive a dose, or several doses, of the novel agent, and then undergo a standard-of-care

surgical resection?

The second question is, to what extent is it known whether principles that apply to patients with primary CNS tumors extend to patients with solid tumors with CNS metastatic disease?

DR. DUKE: This is Elizabeth Duke. Sorry. I had trouble unmuting.

Thanks, Dr. DuBois, for your questions, and I think very interesting to think about. I think the phase zero studies we are seeing, certainly, I think can provide helpful information, particularly when we're thinking about being able to really understand what a particular compound is doing in the brain tissue, which we often don't have that information. We're often using other measures, like I mentioned about CSS, or MRI findings, and things that then aren't necessarily actively happening in the brain tissue. So I do think those can add helpful additional information.

In terms of the primary CNS tumors extending to patients with solid tumors, Dr. Reaman, I may defer to you in terms of how we

would think about that as it relates to the IPSPs.

DR. REAMAN: Hi. This is Greg Reaman. I think, generally speaking, we would probably have similar considerations for those solid tumors where there's a high propensity for CNS metastatic disease, generally a more common problem in hematologic malignancies than in solid tumors.

I think the principles are essentially the same, and I think we elected here to really highlight the issue with primary CNS tumors because of the clear unmet need and the emerging and expanding evidence of specific molecular targets that appear to be important therapeutic targets for certain pediatric brain tumors.

I think in those pediatric solid tumors where there is the risk of -- not necessarily the risk of, but overt CNS metastases for which, generally, there are significant unmet needs as well, then I think the considerations about the CNS penetrance and the importance of the ability of the drug to reach tumors in the central nervous system would certainly be considerations that would

influence our decision making regarding waivers. Thanks.

Does that help?

DR. DuBOIS: Yes, absolutely. Thanks so much.

No further questions, Dr. Pappo.

DR. PAPPO: Thank you very much, Steve.

Our next question is from Dr. Julia Glade Bender.

DR. GLADE BENDER: Thank you, Dr. Pappo.

I think my question is predominantly for Dr. Reaman, but also with a comment from Dr. Karres because I seem to appreciate a difference in the nimbleness of incorporating emerging data from the EMA and the FDA.

So I wonder, Dr. Reaman, if you could comment on the current process, obligations, and consequences of modification to the initial pediatric study plan for emerging data and how it affects the overall drug development timeline; because in my experience, when talking with companies, there seems to be a big resistance to

entering into a modification process. Thank you.

DR. REAMAN: Sure. This is Greg Reaman. I think the concept of a modification process is more a pediatric investigation plan or EMA specific rather than an FDA and pediatric study plan specific situation.

To answer your question, given the fact that we are still pretty early in the full implementation of Section 504 FDARA and the RACE Act, we haven't really had a large number of requests from sponsors to amend their IPSPs, nor have we had the indication to recommend to sponsors or to actually amend initial pediatric study plans, other than the fact that before the full implementation date of August 18, 2020, we did see a number of IPSPs for applications, where the drugs were directed at relevant molecular targets or targets that were relevant to pediatric cancers. Although they refer adult indications, we had to agree with the plan, the full waiver request, because we were still operating in an environment where the driver, if you will, was the adult

indication.

So we would advise sponsors that should their application come in on or after August 18th, that they would have to, either voluntarily or we would require, amend their IPSPs to include their plans for an initial early pediatric investigation.

But I think, in general, we would be open to the consideration for revising a requirement for the investigation of a drug. As I mentioned in my opening remarks, if emerging science or an alternate product became available that we knew about that was the subject of a later application, I think there could be some consideration for revising the requirement of an investigation of a same-in-class product should a, quote-unquote, "potentially superior or more favorable" same-in-class product emerged.

To date, we haven't had that experience, but it may be something that we would consider, and it's something that I hope you as committee members would consider advising us, on how we might do that and what the specific parameters might guide those

kinds of decisions. Thanks.

DR. PAPPO: Hopefully, I answered your question.

DR. GLADE BENDER: I was going to say, thank you, Dr. Pappo and Dr. Reaman. I think that does answer my question.

DR. PAPPO: That answers your question, Julia? Yes?

DR. GLADE BENDER: Yes. Thank you, Dr. Pappo.

DR. PAPPO: Thank you.

We will now proceed to Dr. Richard Gorlick, is next in line.

DR. GORLICK: Thank you. I'm Richard Gorlick from MD Anderson Cancer Center. Thanks for the opportunity to ask a question. This one also is directed to Dr. Reaman, and somewhat brief.

Really, in thinking about same-in-class drugs, with the example of ADCs, I think because of their combinatorial nature, there are a lot of possibilities quickly with multiple different components, like the target, the antibody, the

drug, the linker.

How do you begin to distill a better drug but the same antibody is different, or the worse, or the same? Do you need one, two, or three to be different, to be different drugs? I'm using the ADC example as an example because I think the challenge is defining how much of a difference in property is necessary to make it something new, and just wondered if you had any thoughts about that. Thank you.

DR. REAMAN: Sure. Good question. Again, generally these are developed for the same specific adult indications, so we would really, I think, look to some initial adult experience with the product.

Despite the fact that the payloads may be the same, the linkers might be the same, or different, and the antibody may be the same but may be a different immunoglobulin class, and therefore a different antibody, we look at all of these as, in quotes, "a new active ingredient." Then when they are given in combination -- because you

mentioned the combinatorial approaches -- that would constitute also a new active ingredient.

So we would look to see at whether or not differences in any of those attributes of an ADC might have some impact on the adult experience, as minimal as it might be at the time. As far as antibody binding, hitting the target, the potential toxicity associated with free payload drug and off-target toxicities that may be associated, they would be the things that we would look at.

Unfortunately, the amount of information that is sometimes -- and I would say -- generally provided in the context of an initial pediatric study plan may not always include that. So there are questions that we may have in a written response to a sponsor to provide more information. That's one of the issues that I would like to discuss later today, too, is how much and what sort of specific information do you think we really need to request from sponsors to include, to help guide those decisions, and specifically the kind that that you raised in your question.

DR. GORLICK: Very helpful. Thank you very much.

DR. REAMAN: Sure. A pleasure.

DR. PAPPO: Ira Dunkel, you're next.

DR. DUNKEL: Thank you, Dr. Pappo. This is Ira Dunkel, Memorial Sloan Kettering. My question is for either FDA or EMA staff, and has to do with the oral formulation issue, the liquid formulation issue.

My question is whether this is a voluntary or a mandatory responsibility for the sponsor. If you have a drug where the target is relevant in very young children, where we know that a liquid formulation would be required, and swallowing intact capsules or tablets will not be possible, is the sponsor required to develop an oral formulation suitable for the young children or is that strictly voluntary on their part?

DR. REAMAN: This is Greg Reaman, and I can maybe start from the FDA perspective as far as the requirement.

The legislation, as it relates to PREA and

particularly the amended PREA, specifically states appropriate formulation. If we extend that to other regulation that governs drug development in the pediatric age group, the Best Pharmaceuticals for Children Act, when we issue written requests -- BPCA -- there is a requirement for the development of a pediatric-appropriate formulation, and not only a requirement for its development, but a requirement that it be made commercially available.

It's more than a general suggestion. And again, with the initial pediatric study plans, we recognize that these are initial and limited investigations, and early investigations. We would rarely require the development of a pediatric-appropriate formulation, a definitive pediatric- appropriate formulation, so we would look for some sort of extemporaneous compounding procedure that would make the existing adult formulations potentially appropriate for the pediatric population but require some bioavailability studies to make sure we're not

altering the potential absorption and PK of a compounded formulation.

But maybe Dr. Shord would want to comment further from the FDA side.

DR. SHORD: This is Stacy Shord. Thank you, Dr. Reaman.

I think you addressed the regulatory aspects of the question as far as whether or not an age-appropriate formulation would require it, and I think from my perspective, what I talked about this morning, is just thinking about what formulation would be appropriate for the age group that you're looking at and whether or not the formulation that is commercially available at this point can be given to the pediatric age groups of interest or if some modification needs to be made, and then subsequently, those additional studies need to be done, as Dr. Reaman mentioned, to make sure the PK exposure is what we need it to be.

DR. REAMAN: Thanks, Stacy.

I might just add, Ira, also our reasons for mentioning the formulation specifically was if we

have the same-in-class products where there is a pediatric-appropriate formulation, or there is some suggestion that one could be developed extemporaneously, at least for initial investigational purposes.

That may make that particular product more favorable than another same-in-class product, where a single formulation exists and that formulation can't be compounded, so that children under the age of six or seven, or five or six, who can't swallow large tablets or capsules, wouldn't be able to be enrolled on a study.

Maybe the EMA would like to comment here is as well.

DR. KARRES: Thank you very much. This is Dominik Karres. I'm having in mind that the different objectives here, with the objective of a PIP generating data sufficient for a pediatric indication, quality developments are mandatory in that regard, and I think my colleague, Dr. Wang, will expand on that in her upcoming presentation as well. Thank you

DR. DUNKEL: Thank you all for the responses. I think someone alluded to this maybe earlier in the meeting. I forgot which presenter, but it does seem like there are examples where within same-in-class agents being evaluated in early pediatric case studies, some sponsors are developing the liquid formulation very early and others are not.

I wonder if there's any danger that -- of course, there's an expense and a time and effort obligation for the sponsor who develops the liquid formulation, and I wonder if in any way we'd be penalizing them for their goodwill efforts, and they would be the ones obligated to do a study, and someone else who may not choose to devote the resources developing the liquid formulation might get a waiver and not be mandated to do a pediatric study. It sort of has a potential for a paradoxical unintended reward and punishment or something. Thank you very much.

DR. REAMAN: I really don't think we're too interested in paradoxical rewards and punishments

here. I personally don't see advancing the public health of children as equivalent to a punishment, even for a pharmaceutical sponsor. We wouldn't necessarily provide or agree to a full waiver for a product for which a pediatric-appropriate formulation doesn't exist or could not exist. It might be a partial waiver, and age-related partial waiver, or it could be a waiver specifically for children who are unable to swallow tablets or capsules.

So I think the likelihood that we would be punishing or penalizing a sponsor I think is probably not a significant concern here.

DR. DUNKEL: Thank you very much.

DR. FARLEY: Does that answer your questions, Ira?

DR. DUNKEL: Yes, thank you very much, Alberto.

DR. PAPPO: Thank you.

Our next person on the queue is Dr. Randy Kolb.

DR. KOLB: Thank you, Dr. Pappo. I think

this is a continuation of Dr. Reaman's response to Julia Glade Bender and Richard Gorlick.

As we accumulate phase 1 data, adult and pediatric data, on agents where there may be multiple versions in-class, at some point we have to make a decision about an efficacy phase, and recognizing for some rare subsets of the malignancies we care for with these targeted agents, we may only be able to do one or two efficacy trials inclusive of the U.S. and Europe in a 3- to 5-year time frame.

What's the best mechanism for us to meet with the FDA and meet with the EMA to talk about prioritization of those agents? I know that the waiver deferral discussion is between the FDA, EMA, and the commercial sponsor. Cooperative groups and the academic communities will have opinions as well, specifically on what is feasible for evaluating efficacy, and there may be a lot of information about dosing schedules, CONMED interactions, and all the points that were raised by the speakers today that could be reviewed in

totality to figure out which agents we prioritize for the valuable phase 2 or phase 3 eligible pediatric patient.

So I guess the question is, how do we have those conversations? Is it the ODAC or are there other opportunities that we should be pursuing?

