FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE
ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Wednesday, June 20, 2018
8:00 a.m. to 4:10 p.m.

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland
Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS
Division of Advisory Committee and Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Alberto S. Pappo, MD
(Chairperson, pedsODAC)
Member and Head, Division of Solid Malignancies
St Jude Children’s Research Hospital
Professor of Pediatrics
University of Tennessee Health Science Center
Memphis, Tennessee
Courtney J. Preusse, MA

(Consumer Representative)
Senior Research Administrator and CLIA Operations
Director
Clinical Research Division
Fred Hutchinson Cancer Research Center
Seattle, Washington

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Phuong Khanh (P.K.) Morrow, MD, FACP

(Industry Representative)
Executive Medical Director, Amgen Oncology
Therapeutic Area Head, US Medical Organization
One Amgen Center Drive
Thousand Oaks, California
TEMPORARY MEMBERS (Voting)

Steven G. DuBois, MD
Director, Experimental Therapeutics
Dana-Farber/Boston Children’s Hospital
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Ira Dunkel, MD
Attending, Pediatric Neuro-oncology
Memorial Sloan Kettering Cancer Center
New York, New York

Julia Glade Bender, MD
Associate Professor of Pediatrics at
Columbia University Medical Center
Associate Director, Division of Pediatric
Hematology, Oncology and Stem Cell Transplantation
Medical Director, Developmental Therapeutics and
Precision Medicine Programs
New York, New York
Katherine A. Janeway, MD, MMSc
Associate Professor of Pediatrics
Harvard Medical School
Senior Physician and Director Solid Tumor Service, Pediatric Oncology
Dana-Farber Cancer Institute/Boston Children's Hospital
Boston, Massachusetts

E. Anders Kolb, MD
Director, Nemours Center for Cancer and Blood Disorders
Alfred I duPont Hospital for Children
Wilmington, Delaware

Theodore W. Laetsch, MD
Director, Experimental Therapeutics Program
Children’s Health
Assistant Professor of Pediatrics
Division of Hematology-Oncology
University of Texas Southwestern Medical Center
Dallas, Texas
Donna M. Ludwinski
(Patient Representative)
Research Program Advisor
Solving Kids’ Cancer
New York, New York

Tobey J. MacDonald, MD
Professor of Pediatrics
Emory University School of Medicine
Director, Pediatric Neuro-Oncology Program
Aflac Cancer & Blood Disorders Center
Children’s Healthcare of Atlanta
Atlanta, Georgia

Rajen Mody, MD, MS
Ruth Heyn Professor of Pediatric Oncology and Communicable Diseases
Interim Division Director, Pediatric Hematology/Oncology/BMT
Director, Pediatric Phase-I and Experimental Therapeutics Program
Ann Arbor, Michigan
Kathleen A. Neville, MD, MS, MBA, FAAP, FCCP  
Professor of Pediatrics  
University of Arkansas for Medical Sciences  
Chief, Section of Clinical Pharmacology and Toxicology  
Director, Experimental Therapeutics Program  
Co-Director, Pediatric Precision Medicine Program  
Little Rock, Arkansas  

Elizabeth A. Raetz, MD  
Professor of Pediatrics, NYU School of Medicine  
Director, Division of Pediatric Hematology/Oncology  
Stephen D. Hassenfeld Children’s Center for Cancer and Blood Disorders  
New York, New York
Nita Seibel, MD
Head, Pediatric Solid Tumor Therapeutics
Clinical Investigations Branch, Cancer Therapy Evaluation Program/Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI)
National Institutes of Health (NIH)
Bethesda, Maryland

Malcolm A. Smith IV, MD, PhD
Associate Branch Chief for Pediatrics, Clinical Investigations Branch, Cancer Therapy Evaluation Program/Division of Cancer Treatment and Diagnosis, NCI, NIH
Bethesda, Maryland

Brenda J. Weigel, MD, MSc
Professor
Division Director, Pediatric Hematology/Oncology
University of Minnesota
Developmental Therapeutics Chair
Children's Oncology Group
Minneapolis, Minnesota
SPEAKER (Non-Voting)

Lia Gore, MD

(Participation in Topic 2)
Professor of Pediatrics, Medical Oncology, and Hematology
Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant
The Robert J. and Kathleen A. Clark Endowed Chair in Pediatric Cancer Therapeutics and the Ergen Chair in Pediatric Oncology
Children’s Hospital Colorado
Center for Cancer and Blood Disorders
Aurora, Colorado

FDA PARTICIPANTS (Non-Voting)

Gregory Reaman, MD
Associate Director Oncology Sciences
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND), CDER, FDA
Associate Director for Pediatric Oncology
Oncology Center of Excellence, FDA
Amy Barone, MD  
Medical Officer  
Division of Oncology Products 2 (DOP2)  
OHOP, OND, CDER, FDA

Diana Bradford, MD  
Medical Officer  
DOP2, OHOP, OND, CDER, FDA

Sandra J. Casak, MD  
Senior Staff Fellow  
DOP2, OHOP, OND, CDER, FDA
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Call to Order

Introduction of Committee

DR. PAPPO: Good morning. I would like first to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press context, Sandy Walsh. If you are present, please stand.

I would like to ask all the members seated around here to please introduce yourselves with your name so we can put them in the record. We can start right there.

DR. REAMAN: Gregory Reaman, FDA.

DR. CASAK: Sandra Casak, FDA.

DR. BRADFOR: Diana Bradford, FDA.

DR. BARONE: Amy Barone, FDA.

DR. NEVILLE: Kathleen Neville, University of Arkansas for medical sciences in Arkansas Children's.

DR. WEIGEL: Brenda Weigel, University of
Minnesota.

DR. JANEWAY: Katie Janeway, Dana Farber Cancer Institute.

DR. KOLB: Andy Kolb, Nemours Center for Cancer and Blood Disorders.

DR. MacDONALD: Tobey MacDonald, Emory University, Children's Healthcare of Atlanta.

DR. TESH: Lauren Tesh, designated federal officer.

DR. PAPPO: Alberto Pappo, St. Jude Children's Hospital.

DR. DuBOIS: Steve DuBois, Dana Farber and Boston Children's.

MS. PREUSSE: Courtney Preusse, Fred Hutch.

DR. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer, patient representative.

DR. RAETZ: Elizabeth Raetz, NYU Medical Center.

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering.

DR. MODY: Rajen Mody, University of Michigan.
DR. SEIBEL: Nita Seibel, NCI.

DR. BENDER: Julia Glade Bender, Columbia University.

DR. LAETSCH: Ted Laetsch, University of Texas Southwestern and Children's Health in Dallas.

DR. MORROW: P.K. Morrow, Amgen industry representative.

DR. PAPPO: Thank you very much.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record only 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 with the
media until its conclusion. Also, the committee's
reminded to please refrain from discussing the
meeting topic during breaks or lunch. Thank you
very much.

Dr. Lauren Tesh will have read the Conflict
of Interest Statement for the meeting.

DR. TESH: Dr. Smith, can you introduce
yourself for the record, please?

DR. SMITH: Malcolm Smith, NCI.

Conflict of Interest Statement

DR. TESH: Thank you.

The Food and Drug Administration 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 of 1972. With the exception
of the industry representative, all members and
temporary voting members of the committee are
special government employees 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 committee's compliance with federal ethics and
conflict of interest laws, covered by but not
limited to those found in 18 USC Section 208, is
being provided to participants in today's meeting
and to the public.

FDA has determined that members and
temporary voting members of this committee are in
compliance with federal ethics and conflict of
interest laws. Under 18 USC 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
interest of a regular federal employee is not so
substantial as to be deemed likely to affect the
integrity of the service which the government may expect from the employee.

Related to the discussion of today’s meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC, 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 the review and discussion of a list of molecular targets for which evidence and/or biologic rationale exists to determine their potential relevance to the growth or progression of one or more pediatric cancers, and a list of those targets deemed unlikely to be associated with the growth or progression of pediatric tumors.

These lists are expected to fulfill the
statutory obligation of the Food and Drug Administration Reauthorization Act, FDARA, and provide some guidance to industry and planning for initial pediatric study plan submissions for new drug and/or biologic products in development for cancer in accordance with the amended provisions of the Pediatric Research Equity Act.

The committee will review and discuss considerations other than specific relevance that FDA will include in decision-making with respect to the need and timing of pediatric evaluation of specific new drug and biologic products. The committee will discuss possible criteria and mechanisms for the prioritization by sponsors and the clinical investigator community of selected targeted new agents for pediatric evaluation, especially in the setting of multiple same in-class agents.

Preliminary discussion will focus on approaches to coordination and collaboration for pediatric clinical investigations of new agents that might be pursued to efficiently accommodate
international regulatory requirements in global pediatric product development. The open public hearing sessions are Topic 1, Target Lists; Topic 2, FDARA Implementation; and Topic 3, Mechanisms to Assure Efficiency and to Enhance Global Coordination through International Collaboration.

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 committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they may have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general
and not any particular company. Dr. Morrow is employed by Amgen.

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

Dr. Elizabeth Fox has acknowledged several clinical research grants with Ignyta, Merck, and Novartis, with no personal direct funding. In addition, she serves on the Data Safety Monitoring Committee for Helsinn, Inc. regarding supportive care.

Dr. Hubert Caron has acknowledged that he is employed by Roche and owns stock in the company.

Dr. Christina Bucci-Rechtweg has acknowledged several grants and stocks as part of employment with Novartis Pharmaceuticals Corporation.

Dr. Lisa Bollinger has acknowledged that she's employed by Amgen. As guest speakers,
Bollinger, Fox, Bucci-Rechtweg, Caron, and Vassal will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members 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 other participants to advise the committee of any financial relationships that they may have regarding the topic at issue that could be affected by the committee's discussions. Thank you.

DR. PAPPO: Thank you very much.

We will not proceed with an FDA presentation from Dr. Greg Reaman.

**FDA Presentation - Gregory Reaman**

DR. REAMAN: Thank you, Dr. Pappo.

I'd like to, on behalf of the FDA, just extend a welcome to all of our advisors and to
those guest speakers who have traveled. I'd also like to acknowledge and welcome those colleagues from the European Medicines Agency who are participating remotely, Drs. Franca Ligas, Ralph Bax, and Gunther Egger, and members of the EMA's pediatric committee, Koenraad Norga, Alessandra Janker, Jaroslav Sterba, and Sara Galluzo.

We're here today to talk about implementing the new PREA provisions in FDARA 2017 in an attempt to make precision cancer medicine in children a reality. I think everyone is aware of the fact that there are challenges with cancer drug development in pediatrics, which widely leverages adult drug discovery and development. There are limited opportunities for extrapolation and limited preclinical testing, early preclinical testing in pediatric models, both of which will hopefully change as a result of this legislation.

The impact of the existing legislative initiatives, PREA and BPCA, which support pediatric drug development and support it well in many other clinical areas, has really been markedly less
obvious in oncology given that the paradigm for
cancer drug development is shifting and utilizing
histology agnostic approaches and focused on
targeted agents, many of which are likely
applicable to cancers in children.

I think the most recent evidence of the
immediate mandate for evaluating targeted agents in
children come from these two papers recently
published together in Nature, which evaluate
pan-cancer genome transcriptome analyses of
collectively about 3,000 pediatric cancers across a
variety of histotypes, including acute leukemias,
which definitely demonstrate differences in
mutational burden and differences in specific
genetic and epigenetic drivers. And roughly half
of the various genetic abnormalities are distinct
from those seen in adult cancers.

Nevertheless, there is significant
expression of those targets, up to 40 percent and
higher, of targets in pediatric tumors that are
also expressed in many adult cancers and targets
involving the MAP kinase pathway cell cycle control
and PI3K/AKT signaling pathway as the lead contenders.

Drs. Pfister and Grubner actually looked and evaluated and defined what were actually potentially druggable events in pediatric cancers in their study from the International Cancer Genome Consortium and found that 52 percent of the genomic drivers, or genetic abnormalities, or targets were potentially druggable with currently approved drugs or drugs in development. I think this certainly justifies our need to evaluate these targeted agents earlier in children.

So just as a bit of background, the two legislative provisions that we have are PREA, the Pediatric Research Equity Act, and BPCA, or the Best Pharmaceuticals for Children Act, PREA is mandatory, requires studies only on indications under review and orphan indications are exempt. And essentially, PREA has had no relevance to pediatric cancer.

BPCA is voluntary. Studies are done in response to written requests issued by the agency.
to sponsors. They may expand and generally do expand indications, and again, historically these have actually been issued many years after the approval of a drug in the adult population. And despite our efforts to issue a written request earlier in the development timeline, it's not had a great deal of impact on changing those timelines.

The RACE for Children Act fortunately amends PREA, and it was incorporated RACE for Children Research Acceleration for Cure and Equity, was incorporated as Title V of the FDA Reauthorization Act, or FDARA, enacted last August. It requires -- not a voluntary but requires evaluation of new molecularly targeted drugs and biologics intended for the treatment of adult cancers and directed as a molecular target substantially relevant to the growth of progression of a pediatric cancer. And I think we've had some difficulty with the term "substantially relevant" in defining substantial relevance; more about that later.

As we implement how we're actually going to
apply this law to decision-making, I think there's an opportunity to actually create degrees, levels, and grades of substantial relevance, which should hopefully make things a little bit more clear for all stakeholders.

The statute describes the types of studies which are required. These are not full pediatric development plans, so these are very distinct from the pediatric investigation plans in the European Union. They're defined in the statute as molecularly targeted pediatric cancer investigations that will provide clinically meaningful study data using appropriate formulations regarding dosing, safety, preliminary efficacy that may possibly inform potential pediatric labeling. We interpret this to be early phase studies, phase 1, 1B, phase 2 studies, and there is no requirement for a commitment a longer term development or evaluation.

The important feature of this legislation also is the elimination of the orphan exemption for pediatric studies for cancer drugs that are
directed at relevant molecular targets. The
definition we actually went over at our last public
meeting. We tried to keep this as broad as
possible.

The statutory requirements for the FDA are
to establish with the National Cancer Institute and
update regularly and post on the FDA website a list
of relevant targets. We have a year to do that.
We've done that. We went over that list, reviewed,
and discussed in April of this year.

Establish a list of targets that lead to
waivers, and we interpret this as leading to
automatic waivers. And at this point in time, an
automatic waiver would be appropriate for drugs
that inhibit those targets, which are considered
non-relevant to the growth or progression of a
pediatric cancer.

Work with NCI and the pediatric subcommittee
of ODAC, you all, our internal pediatric review
committee and sponsors, experts, and advocates to
implement the legislation and to make decisions
about required studies.
To convene an open public meeting. This is the second open public meeting that we've done within the year, and issue a guidance on implementation in two years.

So where are we? I mentioned that we had the first meeting in April. We're here today for final review and comment on the target lists, the relevant target lists and those that would lead immediately to waivers; applying the target lists and a process for prioritization, including same in-class agents; how we would work with external constituents, all stakeholders; a process to support international collaboration and coordination given that pediatric cancer drug development is global in nature. And we have non-aligned regulatory requirements and processes and timelines, so we really need to coordinate and collaborate.

Our internal planning has been coordinated through our Office of Hematology and Oncology Products in the Oncology Center of Excellence along with a number of other offices in the FDA. The
focus here, I will point out again, is on accelerating appropriate initial pediatric evaluations and not merely increasing number of pediatric phase 1 studies. So as we think about this, talk about this, and deliberate through the day, please keep this in mind.

The focus here is not just studying every drug and studying many, many drugs in the phase 1 setting and children, but really accelerating the timeline for initial evaluation of those agents that appear to be appropriate. We've been advising sponsors of new conditions and requirements for their initial pediatric study plans for new applications with plan submission dates after August 18, 2020 when the full implementation of the law goes into effect.

Prior to the open public meeting, there was a meeting sponsored by the Friends of Cancer Research, a workshop that was really a forum for scientific discussion and multistakeholder exchange. We considered a framework for defining relevance and came up with a classification tool to
organize our totality of evidence. It's not a perfect classification. There's a great deal of overlap, but it made sense at the time, as we were dealing with a large number of potentially relevant targets.

We talked briefly about additional factors which would impact the decision-making and some anticipated consequences. The discussion again was not focused on any specific diseases or strategies for therapeutic investigation in the single disease area, and there were no regulatory policy decisions, again, other than focusing on the justification for studies to accelerate initial evaluation and not just increase numbers of phase 1 studies.

The target lists have been, as you can imagine, a subject of much discussion. Developing these is a statutory requirement to purportedly -- and I say purportedly -- address regulatory uncertainty for industry and guide, but not dictate early decision-making.

Designation as relevant is not an absolute
or an exclusive requirement for decisions related
to pediatric evaluation, so we can require studies
of products even if the target is not on the list.
And a target may be on the list and waivers may
actually be likely for some of those products, even
though the target is considered relevant.

We envision that target lists are not going
to restrict the authority or the flexibility of the
FDA. The relevant molecular targets were created
or defined independent of whether an agent or
biomarker was currently available.

Candidate target lists were constructed
within the OCE with input from other offices at the
FDA and with the NCI, and input from quite a large
number of international content experts mostly
using published peer reviewed literature, abstracts
and publicly available databases. There was no
prespecified minimum evidence base given the
variability in the types of targets that we were
including.

At the meeting in April, the NCI posted a
request for information so that the target lists
were reviewed at that time, and multistakeholders had the opportunity to provide comments for the addition or deletion of targets on the list. I'm not going to go through all of these. They're actually I think in the written materials that you have, but the gene abnormalities were probably the best validated and available by review of the NCI Genomic Data Commons, St. Jude PeCan data portal, the International Cancer Genome Consortium, the INFORM project, and the Pediatric PeCan.

There are quite a number of these, again no specific agents were defined or discussed. We classified another group as related to cell lineage. Most of these would be appropriate for immunotherapeutic approaches to pediatric cancers, monoclonal antibodies, antibody drug conjugates by specific T-cell engagers, and TCRs, and CAR-T cells.

Another group of targets not on the cancer cells but on normal immune cells or cells in the tumor microenvironment supporting cancer growth, this is an area that I think is still begging for a
biomarker to define those populations in both adults and children who are going to respond to some of these agents, and then a whole host of other targets, some of which may actually have a genetic base, some of which may not, but most of which are thought to interfere with normal cell growth differentiation and development and are at least in consideration for development of drugs in the cancer space. They have potential applicability to a number of pediatric tumors, and some of these are actually currently being evaluated in children; so again, another sizeable list.

The automatic waiver lists, those which we would consider not relevant to pediatric cancer, are listed here. It's small. It may not give quite the degree of regulatory certainty that industry is looking for, but I should point out that there are other waiver considerations which can and will be used in decision-making. So I think other waiver considerations for why we would not require a study, even though a target was on
the relevant list, would be if the target were to be associated with a serious developmental toxicity. Here, however, we might consider partial waivers age-dependent partial waivers, a case in point being bone growth abnormalities with smoothened inhibitors. And limiting evaluation to patients who are skeletally mature would hopefully avoid the toxicity seen in younger children.

Another obvious waiver consideration would be a second or third in-class product unless there's compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies. And then the current waiver consideration, feasibility and practicability due to small study populations may be addressable by limited study requirements and innovations in study design and conduct.

So rather than doing full-scale pediatric studies, including a pediatric cohort on an initial adult first in-human study to define dose and look for signals of activity, or even embed a pediatric
study or cohort within an adult study as we've currently advised a sponsor in a written request to do in a very rare subset of high-grade gliomas.

So as far as publishing and updating the lists, our plan at this point is to hold semi-annual public workshops, and this will hopefully provide an opportunity for stakeholders, clinical investigators, sponsors, advocates to advise on updating the lists and obviously discuss issues related to implementation and decision-making.

I think enabling ongoing recommendations for additions and deletions, we actually plan to open a docket for comments on the existing targets and suggestions for additions and deletions. And hopefully following this meeting, shortly after, we'll post the list of candidate molecular targets on the Oncology Center of Excellence website under the pediatric oncology program, and the web address is listed here.

Other considerations for decision-making and prioritization likely are going to be variable by
the target class and perhaps even the diseases in question and prevalence of target expression in either a single disease or across multiple histologies and evidence that target inhibition, modulates tumor growth, and I think this could certainly be used as a criteria for defining a level or degree of irrelevance.

The extent of unmet clinical needs or potential public health impact, so studying multiple anti-CD30 antibodies in mature B-cell malignancies in children probably isn't going to have a great deal of public health impact, and therefore we would likely not require studies. Availability of access to the agent, obviously, availability of predictive response biomarkers. This would be very helpful in thinking about the study design and conduct.

All of this is really going to require collaboration between industry, clinical investigator, community, and regulators. This multistakeholder input is required to inform FDA decision-making, and that's what we hope and expect
will be accomplished through these open public workshops or meetings.

Other considerations will be any evidence of clinical or preclinical activity, the toxicity profile, as I mentioned earlier, doing a potential benefit-risk assessment; formulation, obviously a major issue; multiple agents in class, and there's going to be required some transparent evaluation of selection criteria in the precompetitive space between investigators and sponsors about which agents when they are multiple in-class should be and can be evaluated in a limited pediatric population. And I think rare pediatric cancers now are not well supported by current study platforms. And again, this is an opportunity to enroll early on adult studies when we're looking at a histology agnostic or tissue agnostic development plans.

Looking at uniform international master protocols for biomarker directed studies will provide efficiency and hopefully high quality data. We will look to increase to the extent possible extramural input in any decisions we make, but
obviously we have to respect the proprietary
considerations of industry in doing so. We might
be able to at these open public hearings have early
pipeline presentations from industry as part of
this collaboration. I think this speaks heavily to
the need for an industry initiated public-private
partnership, which we've been discussing probably
for the last 10, 12, maybe 15 years, to help
facilitate and accelerate pediatric cancer drug
development.

So I think successful implementation is
going to require transparency. We'll do our best
to be as transparent as we can to address potential
adverse consequences. What's going to be required
is initiating early preclinical testing
initiatives. This may require effective industry
academic collaboration when necessary, and I think
this is another potential important role for
public-private partnership.

We have to recognize emerging scientific
discovery, so what's on a list today may not be on
a list two weeks from now, or a month from now, or
a year from now. I think most important is global
development is really going to require
international collaboration in designation of
relevance in prioritization and decision-making
regarding study feasibility and conduct. And we
really need to support and expand robust publicly
shared data sets of genomic, proteomic, and
preclinical testing data.

Priority setting for relevant targets
through periodic international multistakeholder
workshops I think is important. We currently have
pediatric cluster calls monthly with the EMA, the
PMDA in Japan, and the TGA in Australia and Health
Canada to talk about pediatric investigation plans
and study plans and provide written commentary to
sponsors when requested and appropriate.

I don't think that's sufficient; I think
it's very helpful, but I think having a process
similar to the EU's ACCELERATE platform, which is
really multistakeholder, including investigators,
regulators, and sponsors. And there's a clear move
on the part of ACCELERATE to expand this to include
international representation, so we are working with them to accomplish that. And obviously to support and encourage international trials when possible, we have to avoid duplication and competition.

With that, I will close and answer any questions if there are any.

**Clarifying Questions**

DR. PAPPO: Thank you very much, Dr. Reaman, we will now take clarifying questions for Dr. Reaman. Please remember to state your name for the record before you speak.

Steve?

DR. DuBOIS: Steve DuBois. Thank you for that, Greg. How will FDA define a first in-class agent? Is it the first to the clinic, first to declare an adult dose, first to approval? How will that be determined? Because there's obviously downstream consequences of what's second in class.

DR. REAMAN: Right, a very good question. I don't have an exact definition. How we would see them now is first in class, the first application
that comes in for an adult indication that would
trigger, since it would be for a new indication, an
initial pediatric study plan. So it's sort of
first come/first served.

That may not be the best way to actually do
this, which is why I think there needs to be some
discussion pre competitively with sponsors who are
developing same in-class agents with investigators
in the event that there are real differences that
would justify selecting one over another. It may
be that just saying a second in class may not be
too much, but I think once we start getting to
third, fourth, and fifth in the case of checkpoint
inhibitors, we're not doing anyone a favor here.

DR. PAPPO: Ira?

DR. DUNKEL: I wanted to ask for
clarification about two points that you made, one
being the formulation issue. Of course as you're
very aware, it's not uncommon that the
tablet/capsule formulations make it difficult to
study agents in young children, and I'm wondering
how or if the new legislation addresses that.
The second issue is you talked about bringing pediatric phase 1 trials earlier in the process, and I wonder if you could discuss what the FDA believes the most appropriate time would be. For example, does there always have to be completion of an adult phase 1 study before an agent can start an pediatric phase 1 evaluation?

DR. REAMAN: To answer the first question, I think the statute clearly says inappropriate formulation, so it may be an appropriate, extemporaneously, used formulation for investigational purposes that may then require, if we issue a written request, an appropriate formulation, which could and should be marketed. But it is going to be a challenge and it may be that does become a deciding factor about whether we can or can't evaluate certain agents in the pediatric population or at least the ages of children that can be evaluated.

So to answer the second question, which was timing of pediatric phase 1 studies, there is no hard and fast rule. We feel, and as a group, the
subcommittee of ODAC, the pediatric subcommittee, developed a consensus statement that clearly defined that pediatric phase 1 studies should be started immediately after the identification of a safe dose in the adult population. But in some situations they could start earlier, and we could even use a preclinical nonclinical data to justify starting studies without adult experience.

DR. PAPPO: PK?

DR. MORROW: So you discussed the interest of the FDA in an industry-initiated, public-private partnership. I wanted to get your criteria or thoughts in terms of success and framework of such a partnership.