DR. REAMAN: This is Greg Reaman. I will try to address that, Randy. As I tried to make clear, this particular discussion is really not about prioritization beyond which initial same-in-class products, or how many same-in-class products, to evaluate in children in a limited fashion, to evaluate dose and tolerability, and seek a signal of activity. That's number one.

Number two is that not infrequently, as part of the information provided by companies in the initial pediatric study plans, there are references to discussions, and there's information from those discussions that sponsors have had with key opinion leaders and clinical investigators in the pediatric community about the specific attributes of their product, which make it superior

to others, perhaps.

But I think the real question that you're asking, or that I'm hearing at least, relates to the well-known fact that this issue of community drugs for too few patients extends beyond the continuum of drug development in children, and which of these products that are same in class actually make it to more definitive development?

I think that is the discussion that is multistakeholder in concept, and I think there are other platforms for which those discussions can be had. As you know, the ACCELERATE platform includes regulators, as well as investigators, advocates, patients, and industry sponsors. It includes individuals from international cooperative groups, as well as regulatory agencies.

So I think those kinds of decisions are probably best made there, but I'm afraid we wouldn't even be able to have those discussions if we didn't at least have some preliminary information in the earliest possible time frame about some of these new products. If there are

reasons for evaluating multiple same-in-class new products, then I would see that information as hopefully guiding later-stage discussions about prioritization; if that answers your question.

DR. KOLB: Yes, thank you; very helpful.

DR. PAPPO: We have next Dr. Albert Kraus.

DR. KRAUS: Yes. Can you can you hear me?

DR. PAPPO: Yes. Yes, we can.

DR. KRAUS: There we go. You can hear me? Good. It's really a follow-up. I'm representing regulated industry, and I think all these presentations and considerations are really excellent. We certainly don't want to do redundant research and be treating patients when it's not helpful, really, in the broader picture for children's health.

The complication that I'm going to ask you about, Dr. Reaman, is even if we do these things we're talking about here and make all the appropriate decisions, this issue of a lot of mandated work, a lot of regulatory defined requirement work in a very small pool of rare

disease patients of certain types, where we're trying to do even more robust trials than historical larger randomized cases -- which is all good.

But I'm wondering, in all that, even if we do all these things right, if we still have a big problem and require a lot of prioritization that perhaps doesn't meet the timings of regulations, or perhaps doesn't meet what we're trying to do and getting pushed to do as an industry, do we have metrics on -- I know you're close to COG from history as an ex-chair and other organizations. Are we beginning to collect metrics of timings, and accruals, and possibilities of trials?

It's young yet in this concern, but metrics might help see where we are and where we can get to, or can't get to. And I'm just wondering if we're collecting those, or with FDA, if you're beginning to collect timing. We're, as industry -- I can speak from certain personal experience and involvements I've had -- increasingly trying, not just in U.S. and

Europe but around the world, to accrue, and it's challenging. It's really challenging, and I know flexibilities have been drawn.

But are we starting an effort -- it's in a way similar to the prior question, but a little different. Are we starting metrics on timings, numbers, accruals, possibilities, COG issues, et cetera, et cetera, so we can keep track of how we can best apply this sparing [indiscernible] resource?

DR. REAMAN: Excellent question, Mr. Kraus. We are certainly interested in collecting those data. We obviously have a requirement, a legislatively mandated requirement, to report to Congress periodically on the impact of the legislative initiatives on pediatric drug development, and now specifically on pediatric cancer drug development.

As you point out, it's still relatively early with respect to FDARA, Section 504 and the impact, but I think we have definitely seen an increase, which I've tried to mention previously,

with the number of commitments for studies, and more importantly, studies already in progress, which is something that we did not see two years ago, three years ago.

So clearly, this is having some impact. I recognize the challenges, but one of the major challenges to pediatric cancer drug development was getting to first base with respect to being able to do early-phase studies to investigate promising or potential new therapeutic agents. And unlike every other clinical indication, cancer was excluded, basically, from the requirements of the Pediatric Research Equity Act because the cancers of children and the cancers of adults are different.

So I think both in the EU with the mechanism of action requirements and in the U.S., this is addressing an important first step in trying to improve the number of -- and not just the number of studies, but the timing of when those studies are initiated, and hopefully the ultimate timing of when effective drugs are approved for use in children relative to their approved use in

adults.

So to answer your question briefly, yes, we're interested in metrics. We are interested in collecting data to make sure we are doing what we have been legislatively mandated and authorized to do to advance the public health of children with cancer.

DR. KRAUS: Thank you. I appreciate that, and I think, obviously, the industry associations can help participate because I think there will be challenges down the road, and a lot of good progress, as you say, but we're seeing early signs of some challenges, as I think you are.

DR. REAMAN: Yes. I think we have to work together, and I think we're eager to work together to face those challenges, and overcome those challenges, and be somewhat creative and innovative. I think it's going to require some bold steps on the part of industry and regulatory agencies in order to get there, but we recognize that we're in this together, and that's what we hope we're able to do moving forward.

DR. KRAUS: Thank you. And certainly, many in industry are happy to work together, and want to make sure it all works for the right intended outcomes, right?

DR. REAMAN: Right.

DR. PAPPO: Does that answer your concerns and your questions, Dr. Kraus?

DR. KRAUS: Oh, yes, fully answered. Thank you very much, Dr. Reaman.

DR. PAPPO: Okay. Now we have Dr. Ro Bagatell.

DR. BAGATELL: Hi. Thank you so much. My question is really a matter of just information that we can learn from other areas of medicine. I think that many of us are very focused on pediatric oncology and sometimes think about adult oncology, but sometimes think about pediatric medicine in general. But certainly throughout medicine, there are a number of small patient groups in whom it's difficult to do the kinds of studies that we've been talking about.

I wonder, maybe from both the FDA and EMA

representative, if there are lessons that we can learn from patients with rare diseases in terms of defining how much of the same is the same and how much different is different, a little bit going back to what Dr. Gorlick was talking about, both with regards to the structure of molecules, their mechanism of action, and how different is different when it comes to safety profiles.

So, in short, I guess my question is, can we learn from other patients and studies in groups with limited populations? Thank you.

DR. REAMAN: I'll take a first stab -- this is Greg Reaman -- and then let Dominik have some opportunity as well.

Basically, I think in the rare disease space, their situation is decidedly different from what we're talking about here in that there are few, if any, drugs that are actually being developed, or are developed, and under investigation for those small populations.

Here we have an opportunity to develop multiple drugs, or actually to investigate multiple

drugs, in rare populations. It's a little bit different. I don't think there is much opportunity to learn from the rare disease experience about issues or factors that might be helpful in prioritization.

There clearly are opportunities, and opportunities that we at the FDA share with our rare disease colleagues with respect to innovative study designs, doing definitive studies in populations where limited sample sizes may make it difficult, if not sometimes impossible to do randomized-controlled trials, and looking at Bayesian adaptive approaches, hybrid approaches, and the concept of external controls. But that's an issue that's sort of outside of what we're discussing here with respect to having more drugs than we can effectively study, given the small number of patients that we have.

I'll ask Dominik -- Dr. Karres -- if he has anything to add.

DR. KARRES: Thank you very much, Dr. Reaman, and thanks for the question.

I think what we have learned from an EMA/PDCO perspective over the past 10 to 14 years, since we've had the European pediatric regulation, is I think that not always when we think something is the same, it actually is the same; and vice versa, if we think it is the same, at the end we might realize through emerging evidence that it is not.

That's I think something we're trying to take into consideration here through the approach we're taking towards supporting our decision making based on science and evidence and allowing for repeated cycles of evidence generation and reconsiderations as necessary, while at the same time -- and I think that's something where I believe the pediatric oncology community and spaces are really ahead compared to other rare disease areas -- acknowledging that doing this together can only be done successfully in collaboration across all stakeholders. Here, I would argue that, there, the pediatric oncology committee is even ahead.

I'll stop here, and I hope that helped.

Thank you.

DR. BAGATELL: Thank you, Dr. Pappo.

The issues are numerous, and it's interesting to think about the pediatric oncology community being out ahead. Thank you very much.

DR. PAPPO: Thank you for your question. Dr. Ted Laetsch is next.

DR. LAETSCH: Thank you, Dr. Pappo.

My question goes back to what had been previously asked about emerging data, and just thinking not only about emerging data for the specific agents or the specific targets that have been previously identified, but if there are emerging data, that a target may be relevant to a different pediatric cancer or different pediatric marker that had been originally studied, how does that factor into requirements for next-in-class agents that may be submitted to the FDA or EMA?

I'm just thinking that the early nature of these requirements may have made those targets not relevant for the earlier agents in-class that may still be relevant, even if there's a dose and

safety data of one agent in that class.

DR. REAMAN: This is Greg Reaman. I'll try again to answer your question, Ted. Again, I think that's a little bit separate from the evaluation of multiple same-in-class agents, but our evaluation of all of these requirements, with respect to the potential relevance of a molecular target, is something that is evolving and has evolved since the development of the original relevant molecular target list.

As we put that together, there were limited data available, limited publicly available data sets, and they have now certainly increased in the three or four years, or longer, and that information certainly influences decisions initially when there are requests from sponsors about potential waivers or planned waivers, given the fact that something is on the relevant molecular target list.

We made that very clear in the very beginning; that the mere existence of a target on the list wouldn't require pediatric investigations,

and I think we've fulfilled that promise a number of times. We recognize what we thought may have been relatively prevalent associations between a specific target and pediatric cancers, in general, or specific pediatric cancer diagnoses. When we see more data that suggests that's not quite as prevalent as we thought and that there really are a very limited number of patients, then the opportunities to consider waivers, I think, are clearly there.

When it's just an issue of small numbers, but it remains a potentially relevant target, are there opportunities for enrolling some children on early adult trials, looking at safety and early signs of activity or effectiveness? This was never intended to be a static guide to decision making, and we recognized from the very beginning that we would have to make changes as we went along here. The big change that we wanted to see made was that when it's appropriate, consideration of pediatric investigations, or investigation of products in the pediatric population, happened early, not 6 years,

10 years after the fact. That's still, I think, what guides how we adjudicate any waiver requests that still come in, and I would like to think that's how we'll likely continue to do it.

DR. LAETSCH: Thank you, Dr. Reaman. That answered my question.

DR. PAPPO: Does that answer your question, Ted?

DR. LAETSCH: Yes. Thank you, Alberto.

DR. PAPPO: Thank you.

I see a couple of hands that are still up. I don't know if you just forgot to put them down or you have a question. I want to remind you that it's 12:30, so we're going to break for lunch, but we're going to have a second session for questions and answers at 2:15.

So for now, we will break for lunch. We will reconvene at 1:00 p.m. Eastern Standard [inaudible – audio gap] time. Please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. Additionally, you should plan to rejoin

us at around 12:50 p.m. to ensure you are connected before we reconvene at 1:00 p.m. Thank you, and we'll see you in about 30 minutes.

(Whereupon, at 12:31 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. PAPPO: Welcome back, and I hope that you enjoyed your break. We will start with guest speaker presentations. We will now proceed with the guest speaker presentation by Dr. Siri Wang.

Guest Speaker Presentation – Siri Wang

DR. WANG: Yes. Thank you very much for inviting us. My name is Siri Wang, and I am a scientific director at the Norwegian Medicines Agency and a member of the pediatric committee at the European Medicines Agency. I have been asked to share some considerations related to quality and formulation aspects for this discussion, so clearly this will add on to some of the issues already touched upon very nicely by previous presenters. And of course in line with the previous presentation from Dr. Karres and Dr. van Malderen, this will then be the EU perspective, and this is my disclaimer, definitely.

Before we slide into the potential elements that could affect the waiver discussion, or the

prioritization discussion, I would like to take one step back. For every product that comes to our table for potential development in children, this is what we want to see; that any formulation proposed gives the accurate dose and is safe and acceptable. This would apply for the full target age range that we consider in need for this product, potentially, for this specific condition. In this sense, the requirements for an appropriate formulation is the default, and, therefore, waivers based on appropriateness of the formulation as such would really be an issue.

To answer the question raised in the previous session, normally this would really imply a specific formulation, but we also see cases where it could be that the adult form is being manipulated. However, this will normally not be the default, and we would stress the need for any such approach to meet the same requirements as listed here related to accuracy of the dose, including bioavailability data, as was mentioned, including any need for uniformity of those

assessments and acceptability data for any such approach; for example, challenges in taste issues when you open the capsules and so on and so forth; also safety elements to be considered, including safety in handling by the caregivers, risk of medication errors, and these kind of safety aspects. But the default is we would normally require a specific periodic formulation, yes.

Still, although we do normally not then accept waivers based on formulation, when we assess the unmet need for any condition and the potential added value for any new treatment, of course both the route and formulation/quality aspects are, of course, also considered.

One of these two sets is being discussed rather often, is this aspect of the specific route, as has also already been mentioned by previous speakers. The pros and cons of a proposed route are quite often discussed, and the oral versus the parenteral is a good example.

Some factors would favor oral, and listed here are some very brief perspectives, for example,

when comparing an oral versus a parenteral product. An oral product will quite often facilitate home treatment, while a parenteral -- for example, an IV -- would foresee hospital stay. Of course, invasiveness will differ. Access to treatment might be significantly different for oral versus parenteral treatment both for the clinical trial setting, but also potentially for later use.

On the other hand, oral products may also imply some delay that could be not very helpful, so to say, both in the development and in actual availability if a pediatric-specific formulation needs to be developed. This was also very clearly illustrated by one of the previous speakers, where patients de facto are being excluded due to lack of age-appropriate formulation in the clinical trial.

Also, later related to the marketing strategy from industry, the decisions to actually launch the pediatric-specific formulations in all regions could really affect availability of these periodic-specific formulations. For parenteral products, at least when they are identical as the

adult forms, these problems are not really an issue, and the risk for delay is most likely reduced for those kind of products.

From this perspective, prioritization based on route, as such, potentially can be challenging in our view, as the different approaches really have different advantages. Of course, on the other hand, in a setting where we, for example, already have one, two, or three IV products in the same class, an oral product definitely may provide added value for sure.

Trying to illustrate some of the discussions we are having on formulation characteristics -- so the formulations as such, and not the route -- quite often we see approaches where companies are clearly arguing that their products are not suitable for children most often, and then of course the youngest age groups, and therefore asking the waivers. This could be due to dosing issues, acceptability issues, or safety issues, or all three together, definitely.

This approach is, I would say, solely driven

by the adult perspective, so to say, and not really driven by the actual need for pediatric formulation in the target age group, which is where our perspective comes from to decide on the appropriateness of the formulation. In general, as we would normally always request an age-appropriate formulation for each development, this justification would normally not fly from our side.

The second argument we see every now and then is that the development of an age-appropriate formulation would not be feasible, mainly for technical reasons. There could be challenges in taste masking, challenges related to coating, prolonged release approaches that are not that feasible for the age-appropriate formulations, or excipient issues.

I would say that, generally, it's our experience that at the early stage of the PIP discussion, when they come, at their first discussion with us, these aspects are very often not sufficiently justified. They could be, theoretically, at later stage more relevant to

come, but as an initial early stage, these kind of justifications are generally not will justified, and therefore not, at that time at least, a rationale for a waiver.

Of course, sometimes a formulation approach proposed for adults could be considered particularly useful in children, for example, if you have a particularly convenient administration, simplified regimens, treatment durations, or APIs with long half-lives being long-acting, or prolonged released approaches and things like that.

Of course, in these cases, we would definitely like to see pediatric development also here, of course, and in these cases, we could, in theory, discuss pushing development for such products by potentially limiting the deferrals. But I have to say that more often there are clinical and nonclinical issues that are driving our discussions about deferrals and not that much the formulation issues.

To sum up, the formulation characteristics as such are rarely reasons for waiver, at least not

initially. There could be settings and situations where we've had discussions on where the products are, as such, considering their formulation aspects would meet a medical need in children, and therefore should or should not be developed. We've had a couple of oncology discussions on this, and I put here some examples related to fixed-dose combinations.

One of the examples is a product, a fixed-dose combination, consisting of two APIs or two substances intended for intravenous use. In this case, we already had existing products for each component individually, and we also had PIPs, pediatric investigation plans, for each component individually, also actually involving this combination treatment for this product that was presented to us, the combination product.

There were discussions clearly about the added value of any such combination products, and clearly here, in addition, there would not be a question about additional clinical studies, so slightly outside the scope of the problem stated

here where we have a crowded area and unlimited possibilities to do clinical trials. For sure, this type of discussion will not be an early-stage decision or discussion, but really a very late-stage discussion, so limited relevance maybe here, but this was a case where we could have considered a waiver approach, for sure.

The other example is for oral products, also fixed-dose combination, two oral substances, where one of those components were available as an existing product but the other was considered a new API. Here initially, the company proposed waiver lists below 6 years old due to a claim that children were unable to swallow the tablets, as such, that were developed for adults, and that development of age-appropriate formulation was unfeasible and resuspensions were impractical.

We considered this, along with all the other elements of the PIP, not a duly justified approach. After we discussed with the company and also stressed the unmet need in the full pediatric age range, we agreed for a waiver below 3 months and

also agreed on an age-appropriate formulation proposed, an oral solid formulation, oral granules or powder for oral liquid, in addition to some strategies they would approach to enable the adult form and enable dosing until the pediatric formulation was further developed.

Having said all this, I would like to stress that when we do this, we apply some sort of evolutionary approach also for formulations because at the time of the initial PIP discussions with us, it might definitely be too early for the very details of formulation strategy.

One example here, this was an oncology product developed initially for adults and adolescents, being hard capsules, two strengths, size 2 and size zero, which are rather large-sized capsules. You could question whether they would actually be suitable also for adolescents, but that's another story. The hard capsules should be swallowed whole and could not be open or dissolved. The content of the capsules, however, are very bitter, so really not a valid approach, and the

addition to pediatric dosing was not yet fully clear.

So at the early stage of this PIP discussion, we put into the PIP opinion sort of a placeholder PIP measure that they would have to develop an age-appropriate solid dosage form, and then the details of any age-appropriate form needs to be agreed by PDCO before study initiation, so at later stage, and then including more details about the formulation, the excipients, the type of productibility [indiscernible], acceptability studies that we're going to pursue, so on and so forth.

These elements are in the initial PIPS, but at the later modification, then the details and the specifics will be included. They did so, and then decided, based on their evolving knowledge, they would go from coated granules, and also clearly spelled out the acceptability measures, and the nasogastric tube strategies, and so on and so forth. Although we put the requirements, we'll also consider that at the early stage, the details

might not be really feasible to agree on at the early stage.

In conclusion, waiver based on route formulation or quality issues are really considered relevant for us in the EU, but of course later modifications could be possible, potentially also including waivers, of course, but then needs to be really properly justified, but definitely not at early stage.

On the contrary, it's our experience that early considerations regarding the strategy on age-appropriate formulation is really crucial, coming early and thinking early, as it will ensure timely progress of the pediatric studies. I also dare to say it will most likely optimize the clinical trial outcome. You will have more accurate dosing during the clinical trial, you will have, hopefully, better compliance during the clinical trial, and you will include the full relevant age group as also previously flagged by others.

In the end, all this will be important for

the timely authorization and also for the youngest, which altogether would affect access and availability of the treatment, which is our main goal, I assume. But to also answer one of the questions raised earlier today, we are not really considering those who come early with a clear plan as more interesting or more relevant to prioritize, if you put it like that, but we see also some benefit, definitely, in those coming early also for the full development strategy.

So by this, I would like to thank you for your attention and also to thank my colleagues in the committee for their contribution. Thank you.

DR. PAPPO: Thank you very much for your presentation, Dr. Wang.

We will now proceed with our next guest speaker presentation, Dr. Scott Diede.

Guest Speaker Presentation – Scott Diede

DR. DIEDE: Hi. Thank you very much, Dr. Pappo, and thank you to the pedsODAC Committee for allowing me the opportunity to speak today.

My name is Scott Diede. I'm a pediatric

oncologist by training, and I help lead pediatric oncology development at Merck. Today, I'm going to give an industry perspective, but maybe more accurately a personal perspective on waiving requirements for pediatric investigations in the same-class products. These are my financial disclosures.

Briefly, I'm just going to touch on some of the key points of the RACE for Children Act that have already been gone over in excellent detail with some of the previous presentations today, so I'll keep that brief. I thought I would use as a case study the use and studying of anti-PD-1, or L1, inhibitors, checkpoint inhibitors in children, because I think that story is very illustrative of some of the challenges about what we're talking today about same-in-class products.

I think in terms of how we dealt with this as a community, I think there were some very positive aspects of it, but I also do think it highlights some of the challenges for the future, given how fast paced oncology drug development is,

and sometimes we have to act with limited amounts of information to decide what compounds are in fact best studied in children, and how many of those should be studied at the same time, so I'll talk also about the challenges and opportunities around this.

The RACE for Children Act, I really do think what emphasized from an industry perspective, really, I think revolutionized recently how we look at pediatric drug development. In terms of previous to RACE for Children, sponsors could get an adult indication-based waiver or an orphan indication-based waiver, and with RACE for Children, that all changed to trying to determine whether or not your therapeutic, based on mechanism of action, has relevance in pediatric cancer. And then if it did, put it on a list, if you will, to be really strongly considered about should it be studied in children, and what would be the best tumor types perhaps to do this.

The overarching goal of the RACE for Children Act was really, I think, to focus on

accelerating appropriate initial pediatric evaluations, and to have this happen much earlier in the developmental timeline of drugs, as Dr. Reaman has pointed out in some of his comments and questions that he answered.

This legislation has stimulated, I think, a lot of excellent conversations and work in pediatric cancer, but there are still challenges on how exactly best to implement the RACE for Children Act, and that's part of the reason that we're meeting today.

I wanted to touch on some of the considerations for granting waivers that the RACE for Children Act actually allows, and these three are different than the ones that we've spoken of to some degree -- though except for the most recent talk we just heard -- in terms of it would make sense to potentially grant a waiver if there was serious toxicity concerns for a given compound based on toxicity in particular pediatric age groups or concerns around severe developmental toxicities perhaps discovered in nonclinical

models.

Then lastly, when due diligence has been done, it is possible to have the conversation about whether or not a sponsor should be granted a waiver for age-appropriate pediatric formulations for particular age groups, but once again, I think there are a lot of opportunities to actually be able to test, at least in initial studies, what is required for the RACE for Children Act in terms of trying to get some idea of dose finding, safety, and initial PK before launching into the much more extensive and sometimes challenging, more permanent pediatric formulation that could come down the road if in fact there is some activity worth pursuing.

For these two bullet points, this gets more to the topic at hand today in terms of looking at waivers for later generation products that have a lot of these characteristics that have been spoken about today in terms of how do you actually define same in class in terms of looking at pharmacologic parameters, toxicity, and efficacy; and whether or not if there are, in fact, multiple same-in-class

products that for all intents and purposes look very similar, it doesn't make sense to continue to actually have to study this in children.

Then also, for those drugs that actually there already have been pediatric studies that have shown that the target in a way is not relevant to pediatric cancer, it might make sense to also grant a waiver in that particular instance.