DR. REAMAN: I don't really have a framework fully developed, but I think we'll know it when we see it. Right now, all we've done is talk about it, and it goes back to a meeting that pharma and bio had with I believe Friends of Cancer Research several years ago. Actually, maybe it was with the Children's Cause for Cancer Advocacy several years ago. That was great discussion but no follow
through and no real changes. I think now we have a mandate to follow through with this. We have to collaborate. We have to corroborate, industry, investigators, regulators. And the only way we can really do this is through such a public-private partnership in my estimation.

DR. PAPPO: Nita?

DR. SEIBEL: Greg, maybe you could expand a little. You mentioned the master protocols. In some situations, if an agent is included in a master protocol and 20 patients are tested, and nothing is seen, then there's no reason to do a pediatric phase 1. So does that replace it in some places?

DR. REAMAN: Yes. I think that would replace it. The master protocol would be the pediatric phase 1, 1B or 2 study.

DR. PAPPO: I have a question. The prioritization of same in-class agents, for example MEK and BRAF inhibitors, there are three combos now that are approved. Is this going to move forward between COGs, the multiple consortiums, and
investigator initiated studies? Is there going to be a specific agent that will be identified and then the other ones that will just have waivers or is there going to be a process to identify that?

DR. REAMAN: I think we can't change what's already in progress. There are multiple same in-class agents already being studied. There are commitments. There are plans. And depending on the results of those studies, there may be labeling that moves forward. I think we need to prevent something like that from happening in the future, either prevent it or at least not require sponsors when there are same in-class agents.

There may be reasons for doing it, and in that case, we have voluntary mechanisms through BPCA and the written request process where we could incentivize a sponsor if there is a reason for evaluating another same in-class product.

I think Dr. Kolb maybe had a question.

DR. KOLB: Thanks, Greg.

DR. REAMAN: Go ahead.

DR. KOLB: Toby was first.
DR. PAPPO: Please don't forget to state your name, please.

DR. MacDONALD: Toby MacDonald.

Greg, in my experience, contacting some of the pharma, there is a time where they do not know there's an indication for pediatric cancer. And I'm wondering is there a way for the FDA to somehow get the knowledge to them.

DR. REAMAN: Well, part of the, I think, the process of posting the lists, the lists are associated with references and references to databases that they can explore. I think also it's going to be incumbent upon sponsors to do some of this research and investigation on their own in the event that they have to submit a study plan that either includes a plan for a study or provides a justification for why a study is not feasible, or highly impractical impracticable, or potentially unsafe.

DR. PAPPO: Ed?

DR. REAMAN: And again, I think this is something that we would clearly depend on the
investigator community to help with as well. So there could be a series of publications that would be helpful to industry. But again, this is evolving science, and how rapidly can things be published to successfully, and efficiently, and effectively inform industry, I'm just not clear.

DR. MacDONALD: Sorry, a quick follow-up. Could there be a subcommittee of pediatric -- a variety of multispecialists who could look at what they're developing and bring it back to them and say this is a target in this disease of which you had no idea that this was --

DR. REAMAN: I would hope that industry would take that advice. I mean, clearly they have advisory boards. Do they all have pediatric advisory boards, so there may be a role there? I know some forward-thinking companies do, and I think it's been very evident in the kinds of study plans that we have seen. So that may be a real way of accomplishing that.

DR. PAPPO: Ed?

DR. KOLB: Thank you. Andy Kolb.
Thanks, Greg, for the talk and for your leadership in bringing this forward. There are aspects of the Act that will be diminished with the current level of coordination between the FDA and the EMA, and I'm thinking specifically about the PIP process and second and third in-class exemption.

Do you have a sense of what the timeline will be to coordinate better with the EMA so that the European statutes don't undercut some of the efforts that you're trying to move forward here?

DR. REAMAN: Sure. I don't have a good timeline. We've been talking about this already. They're participating remotely as part of how we're going to deal with this. And I'm not sure that we're going to prevent everything, but I think thinking about it early could actually be beneficial.

I think one way that we could help is if this legislation actually results in earlier phase 1-2 experience in children, it could actually inform the pediatric investigation plan process in
the EU, which requires a full development plan from early phase through a more definitive evaluation. And I think making some joint decisions about what products could/should be studied and how, and studying them jointly on both sides of the Atlantic, I think could make things much more effective and efficient as well.

DR. PAPPO: Brenda?

DR. WEIGEL: Dr. Reaman, I have a question with regards to updating and adjusting the lists in a fluid manner. You mentioned there's going to be the opening of a docket, an FDA docket for -- and I'm assuming that's going to be public access for anyone.

What do you envision the vetting of the content of that docket to be within the FDA, and how is that information going to be transparent and utilized to add/delete things from the lists?

DR. REAMAN: I don't have that all worked out yet, but I see it as having our internal process, and then some expert external advice. We could do it as part of the pediatric subcommittee
of ODAC meetings. We could do it at the semi-annual open public workshops. But clearly, there has to be some vetting, and that will be something to think about. We're open to suggestions.

    DR. PAPPO: Katie?
    DR. JANEWAY: Katie Janeway, Dana Farber. I actually have the same question as Brenda, but I'll use my time to extend on that vein of questioning.

    In the context of a new product, when you're assessing the relevance of the molecular target, will there be a process for obtaining outside opinion if this potential target has not been previously considered; in other words, hasn't been thought about in the context of this legislation?

    DR. REAMAN: We always have the opportunity to seek outside opinion and advice. Sometimes it's a little bit complicated if there are conflicts of interest with the sponsor. So sometimes the people who may have the most expertise in a particular area -- in this case with a specific target maybe in a specific disease -- may have shared that same
information with the sponsor, which would make it a little bit difficult for us to get advice from the same individual. But there clearly is more than one expert in most areas in pediatric oncology.

So I think there are definitely ways of safely and without any conflict of interest getting an outside opinion. This is a testament of one way that we do get outside opinion through the pediatric subcommittee.

DR. PAPPO: Julia?

DR. GLADE: Thank you. Julia Glade Bender from Columbia University.

Greg, thank you very much. I'd like to revisit a question that was asked by Dr. Dunkel regarding formulation, in the sense that it's clear that it is part of the legislature, but it's not clear that there is any advice that's being offered to pharmaceutical industry about the process of developing a pediatric appropriate formulation. And the question is whether the FDA will be able to offer advice or recommendation so that each time that this comes up, we don't have to sort of
reinvent the wheel about the steps involved in
developing a pediatric-appropriate formulation and
bioavailability testing in adults, et cetera.

DR. REAMAN: Sure. Yes, and that would
certainly be part of the guidance that we are
required to develop. I mean, it's something that
we have already thought about. It's something that
we already have some templated language when we
issue written requests with respect to
investigational formulations and evaluation of
bioavailability usually in the adult
healthy volunteers or at least in the adult
population.

DR. PAPPO: Any additional questions for
Dr. Reaman?

(No response.)

DR. PAPPO: Thank you very much.

We have no registered open public hearing
speakers for this specific session, and therefore
we will now proceed with the charge and questions
to the subcommittee 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 will start with the first question.

Charge to the Subcommittee

DR. CASAK: This is about the target lists.

"Title V of the FDA Reauthorization Act, FDARA 2017, assigns FDA to establish, publish, and regularly update lists of molecular targets considered on the basis of data the FDA determines to be adequate to be substantially relevant to the growth or progression of pediatric cancers. New drug products directed at these targets may trigger the requirement for pediatric investigations. As well, a list of targets considered not relevant has been developed.

"Comment on the process utilized to construct the list, the classification of molecular targets, the factors utilized to designate a target as relevant or non-relevant and indicate your concurrence with the lists as currently represented."
Questions to the Subcommittee and Discussion

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

I had one minor question. Tumor mutational burden, is that something that will be included at some point or it will just be a surrogate based on other analysis?

DR. REAMAN: I think it's both a surrogate, and I guess it could be included as a specific target as well.

DR. PAPPO: Katie?

DR. JANEWAY: I have a comment and then a question. So my comment is just that although the landscape papers that were recently published are fantastic, they contain only 3,000 cases and some especially rare tumors are missing. And most of the data we currently have is from specimens obtained at the time of diagnosis; so just a statement that there's a need for continued acquisition of data regarding molecular targets in pediatric cancers.
The question I have is on the excluded list of targets, I noted of VEGF and VEGF receptor, and I'm just interested in a little bit more information if it's possible to provide that, of how those ended up on the excluded lists.

DR. REAMAN: I think they ended up on the excluded lists because there's been significant clinical evidence to question their activity in multiple different pediatric tumors in pediatrics in general, not looking at the specific pediatric cancers. But again, I remind you that if there's a reason, just because it's on the automatically waived list or we consider it not relevant, if there is sufficient interest and other preclinical evidence that would refute what we've seen clinically, it's certainly something that could be evaluated and investigated. And it also doesn't preclude our issuing a written request for study of a new VEGF inhibitor.

DR. JANEWAY: Thank you.

DR. PAPPO: Any additional comments? Steve?

DR. DuBOIS: Could you just clarify the
requirement for pediatric investigations? In some cases, will that be a requirement for an industry sponsor to conduct a nonclinical investigation, and is that included in the legislation?

DR. REAMAN: The requirement is clinical investigations. It may be that a nonclinical investigation would be required to support a sponsor's justification for not doing a pediatric clinical evaluation. But there's nothing in the legislation that requires industry to do nonclinical studies.

But clearly, there's an implied need for preclinical studies, and this could be and probably is best accomplished, or could be a very well accomplished, by collaborating between industry and academic investigators. They do it beautifully in Europe with the ITCC P4 platform with a number of industry sponsors working together with investigators to do preclinical studies, so I don't see why we can't do the same thing here.

DR. PAPPO: Elizabeth?

DR. RAETZ: Elizabeth Raetz, NYU. Given the
scope of the lists, have there been any discussions
about potential prioritization within the
subclasses of targets that you’ve identified?

DR. REAMAN: We’ve not prioritized, and I
think that’s something that investigators and
industry working with us, we clearly need to be
informed on what are the priorities of patients and
investigators to best help patients, which is the
only reason this legislation was passed.

DR. PAPPO: Toby?

DR. MacDONALD: Toby MacDonald. The way
the list is currently, it looks like these are
single entity abnormalities. But targeting a
single molecular alteration, rarely if ever, is
sufficient. So is there a plan to develop
combination of synergistic and synthetic lethal
type lists that might be more helpful for
preclinical development?

DR. REAMAN: There is not as a result of
this legislation. It clearly is something that I
think would be beneficial from the perspective of
rational clinical trial design considerations, and
hopefully that would be something that would come from the academic community and maybe working with industry. But there's nothing specific in the statute which talks about combinations, and we clearly recognize that combinations, particularly in pediatric oncology, are going to be necessary. And again, the focus here, and I think the intent of this legislation, was early initial evaluation of single relevant drugs.

DR. PAPPO: Julia?

DR. BENDER: I wanted, again, to go back to Dr. Janeway's question just because of the VEGF and the VEGF-R. I agree absolutely why they are on the prospective list of excluded because we've done a lot of studies in the past. But they don't fail the substantially relevant tests, and they're also in pediatric use to a large extent. So the data that was generated was important.

So the question is, now prospectively, at what point, or maybe there needs to be additional language about when we say it's not substantially clinically relevant, or there is already sufficient
clinical data for that target?

DR. REAMAN: I think we probably used the latter to define relevance here. But maybe there's an argument for it not being sufficient clinical data, and that these were all in multiply relapsed patients across a spectrum of diseases and was the exposure really of significant or appropriate duration to really evaluate efficacy.

So this is an opportunity to take them off the automatic waiver list of if there's a rationale to do so. And again, just because they're on there doesn't mean that they can't and shouldn't be studied. But we'd be certainly open to removing them if that's your recommendation.

DR. PAPPO: Ted?

DR. LAETSCH: I had a different question. Maybe, Katie, if you want to come in first, then I'll --

DR. JANEWAY: So I guess I raised the question because in common use in the clinic and certainly supported by clinical trial evidence is multi-tyrosine kinase inhibitors in relapsed
sarcomas, and it's unclear -- I think there's preclinical data to suggest that VEGF and VEGF receptor are important in those diseases. It's unclear whether there's a relationship between those two things because they are multi-tyrosine kinase inhibitors.

So this is the reason I raised the question. I think additional correlative biology, new agents that are maybe more specific, more tolerable, might answer that question. So I guess I'm sort of addressing -- Julia's, actually, paper is cited for that. By the way, I want to make an aside comment that I think including the evidence and the citations in the lists is fantastic. It's a great resource.

So that is why I raised the question. And I agree it's difficult. I don't think there's a clear answer. I don't disagree that there is clinical data to suggest that the current agents make this not a relevant target, but I worry about future investigation.

DR. REAMAN: I don't think we want to
jeopardize future investigation. I'm hearing that maybe we should reconsider this. Again, we didn't walk down from any mountain with two tablets or anything, so I believe that we could amend the list. That's one of the recommendations here. I agree that it might be a relevant target. It should be a relevant target. It's just that the agents that we've had to evaluate its relevance from a therapeutic perspective I don't think have really panned out.

DR. CASAK: It may be a point that we were really focused on early investigations, and we did not include -- or we excluded VEGF because we didn't think further moving -- we already know the safety. We may not know right now efficacy in combination, et cetera, but it's a very good suggestions, so thanks.

DR. PAPPO: Ted, do you still have a question?

DR. LAETSCH: I was going to sort of ask that question, but more generally, about as we get more data on the clinical experience with agents in
each of these classes, how are we going to decide
whether that data is relevant to that single agent
alone or to the entire class? And when do we
decide that there is enough, either negative or
positive evidence that we stop requiring further
studies of other agents in that class?

DR. REAMAN: Good question. But again, I
think it's a little bit beyond what we do here
because the reason for the list is for early
preliminary evaluations. It doesn't really impact
what's done later. So if there's still a reason to
evaluate a drug in the phase 1 setting, or phase 2
setting hasn't had a sufficient activity signal in
combination, it certainly doesn't preclude those
kinds of studies.

I think you raise a good point. If there is
reason to keep it on the list because of
anticipated synergy or observed synergy in a
clinical trial setting, then it can stay on the
list.

DR. PAPPO: Raj?

DR. MODY: Rajen Mody, University of
Michigan. My question is regarding molecular lists, and I think we discussed that in the April meeting. I'm looking at PTEN, and it seems to be missing from the list, PTEN deletion. And maybe I'm missing that it was added on later on, but I can't seem to find it.

DR. REAMAN: That was one that had the RFI up on the NCI website to post anything. That wasn't something that came in that I'm aware of. So that's also something that can be added if there's a reason to do so.

DR. JANEWAY: Katie Janeway, Dana Farber. I second Rajen's suggestion.

DR. REAMAN: Okay. Yes, I don't see it on here.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel, University of Minnesota. I have more of a comment than a question. I want to go back to, I think, some of the discussion from the April meeting and also the concept of the list is it's a fluid list that is really I think a guide for development rather than
an absolute, a requirement.

I think one of the real opportunities here is to be as inclusive as possible, to go back to what Dr. Reaman just said, to have the impetus to do very early investigation in pediatrics, which is really the goal of the legislation. And I think it's not to say that it's going to work or not work in pediatrics; it's to say we should look at it in pediatrics.

So I think erring on the side of being as inclusive as possible very early on is really what we need to do, and it may serve as an impetus, both for industry and academics, to actually look at doing more research to really investigate the utility of these pathways, targets, agents in pediatrics.

So I think sort of shifting the gear a little bit of saying this may be an opportunity to enhance investigation for pediatric cancers, and we should be as inclusive as possible and try not to be exclusive.

DR. PAPPO: So I will try to summarize our
discussion. We still have another question. The first issue is consider adding a PTEN and also tumor mutational burden to the current list. The second issue that was brought up is that the two pan-cancer analyses that have been published so far lack certain histologies, and certainly additional information would be needed to perhaps update to the current target list.

The other question revolved around the exclusion of VEGF and VEGF receptors, and they're currently listed on the automatic waiver list, especially within the context of multi-tyrosine kinase inhibitors that appear to be very active in sarcomas. So it would be worthwhile reconsidering removing them from this automatic waiver list.

There was another comment as to whether the pharmaceutical companies are going to be mandated to perform nonclinical investigations or preclinical investigations, and as of the current standing of the legislation, that is not part of it, if I'm correct.

Is that correct, Greg?
DR. REAMAN: They're not mandated and we can't mandate it. It's in their best interest to comply with the legislation to consider preclinical studies in a pediatric setting.

DR. PAPPO: There was another comment as to whether there has been a specific process that has been identified to prioritize a specific identified target. And the current answer is no, but it's something that you'll be working on.

There was a question about the potential for developed lists that list either combination agents or synthetic lethality agents. And at this stage, this is not yet in the legislation, but everybody feels that it would be beneficial for sure and to be considered in the future.

There was another comment about -- there were a lot of comments, so sorry for that.

(Laughter.)

DR. PAPPO: There was a comment as to when is enough data enough to say that this agent should proceed or not, and at this stage, this is beyond the scope of the legislation. And I have one more
that I cannot read my writing, but it was something related to a lack of sufficient data in relapsed disease, and when do you say that this is okay to put on the list or put on the waiver list.

Yes, go ahead, Malcolm.

DR. SMITH: I had a couple of other comments to add to those on your list.

DR. PAPPO: Please.

DR. SMITH: One regarding the combinations. There are, for example, DNA damage response modifier type agents or targets that are on the list. For example, ATR is on the list. So that's the type of agent that you probably would develop in combination. So as far as I know, the law is silent in terms of this is a target that's potentially relevant, and how it would be developed is something that the FDA, the research community, would have to establish with the companies that were developing the agent.

So I don't think there's any preclusion of that kind of work, and some of those targets are already on the list.
Regarding the VEGF, I think part of the question is we've studied maybe 10 VEGF targeted agents in children. If there's an 11th one that we haven't studied yet, does FDA need to mandate one of these molecular studies or have we studied enough?

So I think maybe it should be on the list, and maybe it's a separate question as to whether it should be studied. But I would vote that we don't need to study it, probably, unless there's something really novel about it.

DR. PAPPO: Noted.

Yes, Greg?

DR. REAMAN: I think this speaks to coming up with a system of degrees or classes or levels of relevance. If we have 10 studies with clinical experience, we ought to be able to use that. But then again, if there's a specific reason for exploring the 11th, then it's something that could be considered.

DR. PAPPO: We will now move to the second question.
DR. CASAK: Please comment on the process proposed for formally updating the lists least at semi-annual public workshops, the methods for nominating potential future candidate targets, and the required transparency in multi-stakeholder discussions to determine relevance. Comment on additional measures to assure timely discussion of emerging science and its clinical translation, which has the potential to expedite drug development to improve the care and outcome of children with cancer.

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

DR. DuBOIS: Steven DuBois. A couple of issues about the next-in-class agents, I guess a question about the level of transparency. So if an agent is given a waiver because it's second or third in class, how will that information get out to the world? And related to that, often the second and third generation drugs, or in-class drugs, may actually be better drugs. So with the
VEGF in mind, if we had stopped at sunitinib, maybe we wouldn't be so happy.

So if there is a waiver because of a second or third in class, is there an opportunity to sort of revisit that if a much better drug comes along?

DR. REAMAN: I would say the waivers are going to be product specific. So how that gets out to the world isn't from the agency. Our communication with the sponsors is confidential. So if sponsors elect to make that information public, they can do so. But it wouldn't necessarily preclude a third in class that does have some properties that would warrant investigation to either a study required or a study that could be done on a voluntary basis through the written request mechanism.

DR. DuBOIS: But there's not a way, in terms of updating the lists and keeping it current, that agents that have been given a waiver, that that process somehow feeds back to the lists.

DR. REAMAN: The lists that we were mandated to develop our lists of targets, so not lists of
drug products or biologics. And that I think we
have to keep -- I don't think we can do that. The
target wouldn't have to change -- I mean, wouldn't
have to come off the relevant lists if people still
felt that there was a reason for exploring further.
But we wouldn't put a specific agent and identify
compounds by name or industry sponsors by name.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel, University of
Minnesota. I want to go back to what Dr. Reaman
presented as what's the process for updating the
lists because this is an ongoing fluid process, and
I think that's one of the real challenges.

I like the idea of the FDA docket. I think
that's a great idea, and I think that is public.
It's open. Anyone can add information to that. I
think then the key is how is that information
vetted, processed, and how then is that going to
link to changes in the lists.

My thoughts on that are kind of twofold.
One is clearly that's all going to come into the
FDA, and it may be that that information is
summarized. And a good use of the pediatric ODAC would be to say let's look at a summary of that content with references because we have regular meetings. And then at the twice-a-year meetings, anything that's felt to be of relevance coming out of those is put forward for public vetting.

I think then there's transparency. There is also evidence based because I think one of the keys is how is evidence going to be weighed, and I think we have to actually really look at what is the publicly available evidence. So I think that there could be a stepwise process. And it may be that the list is formally updated twice a year because the targets aren't going to change that quickly.

But that may be worth something to think about, is that rather than sort of things come and go at will, is there's a real public vetting twice a year, and then formally things are taken on or off the lists, because I think the FDA has the discretion, as Dr. Reaman has said, regardless of what's on the lists, to have conversation with industry at any time to look at an investigation.
So I think that it's a balance between that and public availability.

DR. PAPPO: Ted?

DR. LAETSC: I just wanted to follow. Ted Laetsch from University of Texas Southwestern in Dallas. I just wanted to follow up on Steve DuBois' question about the second and third in-class agents and your comment that formulation will be one of the things considered to determine whether those need to be studied.

Does that mean that industry sponsors will be required to attempt to make a pediatric formulation for those second and third in-class agents if the first in-class agent doesn't have an optimal pediatric formulation, or how will that be determined?

DR. REAMAN: That's a sponsor decision.

DR. PAPPO: Julia?

DR. BENDER: Julia Glad Bender. I have a question about when a sponsor is required to look at the target list and do a pediatric study. The question is perhaps for those second and third
generation. If they're looking for a second indication, do we go back and ask the same questions about pediatrics once we have more data on their first indication to say perhaps that's the better drug, and now we should go back and ask?

DR. REAMAN: I'm confused. Are you talking about indications for the same agent or indications for next generation? The next generation is a new application and a new molecular entity.

DR. BENDER: Right. No. So I'm asking for a second indication of a drug that's already been indicated for something else.

DR. REAMAN: Good question. So the legislation is very specific. These are for new applications, original applications. So supplemental applications would not trigger a requirement for a pediatric evaluation.

DR. PAPPO: Any additional comments or questions?

DR. KOLB: Andy Kolb. I noticed on the lists -- and I missed this before -- you have several specific targets in the class of MLL
fusions. I think we could expand that to include
NUP98 fusions, ETS fusions. I think there
are -- and when I viewed the lists, I wasn't
thinking about it in those terms. But I think MLL
is probably the most well described and well known,
but with 40 different fusion partners, the targets
may be quite broad.

I think you could say the same with ETS and
NUP98, to name a few. And I think adding those
fusions to the list as the category, recognizing
that multiple targets will fall under that umbrella
I think is important to represent.

DR. REAMAN: So would you suggest adding all
of the currently known fusions or just broadening
it to MLL fusions or ETS fusions?

DR. KOLB: I think that there are lead
fusion partners like MLL, like ETS family, like
NUP98, that probably define a distinct biological
class. And currently, the targets and the drugs
that can target those are not as well known. I
think they're known in MLL to some degree, but not
as well known in the other fusions.
DR. REAMAN: Okay.

DR. PAPPO: Malcolm?

DR. SMITH: Malcolm Smith. There were several additional targets that were submitted, and I'm sure they're on some lists at FDA, but they weren't on the list that was circulated, and I do want to just bring those up. The NUT midline carcinoma fusions were ones, and along the lines of what Andy Kolb was saying, there are a number of different fusions, but they all end up causing midline carcinoma, the fusion for fibrolamellar hepatocellular carcinoma.

The DNAJ1-PRKACA fusion is another one. And then CD206 as an M2 macrophage surface marker would be in the kind of non-cancer cell target class. And then finally, there are several antigens or proteins like PSA, PSCA, and PSMA that are prostate specific that could be in the non-relevant list.

DR. REAMAN: They're on there.

DR. PAPPO: But was not included, correct, on the list?
DR. REAMAN: I thought it was. We'll make sure it gets in.

DR. PAPPO: We have time for two more comments, one for Ted and one for Katie.

Ted?

DR. LAETSCHE: I was just going to make one quick additional comment. I'd also recommend RET fusions, RET point mutations there and also KIT fusions -- sorry, mutations. Yes, they're not KIT fusions.

DR. PAPPO: Katie?

DR. JANeway: I have a couple additions as well, which I think are not there, although it's a little bit hard to make sure you've seen everything, CCND1, 2, and 3; CCNE1. Ted mentioned KIT, which was on my list, and STAG2, and there's histone 1H13B.

DR. PAPPO: A final quick question.

MS. PREUSSE: Hi. Courtney Preusse, consumer rep, Fred Hutch. A quick question. I may have missed this, but will there be any sort of subclassification of molecular targets by new
diagnosis versus relapse recurrence?

DR. REAMAN: That wasn't planned. Much of the data that we have are in relapsed patients, although there are clearly now some and in newly diagnosed patients. But we have sort of included them as an aggregate, so not looking at newly diagnosed versus relapsed.