One challenge is, how do we prioritize studies of several similar targeted therapies in the same pediatric population? Because as we all know, there is a limited number of pediatric patients, and there should be a reasonable expectation for possible direct benefit for a patient when they participate in a phase 1/2 study. This is an excellent problem to have, in a way. One, pediatric cancer is rare, which is a good thing, and now because of RACE for Children Act, we actually have a plethora of possible therapeutics to study in children.

But the question then remains, which ones to study just because you can't study not even close

to them; let alone even within a company, sometimes if you have to study this in a particular pediatric tumor type, you might not actually be able to find enough of those patients to be able to do even the initial pediatric study plan requirement type of studies.

To help sponsors navigate this, especially around this question about same-in-class waivers, the great thing about the RACE for Children Act is that it did actually specifically institute a new mechanism to allow efficient early communication with sponsors and the FDA, and that's through early advice meetings or Type F meetings. These meetings are actually scheduled and held within 30 days of the request, which is pretty amazing in terms of the turnaround. And I would emphasize for sponsors that this is an excellent way to have that initial discussion with the FDA about your plan, be it about same-in-class waivers or otherwise, just for your initial PSP.

I'd like to turn to using a case study of checkpoint inhibitors, which I'm most familiar with

because I was involved with this at Merck. The use of checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 blocking antibodies, really has led to improved outcomes in a wide variety of adult cancers and really has revolutionized cancer care over the last maybe 7-8 years since they were first approved. However, we have a long way to go.

Based on this excitement, what we were seeing about trying to harness the immune system to help the body fight cancer, back in 2015, there were actually three pediatric phase 1-2 studies that were initiated, studying either atezolizumab, nivolumab, or pembrolizumab, and these were all started within about 9 months of each other.

After these studies basically started, enrolled, and then were gathering data, in September of 2018, which is actually pretty fast, there was data from over 250 patients just from these three studies, and as a community of industry, academics, patient groups, it was thought, "Where do we go from here? We really should look at the data to determine what is the

best path for this class of compounds." I just listed the three initial ones here that launched these pediatric studies, and there are greater than -- I think I've lost count -- 20 or 30 different anti-PD-1 and L1's that came after these initial drugs, and the question was, "Are we going to require pediatric testing for all of those?"

There was a forum that was jointly organized by ACCELERATE and also the EMA. This ACCELERATE, a pediatric strategy forum, was created to evaluate the science and to really be able to facilitate constructive dialogue between the many stakeholders involved in pediatric oncology drug development so that we could move forward as a community to develop medicines in the best interests of children and adolescents with cancers.

I'd like to emphasize the multistakeholder nature of ACCELERATE, in terms of it really involves patients and patient advocates; clinicians; academics; industry; and then very importantly, regulators. I started attending these I think back in 2015, and these have been wonderful

forums. We also have yearly meetings to help discuss pertinent topics in pediatric oncology, and in every case, regulators from the EMA, FDA, Health Canada, sometimes TGA, have always come to these to be able to have these types of discussions.

An ACCELERATE pediatric strategy forum was held on checkpoint inhibitors, and this was the finding after looking at the data from those three phase 1/2 trials. On the positive side, there was a high rate of activity for monotherapy checkpoint inhibitors, including even complete responses in Hodgkin's lymphoma, and there was less data on hypermutant tumors; but very impressively because Hodgkin's lymphoma is more prevalent, and we had more data, that it really revolutionized just monotherapy, the responses we were seeing in highly refractory Hodgkin's lymphoma patients.

Unfortunately, there was very limited activity of monotherapy checkpoint inhibitors in the vast majority of other tumor types looked at. All of these phase 1/2 trials were solid-tumor basket trials in addition to lymphoma, and

unfortunately, if you actually take out the responses seen with Hodgkin's lymphoma, the overall response rate was only 2.8 percent.

So one of the important conclusions of this forum was that there really is no benefit to be included in new monotherapy trials of checkpoint inhibitors that use this same mechanism of action unless there is some new piece of scientific knowledge that might make sense to reopen, perhaps studying PD-1 inhibitors in these solid tumors where we initially did not see activity.

Another conclusion of this forum was that academic industry consensus on the scientific merits of a proposal of either a pediatric investigation plan, be it an IPSP or a PIP, would actually be a great benefit to regulators; in other words, the sponsor to bring this information when they're having discussions about their plan for their drug. Having this multistakeholder feedback I think makes a strong case for if a sponsor wants to move forward with why they think they should be studying their drug of interest in children, that

they have the backing of the community.

Then also just as importantly -- and this is getting to the waiver aspect -- is that if the community says, yes, we actually agree that we do not think it makes sense to continue to study this class of drug in children, that's also a very important piece of information.

This I think really benefited the 20-plus companies, if you will, that came after these initial three in that the EMA and the FDA really used the feedback from this forum to help guide those companies about pediatric study plans. So I think this mechanism has worked wonders in terms of really being able to inform on this.

But some of the challenges around this, some of the questions I had is that it worked great for the compounds that came afterward, but one question I had is, how many compounds should we initially be testing in children when we have little data? Should we test one, or two; maybe three? I think there was consensus that 250 children probably was going to weigh too much, if you will, in terms of

was that the best use of everyone's resources, and most importantly, was it the best for children?

Another challenge and opportunity with pediatric drug development is global collaboration is essential, and there's a variety of ways which this could happen, and there's a variety of mechanisms that sponsors can work with health regulatory agencies. Some of these have been mentioned today, and I would encourage early interactions with sponsors to be able to take advantage, potentially, of pediatric cluster calls, common commentary processes, and perhaps even formal parallel scientific advice mechanisms, as well as these international multistakeholder meetings like ACCELERATE.

In summary, I'd like to include that I think the RACE for Children Act, I think, provides a lot of opportunity, and there are some challenges, especially with today's topic of same in class. It's not a trivial question about how do you define same in class, and that is hard, but I think one of the important things is having these early

discussions; and having enough time to have these discussions with multistakeholders, as well as regulators, I think will allow us to come to the best conclusion for how to develop a drug if it's warranted in children. Strategy and the resulting regulatory requirements around this always should be driven by the science because the science always drives what's best, in this case, for children. Thank you.

Clarifying Questions

DR. PAPPO: Thank you very much for your excellent talk, Dr. Diede.

We now have about 10 minutes for clarifying questions for both Drs. Wang and Diede. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked the question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if

possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and that follow-up question with, "That is all for my questions for now," so we can move on to the next panel member.

We have already Steve DuBois as the first person who would like to ask a question.

DR. DuBOIS: Thank you, Dr. Pappo.

Steve DuBois from Dana-Farber. I have a question for Dr. Wang and a question for Dr. Diede, so maybe I'll start with Dr. Wang.

Thank you for that presentation. I appreciated your comment about being able to administer an appropriate dose to a patient. Sometimes in our first-in-child clinical trials, we end up -- because of the available pill sizes, even for children who can swallow pills -- where we're not able to give them an appropriate dose due to rounding between their calculated dose and the dose that we could actually administer with even a capsule formulation.

Is there a precedent where, I guess in your

case, the EMA has mandated different capsule sizes early on in development to enable more appropriate dosing of pediatric patients?

DR. WANG: Thank you for that question. Whether we have been specific on actual capsule sizes for the initial clinical trials, I cannot really remember. But really, the essential, both from an acceptability point of view, being able to swallow a smaller capsule, but also to have the appropriate dose would be essential, indeed.

I cannot remember if we necessarily have requested it, but I definitely would say it would be a brilliant idea, both for dosing perspectives and for acceptability perspectives. Whether this is an intermediate approach or the final approach would probably depend on the setting. Quite often, maybe someone would rather go for a strategy where you could have a formulation that is more flexible, like an oral liquid, for example, or powder, but then, again, taste issues might be an issue, and so on and so forth.

So we are open for different strategies

here. And to answer your question, again, I don't think we have been very specific on exactly that for the clinical trial approach.

But Dominik, also if you have any additions to that, please add if needed. I hope this answered your question.

DR. DuBOIS: Yes, thank you. That's very helpful.

Dr. Diede, thank you for your comments. I really like your idea or suggestion that this be sort of an iterative process and that the science be re-evaluated over time to decide whether a waiver remains appropriate.

I guess one of my concerns is a false negative conclusion about lack of efficacy in the context of an unselected monotherapy first-in-child study; that potentially that type of negative determination of lack of activity to be revisited if there's new data available, that perhaps molecular enrichment would have changed that or that some interesting combination might have changed that.

So I just wonder what your thoughts are specifically about the idea of a false negative conclusion too early.

DR. DIEDE: Thank you, Dr. DuBois, for your question. I think that's an excellent question because, to be honest, it was somewhat surprising and disappointing, the results that we got with checkpoint monotherapy in solid tumors, and we still don't really understand why.

One of the reasons could be around the mutational burden of children's cancers versus adults. We've seen that as a proof of concept in the very rare cases of MSI high cases where that's from a constitutive mismatch repair deficiency. Those children actually have very robust responses, so in a way that's a type of biomarker that is, I think, potentially pertinent in pediatrics.

I don't want to speak for Dr. Reaman or the FDA, but one of the ways in which we have continued to study that, is that when we approach the FDA for approval of MSI high in adults, we actually received a PMR to actually, in a way, re-evaluate

this question in children because we didn't select for MSI high in our initial KEYNOTE 051 study. So I think that's one mechanism after the IPSP has occurred; that the FDA has an ability to readdress that question.

Then the other -- and this is sort of just off the cuff -- is that if there are multiple same-in-class drugs coming down the pipeline, if you will, I think there could be opportunity for maybe not the first ones that went and reopening IPSPs -- and it's amazing how many PD-1's and L1's still are being developed today, literally -- but when they approach the FDA about a waiver, if there is some new information in the literature, I would assume that new information should be taken into consideration about a waiver for the PSP, and perhaps that new same-in-class compound actually might be the one that actually should maybe study a biomarker, let's say, selected population, or if we learn more about just the science and biology, that would be just sort of trying to think of that. But it's an excellent question.

DR. DuBOIS: Thanks so much. Nothing further from me for now. Thanks.

Open Public Hearing

DR. PAPPO: I see that we have Dr. Kim and Dr. Laetsch on the queue, however, we have our OPH speaker ready to go. So we're going to move to the OPH session of the meeting now, and then we're going to come back in a few minutes for additional clarifying questions, and I promise you that I will call on Dr. Kim and Dr. Laetsch first before anybody else.

We will now begin the open public hearing session. Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the

committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors. For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in connection with your participation in this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public

hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, and thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research. Our center is a non-profit, public health think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. Our largest program focuses on cancer treatments.

My expertise is based on post-doctoral training in epidemiology and public health and as a former faculty member and researcher at Yale and Harvard. I've also previously served as a professional staff in the U.S. House of

Representatives and U.S. Senate; at the Department of Health and Human Services; and the White House. I'm currently on the board of the non-profit Alliance for a Stronger FDA, which educates Congress about the need to financially support the work of the FDA.

You are the experts on pediatric cancer, and I am not, so I will focus my remarks on the intended and possible unintended consequences of the FDA policies you're discussing today. I'll start by saying how impressed I am with the careful analysis that was presented today, and I appreciate that FDA is clearly emphasizing how best to improve access to safe and effective treatment for pediatric cancer patients.

However, there is always pressure on any federal agency, including the FDA, to issue waivers even when waivers are not appropriate. The law states that the FDA should avoid, quote, "unduly burdensome requirements," unquote, on sponsors, and you've heard that wording today. Undue burden is not well defined. Even more important, reducing

burdens on sponsors can decrease information available to physicians, patients and parents, and that increases burdens on physicians and their patients when they lack the treatments or information that they need to make the best medical decisions.

There are two issues that I hope FDA and this advisory committee will consider. Number one, waivers for treatments that are very unlikely to be safe and effective for children makes sense, but as you've heard, that isn't always clear in early studies. Waivers may be premature due to pressure from sponsors to issue those waivers.

If the FDA issues the waiver, what happens if it later becomes clear that the drug could be used or is in fact being prescribed off-label for children? You've asked about reopening the issue of a waiver, and in addition to reopening that issue, should there be a mechanism to require that studies on pediatric patients could then be required, and how would that mechanism work to ensure those studies be done as quickly as

possible?

Also, should the label for the medication be required to clearly state that pediatric use is not appropriate until data supports such use? How effective would that label be? We all know that medical care varies greatly across the country, and your experiences as leaders in your field are not typical of all pediatric cancer care.

Number two. How often are waivers being issued if one drug in the class is already considered appropriate for pediatric use? That would seem unfair to patients and their parents because as you've heard, you can't always extrapolate safety or efficacy from one drug in the class to another.

Some drugs in the class would be safer or more effective for children or for children of specific ages or characteristic, and that information would be lost if studies weren't required on at least a small number of pediatric patients. It should always be preferable to conduct studies on small numbers of children who

receive treatment for free under well-monitored clinical trials rather than wider pediatric use of a cancer drug that was not studied on any children.

My final point, a level playing field is very important for sponsors and for patients. Sponsors that aggressively apply for waivers should not be held to a lower standard than sponsors who follow the spirit of the law and do the studies needed to benefit patients. Thank you so much for the opportunity to share my views today.

Clarifying Questions (continued)

DR. PAPPO: Thank you, Dr. Zuckerman.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

As promised, we're going to go back to some clarifying questions. We have about 25 minutes, so we will now take remaining clarifying questions for all presenters, of course including Drs. Wang and Diede who were our last presenters.

Please use the raise-hand icon to indicate that you have a question and remember to put your

hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so we can move on to the next panel.

The next physician on the list for questions is Dr. Kim. Please go ahead.

DR. KIM: Hi. This is AeRang Kim from Children's National in DC. This question is for Dr. Diede.

Thank you for your talk. I found it very interesting, and I really pondered on your comment and how do you define same in class in terms of PK toxicity and efficacy. I also was very interested in the one commonly MEK [indiscernible] classes, checkpoint inhibitors that greater than 30,

different types of products were actually at one point under evaluation, and it doesn't make sense to study all these, obviously, in children at particular -- I don't know if it doesn't, but how can one study all of these in children?

I guess my question really is, in terms of industry, because it is a competitive field, how do you feel industry, in terms of different companies, can work together in order to make selections or the best opportunities to study these same-in-class drugs for pediatrics? How can they work together in order to identify the best treatments to move forward?

DR. DIEDE: Hi. Thank you. This is a Scott Diede from Merck. That's a really good question that I don't have an answer to, to be honest, and I'm still learning and thinking about the best way to do this.

One of the ways I've actually had some of the best conversations with my colleagues, in this example that I gave as sort of a case study that predated RACE -- obviously quite a number of years,

but, once again, I think highlights many pertinent issues -- is in these ACCELERATE forums, I was able to talk with my colleagues from Roche and BMS, as well as the academic investigators involved in those pediatric trials, to be able to try to, in the way that we can, share information because, obviously, there are intellectual property issues and so forth.

I got the sense that while the adult space is very competitive, the pediatric space, I think there is a realization that we're really all trying to work together to try to help children with cancer, which is in a way somewhat different. It's definitely different from a larger financial aspect for industry, and we're doing this to really do the right thing.

I think forums like that have been a good venue to be able to have discussions, and I know there have been discussions about trying to put together some sort of pre-competitive space to be able to have some further discussions, but I haven't seen a lot of those, and to be honest, I

don't know exactly how they would work.

I would be open to trying to better understand that, and I don't know, actually, if any other folks on the committee, or Dr. Kraus maybe, could even elaborate on that. But I think it is an important question about how can we share pertinent information, especially for peds drug development, to be able to make these informed decisions. I, unfortunately, don't have the best answer right now.

DR. KIM: Thank you very much.

DR. PAPPO: You have any additional comments or questions, Dr. Kim?

DR. KIM: I have no additional comments or questions. Thank you.

DR. PAPPO: Okay. Dr. Laetsch?

DR. LAETSCH: Thank you, Dr. Pappo.

My question was almost the same as Dr. Kim's, and was also for Dr. Diede. I don't know if there's going to be an additional response, but I would just highlight that I agree that the ACCELERATE-like meetings, the multistakeholder

meetings, are very important to help align thinking among industry, academic, cooperative groups, and regulators.

I just would highlight the challenge is still -- the example that you gave was after 250 patients had been enrolled to checkpoint inhibitor trials, and it's a welcome input from anyone, my question for Dr. Diede, about ways to do that earlier in development and prioritize the agents up front when there are multiple agents in class being developed with similar timelines.

DR. DIEDE: Hi. This is Scott Diede from Merck. The only thing I might add is I totally agree with you that you can't have an ACCELERATE forum for every, in a way, sort of question that would be pertinent, and it does take time/effort, and we were in a very specific situation there. Once again, I think it worked out very well.

I know ACCELERATE has also tried to work much earlier about not only so much same in class, but what targets are relevant for particular pediatric cancers, and then trying to put

statements out as a community about what targets they think should be prioritized.

It's I think getting to earlier in development and a little bit maybe out of scope for the same-in-class question, but this is incredibly pertinent; that I think similar multistakeholder forums can be more driven before we have any of this pediatric data about what targets actually make sense to study. I think that can help companies, and that can help regulators as well. But I definitely would love to hear any other participants' thoughts around this as well.

DR. KRAUS: This is Albert Kraus, Pfizer and industry representative. Just around the last two questions and what's being said, we do have forums and common activity occurring through organizations like pharma and bio. This is the reason I was asking Dr. Reaman about, basically, data capture around why we ramp all these trials and efforts up, and where do we stand on continued accrual, slowness of accrual, and the ability to complete some of the trials that are more rigorous than

20 years ago when we're looking at this in many cases.

Groups like COG, and Euro [indiscernible] Ewing, and others that we've been working with on various fronts, I think it's important. We're going to probably want to capture that and see where -- we talk about the numbers are a lot, but I think when we started to gather metrics, we're going to see how difficult it is to operate in what manner that we want to operate. We may not be able to do everything that we'd optimally like to do in so many rare diseases with particularly small numbers of patients and targeted molecularly driven subsets of already very rare child tumor settings.

So I think it's a to be continued, but there are mechanisms for data share. ACCELERATE's been mentioned, a very good one in this case, but there are other mechanisms, too, and other groups with data share and common industry cooperation that also should, of course, be beyond industry, with FDA, with academia, and with children's cooperative groups. So I think they're still involved, but

that's just my perspective.

DR. PAPPO: Thank you, Dr. Krauss.

Any other comments?

(No response.)

DR. PAPPO: Ted, does that answer your question?

DR. LAETSCH: Yes. Thank you very much.

DR. PAPPO: Next, we have Dr. Ira Dunkel.

DR. DUNKEL: Thank you, Dr. Pappo.

This is a question I think both for Dr. Diede and for maybe the FDA, EMA, staff members.

To me it seems like there's been a compelling argument that when you have a class of agents that's ineffective in pediatrics for the most part, like anti-PD-1 agents, that waivers of newer agents should seriously be considered to be given. But it's less clear to me what everyone thinks about new agents being developed in a class where the prior agents clearly work.

So if there's NTRK inhibitors, new BRAF inhibitors, new MEK inhibitors, but we have

existing agents that have demonstrated efficacy in pediatric oncology, would that also be a reason to consider granting waivers, or does prior efficacy in the class perhaps mandate more serious consideration of requiring additional trials in newer agents in the class?

DR. DIEDE: Hi. This is a Scott Diede again from Merck. Maybe I'll just briefly comment, and thank you for that question. My hope as a drug developer is let's say there was an MTRK [ph] inhibitor already out there, there was data, it was approved, and then I as a drug developer am developing a, quote-unquote, "new" MTRK, I hope it would be new and different in an important way that could actually help with efficacy.

For example, maybe if there were mutations that arose while being treated with the first generation, this new generation maybe might work to some of those resistant mechanisms. This is an easier low-hanging fruit scenario to say it would probably make sense, then, to study that potentially in children because there really is a

difference.

For some of the, I guess for lack of a better term, me-too drugs, I guess I would really be looking at the current approved drug to see are there some ped-specific issues that really are lacking. Once again, obviously, if there was a formulation issue, and the new compound could help with that, that might be worth studying. But if there really isn't something obvious there, and it is more of a me-too drug, if you will, then I have to admit, I don't think studying it in children, in addition, is that helpful for the field. That's still a very hard question because it is, how do you really get all that information? But I'll stop there and let others from the FDA comment on that.

DR. REAMAN: This is Greg Reaman from the FDA. I would echo, in large part, Dr. Diede's response. I just want to, again, caution -- and I've been involved in the ACCELERATE platform for many years. I've been a member of the steering committee of ACCELERATE for many years, and I want to make it clear here that we're not discussing

prioritization of which same-in-class products to carry forward in definitive development, in pediatric cancer in general or in specific pediatric cancers.

In large part, the example with the PD-1/PD-L1 inhibitors, 250 patients enrolled on studies of three products, three different pharmaceutical sponsors, what we're hoping -- to really come to some agreement and get some insight from the committee -- here is, how could we have avoided that early; not to wait for a strategy forum, but to actually, as product applications come in, associated, or preceded I should say, actually by a pediatric study plan where there's a requirement, unless there's a reason to waive, what characteristics and what parameters can we use to actually say that the studies may not be warranted if multiple same-in-class products have already been studied or are in the process of being studied? And what would warrant the investigation of yet another same-in-class product?

This situation that we're trying to adjust

to is a little bit different than I think some of the examples and discussions that we've had. This really goes back also, I think, to Dr. Dunkel's question.

Again, because there are known products that are active, and there may be targeted products that are actually approved for specific pediatric indication, and if there is a, quote-unquote, "same-in-class" product or next-generation product that is directed at the same target that has evidence of greater efficacy or approved efficacy in a specific population, even an adult population, and if it has a better toxicity profile, then is that a consideration, or should that be a consideration that would warrant an investigation of yet another same-in-class product?

It's the parameters that we would like to use to be consistent and to be fair and equitable that we really need to, I think, be addressing here.

DR. SABER: May I chime in?

DR. PAPPO: Of course.

DR. SABER: This is Haleh Saber, FDA. I think it's crucial to define the class of the same-in-class product. We have defined classes of products for different reasons, but for the topic of interest for today's discussion and pediatric studies, it's what do we really mean by the same class, and it seems like we are discussing the same target.

I think it's easier to discuss that in terms of antibodies because they are highly specific for the target. When it comes to small molecules, there are often multiple targets that are being affected and inhibited. Even if the primary target in drugs 1, 2, and 3 are the same, and there is the same exact binding and affinity, the other targets might also contribute to anti-tumor activities, as well as safety and toxicity.

For the question that was raised in terms of if the drug is negative in a pediatric population, does it really mean drug 2, the so-called in the same class, is also negative; it will depend on the secondary pharmacology and what we know about the

drug. So again, how we define the same-in-class is important, and it's sometimes easier to define it for antibodies, and it's more difficult to define it for small-molecule drugs.