DR. PAPPO: We only have three minutes to summarize, so getting to question number 2, there were a number of new potential genes that partner with other genes that define a specific class that perhaps should be reconsidered on the list. Just an example, it's not the one in CCD206 [ph] RET fusions, KIT mutations, CCND1, 2, 3, CCNE1, STAG2, and histone 1H13B.

There was a question as to how to deal with second and third generation compounds and whether there is an opportunity to revisit the list and the waiver. And from what I could gather, this is going to be primarily related to the sponsor.

Correct me if I'm wrong, Greg, or I don't know if there's going to be a specific mechanism to
evaluate that, correct?

DR. REAMAN: I'm sorry --

DR. PAPPO: I'm sorry.

DR. REAMAN: -- I missed --

DR. PAPPO: In the discussion that we had about second and third generation drugs and how they are going to be incorporated, is it possible to revisit the waiver and is it possible to revisit the lists if there's a specific indication for those?

DR. REAMAN: I don't think there's a need to revisit the list necessarily, unless something should be taken off the list because of the experience with one product in that class. But it wouldn't preclude it coming back on the list if a new product became available for which there was a rationale to study it.

DR. PAPPO: And the final comment was on a process for updating the list, and one of the recommendations was that although the docket is a very good idea to put in potential compounds and potential targets, it would be very helpful to
actually vet this process by having a formal review of the specific target or the specific agent at the twice yearly meetings, and then vetting that specific target or agent at those meetings.

Did I leave anything out or anybody that is really telling me you said the wrong thing?

(No response.)

DR. PAPPO: So good. Okay.

So now we will take a 10-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience, and we will resume at 9:40 am.

(Whereupon, at 9:30 a.m., a recess was taken.)

DR. PAPPO: We will proceed with topic number 2, FDARA implementation, and we will now proceed with the speaker presentation by Dr Lia Gore.

**FDA Presentation - Lia Gore**

DR. GORE: Good morning. It's a pleasure to be here, and I'm grateful for the challenge that
Greg presented to me to talk about some both scientific and logistical conditions that we should think about when trying to figure out how to apply the lists, and I think the conversation in the last questioning session really brought out many of the questions that I hope we can elucidate a little bit here.

So the outline and what I'd like to speak about today is simply to break down things into some scientific challenges that are really biologically driven, and then to think about some very practical applications or logistical considerations that we should consider. Finally, give a couple of just target examples of things that, again, I think the panel outlined their challenged considerations in the question session previously, and then finish with a few reasons that I think we can be optimistic about what this may bring to drug development in pediatric oncology.

Scientific challenges, biology is becoming more and more complex. Some basic considerations really are that targets differ by disease, and
adult cancer biology is very different, and treatments that are being developed for adult cancer types differ from what we may need in pediatric oncology. The vast majority of pediatric cancers involve aberrations and developmentally important pathways or genes and non randomly occurring fusions, as we talked about previously.

Overall, pediatric tumors have very few mutations per tumor, and fusion proteins are very prevalent in pediatric cancers and to date have been harder to target, in general. Those diseases that are considered more adult type cancers seem to have a higher mutational burden and lower frequency of fusions, and as a result, they may be more either amenable to or readily targeted by certain approaches that they're getting lots of attention today in drug development.

So the panel below, in the lower half of this, is a kind of a hallmark paper that really represents a range of tumor mutational burden for a variety of different tumor types. And we know that with an increase in capacity to identify molecular
aberrations in the tumors that we're studying, we have the capacity to understand how that might influence the targets that we're trying to attack.

There is still now a lack of knowledge between the molecular definitions of disease in both pediatric and adult cancers, so we can't apply what we know necessarily about adult cancers to pediatric cancers just by assumption. Pediatric tumors overall tend to be sort of cleaner. They're a little bit more simpler monogenic diseases and a little bit more homogeneous in most malignancies than adults, and they tend to have fewer copy number abnormalities and what we would consider legions per pediatric tumor.

So if we look at the diagram on the bottom, along the X-axis is just a variety of different tumor types and along the Y-axis is the number of somatic mutation frequency. In the solid bars in kind of that fuchsia color are diseases that are typically considered more pediatric in nature, and you can tell that they're at the left end of the panel, meaning that they have fewer molecular
aberrations per tumor.

The ones in the dotted lines, however, are ones that pediatric cancer physicians and adult cancer physicians share with patient populations, and those are things like AML, glioblastoma multiforme, and DLBCL. But I would argue also that within the group of diagnoses overall, there's still quite a few variations among those tumor types, so it's hard to say that a GBM in a child for instance is like a GBM in adults. In fact, we have lots of reasons to believe that those are fairly different. So it's important not just to take diagnostic groups, but to really dig into the molecular underpinnings of those specific tumors.

One of the things that I study most is pediatric acute lymphoblastic leukemia, so I thought I would just give a couple of examples of some genomic subgroups that are under active consideration right now as therapeutic targets, and why we are learning more about them, and why they still present a challenge to us clinically to treat.
So we know that there's a group of mutations in pediatric ALL that have particularly adverse outcomes, at least with the therapies that we've used to date, and those treatments are targets of PTEN, the IL7 receptor, JAK mutations, RAS mutations, those of NF1 or TP53, and AKT.

There's still some confusion around MDM2 as a target, and that is specifically that we do not entirely understand efficacy and outcome results when inhibiting P53 in patients with wild type versus mutant clones, and MDM2 as a target is a very specific example of this, that even though there are now thousands of patients who have been treated with MDM2 inhibitors with adult cancers, we're still not exactly quite sure how to apply this for pediatric tumors.

One of the things that a pediatric oncologist will tell you is that severe hyperdiploidy in patients with ALL is a particularly adverse prognostic factor, and we know now that about 80 percent of hypodiploid patients have TP53 mutations, so this again is a target.
opportunity, but one that we have not risen to the occasion to be able to address quite adequately yet.

IL7 receptor signaling overall we know drives steroid resistance, and this depends on transactivation of a particular domain, R3C1 [ph]. We know that there is a small molecule inhibitor that has been applied successfully to children with cancer and that it can sensitize steroid-resistant cells. But in a patient population that really needs additional therapies that are more promising, those with T-cell ALL and in particular those with relapse T-cell disease, ruxolitinib does not seem to affect T-cell blasts as well as it does other types of malignant cells.

Similarly, we know that AKT activation and phosphorylation is observed in about 85 percent of T-cell ALL. But to date, targeting AKT has been really either an indirect or and upstream target effect. So as we think about how to apply these targets, it's not as straightforward even when we know a very strong disease and target relationship.
Another challenge that I think we have to consider is how do we apply the technology that seems to be exploding in our daily lives. There is ever-advancing technology in genomic landscape that makes the available data on molecular targets rise exponentially and seemingly logarithmically every day. The good news for that is that there are an increasing number of platforms that we can use to study these molecular aberrations, which means that the cost for those studies in genomic testing overall has decreased substantially.

What that also means is that even though we have an increasing number of targets, this does not make things clearer for us necessarily, so we really have to dig into not only the targets but the platforms very specifically as we figure out how to apply these. It's also important to understand that not all targets that we currently define are identified by these next-generation sequencing technologies, so we have to think about how technology can keep up with what we're also learning about tumor biology.
Current technologies depend on an enormous amount of bioinformatics information and interpretation of the data, and as the data explode logarithmically, so does the need for bioinformatics and careful analysis. Despite their sort of super-human skill set, bioinformaticians are still human beings, and there's a very different interpretation of the same data sets at times, and we have to really understand what that means if we're trying to compare data, for instance, from one platform to another and from one bioinformatician to another. This does not make our jobs any easier, but it's something that we have to keep in mind.

Then finally, turnaround times are improving for the molecular testing that's being done, however, it is still not real-time data, and we still have to understand what to do between the time of testing and the time to apply this to patient utilization.

We're pleased to see that one of our panelists has actually provided the figure on the
left side of this slide, so Dr. Mody and his
colleagues presented a very beautiful article last
year about what occurs in a variety of different
tumors and what are the technologies that we can
use to assess different aberrations in the cells
that we're trying to understand.

At the center of this converges the
molecular data that have clinical impact that we
need to understand, and on the right side of this
slide, I've listed just some basic facts to
illustrate that our technologies and the available
platforms differ and how they're being applied
differ. FoundationOne testing for instance is a
nice gene panel by targeted capture, which are a
little over 300 genes on any given day, and the
turnaround time for that is about two weeks.

Dr. Janeway's GAIN and iCat2 panel and the
oncopanel, about 300 genes as well. There is the
option to add in both array compared to genomic
hybridization, FISH studies, and other
histochemistry studies to evaluate in more detail
what a particular tumor aberration might look like,
and the turnaround time is somewhere between two and four weeks for the full testing.

Parallel to that at Dana Farber as well is a LEAP leukemia consortium, that looks at a gene panel called the Rapid Heme Testing Panel, that looks at 95 focus genes active in leukemias. And it may also include additional infusion testing or other drug screen assays depending on the identification of aberrations. Turnaround time for the actual panel itself is quite brief, it's less than 5 days, but to include all of the analysis and the sort of curation of the data, it takes another week or two.

Finally, the pediatric match protocol is an amplicon gene panel conducted through Project Every Child at the National Cancer Institute in the Children's Oncology Group using OncoMine. There are 143 genes that are evaluated in about two to three weeks of turnaround time.

In parallel, CureSearch convened really a survey of pediatric oncologists, scientists, and other experts in the field to say what are the most
important targets you can think of? And this occurred just a little bit over a year ago. It was presented at the CureSearch summit in February of last year.

Along the left side is listed the things that practicing oncologists thought would be the most targetable where should we focus our efforts kinds of genes, and that's a list that's very familiar to many people in the room. The right side of that column is really what's the current status. For PI3 kinase for instance, there are adult studies right now that are not necessarily that promising for certain targeted tumor populations, so the future of the application to PI3 kinase inhibitors in pediatrics is a little bit more challenging.

BRAF and MEK have gotten a lot of attention in pediatric studies right now. There are multiple ongoing studies. I think the last count, there were somewhere around 100 studies of PD and PD_L1 one targeted agents. So the question is -- again getting back to the earlier conversation -- what is
next in line, how many studies did we need to do
with these agents, and what can we or should we not
extrapolate from one to another?

CDK4/6 is a rising target for pediatric
tumors and BCL-2 has active studies ongoing. MDM2,
as I said, is a little bit unclear about how we're
going to interpret those data and in which
populations, but there is a pediatric study
planned. I think many people would agree that if
we could effectively target Myc, that would take
care of a lot of challenges that we have today.
And similarly, EZH2 is a very clean target for a
select patient population. Early studies of that
compound in children have been very promising for
some patients. It has undergone some challenges in
recent weeks, but I think that will continue to
move forward well.

The CureSearch summit actually prioritized
these agents, both the single agents, and they
looked at combination strategies, and finally added
the EWS-FLI1 fusion, MLL-RK [ph], MT2A as it is now
known in PARP, as additional targets that would be
of interest to pediatric studies. So as we think about the lists of targets that were developed that Dr. Reaman presented earlier and those lists that are sort of identified as hot spots in clinical practice, it sets our challenges out for us.

Another thing for us to be aware of is that even when we have a phenomenal target and a phenomenally well-defined biologic driver, it doesn't always work as well as we would like. And the example I'd like to use is that of a small molecule inhibitor of DOT1L called pinometostat, which is a very clean, very specific inhibitors of DOT1L.

The reason that that's relevant is that KMT2A fusion or MLL fusion proteins recruit a histone methyltransferase called DOT1L, and it causes hypermutation at a specific location of target genes that enhance the leukemogenesis or pro-leukemic potential for cells and genes. DOT1L is absolutely necessary for the development and maintenance of these rearranged leukemias, and pinometostat is a very specific potent and
selective small molecule inhibitor.

With all of that biology in our favor, pinometostat still did not give us the kind of results that we would like to see in patients with KMT2A rearranged leukemias, and that tells us that we still have a lot of work to do; not that the science wasn't right and that didn't look promising, but simply that it is not as straightforward as we'd like to even hope that it could be.

So the question is what do we do next with information like this, and then do we go back and evaluate a very clean biologic pathway that should work and it doesn't work the way we'd like it to?

Processing logistical and practical considerations that I think we can't underestimate the importance of, one is that there are a limited number of institutions that can conduct pediatric studies well and cleanly, and it requires a lot of work and effort. That also means that it's very difficult to access these sorts of centers and trials for patients who may need to travel. It
causes a lot of strain on the families. It causes an incredible amount of challenge for people to get to the place where their trial might be available.

Historically, there have been some regulatory endpoints that have sometimes been challenging in a new era of therapies, and I think we've seen some very nice evolution lately of what this could look like in a new generation of therapies. And that is we can't necessarily judge success or failure on overall survival necessarily. We need to take a little bit more carefully about what other endpoints may be meaningful and how to apply them.

Randomized trials are always favored, but randomized trials are not always possible. And there seems to be an evolution toward clinical benefit and overall response for a number of new agents, and those are particularly useful when used in combination with valid historical comparisons and cohorts of data.

We know that a lot of our current therapies and a lot of the targeted therapies that were
discussed and will be discussed at this meeting are less often now traditional cytotoxics. They're more biologically driven, and as a result, complete response or rate at which complete response might be attained may be a different endpoint for us to think about, and we have to question how we want to apply that.

A lot of newer endpoints that are being considered and more commonly used in clinical trials for pediatric oncology right now include things like progression-free survival, clinical benefit, and modulation of targets. I think also at the ASCO meeting earlier this month was a great example of trials that now show that you can have some examples of noninferiority for instance, where you may have clinical benefit, toxicity advantages, quality-of-life advantages that also have non-inferior results compared to more traditional therapies or surgical interventions for instance.

So I think those are important to think about as we consider clinical trials as we're developing this and what our appropriate endpoints
might be for the patient population in whom we are trying to most benefit.

Financial challenges are ones that we can't ignore, and traditionally, investment in pediatric trials has lagged behind those in adults. Just practically, the vast majority of drug development will really only go forward if there's a potential adults indication, and a lack of a market for drugs and pediatrics does exist. It's difficult to recover research and development costs once a drug is on the market, so that has led to lots and lots of social conversation around drug pricing, drug documentation, and marketing, and the majority of those costs are still borne by the companies that develop compounds.

An additional thing that we've touched on very briefly this morning is that pediatric formulations are necessary for many of our patients, but they are costly to develop, and it's estimated to cost at least a million dollars to develop some pediatric oral formulations. If there's a limited market for that, you can see how
that would be difficult to both employ simultaneous
testing, pharmacology testing, and additional
safety that might be required. And that sometimes
has limited implementation of pediatric trials
simply either relatively or absolutely and has
delayed the development of some compounds in
pediatric oncology.

Another consideration is really access to
and what are the operations and practical
considerations. At any given time, there are at
least 8[00], or 900, or a thousand compounds in
development for cancer overall. That's a lot of
compounds, and in fact, we've occasionally said
that there are more drugs in development for cancer
then there are certain diagnoses per year in
children by quite a bit.

The relatively small number that is
available for pediatric trials definitely has
another set of implications for how we would set
about looking at these most appropriately, and a
problem of the success that we have also is that
the vast majority of children with cancer today are
cured of their disease. And that means that overall there are a relatively small number of patients in whom we can apply phase 1 and early phase drugs to use the data that we have and the access to these exciting compounds in a thoughtful way that poses challenges to clinical trial design as well as data interpretation, and the pace at which we can acquire data for patients on these trials.

Another challenge is that pediatric patients who are enrolled in early phase trials are typically very heavily pretreated. They've been through many rounds of chemotherapy, surgery, and radiation. They may have had multiply relapsed or significantly refractory disease, and that is a patient population in which it requires a lot of effort to take good care of them, and they may have untoward complications that could potentially limit our toxicity evaluations in the new agent.

Many of these patients traditionally have had a shortened life expectancy and challenging disease-free survival outcomes, and this not only
is unfortunate for the patients and their family, but it actually imparts a pretty significant difference in our ability to follow the effects of these agents in inhibiting important pathways if we're trying to look at the long-term outcome for these patients.

If we think about moving some of these compounds up front to the front line or early phase treatment, we want to know what happens to inhibiting these pathways after 10 or 15 or 20 years. And that is a very significant difference in pediatrics than most of our adult colleagues have to acknowledge.

Overall, I think what all of these things tell us is it requires a lot of expertise, it requires a lot of focused effort, and it requires very large teams to be able to evaluate all of the important factors that we have to consider. And that, again, brings more costs and burden of treatment implementation for all of the centers that are participating in these both very excitedly and very willingly.
There are some societal and ethical challenges that I think we have to raise. One is that we know that drug development in children's has traditionally lagged behind that for patients over age 18, and there are very good reasons for that. There is substantial concern for exposing what we would consider some of our most vulnerable citizens to unknown risks.

We know that there are studies that require biomarkers that we need to assess most adequately by doing either serial sampling or serial biopsies and that historically has been very difficult to do in children for the concern of putting them through painful or unnecessary procedures if they may not benefit from the treatment which they are receiving.

I think we've received a number of very positive indications that there's very real potential for benefit for children now with some of these compounds, and there has been an evolution to rethinking whether or not that restriction on serial sampling and biopsying is really ethical if
we could offer them a therapy for which they do stand a chance of benefit.

I think there's another consideration that's a little bit of the elephant in the room and that people do have a challenge to think about what happens if a child has a bad event on a clinical trial and we don't have a host of data to support this, or it may be an untoward event that has unfortunately just occurred.

There has been historically reluctance to invest in applying drugs to pediatric trials if there's the potential risk that a very bad public relations event could happen if a child had a bad event on those and further potential killing of that drug if there's a bad event with a child that may actually limit the ultimate access that other patients have to a promising agent just simply because something bad happened, and that's an important event for us to think about how we both deal with that societally and ethically.

So I want to actually draw this to a close by thinking that there are some very good reasons
for us to be optimistic. It's always easy to pick apart the problems and pick apart the difficulties, but I think there is some significant and substantial reason that we should be optimistic.

I think we've seen an evolution, and over the last 10 years I've argued repeatedly that cancer is becoming a chronic disease for many patients. We may never cure somebody entirely of their disease, but we could turn this into a disease that looks very much like diabetes or hypertension. And if you are compliant with your appropriate therapy, you may keep your cancer at bay for many, many years.

As I've told a lot of patients, cancer that does not grow and divide and metastasize and cause organ dysfunction might not kill you. And it's an important thing to think about this as we're thinking about what our appropriate endpoints are. What if cancer becomes a disease that people live with more effectively? That's a very different concept in pediatric oncology, and it requires a frame shift in how we think about things.
I think the newer legislation that was presented earlier today and all of the work that's being done really offers great advantages over what we've done. There has been a learning curve to legislating pediatric oncology, and I think it's important to acknowledge that, first of all, because we are substantially better off today than we have been. But these legislative actions also have limitations, and I don't think we can expect any one piece of legislation to fix everything. So I think we have to be realistic, and I think we have to continue to work to try to define the appropriate degrees of how we're going to intervene.

New approvals and new applications are actually dramatically exciting as we think about what goes forward. There are a number of approvals recently that have been really relatively age agnostic or have allowed access for younger patients under the age of 18 to agents which are extremely promising. And I suspect that most of the members around the table can identify examples
in which they have used an adult drug in a child
and had a very good outcome.

Similarly, I think agents are now getting
tumor-type specific agnostic approvals. And that's
also very exciting as we think about the tremendous
explosion in biologic knowledge that we have the
advantage to apply something that might be a little
bit untraditional but with very strong biologic
rationale, and therefore impact a disease that we
may not have even anticipated an improvement in.

This is a brief chart to get back to the
therapy and prioritization review of targeted drug
pairs, and I think it's important. Just as an
example, I don't expect people to actually see the
detail, but to understand that there's a wide agent
class that's been evaluated. They have been
subject to scoring systems and look at some
potential biomarkers for which these targets may be
able to be applied in pediatric oncology.

There are some example biomarkers that are
listed in the second to the last column for the
right, and then I wanted to include the priority
for the pediatric MATCH trial in terms of how these
were included or not included for a variety of
reasons. I think this is just an example, and I do
think it's important to recognize that these lists
are not static in any way. They need to continue
to be evaluated.

Similarly, along here there were some agents
on the left chart, some agents that were excluded
from the initial evaluation. That is simply, if
you'll notice along these, that there are either
very uncommon targets or targets and biomarkers
that are not known, so it's difficult to know how
to apply them. On the right-hand side are some
example histologies or tumor types for expansion
cohorts. It's important for us to think about how
these apply as we continue to evolve knowledge as
we go forward.

Challenging things to think about and I hope
what will set the stage for later discussions today
are really our tremendous exposure to knowledge
about the cancer genome has led to increases not
only in the molecular targeted agents that are
being developed, but in the sophisticated
technologies and sequencing that we have the
capacity to interrogate biologic pathways to
understand more about what's happening in real
time.

This is truly a new age of biomarker-driven
personalized therapy, and as we learn how to direct
agents, it will allow us to be able to give
patients drugs for which they are most likely to
respond and from which they can most likely derive
benefit. So I think it's important to consider the
limitations. We've talked about some of them
already. We need to think about how to handle
multiple tissue or tumor collections.

We need to really recognize the importance
of disease heterogeneity and complexity, and the
influence of things like the epigenome, the
proteome, the microbiome, and all kinds of other
omes that we haven't even defined yet; to think
about as we increase our knowledge, we have also
increased how we photo divide, and subdivide, and
develop micro cohorts of disease and how we need to
classify them together in order to develop expected responses. Similarly, we need to define pediatrics a little bit differently. We need to think about ethical challenges that will rise as we discover germline mutations. We need to think about costs, and we need to think about availability and formulation.

This is a quote I think from a thoughtful article that was published last year, and it recognizes that as we have had successes and failures in the development of targeted agents, we've done this one step at a time. And I think we can see that the mathematical modeling of what we have presented in front of us and the challenges for the explosion of new applications and new drug development really does require that we shift our paradigm, be creative and be collaborative in how we think about how to do this most effectively because at the end of the day, there is a patient at the other end of these discussions that depends on us to do this correctly.

My personal acknowledgements are those here.
I have the privilege of working with really wonderful people, both in my own institution and across not only the country but across the globe; and again, most importantly, the patients and families that we see every day and trust us to take these responsibilities very seriously. And I think this effort that's going on will allow us to continue to do honor by them and the effort that they have placed in trusting us. Thank you.

(Applause.)

**Clarifying Questions**

DR. PAPPO: Thank you very much, Dr. Gore. We have a few minutes left to take some clarifying questions. Please remember to state your name for the record before you speak.

DR. KOLB: Lia, you had mentioned access to phase 1 development, phase 1 trials as a challenge. If we're going to increase the number of phase 1 trials through the RACE Act, how do we address that challenge?

DR. GORE: That's the million-dollar question, right? I think Dr. Kolb has a very valid
question. The concern is that if we have more
drugs than we have patients, how are we going to do
that? I think part of it is that as we get to
tumor type or histology, biologically driven trials
rather than a trial for neuroblastoma or a trial
for Ewing sarcoma, if we get to biologically
driven -- this is an inhibitor of a pathway that we
know is active in these groups -- it will allow us
to be more creative about our trial design, and we
can probably be more effective and more efficient
in enrolling patients on trials where there's
biologic rationale.

I do think that our study design, our
statistics, are going to have to evolve as we think
about this. The way we used to do trials is not
effective or efficient anymore in this era, so I
think we're going to have to think about that more
carefully.

Dr. Janeway?

DR. PAPPO: Katie?

DR. JANEWAY: Lia, one of the most
challenging aspects of biomarker defined clinical
trials is getting the right patients to the right trial. You talked about availability of molecular diagnostics and the sort of challenges of navigating different types of molecular diagnostics. I think maybe you didn't mention or I'm interested in your thoughts on is actually trial matching, so finding the trial for the patient, because in our current paradigm, we don't list trials by genes or gene variants make you eligible for that trial, and there isn't an easy way to search or access that information.

Do you have thoughts about that?

DR. GORE: I think you're absolutely right. I think one of the things that you didn't talk about is how hard it is to get genomics on a particular patient sometimes, and we know that there are many patients that are limited in their ability to get the best diagnostics available because insurance won't cover it, or they don't allow third-party payers, or there is some great delay.

So that's the social side of this, right?
Just to get even the information is still challenging for a significant proportion of our patients. So under the best of possible circumstances, we have access to this information. I think it's a place where we could have a more national effort, more sponsored ability to have databases that are more searchable, more accessible, a real-time possibility of getting that information. It's almost impossible to have everything captured at any given time. And even if we do, clinicaltrials.gov for instance is a great start, but it's not enough.

I think even if you know there is a trial, it may not be open. There may not be a slot. There are all kinds of other sort of practical application considerations. And I didn't even go into that because it is very complicated, but I think there are probably things that we can do better to make the information more publicly available.

DR. JANEWAY: One major limitation of clinicaltrials.gov is that the eligibility criteria
that are gene or gene variant related are not a
searchable field, actually, so it's a descriptive
entity within that very valuable repository of
clinical trials.

DR. GORE: And I think we've probably all
had the experience where we have looked for our own
trials on databases and websites. We can't even
find out if that's our own trial, let alone
something else that might be an option for our
patients. And if we can't navigate that, that's
probably really challenging for somebody that is
coming at this without of knowing how to look for
it. Absolutely.

DR. PAPPO: Ira?

DR. DUNKEL: I have a comment, although it's
more for the FDA staff maybe then for Dr. Gore. I
think you've provided a really important service.
Some of you have authored papers and statements
saying that adolescents should be included in
relevant adult trials. I just came back from an
adult brain tumor meeting, though, and although
these were highly academic clinical researchers,
this was completely foreign to them. So I just wanted to mention that I think this needs wider dissemination.

DR. PAPPO: You want to --

DR. REAMAN: I'll just comment that -- thank you. We did publish a paper suggesting that this is something that should be considered. We just recently, as of last week or the week before, published a guidance as well. So it's available for sponsors and investigators, including adolescents, on appropriate disease and target-appropriate studies.

DR. PAPPO: Elizabeth and then Malcolm.

DR. RAETZ: Lia, thank you for the excellent talk. Just in terms of your comments that you made about efficiency of trial design, I was wondering if you could comment on any strategies that you've thought about combinations, particularly for disease processes where a single agent activity has been somewhat of an issue and a challenge.

DR. GORE: Sure. For those that didn't hear Dr. Raetz's question, it related to trial design
and thinking about some approaches that might help solve some of these issues, single agent versus combination, those kinds of things.

I think there is always a tricky balance between how to structure, for instance, single-agent windows and then rolling to combinations. How to move some drugs up front if they look particularly promising can be very challenging because you don't want to, in some cases, introduce a new agent that may compromise what we know to be a standard baseline population response for certain patients.

I do think a very simple thing that we could do, if we're trying to introduce a new agent into combination studies, for instance, if we have a backbone that's a relatively accepted backbone for a particular disease type or tumor type, but we know that there is the potential that a new agent targets something that has been discovered recently, one of the things that has been challenging I think is when we're looking at the window period of what data we're trying to
understand and acquire from a new agent, sometimes there has been a tendency to require single-agent windows to be very long, sometimes wonder 1 or 2 months, and then allow rolling over to combination therapy.

I think we are getting to the point where those very prolonged single-agent windows might not be either as helpful as we thought they might be or they might actually compromise the ability to actually see activity of a drug that may have more potential efficacy in combination.

So I think we can consider some models, for instance just as a simple example, where that single-agent window for pharmacokinetics or pharmacodynamic evaluation could be much shorter and still not compromise evaluating the integrity of the drug, both for safety and activity reasons, but also roll in response modifiers to look at single agent versus combination.

I think we can probably accelerate some of the things that we've done more slowly in the past. That might be one approach. And then again, tumor
type agnostic, biologically-driven studies so that we're not lumping everybody together, but at the same time, that we have the opportunity to evaluate a promising compound in multiple tumor types simultaneously.

DR. PAPPO: One final question. Malcolm?

DR. SMITH: Malcolm Smith. A beautiful and thoughtful presentation, Lia. I wanted to query you a bit on your comments about the chronic disease paradigm. I see that for CML plexiform neurofibromas, that those will probably be treated as chronic diseases. It's harder applying that to aggressive ALL or AML.

I guess when I think of the transformative agents from imatinib and nelarabine, ATRA, arsenic, and more recently the CAR-T cells and larotrectinib. What everyone is excited about is that they make the tumors really get smaller or they induce complete remissions.

So I guess it seems to me that's still the coin of the realm and that there's not -- that's still our goal. So maybe we would take something
else if it was the best we had, but I don't see
that there's a real change in what we really want
from a new agent or a new treatment.

DR. GORE: Very appropriate, and I think I
absolutely agree with you. I do think that we
should think about our response definitions,
though, if we have -- for instance, treatment
beyond progression is something that we now do in a
lot of adult phase 1 studies where we're able to
then introduce into -- for instance, a single-agent
phase 1 study, a patient develops some isolated
brain met.

We don't necessarily take them off that by
protocol. A protocol may allow for that patient to
get single-fraction brain radiation and allow them
to continue on, because if we know that this is a
biologic agent that isn't going to work instantly,
it requires a long runway to be able to see the
biologic effect.

If we take that patient off and they go on
to get radiation anyway, we may have limited our
ability to understand what natural history of
inhibiting that pathway or that gene might be. And if we can allow for a more creative trial design where we say isolated progression in one area doesn't mean that the patient isn't benefiting from inhibiting that target or that pathway in a whole bunch of other parts of where they have disease.

So I absolutely agree with you. We still should want to cure patients, and we should want to cure them strongly and deeply and well, is how we've described it. But at the same time, I think we have to think about what do we remove patients from study for and why, and what could we potentially think about modifying as we think about those responses, so that we understand that we give patients an opportunity, a sufficient duration of time exposed to an agent to understand if they're really going to benefit from it.

So I think part of the question is, again, to think carefully and cleanly about what that means, and that does allow patients to live with their cancer for a longer period of time. So we may not be able to use our same judgment criteria
for what we have traditionally.

Thanks for asking the clarification.

DR. SMITH: And that's a great point, and I think just in our preclinical testing, for some agents, we clearly see a progression before we see a response, especially the epigenetic modifiers that may take a week or two to actually modify the transcriptional machinery.

DR. GORE: Right, or four months.

DR. SMITH: So certainly having the response criteria match the mechanism of action of the agent in terms of timing is critical.

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

DR. GORE: Thank you.

DR. PAPPO: We will now proceed to our next presentation, Dr. Lisa Bollinger.

Guest Presentation - Lisa Bollinger

DR. BOLLINGER: Good morning. I'm Dr. Bollinger, and today I will be talking about the implications of the 2017 FDA Reauthorization Act on Pediatric Cancer Drug Development from the perspective of industry. I have the disclosure
I'm going to start with a brief overview of BPCA and PREA that you heard a lot about from Dr. Reaman this morning. They are intended to work together in order to maximize the information in labeling on dosing, safety, and efficacy for products that may be used in the pediatric population. The law requires that even if studies are negative or uninterpretable, study information is still placed in labeling because information has been deemed critical.

We know in the pediatric population we don't often have chances to repeat studies over and over again until we get positive studies. Because of the limited amount of information that gets out there in the pediatric population, it is important for all study results to be included in labeling. And it's also important to note that PREA and BPCA are not mutually exclusive. Those products that are required to be studied under PREA can also qualify for exclusivity under BPCA, although it should be noted that we have increasing numbers of
biologics that are being developed for oncology therapy, and because of the way that the legislation applies exclusivity to biologics, fewer companies actually seek exclusivity for these programs.

Pediatric oncology studies have actually been required by the agency now under BPCA or PREA, and you can see some examples are arsenic, which Dr. Smith mentioned earlier, imatinib, and panitumumab. These are examples from the early 2000's, and a lot of things have changed since the early 2000's in regards to the legislation.

For one, we've had stronger infrastructure and documentation by the agency in how this legislation is applied. In addition, since the early 2000's, we've had improved knowledge of tumor biology that's informing treatment, and precision medicine has delivered more targeted therapies. Because of the targets that are identified, these products may qualify for orphan drug exclusivity, which is actually a critical regulatory pathway for development of medicines in small populations.
Remarkable progress has been made in our understanding of genomic landscapes for pediatric cancers, and products approved for use in adult cancers can provide a health benefit for pediatric patients. Despite the lack of PREA requirements for these orphan products, many of them are actually studied in the pediatric population anyway, although they're not always performed for regulatory review nor product labeling, so that's a big disconnect.

If the studies are conducted and they're not conducted under a requirement or under an incentive program by the FDA, they often aren't submitted for independent review and may not be included in labeling.

I actually went back and looked at Drugs at FDA approval letters and did a sampling and saw that there were approximately 77 new BLAs or NDAs that were approved since 2012. I picked the date 2012 because that was the most recent reauthorization of both PREA and BPCA, and there's really good documentation in the database at Drugs
at FDA about decisions that were made on those products. About 26 applications were waived on the basis that the disease did not occur or was rare in the pediatric population, and another 50 applications were exempt because of orphan designation.

Now, when I cross-reference these 77 products to clinicaltrials.gov, about 62 percent of them had clinical studies listed in the pediatric population. But again, the regulatory utility of those studies are unknown. In other words, it's not known if those are being conducted by the sponsor for submission to the agency or if they're being conducted as independent research studies by investigators.

As we know, PREA was changed under FDARA, and we are now required to study molecularly targeted drugs if they're intended for the treatment of an adult cancer and directed in molecular targets substantially relevant to the growth or progression of the pediatric cancer, and also, it eliminated the exclusion for
orphan-designated products.

Now, these legislative changes do bring new opportunities. For one, PREA now allows industry an early opportunity to discuss these pediatric studies in oncology with the FDA. In addition, the smallest study populations will require the development of innovative study designs, and I think that this will cause a lot of advancement in the way that we study drugs not only in the pediatric population but in the adult population as well. It's also a chance for closer collaboration between NCI, COG, other collaboratives, FDA, industry, and advocacy groups. And you heard Dr. Reaman talk a lot today about public and private work to do in this area.

One of the other benefits is that because studies submitted in response to PREA are required to be included in labeling, the independent regulatory review of data and availability and labeling may increase access to these products for patients. But of course with legislative changes also come challenges.
One of the first challenges that we've heard a lot of discussion about today is what molecule should be studied, and as we all know, this legislation requires lists. The lists in the legislation are a list of products that have substantial evidence that the products would work on a pediatric target and another list of products that should be automatically waived.

The chance to make these lists may represent an opportunity for stakeholders to come together to discuss emerging science, but regardless of whether or not products are on the lists, each one of the therapies that are being developed must be independently assessed for the opportunity to provide benefit in the pediatric population.

So it's not clear if we will continue to have this list or how much benefit it will provide to us in deciding which products need to be studied, or if it will go the same way as the other lists that have been required in previous legislation like BPCA. We used to have lists for drugs that needed to be studied or lists of generic
drugs that needed to be studied. So we'll see if
this actually has utility in helping us determine
which products should be studied.

Now, what the list doesn't do is it doesn't
help us prioritize. Many of these products share
the same molecular targets, and studies could be
competing for the same small pool of patients. And
because recruitment in pediatric trials is
difficult and many centers must be opened,
pediatric studies are often international by
nature, and that does require some level of
harmonization. We'll have to have ongoing
surveillance of pipelines to ensure that the most
promising therapies are studied first.

Oftentimes, FDA and NCI are often aware of
pipelines across companies, so perhaps we can work
with them as we decide which therapies revolve into
studies and which ones to come off. I will say
that at Amgen, one of the things we are doing is
working with internal experts as well as looking at
external experts that we can collaborate with to
assess which ones of our products in our portfolio
may benefit the pediatric population, and then to also determine what types of nonclinical studies we can do to further investigate the potential.

There was also a safety requirement. We do want to make sure that we do have some safety information before we move into the pediatric population to assure that we have all the information we need to help us determine if the benefit will outweigh the risk.

That being said, there are always inherent risks for patients participating in clinical trials, and we have a recent adult example of studies of immunotherapies used in combination with other drugs that were actually placed on hold while safety concerns were examined.

We also know from all the previous studies in pediatrics, including non-oncology studies, that we have identified adverse events that are unique to or amplified in the pediatric population, and we know that some toxicities are hard to predict based on what we know from adult studies or preclinical models.
Of course, industry is always looking for regulatory stability. The intent of the legislation was not to provide prescripted directions for implementations, and lists certainly don't provide certainty. As Greg mentioned earlier, whether a drug is on the list or off the list, it will have to be evaluated independently to see if it will be required to be studied in the pediatric population.

As science advances, it will be incumbent upon the FDA to more clearly define what therapies will have study requirements, because while regulatory certainty is an ideal that's hard to realize, business uncertainty is not sustainable.

Industry must be able to plan for the study requirements for a given therapy over time; number one, to be able to plan the studies. And this is going to be more labor intensive now because as we know, the FDA has been really forward thinking in reducing cycle times of drug development, as well as in reviewing the products for approval. So that actually compresses the amount of time that
industry has to reach an agreed upon pediatric study plan with the FDA.

Of course, we always have to plan for costs. While that's not the primary driver for pediatric studies, we do know that from a business standpoint, we do have to plan for these investments, which could range anywhere from $1 million to $35 million depending on the types of studies that need to be performed.

So where does that lead us? It leads us exactly back to places where we've been before. More than 20 years ago, people said that pediatric studies in any therapeutic area could not be conducted, and what we know now is that there are over 700 products with pediatric information and labeling largely based on clinical studies in the pediatric population. There will be challenges in prioritizing products to study, and the best minds are poised to solve the challenges presented by this new legislation.

The new requirements may provide an opportunity for increased collaboration across
industry, academia, and government, so I'm going to end on this positive note as well. Thank you.

(Applause.)

**Clarifying Questions**

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

We will now take clarifying questions for Dr. Bollinger. Please remember to state your name for the record before you speak.

DR. SEIBEL: Thank you, Dr. Bollinger, for that perspective, which was very helpful. I guess I'm a little -- and this question or comment is both for you and for Greg perhaps, but you alluded to these previous lists that have been present.

Is there anything different about this list that will distinguish it from the ones in the past, where it sounds like they've really failed?

DR. BOLLINGER: I do think that there may be some subtle differences. One is that this is one therapeutic area, although all cancers are obviously very different. And I do think it is an opportunity for all stakeholders to come together...
and really discuss what's emerging in the science.

I think the one thing that's not different is that the FDA doesn't have to stick to what's on the list or not on the list, so there's going to have to be independent assessment of every therapy along the way. So I think time will tell whether or not the investment of time and energy into making these lists is going to be fruitful, but we will certainly be using these lists as we embark on this journey to develop these products in kids.

DR. PAPPO: Julia?

DR. BENDER: Julia Glade Bender. Thank you very much for that really very interesting perspective. And regarding costs, I just want to make sure that both parties understand that many of us who do these trials for industry or for the children, to do the targeted therapies, this is actually a labor of love on the part of the institution because the internal costs to your institution is so much higher than the compensation that you get for doing these trials, that all of us who do them are required to go out and raise more
money in order to satisfy all of the regulatory
requirements of doing these studies.

So I'm concerned that in some ways, while we
try to gain access for kids, the economy is so
different in running these pediatric trials that I
wonder how the institutions are actually going to
manage because if you're looking for the needles in
a haystack, do you have to open up the farm? And
that's part of the issue here that I think we're
going to have to think about new mechanisms of
activating trials for individual patients for rare
targets at an institutional level so that we as
institutions or investigators, who feel responsible
to our patients to get them access, don't go under.

DR. PAPPO: Very good point. Elizabeth?
Brenda?

DR. WEIGEL: Dr. Bollinger, thank you very
much. One of the points that I didn't see your
presentation but I wonder if you might comment on
is that -- and you do state international
collaborations. But also from a regulatory
perspective, how much does -- the new American
requirements, FDA requirements, how does that
balance with the thinking and development of
meeting international regulatory requirements from
an industry perspective?

DR. BOLLINGER: Certainly Drs. Fox, Caron, Vassal, and Bucci-Rechtweg will be talking both
about prioritization as well as international
studies following me later today. But we do have
to look at how we work with the requirements in the
European Union. I think that because of the
cluster meetings, we will have more collaboration.
And actually moving these studies earlier helps to
harmonize the timing of how we prioritize and
embark on these studies. There are still some
differences that we'll need to work out, but again,
I'm sure that we will over time be able to get
through those hurdles as well.

Also, I'd like to say a lot of international
collaborations that are starting up right now that
are very exciting, really do aim to help bring
these two programs together.

DR. PAPPO: Kathleen?
DR. NEVILLE: Thanks; really great talk. I thought it was very thoughtful.

Dr. Bollinger, my question for you -- and I know you can't speak for all of industry -- is I think increased collaboration and cooperation between sponsors would be a paradigm shift and how do you foresee that happening? How do companies collaborate while also protect their and answer to the shareholders?

DR. BOLLINGER: I think that is a very important question and one that we will have to work through. As we look at a lot of these therapies that are not used as sole therapies, a lot of them are used in combination. And one of the questions is going to be with the PREA requirements, how are we going to work with other companies to provide combination studies? But again, I think because in the pediatric space there isn't a large financial driver for getting the studies done and having the products labeled in the pediatric population, that there's probably a little bit more leeway for cooperation.
That being said, as hopeful as we all are, we always run into issues with protecting IP and making sure that our adult programs don't suffer because we're also doing pediatric programs. Again, I don't have any real clear answers, and I think because we're at the very beginning, we haven't had to struggle through some of those issues enough for me to tell you how we're going to define that. The only thing that I can say is, again, we've faced these hurdles in the past and have been able to overcome them, so I have no doubt that all of the companies working together, as well as all the great minds that are focused on developing cancer drugs for pediatric patients, we'll make this happen.

DR. PAPPO: Any additional questions or comments?

(No response.)

DR. PAPPO: I have a comment if that's okay, Dr. Bollinger. As we move forward, I just think that it would be very important just to remember some of the successes and some of the disasters
that we have had trying to develop specific indications for pediatric tumors. I don't completely agree with your slide that said that recruitment to pediatric trials is difficult. I think that if you have the right target, the right population, you will have the patients.

A perfect example is what has happened with the NTRK inhibitor. There is a very rare population that has greatly benefited from this. There have also been very disappointing studies which took a long time to develop, and the two stories are the ipilimumab that was specifically for melanoma patients and opened almost two years after the drug was actually approved for adults. And the second one was vemurafenib also for the BRAF mutant, which was exclusively for pediatric melanoma.

If this would have opened earlier and it would have been just a blanket study for BRAF mutant tumors, perhaps this drug could have been incorporated earlier into the treatment of BRAF selected tumors. So it's just something for your
company to consider in the future as this
legislation moves forward.

DR. BOLLINGER: Yes. Thank you very much
for your input.

DR. PAPPO: Katie?

DR. JANEWAY: Very well said, Dr. Pappo.

Katie Janeway from Dana Farber once again.

How can we get numbers that will answer this
question? Because I agree with your statement that
an accrual -- we gnash our teeth a lot about
accrual, and we worry about accrual, and we do it
so much sometimes that we shoot ourselves in the
foot and slow ourselves down developing trials and
actually answering the question by opening the
trial.

But I don't know how we manage to get data
that supports what you said. And what my sense is
that my problem is not putting patients on trials.
My problem is not having trials for patients that I
see in my clinic who have relapsed cancer, but I
don't know how to actually quantify that.

DR. PAPPO: I'm afraid I don't have an
answer. I don't know if you have an answer for that, Dr. Bollinger.

DR. BOLLINGER: I think I would say the answer probably depends on the type of tumor that you're looking at and how many centers that you're going to have to open. While some studies may enroll quickly, we also have the experience that many others don't.

One of the things that certainly will help is talking about this more and having these types of meetings where people become aware of the different studies that are ongoing. As you said, it's really hard to search clinicaltrials.gov, so perhaps one of the things that we need to start thinking about is a way to either improve that database or develop another one that could help us to figure out answers to these questions.

DR. PAPPO: Greg?

DR. REAMAN: And we just point out that the one important thing about the trials that are ongoing, despite the fact that there were no PREA requirements for pediatric evaluation, and
separating out whether they were industry-sponsored studies that might lead to labeling information or some positive regulatory decision versus investigator-initiated studies where data may not really impact any other patients, I think that's a real distinction that needs to be made.

Again, I just want to stress that we're not hoping or we don't intend to see this legislation result in increased numbers of studies, but just increased timelines for which studies are in fact discussed, considered, thought about, and initial evaluations of dose and looking for activity signals, because I think some of the things that were studied were studied long after the drug was approved in adults.

There are some real challenging examples, and I think very telling examples, with the orphan exemption of drugs for indications that span the pediatric and adult age groups that were approved for adult indications when the same disease occurs in children in two years, three years later we're still doing studies. So that's what this
legislation is really intended to change, I think.

DR. BOLLINGER: And that is actually a really important point that also plays into the ability to recruit into studies. I know what we have seen across the board is if a product is approved in the adult population, it's much easier for a pediatric oncologist to perhaps use that therapy off label in the pediatric population, and they may be less inclined to consider enrolling that patient in a clinical study.

We saw that with our own Neulasta, where it was being used as standard of care in the pediatric population. So because of the gap and the time it was approved in the adult population and the time that the pediatric studies were initiated, we weren't able to enroll enough patients because clinicians believed that the product was efficacious. So that's an extremely good point, that we do need to bring those timelines together in order to actually get better studies. Thank you.

DR. PAPPO: And that you saw also with the
vemurafenib and the ipilimumab trials. Although they were international studies, the accrual was dismal because the drug was already approved and pediatric oncologists could prescribe it. And there were really combinations that were coming along that were much more effective.

Steve and then --

DR. DuBOIS: Actually, something to respond to one of Dr. Reaman's comments. Do you anticipate not necessarily an increase in early phase trials, but a shift in the proportion that are industry sponsored rather than investigator initiated as an impact of this act?

DR. REAMAN: I think they should be industry sponsored, and it's going to be a collaborative effort, obviously, between industry and investigators. Given the patient population that we're dealing with, this will have to be a coordinated, collaborative venture.

DR. PAPPO: Kathleen?

DR. NEVILLE: Just a comment to add on to what Drs. Reaman and Bollinger said, that another
reason to move these studies earlier is the off-label use is often not paid for by insurance, and these agents are expensive. And what we consider adequate data are not considered adequate by payers.

We're running into this over and over, and we've been successful in having sponsors supply drug but the whole landscape is shifting. And until we get these studies done and until the landscape shifts to where payers are satisfied or need to be satisfied with the data we provide, there's going to be an access problem in addition to just access to trials.

DR. PAPPO: Donna?

MS. LUDWINSKI: I'm curious on both the FDA perspective and the industry perspective about moving these trials earlier, which we all agree should be done. What's the impact when these agents are dropped for adults? What do you expect is a likely outcome? Will there be more drugs that are shelved that might have shown some efficacy in children but they're dropped because of adults, and
it doesn't work?

DR. BOLLINGER: I'll go first just to say that if they do move up earlier and they start showing promise in the pediatric population, we'll still have the PREA requirement, although if the submission isn't made for the adult population, I'm not sure where that leaves us. But hopefully if do see signals, we'll proceed.

I know that even with a couple of our molecules that we abandon the adult trials, NCI or NIH was actually continuing to study the products in the pediatric population. But there is that little twist that if the application is not submitted for the adult population, then does the PREA requirement really apply because the PREA requirement comes into effect when the application is approved.

Right, Dr. Reaman?

DR. REAMAN: Actually, the PREA requirement, the requirement, yes, but the initial pediatric study plan, actually that requirement comes at the end of phase 2, so before an application comes in.
And most of those study plans, we would envision that trials are already designed and trials were already approved by the agency and maybe even enrolling patients.

But I wanted industry to go first with the response because we won't have a mechanism that provides the authority for the agency to do anything beyond that. But my hope and expectation would be that despite the fact that pediatric cancer may be a small market and a minimal force, it's still a force, and there are other orphan diseases that some companies have capitalized and used as significant forces to develop drugs for small populations.

So I would be hopeful that something that might be shelved for adult development where there is evidence of activity in the pediatric population would continue to be developed. And that's another potential role for public-private partnerships. I know I'm on a public-private partnership roll today, but that's what it's going to require.

DR. BOLLINGER: One of the other things that
we can consider is if the product is dropped for
development in the adult population but continues
in the pediatric population, there would be an
opportunity for a pediatric priority review
voucher. So there still are some incentives that
would encourage industry to continue forth with the
pediatric studies alone.

DR. PAPPO: Julia?

DR. VASSAL: So I think in terms of
accelerating testing in children, we all look to,
for example, the larotrectinib study as one of the
perfect studies where pediatrics was involved from
the get-go in the initial trial. But oftentimes
when industry and adults are speaking together
about the early phase trials, there's no
pediatrician at the table, so the question is whose
job is it at this point to bring up pediatrics
early in the conversation. And it seems to me that
at least one part of this legislation may be that
it's actually industry's responsibility to request
that when they're initiating a phase 1 study, that
they asked their adult collaborators to involve the
pediatric oncologist who could contribute at the same time.

DR. BOLLINGER: Absolutely. And I do think it is on industry to look at their portfolio and see which products will be required to have pediatric studies. And one of the great things is that there are actually a lot of pediatric specialists within industry. I will say we're taking over the world, right? But there are a lot of pediatricians within industry to provide that advice, although it depends on what company you're talking about.

DR. PAPPO: Brenda?

DR. WEIGEL: Building on what Dr. Glade Bender mentioned -- Brenda Weigel, University of Minnesota -- I think one of the reasons that larotrectinib was so successful in that space was that a pediatric friendly formulation of an oral compound was developed very early and taken into the phase 1 trial at the onset of investigation.

So I think it comes back to an industry prioritization of formulation development as well.
If you really look at that, that's one of the reasons it was so successful to move forward.

I don't know, Dr. Bollinger, if you can comment on that is an industry commitment in certain circumstances, if it's oral, for a pediatric formulation. And I don't know if you can speak to in the timelines how that could affect the implementation of trials for children that are very young age as was exampled in larotrectinib.

DR. BOLLINGER: That's a really great point and something that we will need to be considering in the early stages. What you may not know is that I actually oversee CMC regulatory at Amgen as well, and so I've had a lot of experience working with taking some of our oral formulations and turning them into pediatric friendly formulations. It's a lot more complicated than you would think, especially with solid oral dosage forms because there may be issues with solubility or other excipients that you have to put into the product that may not be great for pediatric patients. So oftentimes with the solid oral dosage forms, it
really does take a long time to produce a product
that can be approved by the FDA.

   Now, when you have a subcutaneous
formulations or IV formulations, that's a much
easier question to answer. But it is something
that will have to be addressed early because of the
time lag required to develop an age appropriate
formulation in younger patients.

   DR. PAPPO: The last question is Katie.

   (Dr. Janeway gestures no.)

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

   DR. BOLLINGER: Thank you.

   DR. PAPPO: We will now proceed to a guest
speaker presentation by Dr Elizabeth Fox.