DR. PAPPO: We're going to move to the next question because we still have three or four members that would like to participate in the question-answer session.

Dr. Kraus, you're next.

DR. KRAUS: If you're speaking to me, my hand's down. I had chimed in previously if you're saying Kraus.

DR. PAPPO: Okay. Thank you so much.

David Mitchell, you're next.

MR. MITCHELL: Thank you, doctor, and I want to thank both Drs. Wang and Diede for their presentations. They were really helpful.

I have a question, actually, for the FDA. I am not clear on the process whereby the FDA decides to grant a waiver. I don't understand internally what you go through and who participates in the decision-making process to grant a waiver. Can you

tell me how that works at the FDA?

DR. REAMAN: This is Greg Reaman. I could tell you. And we're actually not talking about granting waivers because granting waivers is done at the time that an application is submitted for review and approval, and generally for an adult cancer indication.

What we're talking about here are actually early pediatric study plans that need to be submitted to the FDA before a company submits an application for which a decision, with respect to agreement to the plan, needs to be made before an application submitted; and it's the company's plan to request a waiver.

So the considerations for waiver are, to some extent, included in our guidance, and the discussion of these planned waiver requests, or planned deferral requests, are made at an interim review committee, the pediatric subcommittee or the pediatric review committee, which over the course of a year reviews about 180 initial pediatric study plans for cancer products.

We basically review the study plans that have been submitted, and as part of those study plans, there's a discussion of the adult indication for which a drug is being developed. There's information provided on the characteristics of the drug. There's a discussion generally about the prevalence of the indication, the adult indication, like breast cancer, prostate cancer, that may occur in the pediatric population.

Now there is required to be a discussion of the relevance, or potential relevance, of the mechanism of action of the drug at a molecular level; what molecular targets; what pathways; and what cell-surface related antigen drug may be directed at, that maybe is potentially equitable for therapeutic use in a pediatric cancer population.

We review and evaluate what the sponsor's plans are with respect to an initial preliminary pediatric study or investigation that is spelled out in the legislation, a molecularly targeted pediatric cancer investigation; or their planned

requests to waive based on a number of parameters, or generally a plan to request a deferral, and primarily a deferral of the submission of the results of the study because they're generally close to submitting their application, and we don't want to delay the approval of a potentially -- or perhaps potentially, but an effective drug in the adult population who may require it. We agree to those deferrals for submission of results after the application is submitted.

That's the internal process. This internal review committee consists of pediatric oncologists; pediatricians; clinical pharmacologists; molecular biologists; experts in chemical manufacturing compliance, and basically mimics the large pediatric review committee that provides the same sort of oversight for pediatric study plans and proposed pediatric study requests for the entire FDA.

MR. MITCHELL: So if I'm understanding this right -- and I'm a layman -- it's all a part of the review of the new drug application.

DR. REAMAN: It actually precedes the new drug application. So it's a component, and there has to be agreement with the agency for a pediatric plan prior to actually submitting the application. But there has been discussion, generally, between a sponsor, or an applicant, and the review division prior to their submission of an application, and there are frequently discussions about the potential applicability as a product to the pediatric cancer population before that time as well; and as Dr. Diede I think mentioned, the early advice meetings or Type F meetings that we can have with sponsors. This process actually precedes the submission of an application and the formal review of an application for an adult indication.

MR. MITCHELL: Got it. Okay, one more question.

It's often been said by the scientists and doctors on this call that when we say it's the same class of drugs, that frequently we don't know exactly what we mean by that. How do you at the FDA come to a decision and say, yes, this is

essentially the same class of drugs, the same mechanism of action, and what have you?

Many people have said we're not clear, when we say that, what we mean. I'm asking, what do you mean? How do you arrive at that decision if it's not clear?

DR. REAMAN: I think my response to that would be multifaceted, to some extent, and Dr. Saber did make some comment about monoclonal antibodies. But I think it can be extended to small molecules and some situations as well. But generally, when we're talking about a class, or drugs with the same mechanism of action -- and they may not even have the same molecular mechanism of action because an antibody against the target may work differently than a small molecule with a particular target.

So we're talking primarily about targets and inhibition of those targets, and in some situations they are same-in-class drugs. They're antibody drug conjugates and monoclonal antibodies to the same antigen that frequently use the same linker,

and sometimes not associated with different cytotoxic payloads.

So we really are focusing on what makes a drug same in class as much as we are what makes a drug similar enough to another drug where we would have reservations or have concerns about duplicative studies, or requiring studies that we know might not be able to be completed, and we are, in essence, potentially wasting precious patient resources. I guess that's how I can best answer same in class.

DR. SABER: Yes. And to add to Dr. Reaman --

(Crosstalk.)

DR. PAPPO: Sorry. We're going to have to go to the next -- we only have time for one more question, and then we have six different topics to discuss. Sorry.

I'm going to allow Dr. Ro Bagatell to ask her question, and then we're going to move to the discussion points of the meeting.

DR. BAGATELL: Thank you so much, Dr. Pappo.

Most of the discussion has quite appropriately been about the process for thinking about same-in-class designation for agents that are developed for adult oncology purposes with kind of a P.S. about pediatrics. As I've been listening to this, I've been thinking about the few situations in which drugs are developed specifically for pediatric cancer targets, for pediatric indications. They are very similar to each other and maybe have different formulation, maybe different routes of administration or duration of administration, but it's the same patients, and we run into the same problem of not enough patients, which I guess is a good thing, but still we want to have the best drugs for kids.

So my question is, what are the implications of this discussion for those kinds of agents, specifically for the pediatric population?

DR. REAMAN: This is Greg Reaman. Can you provide an example?

DR. BAGATELL: I guess the one that comes to mind most immediately is something like an anti-GD2

antibody. I'm totally biased by my neuroblastoma background, but I'm sure there are others.

DR. REAMAN: Sure. I think our considerations apply to products that are developed for adult cancers, as well as pediatric cancers. As you, hopefully, well know, there are many more of the former than the latter. I think any requirement that we would have for investigation of a drug that may be directed at the same target would, again, have to include the same principles: the potential differences in activity; differences in toxicity profile; route and frequency of administration; its activity as a single agent versus its activity in a combination setting; and when and where the drug is going to be utilized in the early part of therapy, the induction phase of therapy versus a post-consolidation phase of therapy.

So they would all be, I think, considerations for evaluating, at least making reference to the example that you provided.

DR. BAGATELL: Thank you very much. That's

helpful.

Questions to the Subcommittee and Discussion

DR. PAPPO: Okay.

Thank you very much for a very lively discussion. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We're going to start with question number 1. Would the FDA read the first question?

DR. REAMAN: Yes. Sorry. I'm double-muted here. I apologize.

Consider the degree of unmet clinical need in a specific disease context that should influence decisions related to planned waiver requests for pediatric studies of multiple same-in-class novel

agents, given the proviso that same in class may not be the best way to actually describe these products.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion, and Joyce is going to help me here prioritize your questions.

Let me see. Okay. David Mitchell, do you have a question? No, I meant on -- put your hand down. Put it down right now.

MR. MITCHELL: Sorry.

DR. PAPPO: Okay. We have Dr. Gorlick.

DR. GORLICK: It's Richard Gorlick. Sorry. I put my hand down as well. I have a comment, but not a question related to the question.

DR. PAPPO: Okay.

Does anybody have any consideration as to the unmet clinical needs for a specific disease [inaudible – audio gap] and how decisions could relate to planned waiver requests for pediatric studies?

Does anybody feel that [inaudible – audio gap] data might be important to decide which agent to move forward and whether there should be waivers issued for that, just as the availability of the drug, PK, CNS penetration, and things like this?

I'm just trying a little bit of discussion on this first question, so we don't go blank without any recommendations for the FDA.

Julia?

DR. GLADE BENDER: Hi. Thank you, Alberto. Julia Glade Bender from Memorial Sloan Kettering. The way I am interpreting this question is should the unmet clinical need of the potential diseases for which the agents are being developed weigh into whether something might be eligible for a waiver request, et cetera.

I think my problem with the idea of unmet clinical need is we have a lot of unmet clinical needs in pediatric oncology, and hopefully that is what drug development is all about. But there are some very, very rare pediatric cancers like rhabdoid tumor, or pleuropulmonary blastoma, and

some very, very rare entities, where even though there is huge unmet clinical need, there are certainly not enough patients to test many drugs. So it's this balancing of unmet clinical need with pragmatism about what can actually be done regarding these decisions and how similar, then, is the next in-class agent to the agent that may or may not already be in clinical trials.

So I understand that it's the sponsor who brings the proposal, but they may or may not truly appreciate the context of the rarity of the patients and whether or not the proposal is actually feasible, if that makes sense.

DR. PAPPO: So you think that in the development of a specific waiver and also in consideration of multiple in-class agents, the sponsor and the FDA should take into consideration the specific disease and the need for the specific disease, especially in very rare diseases such as rhabdoid or PPB? Did I get that right?

DR. GLADE BENDER: That's right. There's a large degree of unmet clinical need, perhaps, but

there's also a very limited number of patients. So it's that context of rarity that needs to also be balanced in with the unmet clinical need.

DR. PAPPO: Okay.

I believe Dr. Gorlick wants to comment also.

DR. GORLICK: Yes. It's Richard Gorlick from MD Anderson. I did want to comment. Sorry about the earlier confusion.

I actually am going to make the case that it isn't the degree of unmet clinical need that should be the predominant definer of a waiver request. In clarifying that statement, I think there are poor prognosis malignancies where clearly there's a clinical need. So whether that's metastatic solid tumors, CNS tumors, or other diseases with poor prognosis within the pediatric space, those are certainly areas where additional drug development occurs.

The implication is there's unmet clinical need in a domain where the prognosis may be better. So in those categories, we're talking about diseases with cure rates in excess of 90 percent.

And I will argue in the diseases where we have a favorable cure rate, much of that is accomplished with cytotoxic chemotherapy that is traditional. Many of the novel agents that exist today have much more favorable toxicity profiles. I think there are certainly selected cases where an agent has a lot of promising activity and favorable prognosis disease where it may be associated with less toxicity. I think granting waivers in that case would also not be advisable.

So responding specifically to this question, unmet clinical need could be a factor, but I don't think it should decide exclusively whether a waiver is granted. It's other factors that define that. Thank you.

DR. PAPPO: Steve, do you have a comment?

DR. DuBOIS: Yes, thank you. Steve DuBois from Dana-Farber. I'm reflecting on the very interesting discussion earlier about how many patients are needed to be treated to feel comfortable that we've potentially reached the right conclusion. It was 250 patients treated on

the checkpoint inhibitor trials. Was that too much or is that too few?

I think it sort of depends, in my view, a little bit on the level of efficacy in initial adult testing. In the case of the immune checkpoint inhibitors, it seems like we needed to be really sure of the level of activity in pediatrics before making a conclusion, given the really transformational activity seen in adults. So I would think that some of this thinking about waivers and concluding that an agent is not active in pediatrics probably depends on whether we're talking about a really transformational modality versus something that maybe extends PFS by 2 months in adult malignancies.

DR. PAPPO: I think that's something that can also be based very strongly on preclinical data if somebody's studying a very, very rare cancer, like Julia Glade Bender was saying, rhabdoid or PPB, and you find a specific target that is being developed in adults for another specific disease. I think that that should be taken into

consideration whether a waiver should be requested or not, unless anybody else disagrees.

Do I have any other comments or any suggestions?

Greg, do you want to comment at all?

DR. REAMAN: No. It was just a question as to what role, if any, unmet clinical need -- however one defines a clinical need, poor prognosis or current standard of care is very toxic -- how that, or should that, actually influence any decisions about evaluating more than one drug with the same mechanism of action in an early investigation, and I think there's been some discussion about that.