       Guest Presentation - Elizabeth Fox

   DR. FOX: Thanks, everyone, and thanks to
the chair for this opportunity to speak and address
you from the investigative perspective.

   My disclosure information was discussed at
the beginning of today's meeting. I would also
like to state that all the data that I'll present
on slides today is publicly available, and the references to those studies, some of which were done very well by people in this room, are referenced on each slide.

My interpretation of this data and my opinions, however, are not intended to reflect the opinions of my institution or cooperative group affiliations or trial sponsors, and I will discuss many off-label uses, as is the first statement, in what we're trying to improve with the RACE Act.

We've talked today, and just as a reminder, research to accelerate Cures and Equity for Children's Act as part of FDARA 2017 mandates earlier discussion of pediatric plan for our oncology drug development or biologic products directed at specific molecular targets in cancer that our germane to children. As we've heard repeatedly this morning, the agents are classified using a list system, which is very fluid, which includes relevant, non-relevant, or other. I see this as an important next step in the opportunity for collaboration among U.S. government agencies,
the European Medical Association, PDCO, global pharmaceutical industries, academic investigators, patients, and policy advocates.

This issue is particularly important, as we can see on this slide, on oncology drug approvals over the decades with cumulative oncology, new molecular entities plotted as a function of the decade, and as you can see, the rapid exponential growth and annual average of oncology drug approvals. Back in the 1950's, the average was about one per year. Between 2011 and 2018, that average is nearly 11 per year.

When we look at this more closely at anti-cancer drugs, we can see that these are falling into the two classes we'd expect, this early rise of small molecules, primarily tyrosine kinase inhibitors, and in recent years the increasing prevalence of biologic agents. The chart on the left-hand side of the slide just looks at the mechanism of action and the generic name stem that helps us organize these drugs with some degree of precision.
This slide is well known to many in the room and reminds us that cancer is a rare disease in children. Each year, under 16,000 children in the United States are diagnosed with cancer, and it's important to remember that the average age of diagnosis is 6 years of age. If we look more carefully at how these 16,000 children are divided by diagnoses here in the color-coded pie graph and the corresponding color-coded chart, you can see that children with lymphoblastic leukemia comprise 20 percent of those children diagnosed. And if we look a little bit more closely, we can see that the common age for those children is less than 8 years of age.

Skipping down the list, you can see that there's a subpopulation of children with AMO who are very young. Patients with neuroblastoma tend to be young. Patients with Wilms tumor and other kidney cancers tend to be young, but there is an older age population for some specific types of cancer of the kidney, and patients with retinoblastoma are also very young.
If we look a little bit more closely at Hodgkin's lymphoma, the other end of the spectrum for acute myeloid leukemias, osteosarcoma, Ewing sarcoma, thyroid cancer, and melanoma, these are older children and adolescents. Really beginning to speak to if you look carefully at the disease you'd like to treat or the molecular characterization, you may be able to understand what age group you should target, and this will directly impact questions such as formulation and patient access to drugs.

Finally, if you look at some of the other listed diagnoses here, you see that non-Hodgkin's lymphoma, rhabdomyosarcoma, and a few others have a large age range, zero to 19 years of age, which is how these 16,000 children were categorized in that age group. You can see these diagnoses span the entire age group. But if you were to look carefully at the subtypes of these types of cancers in children, you would see that these two have age distributions. And as we learn more about the molecular diagnosis of these, we are likely to be
able to really hone in on what age group we're actually talking about for new drugs.

So one of the tasks I was given was to talk about single agents same in-class prioritization. I think this is among the places where we may likely have the biggest impact for single and individual patients, but from a clinical trials perspective presents many challenges. As we think about single agents, same in class, we need to consider the unique aspects of biomarkers in cancers of children and adolescents; specifically what is the strength of the oncogenic driver in each of these specific diseases.

Finally on the prior slide, there were 16 percent of the children who are diagnosed with cancer between the ages of zero and 19 years of age who are classified as having rare tumors. These are specifically rare tumors, and addressing those may be a place where single agents are particularly relevant as we've heard for larotrectinib. The number of agents in trials in this rare patient population will depend on the agent properties and
the efficiency of trial design. This relies on our endpoints, whether they're safety, dosing, or pharmacokinetics.

The status of the biomarker and companion diagnoses for these various molecular entities is going to be critically important to how we apply that to children and how we conduct these studies. And finally, a topic that we've touched on slightly but not really delved into is in pediatric cancers, we have disease-specific response criteria. How we declare complete response in a patient with neuroblastoma is very different than how we declare that in a patient with rhabdomyosarcoma.

From an investigative perspective, I really appreciate the acceleration of new agents into our patient population. Access is a major issue. However, I will remind everyone that the RACE Act for Children defines cures, and in my mind, it defines cures as the ultimate goal.

The majority of childhood cancers will require assessment of combinations. These we will need to look at disease-specific backbone therapy
because our current curative therapies are multimodality and cytotoxic. They come at the cost of high late effects rate, and we would love to be able to decrease the amount of cytotoxic drugs that we use, but that is going to be a process over time.

In addition, we're also very interested as investigators in combinations of targeted agents for pathway inhibition, which has been alluded to in this and I understand is likely beyond the scope of the list, but certainly as an investigator, the places where we're looking. Finally, as I mentioned, the consideration for aged distribution of specific cancers, histologic and molecular subtypes, should be carefully tracked over the next few years.

In terms of prioritization, there are a few key points that I think are worth highlighting here. The evidence of the target drug/response relationship will need to be looked at in order to determine how to move forward in children. We're going to be doing this with less data from trials
in adults if we accelerate the pipeline. That will likely mean an increased reliance on pharmacokinetic and pharmacodynamic endpoints in modeling.

In addition, physiologic based pharmacokinetic models and the assumptions that are used in those to help predict how to start doses in children need to be looked at carefully. I think there are emerging data on what some drugs are doing and some of our sponsors have done to try to use PBPK modeling, and we need to monitor that carefully. As I mentioned, the biomarker validation and companion diagnostics and the status at the time we enter into pediatric trials will be important, and I'll have an example of that a little later.

The resources for pediatric cancer specific animal models should be clearly addressed. As we've heard, this is likely going to be a private and academic partnership to bring these forward with some interesting cooperative groups in the mix, but I think this is going to be something
we're going to need to address as part of prioritization.

As we've heard, toxicity in children is something that we take very seriously, and the toxicity profile of new agents must be carefully looked at, primarily from developmental considerations and careful assessment of the role of juvenile toxicology, its pros, its cons, and its timing in relationship to the cost of those types of studies. Most importantly from a clinical perspective, the severity and reversibility of any toxicity is a key consideration. And finally, as we think toward combinations that are relevant to childhood cancers, we need to think about additive toxicity.

Finally, I think pharmacologic properties of each of the agents and assets need to be looked at as well as the formulation, and we'll discuss some examples shortly. And finally, I think agents where we have a goal for global collaborations could be and should be prioritized, particularly as we're working in smaller and smaller groups of
patients.

With respect to preclinical models, in my opinion, they are a prerequisite for prioritization. Some of the best practices that should be considered when looking at preclinical models are the selection of the models with fidelity of the oncogenic drivers of disease and their ability to evaluate the biomarkers in this preclinical setting.

Drug distribution should be considered; specifically do we need drugs that cross the blood-brain barrier for CNS penetration, central nervous system penetration, particularly for patients with brain tumors; validation of concentration thresholds and necessary duration of inhibition. Demonstrations of the relationship between target inhibition and activity is something that clearly belongs, at least in the starting point, in the preclinical realm.

Within our preclinical models, we need to demand clinically meaningful efficacy thresholds. Those thresholds cannot be determined in our
smallest of patients. Evaluation of pathway redundancy, innate and acquired resistance, these can be secondary steps after the initial prioritization but are really important to understanding how we're going to move drugs forward. And finally, if we're going to consider combinations, the mechanistic rationale for synergy should be fully explored.

Biomarkers are going to be an important part of how we move molecularly targeted agents into pediatric patients and are doing so now. As we've discussed, childhood cancer is a rare disease. Biomarker selection will further limit the number of eligible patients and that we have the need for resources for assessment of agents in pediatric preclinical and in silico models.

We may have to consider limited revalidation of biomarkers and companion diagnosis in our pediatric populations; as Dr. Gore discussed, the role of tumor biopsies and consideration for recurring tumor biopsies if they can benefit our patients, and the hope that someday maybe
circulating tumor DNA can be part of what we use in children.

The relevance of single genetic aberrations and genomic signatures from carcinomas in adults are going to be challenging to use in our pediatric population, and efforts to look for genomic signatures in pediatric cancers are going to be limited by the lack of genomic variability in those tumors. And finally, the complexities of fusion transcripts and multiple fusion partners, as was alluded to by Dr. Janeway, as we look at the different panels that we are using in our patients, are we really finding pediatric relevant targets and are we looking for them?

So as an example, I'd like to walk through the checkpoint inhibition in childhood cancer or at least a piece of this study. These are three studies that were presented at the American Society for Clinical Oncology meeting last year in 2017, and what you can see is three separate trials were done. The age for the enrolled patients was similar. Two of the three trials did not have
biomarker selection and did not ask for centralized PD-1 screening of archival tissues. The pembrolizumab study did. The adverse events were fairly comparable across the three agents, and the first look at the overall response rate in these patients was very similar and quite frankly disappointing.

When we look more carefully at the pembrolizumab study, which was biomarker selected or what we thought was a biomarker selection when this study opened, it was updated this year at ASCO, and it was clear that over 800 patients had tumors screened for this study to enroll 127 patients. And in doing this, the response rate was still very low, and those responses were in the disease that we expected to have response, Hodgkin's lymphoma.

So checkpoint inhibition, where we started. We started with huge enthusiasm from studies in adults, and we had a lack of preclinical models that led to multiple large multistrada clinical trials in children. We were uncertain of biomarker
selection, but we certainly learned along the way. What we learned from these studies is that single-agent PD-1 or PD-L1 inhibitors are tolerated for short durations. Many of the children were exposed, but few had clinical benefit. One of the important things we learned, however, in this experience is that multiple studies can simultaneously accrue when the effort is global.

What we would still like to know, with respect to the Hodgkin's lymphoma cohort, some of these trials included those patients down to age 12 of what we would consider adult trials, and the real question in my mind is, can we realize true collaboration between medical and pediatric centers overcoming the logistics, the different care aspects, and the different care models in order to allow patients in the older age groups to actually have access to these drugs? Can we define the new biomarker for PD-1 inhibition, hypermutated cancers in children, and will those children benefit? And finally the lingering question of will combinations work better?
So as I think about dose-finding trials or the earliest trials we're going to be likely asked to do as part of the RACE Act for Children, we think about whether we need to do dose escalation trials or what we would consider dose confirmation trials, meaning bringing the adult dose directly into children, and I've outlined a few points here that are worth considering.

We should consider dose escalation in scenarios where the recommended adult dose is determined by maximum tolerated dose; that is there is associated toxicity with this drug. And if this toxicity is part of a central nervous system complex or is irreversible or serious organ damage, we certainly need to understand what the lowest and appropriate dose is for children.

For drugs that are myelosuppressive, there are fewer and fewer of those in development, however, we do have to recognize the impact of our upfront prior therapy in children with relapsed cancers will impact the role for myelosuppressive therapy, not only in the future but our ability to
assess that in a phase 1 study or early phase trial.

Highly variable pharmacokinetics, age-related metabolism, or saturable clearance would lead us to think that perhaps dose escalation is necessary in a younger patient population. If we're going to test the formulation or an untested schedule, we may need to consider dose escalation. And for childhood cancer that requires a different target concentration to achieve an end result as determined in a preclinical model, we may need to escalate to get to that dose. And finally, as we heard earlier today, if there's a rationale for early combination, we could consider that in a dose escalation trial.

If we don't have these things, if the recommended dose in adults was determined by pharmacokinetics and was not an MTD, if the toxicity profile is easily reversible, if the pharmacokinetics are dose proportional and have limited variability, and the other factors here listed, I think we could begin to consider how many
trials we need to do or if we can just do a dose
confirmation and immediately try to expand.

As we look at the challenges of same
in-class comparisons, I will put up some of the
data that's been presented in publication form by
Dr. Laetsch, as well as abstract form this past
year at ASCO regarding the NTRK inhibitors. As we
know, the larotrectinib study was a biomarker
enriched study. Twenty four patients had been
published from that study; 17 had tumors that
harbored NTRK fusions, and the median age was
4.5 years.

As we look at entrectinib for those
features, we see that this was not a biomarker
selected dose escalation study. Sixteen patients
were required, 3 of whom who had tumors which were
fusion positive, and the median age was 10. The
dose-limiting toxicities were really limited in
larotrectinib, but a number of dose-limiting
toxicities were found in entrectinib, and in fact,
the dose of entrectinib that's recommended in
pediatric patients is based on a maximum tolerated
dose. And it's 550 milligrams per meter squared daily, which compares to the adults recommended phase 2 dose of 600 milligrams per day, which is approximately equivalent to 350 milligrams per meter squared, so above the adult recommended those as a fixed dose.

The pediatric recommended phase 2 dose of larotrectinib is 100 milligrams per meter squared twice daily with a maximum dose of 100 milligrams, which is the adult recommended dose, and that is given twice per day. The most important thing to our patients is objective response, and through biomarker selection, larotrectinib produced objective response in the majority of patients with fusion-positive tumors. And in the entrectinib study, all three of the patients who had fusion-positive tumors did benefit from this drug, indicating the true need and actual data to support biomarker selection works, and patients can be enrolled.

The biggest difference between these two drugs, besides toxicity and the way the trials were
conducted, is, as Dr. Weigel pointed out earlier, the presence of an oral form solution and formulation for larotrectinib allowed them to target the appropriate population. You see that the median age on that study was 4.5 years compared to 10 in entrectinib. This is in large part because infantile fibrosarcoma is an important tumor for NTRK fusions, and those are young and infant patients who require the oral solution.

The pharmacokinetics of these two drugs were looked at in each of the trials, and target concentrations were easily achieved at the doses that were administered to pediatric patients. You'll notice in the larotrectinib study, the vast majority of patients got their target dose because they were able to accurately deliver it with their oral solution.

Formulation has been mentioned a number of times today, so I'll spend a moment talking about the important features of formulation. We recognize as investigators this is an expensive endeavor. We also recognize as pediatric
oncologists what it means to walk into a room and have a child spit and oral drug back at you.

(Laughter.)

DR. FOX: This graph on this slide is actually from an ALK inhibitor study where we looked at a series of different formulations, investigational formulations including powder in capsule, powder in bottle, the formulated capsule, which is the commercialized form of this drug, and a pure oral solution.

As you can see, when we looked at the dose normalized exposure area under the concentration curve on the Y-axis as a function of age and each of the different colored dots, there's really no association between these things, which really helps us to understand that these formulations were all from an exposure perspective interchangeable. They were not, however, interchangeable in the patient's mind.

Bioavailability is an important consideration, and small bioavailability comparison studies can be done within pediatric studies.
However, major bioavailability studies need to be done prior to pediatric testing. In part, we need to know if we're in the right target range.

Taste and palatability are critically important to our patients. They're critically important to the ability to get the drug to the patients, and some of the other things we've heard about, the concentration of the oral solution is important.

Taking large volumes of anything, even if it tastes good, is not going to go well in a 3 year old. The stability of that formulation, how it is prepared, what the expectations are for the family, and how it is administered, and if it has to be administered immediately after preparation, this can really constrain a formulation in the long term.

To look carefully at one example of how formulation impacts how we design trials and how we interpret the results, this is the drug cabozantinib, which was recently published. And in this is the pharmacokinetics. This was a
dose-finding study in children where the area under
the concentration curve or exposure is plotted for
each dose level.

You can see that although we endeavored to
treat patients at three different dose levels, 30,
40 and 55 milligrams per meter squared, the
exposure in the actual patients when it was
measured was highly variable and probably didn't
differ.

When we looked at the average daily dose
that was actually administered to these patients,
you can see that because of the constraints of the
formulation, cabozantinib being delivered as 20
milligrams or 60-milligram capsules, that the
actual daily exposures didn't differ in the first
two dose cohorts. So this was an important lesson
about what we think we're accomplishing with those
escalation and the ability to deliver drugs.

Toxicity profile is an important
consideration. As we move into the targeted
therapy age, we can look at both small molecules
and biologics. They are no longer primarily
myelosuppressive, but they do have a major impact on important features particularly for children such as metabolic changes, such as hyperglycemia, hyperlipedemia and dyslipidemia. Cardiac impact with arrhythmias, QT prolongations, changes in injection fraction, and the changes in growth and development are something we're all aware of.

Similarly for the biologics that are now later in development in pediatric patients, the cytokine release syndrome, neuropathies, and capillary leak, I think the lesson from biologics in children is that as pediatric oncologists, we can adapt and we can manage these toxicities with careful observation.

The unique toxicity of growth plate abnormalities is well described and known and an ongoing issue for many of these agents. Here is the comparison of pazopanib, a VEGF and multityrosine kinase inhibitor, and vismodegib, a smoothened inhibitor.

What you can see here is that for pazopanib, even though on therapy there was a widening of the
growth plates, and a fusion of the growth plates, that was reversible. However, for the smoothened inhibitor, it was not. And Dr. Reaman alluded to this in his opening comments, that this was managed not only by understanding the toxicity but also understanding the toxicity and limiting the age range of patients who could go on to those who were skeletally mature.

I think the best way to manage toxicity profiles, particularly if we move agents into children with less adult data, is that serial evaluations are very important, and the use of pediatric-specific grading criteria -- for example, things like hypertension and neuropathy -- are important considerations as we move forward.

So I would say the attributes in my mind for prioritization and collaboration include adaptability. The expected prevalence of biomarker and disease and the primary endpoint determine the number of sites that will be necessary to conduct these trials. And perhaps we can move into a model where additional sites are added after initial
safety cohort.

Agility. We need to have timely, scientifically and clinically relevant results and require shorter protocol lifestyles with rapid readouts of endpoints and outcome measures.

Allegiance. We all have allegiance. We need to recognize it. We need to recognize it as stakeholders. And as an investigator, the goal of cure rather than an individual drug or trial is very important to me, and I recognize others in the room may have other allegiances and goals.

Importantly, and as was alluded to, a mechanism to continue assessment of agents without adult indication is critically important, especially as we're going to move these evaluations up sooner, and the pediatric oncology population and our patients are going to want to have continued development of some of these agents.

Finally, alignment. There is already academic international alignment on goals and risk stratification and strategies that is happening. One example is the recently activated, newly
diagnosed hepatic tumors trial, which is an international trial to address the issues of hepatic tumors and treat those tumors, which are very rare, on several continents using the same risk stratification and the same outcome measures.

Notably, there are no investigational agents on that study, but it demonstrates that academics and pediatric oncologists are willing to work together to align our goals and to negotiate to have international standards.

Finally, the future of cancer therapy in children, increases in preclinical modeling, both in vivo and in silico, will be helpful to us. We expect that personalized individualized therapy will be based on tumor biology. We look forward to the day where cytotoxic chemotherapy with its acute and late effects can become extinct and increasingly a role for all molecularly targeted immunotherapy drugs through clinical trials.

We'll have to accept some of the challenges of looking at combination therapy and what it will mean to transition from a cytotoxic backbone to
more molecularly targeted drugs. As I've discussed, age appropriate formulations can be considered, and it doesn't necessarily have to be considered for every single drug we want to test earlier.

Finally, toxicity is always an important consideration for all stakeholders. Chronic oral outpatient therapy with targeted drugs -- so drugs with a long half-life -- means that we do have to watch some of these patients for longer to understand the toxicity profile. Non-myelosuppressive, chronic non-hematologic toxicities will be prevalent in this group of drugs, and we'll have to watch carefully for the impact on growth and other development.

Finally, unknown late effects of this drug is something that will need to be followed possibly through registries as we expose children to these drugs and hope that we improve their quality and duration of their lives. So with that, I'd like to thank you.

(Applause.)
Clarifying Questions

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

We will now take clarifying questions for Dr. Fox. Please remember to state your name for the record before you speak.

DR. DuBOIS: Steve DuBois. Thanks so much, Beth. I wonder what your thoughts are on overcoming this challenge of novel-novel combinations when both agents are not owned by the same company.

DR. FOX: Thank you for that question, Dr. DuBois.

DR. DuBOIS: It's extremely straightforward.

DR. FOX: I want to be optimistic that as we see the single agent success stories like larotrectinib and the NTRK tumors, that we can move to a place where whether it's through some investigator initiated trials or other mechanisms in which patients get drugs, that we can garner enthusiasm for pathway inhibition. And in my mind that's truly what we have to show, whether that's through preclinical models or other ways with our
patients who understand those, what does it mean to inhibit the pathway? And I would hope that once we can determine that we really need to be able to inhibit multiple nodes on the pathway and through the legislative efforts to get us early data, that there may be an increasing opportunity for collaborations either within the industry or outside of industry to get those combinations to our patients.

DR. PAPPO: PK?

DR. MORROW: P.K. Morrow. I had a question for you about your slide related to doses and the dose confirmation trials. And my question was related to your criteria for non-myelosuppressive therapy, and the reason I'm asking is because oftentimes, particularly in the HE [ph] malignancies, we're able to accept some degree of myelosuppression, especially when it can be supported. And I just wanted to get your thoughts as to whether you would differentiate between the two types of malignancies for that.

DR. FOX: I certainly would. And
traditionally in dose-finding studies, we have separated hematologic malignancies from solid tumors precisely for that reason in that in the solid tumor population, myelosuppression is something we do need to be aware of, particularly if we want to move down the line into combinations. But in the hematologic malignancies, obviously that is not something we can either track, nor do we want to track.

DR. PAPPO: Elizabeth?

DR. RAETZ: Beth, thank you for a wonderful presentation. Just in terms of your thoughts about agility, I was wondering if you could comment on the process. So if an investigator at an academic medical center has what they believe to be promising preclinical data and they want to bring that to an industry partner potentially or to a cooperative group, retreating consortia, do you see that as a place where there could be some opportunities for greater efficiency, and any thoughts on how that process might be more efficient?
DR. FOX: I think that the ability to bring those ideas forward, in my experience and in talking to others who do a lot of preclinical work, the agreements that are set forward with whoever owns the asset or controls that asset are a very important key piece to this.

So when individual investigators in academics partner with pharma to test in a pediatric animal model or other models systems, agents and assets, if there were a mechanism to broaden those types of studies so that perhaps we could include other agents that aren't necessarily from the same sponsor or a way to compare those agents would be critically important.

That is a large ask in a time when there's a lot of proprietary information that needs to be protected, but I think it's going to become critically important, or if there were mechanisms to have similar -- and I know that through the PPTC, there are mechanisms to have potentially different labs working on using the same type of strategy to evaluate drugs, so the outcome is a
little bit more comparable.

DR. PAPPO: Ted?

DR. LAETSCH: Beth, thank you for a very
nice -- this is Ted Laetsch from UT Southwestern.
I just wanted to ask you your thoughts on trial
design. And as we may be studying more agents if
this legislation is successful and bringing more
agents to phase 1, do we need to think about where
we set the bar for those early trials in terms of
early signals of efficacy -- noting larotrectinib
as an example, but also crizotnib for ALK fusion
tumors and CAR-T cells for ALL where there was very
early evidence of lots of efficacy -- and avoid
what we've potentially done with the PD-1
inhibitors, where we have exposed hundreds of
patients and use a lot of resources to study agents
that show little efficacy, at least across the
board, do we need to raise the bar in this setting?

DR. FOX: In my opinion, Dr. Laetz, I agree
with your statement, and I would say that we do
need to raise the bar. I think that biologic
selection, using biomarker selection is going to
put us in a unique place to expect the bar to be higher. Where exactly that bar is, certainly we do not want to discount drugs that have -- for example, as Dr. Gore pointed out, we need longer periods of duration to know if they're really effective.

When we look back at the PD-1 and PD-L1 inhibitor experience, if you look at how long patients were on study, very few of them continued on for a long period of time, one could say we just weren't patient enough with the drug. But I do think patients are one of our most valuable resources, and we have to respect that, and we have to respect how they move forward. I think the bar has to be a little bit higher in our clinical trials. I think it has to be a lot higher in our preclinical models.

DR. PAPPO: Toby?

DR. MacDonald: Toby MacDonald. A lot of these targeted therapies also hit the normal host cells, namely the microenvironment cells, like tumor associated macrophage. These are not readily
addressable in preclinical models. Just what are your thoughts on how we can get at that side of the coin?

DR. FOX: Yes, I don't have a great answer to that question, Dr. MacDonald. I do have -- I'm thinking very heavily about the experience in the PD-1 inhibitors, where we accepted the fact that we didn't have good preclinical models and expose a large number of patients; so I think working towards some of those models or non-traditional models. I don't mean to imply that every drug needs to be in a mouse before it gets into a child. I'm just implying we need some indication as a way to say for our pediatric targets, this makes sense.

DR. PAPPO: Katie?

DR. JANEWAY: Very nice talk, Beth. Katie Janeway from Dana Farber Cancer Institute. One thing that I have grappled with since this regulation was passed and as we've developed the molecular targets of relevance list is the molecularly targeted agent where the biomarker is not yet clear and the biomarker is being assessed
in the context of early phase trials. The best example here probably is the DNA damage response inhibitors right now, ATR inhibitors, checkpoint inhibitors, PARP.

In that setting, the biomarker's not yet defined, but it will be defined in the context of the trial, and I worry that that will be to delay in incorporation into trials in pediatrics because we won't -- the testing for the biomarker is done in the context of the trial. We'll then have to catch up in figuring out whether that biomarker is present in children.

Do you have thoughts about how we do that? The best example of that is tumor mutational burden where -- or even PD-1 and PD-L1, where because kids were not included in those early trials, the biomarkers were never tested in our cancer types, so we didn't know how frequent they would be and whether or not they would predict response.

DR. FOX: Obviously, Dr. Janeway, that's an important question, and I would hope that in the RACE for Children Act and the mandate to begin
discussions earlier, that's part of the discussion. I think as pediatric oncologists and clinical trialists, we may need to consider that very heavily. And I have no problems with trying to do things in a non-biomarker; if we don't know what the biomarker is, should we make a leap that we do? Or should we just constrain the studies so we don't enroll 150 patients without a biomarker?

So could we do these things in parallel as we're learning more about the biomarkers and perhaps do a stage study where at the second stage of the study, before we expand to large patient populations, should they exist? We know precisely what the biomarker companion diagnostic is and how it relates to the pediatric patient population.

DR. PAPPO: Steve?

DR. DuBOIS: It seems to me that that really highlights the ongoing critical importance that academia and academic pediatric oncologists are going to continue to play in pediatric cancer, drug development, and biomarker development. So I think we're going to have to obviously continue to
publish our work on biomarkers and continue to pool our data into national resources, so that as new potential biomarkers become highlighted by studies in adults with cancer, we're able to very quickly say, oh yeah, that does seem to be relevant because here it is in this database that we've already built.

DR. PAPPO: Malcolm?

DR. SMITH: Right. And I think to the PD-1 question, you know, even as these studies were being done, there were efforts of collecting pediatric tumors and analyzing for PD-1 by a number of companies. So it's really important to be doing that either prospectively before or in parallel. I do think there will be -- if we're going to be moving forward in children early, there is going to be this uncertainty like there was with the PD-1 and PD-L1 targeted agents.

In retrospect when we look back, it's what tumor mutational burden seems to be really, really important, and our cancers don't have -- and the childhood cancers have low tumor mutational burden.
But going into it, that wasn't necessarily obvious, and there could be other hypotheses for why a checkpoint inhibitor might work against the tumor's expressing an embryonal antigen.

So I think there's both a risk and a potential for gain going in early, but there's certainly going to be more uncertainty like there was with the PD-1 and PD-L1 inhibitors.

DR. PAPPO: Donna?

MS. LUDWINSKI: Donna Ludwinski. I had a question about what is your opinion with affecting standard of care? So what's laid out here is introducing agents that might have efficacy early, but what is it going to take to do smarter phase 3 studies so that it doesn't take 10 years to answer a question with this potential for lots of new agents? And I'm referring back to you pointed out the goal is cure, and I really appreciated that.

DR. FOX: So I think every investigator in this room would agree that having trials that take five-plus years to accrue and have endpoints that read out in three or four years is extremely
challenging for our patients. But I do think part of the answer to that question lies in how we do the study before phase 3. In some ways, phase 1, 2 or 3 is becoming a little anachronistic, and I'm feeling a little dated using those terms.

But in terms of how do we compare and how do we get the very best agent to the most number of patients, I think part of that challenge is going to lie in the rarity of some of the molecular signatures and the molecular changes that we're trying to target. So when we talked about large MATCH studies or master protocols, those begin to address in my mind, in part, the logistical challenges of opening multiple studies.

In some ways, perhaps we could do more effective phase 3 studies with better endpoints, but we also probably need shorter protocol life cycles, not only in the phase 3 but also in the earlier phases 2 and dose finding.

DR. PAPPO: Any additional questions or comments?

(No response.)
DR. PAPPO: Okay. We will now break for lunch. We will reconvene in this room in one hour, approximately 12:40 p.m. Panel members, please remember that there should be no discussion of the meeting topics during lunch amongst yourselves or with any member of the audience. Thank you very much.

(Whereupon, at 11:42 a.m., a lunch recess was taken.)
AFTERNOON SESSION
(12:51 p.m.)

DR. PAPPO: Good afternoon. Welcome back.
Please take your seat.
We will now proceed with a guest speaker presentation by Dr Hubert Caron.

GUEST PRESENTATION - Hubert Caron

DR. CARON: Thanks for inviting me to speak here. It really is a pleasure to be present at this meeting and meetings before to really help and push for the best implementation of new legislation. I'm going to talk today about the industry perspective of prioritization pediatric relevant targets and molecules. I'm a principal medical director at Roche/Genentech, and I lead the pediatric development group of our late-stage portfolio.

So I'm a full-time employee of Roche, I own some stocks, and I will not be discussing off-label use or experimental [indiscernible] use of any of our pipeline agents. Explicitly, this presentation describes our views on pediatric drug development.
and not necessarily the views of companies or other entities.

I will be going through -- I'll skip the perspective on the current regulatory landscape. I'll do very short, one or two slides, on revisions to PREA because the presentation of Dr. Lia Bollinger -- has done this better than I can. I'll give you a vision on pediatric drug development, then I'll focus the majority of my talk based on pediatric target and molecule prioritization based on the MOA approach, pediatric developability, and then touch upon across company prioritization as well.

I'll give you a quick case study, how this works internally, but also how we can make this work externally, and then I'll end with the key messages.

The Research Equity Act and the revised PREA coming out of it, post-FDARA 2017 -- we're crystal clear as we implement it on both drugs and biologics. Pediatric studies will be mandatory in the future. That will be required to develop
molecularly targeted cancer investigation plans for those molecules which are on the lists but also potentially molecules which are not on the lists, and that the list of non-relevant targets is getting smaller and smaller.

It's important to realize that for pharma, there's a big change that our orphan exemption studies has gone. As you saw with the numbers Dr. Bollinger presented, it was a real big loophole in the previous regulation for pharma, that the ODD designation for the adult indication was a real quick possibility to go for a waiver in pediatrics, and this loophole is now repaired with the Research Equity Act.

What's also important to realize is that studies under the new legislation will have to be intention-to-file studies, and intention-to-file studies are very different from what in academia [indiscernible] trials. Intention to file requires much more rigor and other ways of implementing trials than for academic purposes only.

The change in landscape tells us that we
will be required to submit initial pediatric study plans for new market implications, submitted after August 2020, which is pretty quick from a follow-up point of view, and that those iPSPs have to outline clinical study designs to evaluate dose finding, safety, and efficacy of the drug. This will require relevant preclinical data that would require pediatric formulation.

Although we heard Dr. Reaman comment on the timing of the actual pediatric formulation used, we could potentially use a research-only formulation during phase 1-2, and then time the development of a definitive pediatric formulation underwritten request, which would be helpful because you've heard many times now during this meeting that pediatric formulation can be relatively easy, but solid-phase molecules are going to be pretty challenging and pretty expensive to develop a definitive pediatric formulation.

It might be difficult to get companies to do this without having any pediatric data. And to do this before any child has been dosed might be a bit
of a stretch, so then phasing it to start with an
temporaneous formulation for research purposes,
and as soon as the molecule starts to become
promising, then start redevelopment of a definitive
pediatric formulation might be a good way forward.

The vision we hold at Roche for pediatric
development is that we really want to provide
children with unmet medical needs with innovative
safe and life-saving therapies. Our mission to
accomplish this vision are that we work towards
early access to medicines with a strong scientific
rationale for children, especially for children
with high unmet medical needs that will increase
treatment options through clinical trials aimed at
pediatric product labeling for children with
cancer. And sure enough, these activities will
also work to ensure that we meet our regulatory
obligations so we can facilitate timely
registrations in adults.

Last but not least, one of our
[indiscernible] missions, not only from watching
the science folks but also from our regulatory
people and legal department, they said we're going to facilitate industry innovation and change in policies in collaboration with all the stakeholders, including regulatory authorities, to increase the potential for drug development in children with cancer.

Let's just say the big scheme of things we think of in Roche for the entire late pipeline in oncology is how are we going to make decisions here for children with cancer. The first step is that we will assess pediatric developability for all our oncology molecules in late stage to select those, which we prioritize for inclusion in our iMATRIX trial, and I'll come back to the details of that.

Then we develop phase 1-2 data for children, and then decide whether not an exceptional case, there's data potentially enough for direct labeling or that we add an additional sponsored pivotal trial or supported academic investigation pivotal trial. Or too often we'll have to terminate development due to toxicity reasons. But all of this is aimed at the endpoint of pediatric
labeling.

Here is the overview of the iMATRIX design, which is a gated phase 1-2 approach, which can go across molecules, which can go across broad indication of diseases, and which can incorporate early combinations as well. But the setup is similar or is identical for different molecules. It starts off with limited dose finding, including PK and safety until gate 1, either across all disease where it makes sense to go or a limited set of diseases depending on the context of the molecule and the adult data.

As soon as we establish a single molecule safe dose, then we branch out in different diseases or different clinical biological entities, where it makes sense to study the molecule for early efficacy. We've put an early gate 2 in place where after 10 to 12 patients, we will assess if there's a sufficient efficacy signal to move forward in additional cohort expansions or not.

At the end of full phase 2 expansion, the iMATRIX stops and is on its goals for phase 1-2.
And the [indiscernible] of the data will then go into discussions with academics and health authorities to decide on pivotal trials for the molecule in one or more indications.

The pediatric molecule developability relies on four major categories of questions or data. The first one from a pharma perspective is do we have or do we expect a regulatory obligation, Which with revised PREA, that landscape has changed considerably. And it's not only the EU which is not driving these assessments, but it's also now in the U.S. with the new obligations very likely that the U.S. will deliver more obligations to pharma than Europe or at least earlier obligations to pharma to develop the molecules.

The second set of questions focus on molecule feasibility, do we see a strong match based on mechanism of action with pediatric biology; is this match then happening in diseases with a strong unmet medical need; is the safety profile we can deduct from our preclinical juvenile toxicity studies in the adult profile suitable to
move forward in children; and is the PK and formulation appropriate to be able to start development in children?

The pediatric clinical feasibility assessment relies mainly on feasibility, can we recruit sufficient patients for full phase 1-2 development, which hinges on prevalence of matching patients, but also it's perceived improvement of standard of care, which really makes a major difference both in the endpoints we use and the statistical power, but also in the interest in academia to recruit patients into trials with agents with a large perceived improvement over standard of care.

Last but not least, are the competing molecules in class, either we don't go in pediatric development or where we expect pediatric development. And fourth, we checked the potential for capitalizing on incentives. It's not a major driver for pediatric development, but it does help if we can show that there's at least some likelihood of partial or recoup of the investments
we have to make in pediatrics.

What I'll focus on now in the next part of my talk is the more detailed approach and how do we match the MOA of a molecule with pediatric biology and what kind of methodologies to put in place both in the company but also in collaboration with academics and other companies, which could be useful for thinking about the list under the new revised PREA. It all relies on matching of the molecule biology on that side, and on the other side, the pediatric biology and actionability of the target in pediatrics. The stronger the match, the better the potential.

We use this set of questions to determine if the target is actionable in a pediatric setting. These questions are not unique. They're used in [indiscernible] medicine trials as well. It's a target activated in tumor of interest. Is tumor survival dependent on the target or the other way around. If you block the target or hit the target, does that lead to tumor kill? Less important but interesting to have is an idea on how resistance
occurs when you treat with molecules aimed at a
target, and do we have information on combinations.

We categorized our targets in three main
categories because that makes a difference in how
we think about activation of targets, about tumor
dependence on targets, and efficacy data. We
defined this as tumor dependence targets, tumor
delivery targets, and tumor microenvironment
targets.

Then tumor dependence splits this in genomic
aberrations and targets with expression, potential
lineage to specific targets. Tumor delivery
targets are mainly the ADCs, but also amino
conjugates or antibodies used to deliver the
molecule tumor target or other means of delivering
to the tumor. And then tumor microenvironment,
immunology, and angiogenesis are the major
components there.

The target list is split what you’ve seen
today in gene abnormality targets, cell lineage
targets, which nicely overlap with our first tumor
dependence classes, and then non-cancer cell
targets, which is both tumor delivery and tumor microenvironment. And the other targets we have not listed, but they mainly go under microenvironment or delivery targets as well.

For the target actionability, we split in three major activities. The one is systematic literature reviews of target actionability, and I'll show you more details on that. The second one is an additional in silico work to check for target prevalence in preclinical series to large databases. Dr. Reaman showed that there are more databases out there which we can tap into, both publicly but also in collaboration with academic groups.

When we have all these data analyzed on one of our targets or target pathways, we not only can identify where we have sufficient evidence to move forward in clinical trials, but also more often where do we have [indiscernible] evidence, and do we have gaps in our knowledge, and do we need to add additional preclinical proof-of-concept testing, which will then actually reach out to
other CROs or academic groups with the right expertise and the right models to develop additional data to help us move the molecule forward in the best way.

To structure our thinking on what is preclinical proof of concept, we came up with eight modules of data, which ideally would constitute a complete preclinical proof-of-concept data package. In practice, things are more patchy and we often don't have data in all eight modules.

Target activation status in clinical series, then we approve of in vitro models that raise molecular validation of tumor dependence. The third one is, as has been done, in vivo models showing that molecular means target dependence. So essentially, these are transgenic models that are in mouse or in zebrafish, or others; and then molecule sensitivity patterns in vitro, molecule efficacy data in vivo models, biomarkers, mainly predictive biomarkers, potential biological efficacy biomarkers. And then the resistance mechanisms we studied are rational combinations.
tested in preclinical models.

The approach to target actionability reviews comes out of my time when I was still in academia until 2014 and was part of ITC, which is the European phase 1-2 consortium in pediatric oncology, where I was leading biology, which was a large clinical network of academic labs aimed at bringing these proof-of-concept data packages. And we didn't have to do the work all over again. There was potential to use the literature review.

The academia was also leading to the Cochrane group for systemic reviews and clinical care for pediatric oncology. So why don't we try to use the Cochrane approach to redo this for biology to find a way that we at least can describe, as objective as possible and as complete as possible, what do we know what do we not know about a target in pediatric oncology?

The steps start with finding reviewers, potentially two but prefer three or four reviewers so they can share the work, and then together perform a very sensitive literature search to find
all the papers there are in pediatric oncology on that target pathway, and agree on which are the relevant papers which describes the right target in pediatric tumors. The reviewers independently then take all those papers, review the papers, extract the main findings, and categorize the main findings based on the modules I showed early on and the disease type, which is described in the papers. Then particularly appraise the evidence in the main finding, and any paper can use 1 to 10 or so main findings.

Every main finding calls for experimental quality, so how strong and how well it's done, and on the other hand, what is the effect, what's the quantity of the evidence described in that paper? Then come back and independently check with the reviewers for discrepancies, and then adjudicate the discrepancies based on discussions. Then all of these main findings per disease per module are merged together in a final score on how strong the data are for that tumor, for that specific module.

All of this is supported by the R2 data
platform, which is in ITCCP4. I forgot to mention it is no longer academic work, which I took forward in Roche. This is now within the ITCCP4 consortium, which is a large consortium with 5 pharma, 11 academic sites, and 3 CROs working primarily on a PDX platform for standardized strong testing, clinical testing. But a part of the work they do is also aimed at target actionability, so we use those investigators to develop the methodology for these reviews and to also develop the bioinformatics support of performing those reviews.

So this R2 tool is a pretty intuitive and nice tool primarily aimed at analyzing genomic and transcriptomic and epigenic data, but those guys have also built the tool to support the reviews. So you can enter the paper references in the tool with all the reviewers, and each reviewer can extract its main finding and upload in this tool. Instead of uploading the [indiscernible] cell file, you upload them here and score them from quality and quantity, and then the reviewers can come
together. The tool will support checking the
different main findings between reviewers and check
for discrepancies in those findings, and then
adjudicate.

We will put together to support and be as
objective and as reproducible as possible. We put
together guidance listings for the evidence quality
in the 8 modules, and we also put together evidence
quantity, rules or cutoffs, to help reviewers be
reproducible in the way that's called, which
doesn't mean these are the perfect truth, but this
is the guidance we use. The endpoint is based on
what reviewers make of it and what reviewers then
discuss together, and what they adjudicate as their
final agreed upon scoring of each of the main
findings of each paper.

What then happens behind the scenes is all
of those individual main findings, which address
one disease and one of the 8 modules, those are
merged, and then based on the quality and quantity
scores, averaged across those main findings, and
lead to a final score, which you see here in a kind
There are two ways we can use these heatmaps, either with the 4 colors I show here, green as being sufficiently researched. Yellow with evidence, but it's patchy, it's not strong enough. Red is, yes, that's been research, but there is no support in that module for that disease for this specific target, and then white, it is missing evidence, so there is nothing.

What you can see is, for example, this is MDM2-TP53 review, where we split the target amplifications in three different findings, p53 functional; is MDM2 amplified, is MDM2 highly expressed in clinical series. You see the neuroblastoma, for example. In general, P53 is functional. MDM2 amplifications occur at a rather low frequency, and high MDM2 expressions occur pretty frequently.

There is good vitro and vivo molecular dependence model data, so no molecules involved but molecular data involved. Compound efficacy in vitro is [indiscernible] with P53 status, but
in vivo, single molecule efficacy is not great.

That's the red. But then in combinations, there is again strong P53 status dependent efficacy.

This is how this quickly reads. It serves nicely to come up with discussions on which disease has sufficient evidence to move forward into a clinical trial, also depending on the assessment of the medical need in that disease. In some disease, there is patchy evidence. For example, in synovial sarcomas, you will notice that there is some vitro work and some evidence from [indiscernible] expression, but there is no strong vivo work either for molecular tumor dependence or for compounds. So it will typically be a target disease to add additional data in collaboration before we move into clinical trials.

One more thing we have been adding is, for example, if you look at high grade gliomas or medulloblastomas, or neuroblastomas, we know there are several different biological subsets hidden under this one histotype. What we've been developing now is to ensure we can split the main
findings into different biological subsets. If you now would click on a disease name, it splits in 3 or 4 subcategories, which are agreed upon by our academic experts in the ITCCP4 consortium as relevant biological subsets, so it can split quickly and see which evidence is for which subset.

On the other hand, if you would click on one of the colored squares, it will open up the underlying evidence. So here is the main findings, which constitute the green score for MDM2 expression neuroblastoma. So you can quickly assess which are the individual papers and which are the main findings which underlie the combined green score here. And you'll see that for each main finding, there's a description, and the right upper-end corner, the main finding is the Q, which is the quality of the evidence score, which is minus 3 and plus 3, and then the extent of the data, minus 3 to plus 3, and then the product of those two in the colored box.

What we are currently doing is ensuring that we look at all academic investigators to ensure
that they agree on this methodology, which we've
developed the neuroblastoma as a pilot; that all
our academic investigators of the 11 institutions
now are joining to review the methodology and the
guidance tables so that we then can put together a
white paper on this methodology, including one or
two product reviews we have been performing, so we
then can make this methodology, including R2
support, available to external investigators or to
anybody who wants to use it.

The timing is that we are finalizing the
methodology over summer and that the paper should
be written Q3 Q4, and submitted for publication
before the end of the year. So as soon as we
finalize the methodology, we're open to share this
before publication of the paper with any interested
investigators and/or rater authorities, or based
[indiscernible].

So this is what I wanted to tell you about
the target [indiscernible] reviews, which together
with in silico work compose the basis of MOA-based
rationale for pediatric development, which is an
important part of our pediatric developability assessment.

Here is the example of how we have structured our developability assessment in peds within the company. And again, you see the four categories I discussed with you earlier on: the regulatory obligations; the molecule feasibility; the clinical feasibility; and the incentives.

We tried to summarize this in one slide so you get a quick overview per molecule, but also this is an opportunity to go across our portfolio three to four times a year to see which molecules are either ready or strongly enough supported to move forward in pediatric development, or which molecules do we have as showstoppers for pediatric development, and do we need to put a regulatory de-risking [indiscernible] strategy in place.

What we're going to move towards next is prioritization across molecules and companies because this works internally, but this also works across companies and across molecules. And the example I'm going to use is the accelerate
multistakeholder strategy forums, which Professor Vassal will discuss in more detail. But this is our experience with how those forums worked with Roche participation.

The accelerate multistakeholder strategy forums either concern the molecules in the same class or disease specific forums with different molecules, different in ways, but then disease specific. They are truly multistakeholders. There is an independent organization organizing them, and they bring together academia-based advocates, pharma, and health authorities to exchange information on the molecules and the disease where they pertain to.

We have nicely formatted data showing, based on description of MOA, safety, pharmacokinetics, adult efficacy data, stage of adult development, and availability, or what's the formulation, and is it suitable for pediatrics, and is there pediatric formulation available? And then if available, do we have any pediatric preclinical data or pediatric clinical data?
This kind of formatting really helps in being able to think across molecules, because if we leave this to the different, say, molecule content owners or companies, the format differs widely, and then it becomes very difficult in a compressed fashion because these forums typically take a one and a half day, and if you then do 20 molecules, it becomes very difficult if there are different formulas all over the place. So this formatting thing really helps in being able to quickly go through different molecules and see similarities but also see differences between molecules.

Up until now, two of those forums have been run. We've participated in both. In January 2017, there was a forum on ALK inhibitors from six different companies, and in November of last year, there were an accelerated around a BNHL study forum, which was disease specific, where there were 20 molecules discussed with different MOAs across 15 companies. And in both instances, there was pretty clear output on what was the most likely strategy to be successful for children, where it
was a clear difference identified between molecules based on the stage of development, based on PK and formulation, and also based on preclinical efficacy data.

In September 2018, the preparation was ongoing to run an immuno checkpoint inhibitor forum, and Gilles will give much more detailed data on ACCELERATE, how it works, and what is the potential for connection between the groups represented here and ACCELERATE.

What I want to give to you is a flavor of how this works in practice and what has been happening with our BNHL portfolio and using ACCELERATE platforms as well as part of our, say, prioritization exercise there. We need a pediatric BNHL strategy because BNHL is a relatively rare disease and is very curable. So that mean that in relapse refractory BNHL, it's difficult to develop new molecules. And as you can see, there's a plethora of molecules targeting BNHL in adults, which makes prioritization something we need to do because we can't develop all those molecules in the
future, which constitutes an unmet medical need.

Here are numbers taken from Tom Gross' presentation at the ACCELERATE BNHL forum in November of last year. In adults, there was a pretty sizeable fraction of BNHL patients, and also prognosis in adults is less favorable than it is in pediatrics. In adults, we're looking at 54,000 DLBCLs in Europe and about two-thirds of the number of patients in the U.S.

In pediatric, BNHL is much more rare. There are only 250 cases in Europe per year, and there's 800 Burkitt lymphoma cases a year, which is pretty sizable. But if you take into account that with LMB chemotherapy and with the successful phase 3 with Rituxan [indiscernible] 2 to LMB chemotherapy, we are now looking at 94 percent one year EFS, which essentially is cure. So that means that the relapse/refractory numbers in the middle column are going down considerably.

So we're looking at 40 relapse/refractory Burkitt patients and 12 DLBCL patients in Europe. Add to this about two-thirds of those patients in
the U.S. So we're looking at around 20 relapse/refractory cases a year of very ill children who in general will relapse during chemotherapy or just after the chemotherapy, so a very difficult group to recruit into relapse/refractory studies only. You saw on the previous slide that there are more than 20 molecules in development in the adult space, so really too many drugs to test and by far not enough pediatric patients to go around.

This was the basis for ACCELERATE to push for BHNL. And as I showed you, 20 molecules, 15 companies, and the ACCELERATE organizers managed to compress the whole academic part of the description of the disease and the medical needs biology into half a day. The industry presentations took up about three-quarters of a day, and then there was one-quarter of a day left for very structured and good discussions on what comprised molecules with a potential to move forward in this space and what were molecules, which were deemed less relevant for the pediatric space.
In our own pipeline, Roche's three molecules are so-called BNHL-only molecules. So the MOA is such that it can only be developed in BNHL, and there are three or four more molecules where the MOA is broader, but rare are developments in BNHL as well. So those broader molecules we reason will go in other diseases, and we don't want to go in BNHL. But there are three molecules where the only development option is BNHL.

We used the same approach as I described for ACCELERATE, described earlier, to assess which of those molecules for us would be the most relevant for children and which molecules would be less relevant. We use a stepwise approach to test or to get feedback on our assumptions and our assessments.

First, we conducted a so-called pediatric oncology portfolio meeting with EMA, and then we had an advisory board a month later, and then we presented at the study forum from ACCELERATE in November. And this really helps to make our assessment of the molecules and the prioritization
much more explicit.

The feedback was pretty clear that only one class of molecules was deemed to be relevant out of the three molecules we have in the pipeline, which was in the T cell specific MOA. And it was also made clear that in Europe feasibility could not be a specific ground for a waiver, but with the right augmentation and the right discussion about relevance of the MOA and unmet medical needs, this could be considered, which is clearly different from the FDA position.

This worked quite nicely. In the end, it was possible to keep up our prioritization to move one molecule into the planning of clinical development and put two molecules on hold, on the back burner.

We were successful in negotiating this with the EU regulatory agency as well, which really helps, so we don't get a PIP situation as we had earlier on with the melanoma BRAF situation. So we now are able to focus our resources on a molecule not only for us but also to patient advocates and
academia, and this makes the most sense. And we're in the process of activating that clinical development.