DR. PAPPO: Will, do you have a comment?

DR. PARSONS: I do. This is Will Parsons from Texas Children's Hospital. Most of my comment has been [inaudible – interference], but my first comment was that we really need to be thinking about clinical need broadly, which I think several folks have emphasized, so not just talking about poor prognosis tumors, but tumors where the

therapies are toxic, and a number of the targeted therapies were unclear on the long-term toxicities because we just don't have data.

So we need to think about it pretty broadly, and once we do that, I think clinical need is unlikely to be a high-level determining factor for many of the agents being considered, given the large number of areas that we have clinical need in pediatrics, specifically for some of these rare tumors. So feasibility and some of the other concerns I think are likely going to override this.

Presumably in cases where there's a less compelling clinical need, there's also less compelling motivation for everyone involved in this partnership to cure pediatric cancer patients and developing new therapies for those patients. That's all I have to say.

DR. PAPPO: Steve, do you have another comment?

DR. DuBOIS: No, I've lowered my hand. Thank you.

DR. PAPPO: Basically, just from the

discussions that we've had, I didn't feel that the panel felt very strongly that the degree of unmet clinical need should significantly influence decisions related to planned waiver requests for pediatric studies.

Is that a fair statement?

(No response.)

DR. PAPPO: Anybody?

DR. PARSONS: This is Will Parsons. I believe so.

DR. GLADE BENDER: Yes, I agree.

DR. PAPPO: Based on what I've heard from Julia and from others, and Richard, I believe that pretty much encapsulates what we discussed for question number 1; is that correct?

FEMALE VOICE: I think that accurately --

DR. PAPPO: Okay.

GLADE/BENDER FEMALE VOICE: I think unmet clinical need in its broadest sense.

DR. PAPPO: Okay.

We will now move to question number 2, and the FDA is going to read the question for us.

DR. REAMAN: Question number 2, consider the importance of any comparative efficacy results of same-in-class agents in one or more adult cancers, as well as any available comparative toxicity data -- the type, the magnitude, and the frequency -- that could contribute to a decision where evaluation of more than one same-in-class product in children might be warranted.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion. I'm going to wait for Joyce to help me with this.

I personally think that it's a very important point to consider when you are developing or trying to study same-in-class products based on the adult data. For example, a perfect example would be, for example, ALK inhibitors and what was learned from crizotinib, and then more recently lorlatinib; and comparative studies, for example, with NTRK inhibitors and the incidence of a variety of complications that may be particularly pertinent to pediatrics, for example, multiple bone fractures

with entrectinib.

I have Andy Kolb here. Any comments?

DR. KOLB: Yes. Thank you, Alberto. I think the ALK inhibitors are a great example of the importance of comparative efficacy/comparative toxicity. I think that with the RACE Act, though, we are seeing agents earlier and earlier in phase 1 development in adults. At least we're having conversations with companies long before the end of phase 1, and comparative efficacy data are either insufficient or non-existent, and we're often making decisions about pediatric development before we have that data.

When available, I would consider it to be of utmost importance, but I have a feeling it's going to be less and less available at the time we're considering pediatric trials, and really making sure that we have dosing and drug interaction data in adults I think will be a primary driving factor in which drugs we're most enthusiastic about in children. Thank you.

DR. PAPPO: Thank you, Andy.

Richard, do you have a comment?

DR. GORLICK: Thank you, Dr. Pappo.

I think the comparative efficacy results in adults is immensely important in the context of pediatrics. If we think about efficacy data, we know we have a reasonable biological understanding of when pediatric malignancies are similar or different to their adult counterparts. When they're similar, relative efficacy is likely to be similar.

I think toxicity also is very, very informative, but I think at the same time, there you have to take note of the specific differences between adults and kids. As an example, kids tolerate myelosuppression, or at least the peds oncologists tolerate myelosuppression to a greater extent. But the results from the adults are likely to be similar as the kids, and as long as that's filtered appropriately to a pediatric context, it's very, very relevant. Thank you.

DR. PAPPO: Thank you very much.

Dr. Glade Bender?

DR. GLADE BENDER: Julia Glade Bender, Memorial Sloan Kettering.

I wanted to echo what Andy Kolb had said and what Dr. Gorlick had said. When available, comparative efficacy in human adults and comparative toxicity in human adults is very important. But sometimes at the point that these decisions are being made, that doesn't exist, and it's being extrapolated from either preclinical testing or from basically the, for lack of a better word, pitch from pharma about trying to explain why their drug isn't a me-too drug but rather an improvement on an old drug.

So I feel like early on in drug development, before a new agent has its first adult indication and there is not necessarily the preponderance of data to support it, to me, that part should not influence. It should be actual real human data that carries significant weight as opposed to theoretical comparative efficacy and toxicity data, based on preclinical testing or molecular chemistry, if you will.

DR. PAPPO: Thank you very much.

Dr. Kim?

DR. KIM: I just want to echo, and I agree with all the prior discussants. I do think that when we think about the later generation products and these same-in-class products, many of these considerations for waivers would be the importance of the comparative efficacy of adults in both efficacy and toxicity, and would be a clear importance when we're thinking about whether or not to evaluate in the pediatric population.

DR. PAPPO: Thank you very much.

Donna?

MS. LUDWINSKI: Thank you, Dr. Pappo. This is Donna Ludwinski from Solving Kids' Cancer.

Just following on your comments, Dr. Pappo, about the crizotinib and lorlatinib example, I saw what was an additional interesting thing about what happened in the adult data before lorlatinib was tested in children, was the fact that not only was efficacy quite different -- the results in the adult lung cancer patients -- but the toxicity

profiles radically different between the two drugs, and the property of penetrating the blood-brain barrier, in that some of the lung cancer patients had brain metastases that resolved; and lo and behold, brain metastases can happen in neuroblastoma, albeit rarely.

At least from a patient or an advocate perspective, I think those are extremely compelling issues that would weigh in on the decision, even those interesting property differences. Thank you.

DR. PAPPO: Thank you very much.

Will?

DR. PARSONS: This is Will Parsons from Texas Children's. My comments are very similar to the rest, but I guess the one thing that really is striking to me about this discussion is, in the context of quite rare subsets of pediatric cancers -- which is what I've spent much of my time thinking about the last few years through the NCI-COG Pediatric MATCH trial and others -- there are really two different decision points. One is likely to be, as Dr. Kolb first pointed out, making

a decision about a very small number of trials in an early situation where you have very limited data on comparative efficacy of the agents in adults or the rest of the things we're discussing.

So some rational decision needs to be made based on those preliminary data, but then perhaps the equally critical point is how to then incorporate and systematically review and take into consideration the ongoing generation of data over the next handful of years; for example, as the adult trials are being completed, the very first pediatric trial or two is being completed, and how to make the decisions from that point.

So I think in some ways it's the same goal, but in some ways they're different tasks and a more limited information situation, and then one hopefully down the road where there's ability to make a decision, incorporating much more extensive, hopefully, adult data, as well as at least some modicum of pediatric toxicity and efficacy data.

DR. PAPPO: If I can encapsulate some of what the panel believes, we believe that definitely

comparative efficacy results in adults are very important in deciding when to move to different compounds that are in the same-class products in children with cancer. Sometimes there is a lack of data in the adult world, but it would be nice to have that to complement our decision.

We also need to take into consideration preclinical studies. Also, when we evaluate the toxicity of some compounds in adults, we need to take into consideration the pediatric population. Some of the pediatric population might involve the more vulnerable to some of the toxicities that are seen in adults, and some of the toxicities that are seen in adults might not be as relevant in pediatrics; for example, the incidence of neutropenia.

The other, I believe that's pretty much what we talked about unless anybody wants to add anything. I think that pretty much encapsulates everything on question number 2.

Anybody else want --

DR. KRAUS: Dr. Pappo, this is Albert Kraus,

Pfizer, industry representative, and one comment. I did put my hand up, and really I almost said it very early around the question.

I agree with everything people were saying, your summary, and all that. One thing I wanted to bring up, though, being somebody who grew up on the research side of things and then participated much more in the development side of things, is we have a lot failure. Even though comparative efficacy in adults is interesting and important, I looked through the questions, and the precedent or lack of precedent of activity in pediatrics, particularly given its often changed tumor settings, may be a very important element as well in this.

You can have a lot of comparative efficacy in adults, but if your first three agents out the gate of same class all failed in a bunch of deep [indiscernible] settings, perhaps that's a big factor in this discussion. I didn't see it in other questions. I wanted to bring that out because I think it might be an important kind of extra element in this question.

DR. PAPPO: Thank you, Dr. Kraus, and I apologize for not seeing that you raised your hand.

DR. KRAUS: No problem.

DR. PAPPO: If there's no further discussion of this question, we will now begin with the next question, and we will ask the FDA to request number 3.

DR. REAMAN: Thanks, Alberto.

Consider whether differences in specific product quality indicators, dosage forms, route of administration, impact clinical benefit considerations and might influence a decision to investigate multiple same-in-class products.

DR. PAPPO: While I wait for Joyce to start the comments, I would say that it would be very important, in my opinion, to consider these differences, for example, CNS penetration; oral versus IV, cost; the patient that has to be admitted to the hospital or can be based on outpatient; CNS penetration, but let's see what our panel thinks, and Joyce will let me know. She will start typing.

I see a lot of hands there, and I start with Will. That is the first hand I saw go up.

DR. PARSONS: It's Will Parsons from Texas Children's.

Alberto, I agree with you. That's critically important, especially for these patients. All of those factors play such a huge role both in terms of our ability to effectively use those agents over the long term, our ability to ethically and kindly conduct clinical trials in the shorter term, and then identify based on an example. For example, in the CNS penetration, particular drugs for particular populations, I think this is absolutely critical.

DR. PAPPO: Andy, I see your hand up.

DR. KOLB: Yes. Thank you, Alberto. I don't think I was the first, but I would just like to add my endorsement. I would add to this list interactions with common concomitant meds in children, CYP3A4 for example, and how that may impact dosing and ability for chronic administration of these drugs. Thank you very

much.

DR. PAPPO: Thank you very much.

Joyce Yu?

DR. YU: Hi, Dr. Pappo. This is Joyce. Did you have a question?

DR. PAPPO: Okay.

DR. YU: Dr. Pappo, can you hear me?

DR. PAPPO: Okay. I saw you. Sorry.

Ro Bagatell is next. Sorry.

DR. BAGATELL: Yes. I agree with what everyone has said, but also on one of the slides I noticed one of the speakers had put in the number of times per day that you dose medicine, so that's kind of dosage form, but it's more dose schedule. Trying to get a kid to take a nasty tasting drug once a day versus 4 times a day is actually significant.

DR. PAPPO: Okay.

We have Julia Glade Bender next.

DR. GLADE BENDER: Yes. Julia Glade Bender, Memorial Sloan Kettering. I was going to make the same point as Ro, that schedule is an important

quality here that is missing, not only taking a drug fewer times per day, but even if it's dosed fewer times per week orally. Obviously, palatability is in here as well, but even IV, if the schedule -- for example, with the PD-1 inhibitors, the difference between an IV once every 2 weeks, once every 3 weeks, once every 6 weeks, these are major quality-of-life improvements for our patients.

Then I agree with the potential for the agent to be used in combination with agents that are classically used in pediatrics because, ultimately, what we really want to do is cure more patients up front, and upfront therapies are quite complicated, so the ability to use them in combination would be very important.

DR. PAPPO: Dr. Laetsch?