So with that, I'm going to leave you with the key messages from our perspective. We expect that the revised PREA will lead to the right approach from our perspective, more MOA-based rational pediatric drug development and; and earlier, that we will be forced to be more proactive and more early, which is a good thing; and that we really need a strong collaboration between regulators, sponsors, academic partners, and patient advocates to perform detailed preclinical proof-of-concept testing; ensure that we harmonize our study designs so we don't start competing our patients; and that we perform strong molecule prioritization to be able to successfully implement the new legislation in the U.S. and at the same time fulfill regulatory obligations in the EU.

We expect innovative trial designs; establishing clinical development matching
pediatric potential; use molecule developability in an explicit way; and shift mindsets to portfolio approaches based on MOA, which is really needed to ensure that we develop the right molecules for the right disease and thereby contribute to improving the outcome for children with cancer.

With that, I thank you for your attention, and I'm open to questions.

(Appplause.)

**Clarifying Questions**

DR. PAPPO: Thank you very much.

Before we proceed to clarifying questions for Dr. Caron, I would like to ask if there are any public hearing speakers here in the room, to please go register in the table across the hall and then come back.

We will now take clarifying questions for Dr. Caron. Please remember to state your name for the record before you speak.

Steve?

DR. DuBOIS: Thanks so much, and I've got a couple of questions. It's terrific that Roche has
an IPODD [ph] team because as an investigator, it
makes it very clear who to talk to at your company.

How common are these sort of dedicated teams? A
lot of the pediatric oncologists I know who have
gone into industry are sort of dispersed throughout
industry and not clustered in a team really devoted
to thinking about pediatric drug development.

So that's one question. Maybe we'll just
start there, and then I can ask my second.

DR. CARON: Yes. As far as I know, we are
the only dedicated team in the sense of having the
responsibility for the full development of the
portfolio in children. But talking to Mark Kieran,
who recently moved to BMS, his expectation is that
he will be putting together a similar team at
Bristol-Myers-Squibb, so that's going to be helpful
because I recognize the difficulty for academic
investigators to connect with the right people in
these huge pharma organizations.

In many other companies, there are true
pediatric champions. I'm not aware of any, say,
listing of who those people are in companies,
potentially something we could consider developing through ACCELERATE or through health authorities, because those tend to be relatively stable but not always known to all investigators that those are the people to reach out in the companies. And they're not necessarily the ones who are responsible for development because, in general, pharma is organized by molecule, but there are great assets to guide investigators to the right person for a molecule or for a set of molecules, and to align.

What will be helpful thinking from the pharma side is to return the favor and have the academic community coordinator as well. Because it's interesting to see, now that I'm in pharma, how much duplication occurs in communications.

One complicated molecule -- and my team is developing -- is also co-developing with another molecule from another company, and it's really interesting to see that we are being approached four or five times, but then the other company from the same people also get requests for their
molecule individually. And that really takes a lot of time to ensure that things calm down and we don't get different teams activating discussions.

So from both sides, I think that coordination of communication would be great. And I can take it on to work with ACCELERATE and/or bio and FDR [in] in Europe to see if we can come up with some kind of repository or listing for pediatric experts in different companies.

DR. DuBOIS: Terrific. And my second question was about the guidance that Dr. Reaman talked about this morning about encouraging adolescent age of eligibility to, quote, "adult clinical trials," or trying to move that age range down closer to 12 years of age. And I wonder if you might comment on how Roche-Genentech is thinking about that guidance moving forward.

DR. CARON: Given the fact that our vision is that we want to develop all our molecules where it makes sense in children, we are trying to push to be able to start up pediatric development earlier. So for the diseases where we're talking
pediatric tumors, the typical embryonal tumors and pediatric leukemias, it's not very useful to try and enroll one or two patients in an adult trial if we are planning on pediatric development.

We have disease I call overlap disease, Hodgkin's or sarcomas. There it depends on the patient's size. It depends on the adult development program. If in the adult development program, those diseases would already be in their development view, then it could make sense to lower the age range because those also have an epidemiology, which the majority of relapse/refractory cases will be over 12, and it's unlikely that we're going to put a pediatric-specific development together.

The third is adult epithelial tumors -- colorectal, breasts, where the indication is very, very low, which makes it impossible to develop specifically for children, but where labels in general are over 18, so access to molecules for those patient groups is very difficult. So there we are pushing to help our adult teams to lower the
age range to 12, which logistically is not as easy as we from a pediatric point of view think.

Sure enough, we can help with and with sense and with taking away the belief that it's dangerous to go in children and that they need different PK. For adolescents, that's not an issue. But finding the operational possibilities, general adult studies are much smaller in number of sites; finding overlapping site where we can include adolescents; and find a right co-investigator at a site. Then again, it's knowing the playing field.

DR. PAPPO: Brenda?

DR. WEIGEL: Dr. Caron, thank you very much. That was a great talk. My question actually is around the Cochrane-like methodology, and I love it. But do you have any data on timelines and learning curves? This is a process, and how much time it takes actually to get to that prioritization piece and the people involved in it that's required at training, or how has that been really implemented?

DR. CARON: So in general, the amount of
training, I would say we typically try to use pediatric oncologists to do those reviews, but essentially those are biology reviews. So what you need is oncologists who have enough biology knowledge to be able to perform those reviews.

On the other hand, it's the same time kind of methodology that occurs all the time. What I did at Roche is run a hallmarks of cancer course first to educate my clinical scientists, and then got them into reviews. But with the people who will be interested in these things in early drug development, the majority of people are involved in pediatric [indiscernible] medicine trials. The majority has been doing preclinical work themselves.

So I would think training is very limited, as such for the [indiscernible], what you do when you read an investigational paper and want to find out whether not for this specific patient a molecule A or B or C will be a good match. So I wouldn't say there's a lot of training involved, but the different mindset is to get all the
information and summarize all the information.

Now, it depends on the pathway. The MDM2 one, it was 150 papers with three reviewers, and then there was about three to four main findings per paper. On the other hand, our 4/43:12 review was 12 papers or so, so it's relatively easy; PI3 kinase, 350 papers, so it depends a bit. But that's where three reviewers come in handy. Larger reviews would take two to three months or so. Smaller reviews, a BID-4 review I did in two days because I had to talk to the company.

DR. WEIGEL: Because there wasn't much there, right?

DR. CARON: Yes.

DR. WEIGEL: And it's very -- I forgot to identify. Brenda Weigel. Thank you.

DR. PAPPO: We have time for two more questions. Kathleen?

DR. NEVILLE: Hi. I enjoyed your talk as well. One question is about the master protocol and have you used that just within Roche or are there any plans -- I'm going to go along the lines
of what I did with Dr. Bollinger. Are there any plans to roll that out to other companies or to do that collectively?

DR. CARON: So two things. Currently, we use this as stand-alone CTA-90 [ph] not because of the U.S. situation because there we potentially could handle this as a master protocol and bring in new molecules as amendments. But in Europe, the review process and amendment process doesn't allow to use major amendments as a process to bring in entire new molecules because there's not enough time and not enough discussion in that amendment procedure to allow for solid evaluation of a new molecule arm. So that's why we're currently using -- and two-thirds of our patients we recruit in Europe, so for us it's not feasible to run as a master protocol.

What we have done is template all the language and all the approaches we can, and we're completely open to sharing these templated things with other companies, and at the last ASCO, at, at least, two meetings with other companies to discuss
sharing. So anybody interested, please approach me. We're open to sharing.

With new insights coming from academia, where Dr. Vassal is running a precision medicine trial, he recently told me that he'd been successful in amending new molecular arms into his EASMARK [ph] trial. So if this holds for different countries, then we might reconsider and bring it again back as a master trial protocol.

We also explored potential collaborations with other companies to bring in different molecules from different companies into these CDAs or INDs or master trial. There was some interesting discussions on legal stuff and IP, and specifically sharing safety data and sharing investigative brochures across companies. But with the new RACE Act, there's a new drive, sort of new potential to open these discussions again and see if we can consult [indiscernible].

We see this coming now with our own development and working with another company for co-developing combinations. If we want to do good
combination studies, we cannot go with portfolio molecules only from whatever company. We need to be able to go across companies.

DR. NEVILLE: And to your point, it doesn't make sense for three companies to each be getting four and five phone calls if it's not in anybody's best interest, especially the patients.

DR. CARON: The discussions is one, but then putting a coordinated trial together with molecules from several companies, that will be interesting. We are doing so now for one of our future trials with one of our molecules, so the lessons we learn from that I'm going to bring into opening up new discussions with other companies to see if we can bring together pipelines and develop across pipelines.

DR. PAPPO: Donna, and then Greg, and then we're done with questions.

MS. LUDWINSKI: Donna Ludwinski. I'm curious about how you choose your topics for the strategy forums. I think that concept is a very exciting idea, and I was just curious how you're
choosing those and the timing.

DR. CARON: Roche is an active member of ACCELERATE, but we do not choose the topics. That's really a cross-stakeholder process where essentially the steering committee -- which is composed of 4 regulatory representatives, 2 out of the U.S. and 2 out of Europe; 4 patient advocates, 2 out of Europe, 2 out of the U.S., 4 pharma, 2 and 2; and 4 academia, 2 and 2. And the steering committee is the committee where these discussions about the next forum and the frequency of the forums takes place to avoid any shred of doubt about the independent way of how this is done.

So I'll leave this to Professor Vassal to comment in his next talk.

DR. REAMAN: I just wanted to follow up on Dr. DuBois' question about the adolescent guidance and one of the other potential benefits of enrolling adolescents on appropriate adult studies. And really the impetus for this was because of the orphan designation for many of the diseases that span the adult and pediatric age group, which
exempted PREA requirements for pediatric investigations. But enrolling adolescents on those trials allows us to potentially extrapolate data from older children, adolescents if you will, down to a younger age group.

So that's another possibility for accelerating, if you will, the evaluation and even potentially the approval of appropriate drugs for the pediatric population.

Open Public Hearing

DR. PAPPO: Thank you very much. We will now move to the open public hearing session.

Both the Food and Drug Administration 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 related to
the topics of this meeting.

Likewise, the 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 in 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 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. Thank you for your
cooperation.
Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. PAPPO: Okay. We will go to speaker number 2.

MR. AGIN: Good afternoon. My name is Jonathan Agin, and I am the executive director of the Max Cure Foundation. I sit on the NCI Brain Malignancy Steering Committee. I'm an attorney by trade. I'm also a member of Oncokids Biosciences. I have no financial conflicts. Much of my comments are to thank the members of the committee and the advocacy community for coming together to try and push forward the efforts under the RACE Act.

I lost my daughter to DIPG, a diagnosis that has had little to no improvement since classification. So as a member of the advocacy community, as I've seen so many improvements moving forward, and then I look at other forms of childhood cancer that have had little to no
improvement, what we try and do is balance out the
success stories with the failures. And I've been
to meeting after meeting in the DIPG community
where the first line of everybody's talk, or
everybody's presentation, or everybody's paper
talks about the dismal prognosis.

Juxtapose that with the great stories that
are told about the 80 percent cure rate for
childhood cancer, and we have to ensure that
efforts such as the RACE Act are implemented in the
most aggressive fashion possible without excluding
those cancers which have had little to no
improvement.

So whereas on the one hand, I want to
applaud everyone for their efforts in moving this
forward and in understanding the need to have such
efforts from the clinical side of things, the
regulatory side of things, and industry, I implore
everyone involved in implementing the Act and
implementing the strategies behind ensuring that
pediatric drug development does not continue to
lag, to act aggressively, and to ensure that
childhood cancers with poor prognoses like DIPG, or refractory disease, or recurrent disease, metastatic disease, anything that does not fit within that tight little pretty bow that can be captioned as 80 percent survivorship, I implore everyone to ensure that the Act is implemented aggressively to ensure that studies move forward without the amount of wiggle room for waivers so that drugs are developed, so there is access earlier to be able to test drugs.

I also fully believe that what the RACE Act does is provide a potential new channel or pathway for creation of commercialization avenues for drug development for rare disease populations. And I think that we'll see, hopefully in the coming years, avenues for financial resources to be provided into this avenue of drug development.

So at conference after conference and meeting after meeting, when people talk about limited disease populations, and they talk about the fact that for biotech and pharma companies, the revenue sources, the equation isn't there, I think
that through some of these new efforts and some of these efforts that I'm involved with, and other members of the advocacy community are involved with, there is going to hopefully be a new pathway for commercialization of drugs, which aren't moving across the goal line in the adult population, and avenues for incentivizing pharmaceutical companies and biotechs to develop drugs for smaller disease populations.

Other than that, I appreciate everybody's attention to this issue, and I think we're moving in the right direction. Thank you.

DR. PAPPO: Thank you very much.

(Applause.)

DR. PAPPO: Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. GOODMAN: Thank you. My name is Nancy Goodman. I have no conflicts of interest. I am the founder and executive director of Kids v Cancer, and I'm also a parent of a child who died
with cancer. I can speak today on behalf of not
only myself but on behalf of the many families
whose children were afflicted by cancer and who
joined together to advocate for the passage of the
RACE for Children Act.

Until now, parents of children with cancer
have watched in frustration as companies developed
novel and promising cancer therapies often for
adult indications only. And I know all of you here
in the room, researchers and even pharmaceutical
executives within industry, have shared my
frustration that access to these experimental
therapies has been quite limited for pediatric
indications.

So in response to this concern, we the
pediatric cancer community undertook academic
studies to understand how this policy of the
Pediatric Research Equity Act could be updated,
what the challenges were, and why it didn’t match
the scientific advances we have now. We drafted a
bill. We created a grassroots opportunity. We
asked members of Congress to join, and they did.
Congressman Michael McCaul; Congressman G.K. Butterfield; Senator Michael Bennet; and Senator Marco Rubio were real advocates on our behalf, and we're grateful for their support.

We would also like to thank the FDA, which was instrumental and critical in the technical assistance it provided to structure the bill and to provide input into how this new proposed policy change would be implemented in their communications to members of Congress, and we are very grateful for FDA's support.

There are just a couple of substantive points I would like to add here with respect to the question today of public comments related to the guidance that the FDA will be directed to publish on the RACE for Children Act.

First of all, from an advocate's perspective, the best way to achieve studies that really will benefit kids is that we protect FDA authority to make the decisions that it determines should be made. So to that end, I hope that the FDA and the stakeholders will all agree that we
should interpret the statute to maximize FDA
discretion, so that we don't have the situation
again like we had before, where PREA did not match
the science and we couldn't get pediatric study
plans undertaken because cancers in kids and adults
occur in different organs.

Going forward, we don't know where the gaps
will be between the language we drafted and what
scientific opportunities present themselves, and I
really hope that we as a community can agree that
maximizing FDA discretion will achieve the best way
to get the best pediatric study plans for kids. We
know historically looking back that FDA's use of
discretion has been appropriately handled by the
FDA and that we have a lot of confidence in their
expertise, so I thank you for that.

I would just like to make one other comment.
I understand that in advocating for the RACE for
Children Act, many members of industry express some
concern about clarity of the legislation, whether
there would be a burden associated with
understanding whether there were standards
associated, with whether a molecular target was
substantively relevant to a pediatric indication, for example, or when a target was on an automatic waiver list.

Again, I just want to assure industry and ask FDA to continue to apply the processes and procedures that are already in place under the Pediatric Research Equity Act and that have been used by the FDA for non-cancer drugs since 2003. And those processes provide that the sponsor submit to the FDA an initial pediatric study plan, a proposed discussion of how to think about a particular drug product, and that the FDA and the sponsor together consider the particular facts of that drug product so that they can make the best determination of whether there should be a pediatric study plan.

This has worked since 2003, so there is no reason to think it can't work now, that the FDA looking at each initial pediatric study plan can't make a fulsome and robust and detailed analysis of whether there is substantial relevance and whether
a pediatric study plan should go on.

So thank you very much. I appreciate the opportunity to speak, and I want to thank in particular the medical officers of the FDA, but all of you here in working on this very exciting new venture.

DR. PAPPO: Thank you very much.

(Applause.)

DR. PAPPO: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The subcommittee 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 now proceed with the charge and questions to the subcommittee on 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.

Would you like to read the next question?
Charge to the Subcommittee

DR. BRADFORD: Please comment on the proposed additional considerations for which the FDA might engage with industry, clinical investigators, and advocates when making decisions regarding the requirement for pediatric studies of new drug and biologic products based on molecular mechanism of action and their timing.

Questions to the Subcommittee and Discussion

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question to discussion.

(No response.)

DR. PAPPO: I guess I'll take a first shot at it if nobody has -- I didn't interrupt anybody? No.

So one of the questions I have is what is the level of evidence that is going to be needed to incorporate a specific agent based on the target list that we have? We for example saw in the presentation from Roche that this IPODD committee identified, for example, rhabdomyosarcoma. If you
look at MDM2, there was a lot of variability on the expression of MDM2.

What are the metrics, and what is the role for the FDA or for this legislation to say this is a go or no-go, or is that left up to the sponsor and the investigator? And what is the minimal level of evidence that we will have to do to move this forward?

DR. REAMAN: Well, I think what was presented is somewhat tangential to what is actually required in this legislation, which is really evaluation of agents, not necessarily in a particular disease since we do know that some molecular targets, many of these actually cross various histologies. So what is mandated by the legislation is that if the target is relevant to the ideology, progression of a pediatric cancer, of one or more pediatric cancers, then a limited pediatric molecular target investigation is required.

So the level of evidence is something that I think would be discussed in each individual case
that comes before us with the sponsor's initial pediatric study plan. Hopefully, they have received input from clinical investigators and received adequate information to formulate their plan, which is then evaluated by the agency, and a plan to proceed with a pediatric investigation, or a justification for why there is no need or why a pediatric investigation should be waived. And that decision would then be made by the FDA.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel, University of Minnesota. I want to go back to I think a point that Dr. Fox and Dr. Caron made with regards to just how we move quickly into early-phase trials. And I think the real goal -- and I think Dr. Reaman made this point -- is that the real goal of this legislation is to move quickly into an early-phase trial. It's not the end goal of a big randomized phase 3 trial.

One of the issues -- and I come back to the figure that Dr. Fox demonstrated with the age distribution of pediatric tumors. And I think that
really should drive some of the thoughts here of how we move forward. And if the target is something that's really going to occur in very young children, that should drive a formulation discussion very early on.

I think if it's a tumor type, even if it spans all the ages but does occur in older children and adolescents, existing formulations developed in the adults may be sufficient to do that initial trial in the pediatric patient population at the same time when the formulation questions are being considered by the pharmaceutical industry.

So I think what we need to do is really come at this with as much information about the target, the age appropriateness, and recognizing the burden on industry of developing formulations, but also saying we can probably get enough signal information in some of the pediatric populations. But I think learning from the larotrectinib data, that in infants -- and if that's where you're really going to have your patient population -- we have to have formulations from the get-go. And I
think that requires the biology to be done in the preclinical space, and as much as we can encourage that, the better.

So I would encourage the FDA to really work with industry to say what do we know about the patient populations and require those early trials, those very first trials, in the setting that makes the most sense.

DR. PAPPO: Julia?

DR. BENDER: Julia Glade Bender. I'm wondering what the mechanism will be for the communication between the investigators and industry vis a vis this legislation in the sense that oftentimes, we don't know where an asset is in its pipeline, or there are multiple assets in the pipeline, and we don't know which will hit the FDA first because we don't know where they are in their development.

In order to -- I was struck by Dr. Caron's comment about companies getting calls from the same investigators, three different companies. And I think that's really because in the past, if you
wanted to test a drug, the drug you tested was the
one you got, and we'd take any drug. So I'm
wondering if there's going to be a mechanism to
allow investigators to know where things are in
terms of development so that we don't call
everybody. If there's a lead compound, I've got to
be honest with you, I usually find out from the
financial literature. I find out from Reuters
before I find out from the drug company. So I
guess it's really about how that's going to be
communicated.

DR. REAMAN: Unfortunately, I'm not sure
that that's a mechanism that falls within the
authority of the FDA. I suspect that now that
there will be a requirement for companies to think
about pediatric plans, so when appropriate, when a
target is relevant, they'll have to start
communicating with the investigator community,
hopefully earlier rather than late; and if and when
necessary, communicating with regulators at the
same time. And hopefully doing this on a global
perspective so that they speak with U.S. -- or
North American -- and European investigators, and other investigators from other parts of the world since products are globally developed.

But I don't think there's a mechanism that we can definitely put in place unless we use these open public meetings, which we have semi-annually, to talk about what drugs should remain on the lists, what we should be adding, and what we should be deleting. And some of that would, I imagine, be informed by what might be in the pipelines of various companies.

DR. PAPPO: Katie?

DR. JANEWAY: Katie Janeway, Dana Farber.

Dr. Reaman, in your comments, you mentioned, both under waiver considerations and also considerations for prioritization, about frequency of a particular molecular target. And I just want to issue a word of caution about frequency because our current estimates of frequency of potential molecular targets in pediatric malignancies are very imprecise given the number of tumor samples and the range of cancers that have been sequenced.
Also, many potential molecular targets are not recognized or identified and reported on until there's a good drug. For example, to use the topic that's come up many times, NTRK fusions, fusions are very hard to find and people weren't looking for them until there was a good drug. So I just want to be careful -- I think implementation of waivers for rare variance or rare genomic alterations and de-prioritizing something because of low frequency I think should be done very cautiously.

DR. REAMAN: That wasn't actually the nature of my comments. It really related to whether or not -- not from the standpoint of granting waivers, but in the context of prioritizing with limited numbers of patients. And it may necessitate waivers, but it really was a question of prioritizing. And I certainly agree with you that we may not have adequate numbers and adequate evaluation of the numbers of molecular targets related to specific gene perturbations, but we certainly have more than adequate knowledge about
some molecular targets and their recurrence in pediatric cancers like CD19 in ALL as an example.

So it was a question of prioritizing and not necessarily granting waivers just based solely on prevalence.

DR. JANEWAY: Thank you for that clarification.

DR. REAMAN: Sure.

DR. JANEWAY: One could even imagine being creative about trial design such that the first trial is really to assess the frequency. That could even be an end point, how frequently does this occur and how large is the patient population in pediatrics for which this is a relevant drug.

DR. REAMAN: But I will also say that one of the written comments that we received very late from the Pharmaceutical Manufacturers Association, PhRMA, the trade organization, in response -- we didn't really have a chance because it was received literally the day before the docket closed -- was about prevalence and their perception that just because the target has been demonstrated in a
single patient, that that would be enough or sufficient evidence to say that it's irrelevant to pediatric cancer.

So that was another reason for just expressing the importance or the reason for consideration of prevalence in decision-making, but really more from a priority setting perspective rather than absolute go/no-go decisions.

DR. JANEWAY: I do think we want to prevent the example at the PD-1/PD-L1, where you screen 800 patients and find out there's a very small number of patients who actually have that biomarker. So you might even, as I mentioned before, think about trial design more broadly in terms of assessing biomarker in a particular patient population and deciding that it's actually not feasible; that that's actually an endpoint of your first pediatric study, that studying that target is not relevant.

DR. REAMAN: Absolutely. And there are many targets on these lists for which there are no existing biomarkers that I am aware of. So not all of these studies are going to be biomarker
directed. When there's a biomarker and when we can
do biomarker-directed studies, I think it's
appropriate to do so. But that again shouldn't be
a limiting factor and a sole deciding factor.

DR. PAPPO: Malcolm?

DR. SMITH: Malcolm Smith. I had two
things. One was a clarification from Dr. Reaman
that I thought I heard the statement that molecular
targeted pediatric cancer investigation should all
be sponsored by industry.

So I just wanted to clarify what role the
groups -- like the current Children's Oncology
Group phase 1 consortium and other academic groups,
what role the data that they generate in their
clinical trials could play in meeting regulatory
requirements for these molecular target pediatric
cancer investigations.

DR. REAMAN: Well, the confusion might be
around the word "sponsors" and "regulatory
responsibility." The statute refers to industry
requirements, and it's well recognized that many
industry studies are actually performed by the
academic community. Clearly, in pediatrics, I would say most are performed by the academic community.

So studies performed by the COG phase 1 consortium, other early-phase consortia, would certainly be included in here. But when we talk about sponsors, we're talking about sponsors who are planning to submit licensing applications. And it's for them that the requirement is who's the sponsor of the study, not necessarily who's conducting it.

DR. SMITH: Okay. Thank you.

DR. REAMAN: If that clarifies things.

DR. SMITH: Yes. And my second point was to get back to the issue you raised, Alberto, about prioritization. And I do think it's an issue that we really are going to have to grapple with as this is implemented. When you, again, look at that list of targets and then think of all the agents that might meet those targets, too many of the agents, if we brought them into the clinic, probably would have very little activity depending on how we did
it. Too many of the clinical trials that we did
wouldn't be able to be completed, and then it would
crowd out the most important clinical trials and
the agents that really are kind of the cream of the
crop.

So I think the prioritization issue is
really going to be critical. I think the kind of
strategy Dr. Caron described, while we may not all
be able to do it in such detail, I think we'll all
be trying to think of those factors as we say we
really need to focus on this agent for this disease
or for this molecular biomarker.

The final point, I think, is it will matter
by disease, and the biomarkers tend to distribute a
lot by disease. Not all are kind of agnostic to
disease. And I think for certain things like ALL,
the bar is very high, so I think unless an agent,
you have some hope that it's going to be inducing
remissions in a substantial proportion of patients,
it's going to be really hard to interest people in
studying that given the alternatives of various
flavors of the CAR-T cells.
So for a disease like that, the bar is going to be very high. When you look at tumors like Jonathan Agin talked about with the DIPG, the bar's not going to be nearly as high, so I think that's another factor that we have to consider. But prioritization is really going to be the biggest challenge for the people around this table, FDA academic, and the pharma and biotech sector.

DR. PAPPO: Thank you for your comments. Courtney?