DR. LAETSCH: Thank you. It's Ted Laetsch, Children's Hospital of Philadelphia. I agree completely with what everyone else has said, that these are very important considerations. I would just say that I have, I think, the same concern

that Dr. Dunkel expressed previously about some potential inadvertent consequences if we overly wait the current availability of an oral liquid formulation for young children, in terms of discouraging sponsors from early development of that if they want to avoid the requirements of this act.

I agree with Dr. Reaman that I certainly don't view child drug development as a punishment, but I do think there may be some sponsors who would prefer to have a waiver, and we certainly don't want to provide a disincentive to development of a liquid formulation.

DR. PAPPO: Thank you very much, Ted.

Steve, do you have a comment?

DR. DuBOIS: Yes. Steve DuBois, Dana-Farber. I agree with what's been said, and just to highlight the dosage form, I think it's really a key factor. If another in-class compound came along that, for example, replaced isotretinoin, I think our families would be grateful not to have to try to figure out all sorts

of ways to administer isotretinoin to toddlers. Indeed, there's data from the UK that the PK with the way we're currently administering isotretinoin is not optimal, so I think there's a lot to be thought about in terms of dosage form.

DR. PAPPO: I don't see any other hands up, so I'm going to try to encapsulate the discussion of the panel for question number 3. I believe that everybody believes that the product quality indicators should influence a decision to investigate multiple same-in-class products.

The important things should be the schedule of the drug; the pharmacokinetics; the palatability; the impact of this specific drug on the quality of life that brings in a schedule; outpatient; frequency of administration; and the potential consequences of not having an oral formulation for some of these patients, and the panel believes very strongly that that should be considered in the future.

I believe that's about it unless I missed something.

Did I miss anything else or does anybody want to add anything to what I just said?

DR. GLADE BENDER: Potential to use in combination.

DR. PAPPO: Ah, that's right. Okay, the potential of this drug that could be used in combination with other agents.

Thank you very much, Julia.

Okay. If there is no further discussion on this question, we will now begin the next question, which is question number 4, and we will ask the FDA to read the question.

DR. REAMAN: Thanks, Alberto.

Consider the importance of nonclinical efficacy data on whether pediatric investigations of more than one same-in-class products are warranted in children, and if/when preclinical studies in pediatric-specific models might be required.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion. I'm

going to let the panel lead this one, and I'm going to wait for Joyce to tell me who is raising their hand. I don't see any hands raised yet, but I'm sure that it'll become relatively soon.

Please? I see one.

Ira?

DR. DUNKEL: Thank you, Alberto.

Ira Dunkel, Memorial Sloan Kettering. I think that the clinical data certainly would be much more important than the preclinical data, but if there were relevant pediatric clinical models demonstrating significantly different efficacy and/or toxicity, I think that should be taken into consideration.

DR. PAPPO: Thank you.

We have Julia Glade Bender.

DR. GLADE BENDER: Thank you very much. I agree with Ira that clinical data should trump preclinical data, but in that space that we discussed of really very rare tumors, where the opportunity to study multiple agents will be very difficult.

I think the nonclinical data is very helpful. For example, there are very few pediatric patients with ALK mutations, so I think preclinical data on neuroblastoma ALK and certain ALK mutations, neuroblastomas, preclinical data I think contributed significantly to moving forward some of the newer agents in class. So I think this helps us with the rare disease issue.

DR. PAPPO: Thank you very much, Julia.

Anybody else that would like to express their opinion? Joyce is typing, so somebody else must be interested in saying something. Hold it just for a second.

DR. YU: I don't see any other hands raised.

DR. PAPPO: Okay. This was a relatively straightforward question. We believe that clinical data is significantly more important than others to evaluate same-in-class products. However, for very rare diseases, clinical data should be taken into consideration.

Does that encapsulate your views, Ira and Julia?

(Inaudible response.)

DR. PAPPO: That's probably yes.

If there is no further discussion of this question, we will now move to the next question, which is question number 5, and FDA will read this question.

DR. REAMAN: Thank you, Alberto.

Consider the specific pharmacological parameters that should be considered and the importance of central nervous system penetration when primary CNS tumors may be key target tumors of interest when evaluating the need for pediatric investigation of more than one same-in-class agent.

DR. PAPPO: I have to say, if there are no questions or comments concerning the wording of this question, we will now open the question for discussion.

I believe that it's very, very important to take into consideration CNS penetration, not only for primary CNS tumors, but as Donna was saying, for diseases that may metastasize to the brain that may respond to targeted therapies; for example,

lorlatinib or other agents like NTRK inhibitors, and whether some have better CNS penetrations than others. So I think it's a very, very important consideration when we're going to do a pediatric investigation of more than one same-in-class agent.

Let me see; who do we have here?

Will, I think that you are next.

DR. PARSONS: Will Parsons of Texas Children's. I agree with you, Alberto. It's a very important consideration. I'd just like to emphasize that these should also be considered more broadly with any available clinical data in adults -- for example, where there's experience with efficacy, or lack of efficacy, or any evidence in patients -- in whether the drugs have CNS penetration in addition to laboratory and model parameters, to evaluate that.

DR. PAPPO: Thank you very much.

Do I see Ira?

DR. DUNKEL: Thank you, Alberto.

Ira Dunkel, Memorial Sloan Kettering. Of course, I agree, too, and I just was also going to

make the point that the converse could also be true. For a drug that has central nervous system -- or a class of agents that has potential central nervous system toxicity, if the disease that's being considered is not one with CNS metastatic potential, or not a primary CNS tumor, that lack of blood brain barrier penetration could be advantageous. So it could work in both directions.

DR. PAPPO: That's a very, very good point.

Anybody else would like to comment on question number 5?

(No response.)

DR. PAPPO: Joyce, do you have anybody that has -- I don't see anybody here, but I will --

DR. YU: I don't see any hands right now.

DR. PAPPO: Okay. So based on the limited panel discussion, we do believe that CNS penetration is an important factor when considering evaluation of pediatric investigation of more than one same-in-class agent. Not only related to efficacy of the drug, but in cases where there is

no need for significant CNS penetration, if you have a drug that has significant side effects in the CNS, that should be taken into consideration when you're evaluating this class of agents.

If there is no further discussion of this question, we will now begin with the last question, which is question number 6, and we will have the FDA read this question.

DR. REAMAN: Discuss the extent to which sponsors should include sufficient data to address the features discussed in initial pediatric study plans to inform assessment and decision making, and whether other features should be considered in decision making about waiving requirements to investigate multiple same-in-class drugs.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open for discussion, and I'm going to start looking for some hands here and for Joyce to help me.

We have Ted Laetsch.

DR. LAETSCH: Hi. Ted Laetsch, Children's

Hospital of Philadelphia. I would agree that sponsors should certainly include the data that's available in their initial pediatric study plans relative to the items we've discussed. I would just highlight the discussion we've had about the early decision-making time frame during which these are developed, and the need to be respective of emerging scientific data over time. So the use of things like deferrals versus waivers and/or flexibility in these plans if the science changes will be important as well.

DR. PAPPO: Thank you very much.

Dr. Kraus?

DR. KRAUS: Albert Kraus, Pfizer, industry representative. I guess this could be a place where my prior comment goes, which is to me it seems perhaps very pertinent in same-in-class drugs, given the data, flow [indiscernible] will be different on different drugs.

If there's a good drug in adults in tumor setting X, if it's inactive in multiple places in pediatric settings that are logical, as well as,

say, a second one, I think the lack of pediatric activity, regardless of comparative adult efficacy, is a big driver. I think Dr. Reaman had it in his slides, but he didn't ask a lot of discussion in the questions on it; maybe because it's obvious. But I would lay it out there because this is a situation that occurs and impacts the industry around decision making, and what makes sense, and what proposals. That's a comment. That's all.

DR. PAPPO: If I understood correctly, if there is lack of efficacy on one specific drug in a specific class of drugs, try to be a little bit more thoughtful about investigating additional drugs that are in the same class given the lack of efficacy in pediatrics, based on a limited number of patients and a limited number of drugs?

Did I get that right, or not really?

DR. KRAUS: No, that's right. And it might not be just one, but it might be a couple who've tried efforts in different places even, and often were doing multiple tumor types in initial trials. So it might not just be the first one in one, but

it might be a couple same-class drugs that just aren't having success in areas we'd hoped.

DR. PAPPO: Correct.

Then just to supplement that with Ted's comment, the only other thing I would add is also try to have some flexibility as we evaluate data over time, and also consider the possibilities of deferral, some certain drugs.

I do not see any other hands, but I will ask if anybody has any additional comments on this question.

(No response.)

DR. PAPPO: If not, we'll now proceed to FDA closing remarks from Dr. Reaman.

Closing Remarks – Gregory Reaman

DR. REAMAN: Thank you very much, Dr. Pappo, and thank you to the committee for your time and efforts and the thoughtful discussion. This has been very helpful. It will be very helpful as we attempt to put together the guidance for industry and investigators, and the criteria that we'll evaluate and how to evaluate in the decision making

with respect to early planned requests for waivers.

So I, again, just want to clarify that these are decisions that are made early in the process, and not decisions that really lend themselves to large multistakeholder platform discussions like those that occur at the ACCELERATE strategy forums. So again, we need to come to agreement with these initial pediatric study plans before applicants can submit their applications. While we clearly want to accelerate and facilitate pediatric development, we also are conscious of not wanting to do anything that's going to delay access to effective cancer drugs in the adult population as well.

I think some of the discussion around the questions were helpful to us, particularly the area of unmet need, which was intended to be broad and not just think about unmet need in the context of the diseases with suboptimal outcomes or poor prognosis, but also recognizing the fact that many children with diseases with a favorable prognosis suffer from the unattended consequences of unsuccessful therapy. So looking at opportunities

to evaluate and develop less toxic therapies is really important.

As far as the quality indicators -- and I guess equally or more importantly the pharmacologic considerations -- looking at issues related to dosage form and scheduling administration and route of administration are important. We use those, and we will continue to use those, looking at drug-drug interactions, and particularly the interaction with drugs that inhibit or increase the cytochrome P450 function; looking at relationships between exposure and response in adults, and then potentially extrapolating that to children; and clearly the importance of CNS penetration both from the standpoint of potential applicability to tumors that are primary in CNS, or those that may metastasize to the CNS, and then the contrary potential risk for enhanced CNS toxicity.

We would certainly agree that the clinical data trumps preclinical data, but as was pointed out, there may be information that is, in fact, important in decision making that emerges from

comparative nonclinical data in adult models, as well as preclinical models. Whether or not there may be sufficient data to really glean this kind of information we need is clearly another question.

But I think this discussion has been very helpful, and I want to also continue to mention that this is an evolving process. All of this, when we initially even put together a list of relevant molecular targets, we made it clear that these were tables that were on the FDA website that were not necessarily cast in stone, and that changes could occur and would occur, and, in fact, have already occurred, and there is flexibility with respect to decision making.

We, in fact, really have to exercise working with all the stakeholders here, but at the same time keeping in mind that our primary responsibility is assuring the public health, and in this situation the public health of children and children with cancer.

So I would, again, thank you for your participation, and we look forward to tomorrow's

session with most of you on a completely different topic, but thanks again for your invaluable input and discussion today. Thanks.

Adjournment

DR. PAPPO: Thank you very much, Greg, and I want to specifically thank the FDA staff for making this conference go very, very smoothly and a seamless transition, so thank you.

We will now adjourn the meeting for today and continue for the next session tomorrow at 10:00 a.m. Thank you very much, and have a good evening.

(Whereupon, at 3:14 p.m., the meeting was adjourned.)