MS. PREUSSE: Hi. Courtney Preusse, consumer rep and Fred Hutch. Most, if not all, of the discussion so far from a layman perspective has been around drug development as well as clinical trial design, so I hope I'm not too off the mark with my commentary.

Re-reading the discussion point to comment to the FDA on additional considerations for drug development and new biologic products to support pediatric cancer, I just wanted to put out there to the entire committee to take into consideration other things that support the development of drugs
as well as could improve on diagnoses and perhaps longevity in these patients.

What I'm specifically referring to is attention to molecular diagnostics, attention to companion diagnostics, to point of care devices, things that will help us get deeper into the scientific questions as to what is causing these -- anyway, as well as support for bioinformatics.

We see in research studies enormous amounts of data come out of NGS testing, but then there's not always the manpower to support interpretation of that data. And finally, new essays around prescreening, some of these patient populations before the clinical trials even open, so that you know in advance whether or not those patients are actually going to benefit from the drugs and chemo sensitivity testing.

There's just so much more that goes into it beyond just the development of the compound, so I just don't want that to be omitted from the conversation. I hope that was helpful.
DR. PAPPO: I don't think we have any more time for questions. And I'm sorry, Kathleen. Is it a really, really important question? Okay.

DR. NEVILLE: It's just a quick comment, and I couldn't have been teed up faster. We've been sitting over here sort of thinking and talking, and this is a plea to regulators and advocates that in an investigator's opinion, there needs to be a paradigm shift of what is standard of care for biopsies at relapse. It's standard of care in adults. It is not standard of care necessarily in children, and it for sure is not allowed as part of research protocols.

We're sitting here saying we don't know the prevalence of molecular aberrations, in particular tumors, yet as an investigator, my hands are tied behind my back to get that information, and I think that will greatly slow us down. So as investigators, we're going to rely on advocates, industry, and regulators to help push this forward.

Thanks, Alberto.

DR. PAPPO: I hope you're not upset. Was it
a really, really important comment? Okay. If not -- I want to be fair.

(Laughter.)

DR. PAPPO: So I'm going to try to summarize some of the points. A lot of it was just discussion and clarification, but some of the points that were brought up is how to move some of these new compounds into phase 1 trials. One consideration should be age and the prevalence of that disease and a specific age group, and that could potentially dictate which agent is going to be moved for that specific population.

Similar to that, also the tumor type and what we expect of that specific drug, whether it's a very highly curable disease and if your bar is going to be very high to move that agent forward; or if you have a uniformly fatal tumor, that your bar is going to be relatively low, and that may affect how you prioritize a specific agent.

Another comment was about communication between investigators and industry. Although it is not a direct responsibility of the FDA to address
this issue, it is hoped that with this new legislation, it will be much easier to get information on which agents are on the pipeline and that there will be increased communication between investigators, the FDA, and the EMA.

The final issue that was brought up was that we are not aware -- or we really don't have a very good idea on the prevalence of specific targets in the pediatric population, and that perhaps a strategy of a protocol would be actually to try to validate or to interrogate what is the prevalence of a specific target in that population that is being studied to further plan future clinical trials.

The final comment was to consider other issues other than drug development itself to address the clinical trial enrollment and identification of patients for potentially useful drugs. And that would be by the development of molecular companions, expanding bioinformatic support, and developing novel essays, prescreening a population that we are pretty certain could
potentially benefit from a novel agent.

Did I quote everybody correctly? Did I miss anything, or does anybody want to say anything else?

(No response.)

DR. PAPPO: Okay. So now the good news is that we will now take a 10-minute break, and with all this water, we will need it. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any other members. We will resume at 2:15, 2:16, something like that.

(Whereupon, at 2:07 p.m., a recess was taken.)

DR. PAPPO: We will now proceed with topic number 3, Mechanisms to Assure Efficiency and to Enhance Global Coordination through International Collaboration. We will have guest speaker presentations by Dr. Vassal and Bucci-Rechtweg. We will hold all of our questions until those two presentations have been done, and we will start with Dr. Vassal.
Guest Presentation - Gilles Vassal

DR. VASSAL: Good afternoon. Thank you for giving me the opportunity to share some thoughts on the collaboration and coordination at an international level. I am Gilles Vassal, a pediatric oncologist, and clinical research at Gustave Roussy comprehensive [indiscernible] cancer in Paris. I am president of the ITCC Consortium and chair of the ACCELERATE platform. I will not discuss any drug or any off-patent use of drugs.

We are in the 2018 specific paradox. On the one hand, there are many drugs developed in adults. So far over the last years, it has been waived for the pediatric development of disease of children and adults. And after 10 years of such development, we can say that too many waivers delay pediatric development [indiscernible]. And in addition, there is quite poor access to pediatric patients for those plans run by pharmaceutical companies.

On the other hand, patients with cancer are rare, but they do not [indiscernible] poor access
to innovation. Around 10 percent of children with relapse malignancies have access to innovative drugs. So the goal is first to base the development of new drugs for children on science, matching the knowledge of the science and the biology of the tumor [indiscernible] with the mechanisms of action of the drugs in order to meet the needs of the patients.

But this cannot be done without prioritization, and prioritization should include biostatistical data but be considering the needs of the patient, which will be different from the disease to another one. But the other goal is also to incentivize the development of specific pediatric drugs targeting the alteration which are specific of the pediatric treatments.

Now, in 2018, we are a favorable regulatory environment. On one hand, the RACE for Children Act, and on the other hand, the implementation in a few weeks of the Revised Class Waiver List that is defining in which situation a drug systemically can be waived. This gives a very favorable regulatory
environment to drive the development of new drugs for children with cancer through science, meeting the needs.

A few years ago, we set up this figure proposing that at the time a drug is being evaluated at the preclinical level and enters the phase 1 setting in adults, generating biological and preclinical evaluation in pediatric cancer, we do know to provide sufficient information and the relevance of the target in order to define whether or not these drugs should be developed in children and be the subject of the pediatric development plan.

So early evaluation or mechanism of action relevant for us, crucial in this setting, to do that, we need first early pipeline discussions between scientists, pediatric oncologists, and pharma. This is not in the scope of FDA or EMA, but a real need of early interaction between the scientists, the pediatric oncologists, and pharma just to generate as expected with the evidence of the relevance of a target.
There is a need for easy access to data but also to high-quality clinical platforms. And finally, there is a need to agree on an international consensus on what is required in terms of biological data and preclinical data to define whether a drug should be developed further in children. The FDA target lists will guide this early discussion about the relevance of the target with regard to a drug being developed for adults.

In terms of easy access to the preclinical platform, there are at the moment two very important programs, one in the U.S., the Pediatric Preclinical Testing Consortium and one in Europe, the ITCC Pediatric Preclinical Proof-of-Concept Platform, two programs building the assets to generate preclinical evaluation of compounds. And recently, at the American Association for Cancer Research annual meeting, the two programs first met and defined how to collaborate and [indiscernible] these important assets to make the generation of preclinical data most systemically done to [indiscernible] siege the decision on
[indiscernible] of the targets.

In addition, we will host in Europe at the end of September a meeting with international experts from academia, from industry, as well as regulators and advocates to define together the international scientific consensus on preclinical evaluations that can be used further as a guidance by the regulatory authorities.

Access to molecular data at diagnosis and at relapse is now feasible because we have generated a lot of molecular data for pediatric malignancies. I just mentioned in this slide, on one hand, the paper by Grobner in Nature gathering data from 961 pediatric malignancies, which is now accessible on this website, but also data at relapse; as an example, the MAPPYACTS program in France and other countries, generating molecular data at relapse when patients are [indiscernible] tumor when their disease relapses or progresses, or the other program called INFORM developed in Germany, which is generating at relapse as well as molecular information.
There is a certain need for international cooperation to run trials where we are addressing rare diseases in rare patients. To this point what I think is very important to have in mind is that there is a quite nice track record of successful phase 3 academic trials run at the international level looking at Burkitt lymphoma, hepatoblastoma, osteosarcoma, and Ewing carcinoma [indiscernible] tumor. But in terms of academic trial, we are facing major regulatory and administrative hurdles that will need, if possible, to be addressed to facilitate this academic program at the international level.

In addition, most industry trials at the moment are international, so clearly in terms of implementation, it is already at the international level that it is done and it is feasible.

But the strong message is that pediatric oncology drug development is global, and the other point is that this is necessarily a multistakeholder endeavor. Indeed, it has been brand new for everyone around the table to figure
out how to develop drugs for children with cancer and make them available to marketing with organizations. This was a learning curve over years but that is now to be pushed forward and implemented in order to really make this a new regulatory environment most successful for children and adolescents with cancer.

With this background, we created in 2015 the ACCELERATE multistakeholder platform. This is an international platform with academia, with industry, with parents and patient advocates, and with regulatory burdens. And we have in this setting participants from Europe, participants from the U.S., and even participants from Japan. And the idea was really to get together all the stakeholders and figure out how to improve new oncology drug development for children.

The motive of this program is first, there is a value of working together. The principle, there is no blame, no shame of what was done. But the goal is to look at what was done to generate data and to find solutions. So we've been working
on several topics. One is the teenager participation in trials. The other one was the implementation of mechanism of action biology-driven early drug development in children with cancer. These together define the feasibility of running such plans.

But without, as we said, mechanism of action, driven development plans cannot be effective without prioritization of compounds among all those developed in adults. This is why we propose to develop a new type of asset, which is the Pediatric Strategy Forum that Dr. Caron already presented in his talk.

What is a forum? It's a scientific meeting to share information and to advance learning on a given topic with everyone around the table. This is meant to further inform subsequent decisions, including regulatory decisions. So it's not a regulatory meeting, but is a meeting where everyone is in the same room and discuss a topic, and to really add positive subsequent decisions.

In this meeting, we define the need for a
given population because clearly the need for new
drugs for children with B mature and mature B-cell
lymphoma is absolutely different from the need of
new drugs for children with DIPG. And this meeting
is to facilitate the prioritization. They don't do
the prioritization, but they facilitate the
prioritization. In this meeting, there is a
dialogue and interaction with all relevant
international stakeholders, and we make it visible
on the website and will publish this in the
peer-reviewed journal.

This program is called an agent
[indiscernible] implemented by both the ACCELERATE
platform and the European Medicines Agency. We
demonstrated the proof of concept of this platform,
the first one January 2017. And you're looking at
ALK inhibition pediatric malignancies with a clear
situation where there is evidence of the relevance
of the target. There are many drugs approved or in
development but not a single pediatric
investigation plan in place, and clear activity in
academic trials to treat anaplastic large cell
lymphoma and inflammatory tumors.

The second meeting was orientated on disease, and I will not go into the details. But this was clearly defining that in this population, 94 percent cure rate can be achieved under treatment, and there is a need for defining how to address the development of 20 compounds.

Based on the positive -- the reason for these forums would be the third one, which will be in September, looking at checkpoint inhibitors in combination. And stemming from the facts which we see there are many PD-1 and PD-L1 inhibitors, which are approved and all in development and likely to be approved later on, where at the same time there is very limited activity in pediatric malignancies for the data already generated by such drugs, and those malignancies are qualified as cold tumors. So the key question is, should we stop evaluating these single agents? Should we move more rapidly to combination and what will be the best way to do so?

We are already anticipating and preparing
the fourth meeting in April 2019, which will address pediatric acute myeloid leukemias. Why? It's a rare condition. There are many drugs, and now there are plans, which at the time of their development, they need to set up phase 3 trials. And there are clearly not enough patients to really participate in all these trials.

So these forums are very much on a given topic discussing with each stakeholder at EMA, including the participation of the representative of FDA, of the cooperative group from the U.S., and in addition, U.S. advocates. Based on that, we propose in the context of the implementation of the RACE for Children Act, that this will be of value to have this forum further implemented and more systematically done.

The proposal that we made to both the European Medicines Agency and the FDA was to organize these forums based on the processes that were established over the last 12 months in a way that there will be a preparatory panel and team, and for each topic a dedicated program committee.
with experts from the U.S. and from Europe, and
from the cooperative groups in order to have a
single international forum for each topic.

The principle is invitation of people
following expression of interest for academia, for
pharma, and for patient advocates. We propose that
the venue will be in Europe and in the U.S., and
the goal will be to do up to four forums in
pediatric oncology per year. So we think that it
could help discussing about the issue of many drugs
for the same targets and how to best define the
strategy for their development in the pediatric
population.

In addition, we will reorganize the
ACCELERATE platform to make the steering committee
international, and this platform is working through
interactive meetings and working groups. It's an
international platform to facilitate and accelerate
the development of pediatric oncology drugs, and we
think that it can help to accelerate the
coordinated global agenda in order to implement
further the development in the new context of the
regulatory environment in the U.S. and in Europe.

The goal will be to engage more pediatric oncologists and scientists. The patient advocates are extremely present, and we are very pleased that they are working very closely with us. And we would very much like in this platform further to engage more pediatric oncologists and scientists because over the next year, clearly the new environment is an opportunity to completely change the way we develop drugs for children based on science, better meeting the needs of the patients in order to accelerate starting early the development of these drugs for these children.

In conclusion, I would say that the oncology drug development for children is definitely an international initiative and should be done through international collaboration to better meet the science and the needs of the patients. And we I think showed the value of working together with all stakeholders in what is now favorable regulatory environment, which I think will change significantly the landscape. I would like to thank
you for your attention.

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

We will now proceed to the presentation of Dr. Bucci-Rechtweg.

**Guest Presentation – Christina Bucci-Rechtweg**

DR. BUCCI-RECHTWEG: Good afternoon. I'd like to express my thanks to Dr. Reaman for the invitation to present to you today and also for the important discussion that we've been having so far. I've been tasked with addressing the challenges to global coordination.

This is a bit of a take from some of the previous presentations, but you're going to hear this presented from the context of how do we get to global cooperation on agreement of a plan to develop pediatrics. So it's going to turn a bit from the science focus to more the regulatory procedure, the regulatory process, and how we can actually get a place to in fact even getting to the point of us getting to our clinical trials.

For my conflict of interest, I am an employee of Novartis Pharmaceuticals, and I am a
stockholder of Novartis and that the opinions
expressed in this deck are mine. They are not
representing an industry perspective or even a
compny perspective.

What I'm going to do is set the scene, the
context, in relation to the regulatory process, and
then what I'm going to do is offer some
considerations for how to implement a global
solutions focused approach, looking at
population-specific opportunities, need-based
opportunities, and also to how we can better think
about streamlining our regulatory pathways, and
then I'll leave with just with a brief thought.

Our colleagues so far have done a wonderful
job of spending every presentation previously
talking about this slide. If you look at the dark
blue, we've talked about the fact that in oncology
drug development, there has been this escalation of
pace around the knowledge that's been building
regarding the underlying biological mechanisms
promoting cancer cell growth. And then if you move
to the light blue, this has clearly led to avenues
for promising new therapies. And you'll see in the future slides what this has been doing in terms of the opportunities for development of numerous products within certain therapeutic areas.

Then when we move to the orange, there's also been this explosion of understanding as it relates to genomics and certainly embracing of precision medicine, which has changed the ways we've thought about our pipeline, development in our pipeline expansion. And as a result of that, it's required us to really think about how to move the regulatory science base forward, thinking about smaller and ever smaller populations of patients for us to be able to evaluate within our development programs.

Critically, as we get to the dark red piece of the pie, this all needs to be integrated into the policy that we use as our guide to develop our therapies in the regulatory policy space, and importantly when new policies, such as what we've been discussing today related to the FDARA Section 504 changes to PREA, we have to understand
how best to incorporate all of this into the regulatory procedures that will help us get to agreement on the development of these programs.

This in particular is important because as previous speakers have mentioned, when you look just at immuno-oncology medications and you look at the promise in the pipeline, just within pharma's trade organization member companies, we have more than 200 potential compounds in our pipelines from phase 1 through the point of application being submitted, that we have to think about how to apply this new regulatory process, too.

When you think about what that means for pediatrics, we've even seen that within the pediatric oncology space, that for relapse/refractory ALL, we've even been able to see that these advances have been able to be made in this population with response rates that we could have only dreamed of 10 years ago but we're clearly seeing in the populations when we've got targeted therapies that can address the pediatric population of interest.
How do we think about this as companies when we have to put all of this into our considerations for how we build our pipeline development? I'd like to thank the IHME, the Institute for Health Metrics and Evaluation, for allowing me to use their data. This is a group with funding from Bill and Melinda Gates Foundation and whose data metrics are evaluated by the University of Washington.

What the IHME does is they calculate model and forecast based on metrics that are available through census data, vital statistics and surveys, publications, registries, and research and government data. For example, in the U.S., they use CDC data, and as a result, they're able to create a global health data exchange. In doing so, this is how places like the World Bank, the World Health Organization, is able to look across regions to really understand the global burden of disease and where to direct action in order to change outcomes.

So if you look at this slide, look all the way to the left, what you see is the world. And if
you look at the global burden of disease for children under the age of 5 and the causes of death in children, there clearly is a huge burden as a result of what you would expect in this population: malnutrition, infection. When you look to see where does neoplasm fall in terms of the world, there's a light blue bar that's in the middle. And what you have to look at is how is this disparate across the regions of the world.

So when we've be using global here today and international here today, we've been talking about the U.S. and the EU. And clearly there's a huge disparity in what is global even when we think about oncology. So we have to think about, when we are talking about very novel therapies and the race to ensure we can get to cure, or we can get to advancing disease, that what we are thinking about for the U.S. may not be applicable to other regions of the world where our development pipelines need to reach into and where access issues are actually even more profound for our patients who are desperate for our therapies.
There is a slide -- and you'll have access
to these decks -- which goes through and ranks then
where do these different impacts and the global
burden of disease really fall in the rank order and
how they're impacting the population. Neoplasms
range from 6th to 13th in this population. But not
surprisingly for all the experts in this room, you
know that as we go to the 5 to 14 year olds, you do
see a change. We do see a difference in terms of
the global burden of disease.

Again, the world all the way over to your
left, the U.S. immediately following, the European
region is about the sixth bar in, but you do
continue to see this great disparity between our
regions. So as developers, when we think about the
global coordination, the global cooperation,
clearly we need the science to drive our strategic
imperatives behind a pipeline, but we do have to
think about these implications for other regions
and where our therapies are going to reach into.

So what does this mean, then, overall?
Well, if we expand between immuno-
oncology -- again, go to the pharma organizations, member companies -- and we look at just the therapies that are in development for various cancers, there's in fact over 1100 at this point. And this is just, again, the pharma member companies across the phases of developments. We have to think about how do we best target to meet the needs of children that will have the greatest impact for populations around the world.

But this is critically important to understand. That's just a snapshot of pharma because if you actually look to the publicly available data that's in pharma projects, there's over 5,000 active drugs in development pipelines for anti-cancer therapist, 5,000. We have to think about a rational way to move forward and what makes sense for a pediatric populations because we hit a situation like this.

I acknowledge that this is pooling every type of variation that could be there for ALL, but when you look just in clintrials.gov, as in a snapshot, currently with what's in the database for
planned or active studies in and across all types of sponsorship, there currently is a requirement for 23,000 patients with ALL. And if you look at the U.S. pediatric patients diagnosed per year with ALL, we've got 2600 patients, or if we're looking at recurrent and relapsed pediatric patients per year, we have over 500 patients.

We can't possibly do this alone in the U.S., and clearly we've already heard the statement made earlier that even these trials are not necessarily adequate to meet the needs of the patients that are actually in the clinic. So how can we target what we need to do to prioritize the right studies, prioritize the right products, to prioritize the right mechanisms to be able to in fact impact change?

I had mentioned global for us goes beyond the U.S. and the EU. This is a paper, the Financial Times, an article at April 2018, where it clearly notes -- and if you look at the data, the Chinese are now emerging as the industry leaders in the CAR-T space. And in fact, they're already more
clinical trials going on right now in China than we have in the U.S. In fact, there are 116 CAR-T studies going on in China alone as we speak. And this is not a surprise. We know what the population growth is in China and other regions of the world, and in fact, businesses are pivoting. There is a change in direction of how we're thinking.

So when we think global, we do have to think about the influences that go beyond the U.S. and the EU because this in fact will come more and more into play for strategies for products that we're bringing into our pipeline that will ultimately be available to us to develop for children.

I bring up the next slide as an example of this because as you look across the regions and you look at how there has been a clear maturation of the regulatory environment in many regions around the world, and as companies are beginning to change their strategic focus based on the emergence of populations around the world, we're seeing other markets besides the U.S. and the EU really emerge.
In Japan, I focused specifically because in the 2017 report on the R&D outcomes in marketing approvals, we saw that in Japan, 18 percent of the new active substances were approved in 2017 first in Japan. This changes our dynamics. We have to think beyond the U.S. and the EU. We can certainly drive the science with where there's a critical construction, but we do have to think about the other markets that are in play.

So how can we be solutions focused understanding this background context for regulatory strategy? Well, you think clearly we've heard both from our speakers at the microphone and the public session, and we've heard from our panelists and from our members of the committee. There are some population-specific approaches we need to take.

There are pediatric-only cancers, there are ultra rare cancers, there are cancers with high mortality despite research investment, and there are cancers that are occurring in both adults and children. And what we need to do is think about
solutions that can address all of these needs
because a single policy solution will not possibly
be able to address and solve the issues that we
have.

So number one, we've heard very, very nicely
from many of our speakers today about the role of
cooperative groups and importantly how do we expand
and continue to grow our global cooperative groups.
But when we think about pediatric-only cancers such
as retinoblastoma, we have to critically think
about what are the market drivers because what is
really needed for these cancers is a solution that
will continue to drive interest from the innovators
into this space. PREA will not be a solution to
address this issue.

For ultra rare cancers such as infantile
fibrosarcoma, clearly market drivers are at stake,
but we also have to think, just as some of our
speakers have spoken about, about non-traditional
quantitative approaches, non-traditional design
approaches. We have to think about the potential
for introducing new regulatory pathways that we've
never seen before, such as dedicated pediatric regulatory pathways that are specific to pediatrics.

Importantly, when we think about these ultra rare cancers -- I'm going to go back to access very quickly because it's not on this slide -- we know right now that we have experiences in Europe where these alternative approaches are not necessarily leading payers to reimburse, so we have to think about those other forces that are out there. We can develop these therapies. We can get them to the market utilizing these alternatives and innovative approaches. But we need the other players to be engaged. Now, I'm talking about payers to be engaged, so that they understand this is our only solution to being able to get this information for patients.

Then we have the cancers with persistently high mortality such as DIPG. We need to take a concerted effort to really drive the research and understanding here, so we can use better target our molecules, so we can better target our designs to
find solutions, which means we need to make a concerted global investment in the foundational science to find the solutions.

Then finally for cancers occurring in both adults and children, I think that we've seen wonderful progress just with the last week with the FDA draft guidance for industry to consider the inclusion of adolescents and adult cancer drug development, but this is the first region in the world that has such a stated guideline. We have countries in Europe whose review bodies will not allow pediatric inclusion until there is adult data to proceed forward. Again, the environment around us can be a critical roadblock. We can't just focus on the science. We have to move the bodies that can sometimes get in the way of our making forward progress.

We also critically need to think how do we get to a place of regulatory agreement on key program design elements; not all of them, but key program design elements that will facilitate high-level pediatric plan agreement, and therefore
earlier movement of a pediatric plan through a development pipeline.

So we've heard quite a few speakers talk about global coordination as it relates to unmet need. We've talked about the fact that this is a highly competitive environment in cancer drug development. We've also talked about the complexities of early-phase drug development planning primarily because of two issues. Number one, when we're really early in investigational drug development or innovative drug development, we're working with a tremendous number of assumptions.

We don't have a lot of data in hand to drive some of our trial considerations, and secondly, we know right now there's an 80 percent attrition in early-phase drug development. So how can we target the right, the most likely to be successful, so that we can really preserve our precious commodity of patients for the right trials at the end of the day?

Then finally, we don't have a consistent
standard of care. That's okay because regionally there are regional-specific needs, but where can we agree in some of our key global markets on a standard that will allow us to have a harmonized approach to developing these therapies?

So number one, we have to continue the efforts that have already been started. I always love following Gilles, because he laid out exactly where we're going right now from the standpoint of internationally bringing the conversation together. We need to continue that engagement, but we need to move this forward. And again, we need to move beyond just thinking about the U.S. and the EU because there are other markets that are applied.

To that end, I'm going to focus on the EU because this is the only other region where there is required development work in pediatrics. And as everyone in this room I think is well, there's a very high number of discussions going on with the European Medicines Agency with companies, almost 400 discussions last year alone on pediatric programs. And when we look at it by therapeutic
area, specifically at what therapeutic areas are these discussions taking place, with oncology alone, there were 17 pediatric plans agreed for commitments in pediatric oncology. So we do need to think about coordination between our regions.

So what does this look like for a company? To be frank, it's not a straight journey. It's very complicated for us to figure out how to go forward, who to move forward with first, who to speak with first so we can get the best advice to be able to proceed forward. So if we start with our product, we know we have two sets of regulations that compel research. We've got the European pediatric regulation, and then we've got the legislative vehicles and the U.S. under PREA and BPCA.

That this then brings us to actors, clearly the sponsor or the future applicant. And then within the European Medicines Agency, who do we target first? Do we target the pediatric committee, the scientific advice working party, the CHMP, or even the committee on orphan medicinal
products because many of these programs working on developing are going to go through comp. And at FDA, it's nice because we can work directly with the division.

But when we think about our strategy, our strategy shouldn't be based on what is PREA telling I have to do. When we're thinking as innovators, we're truly thinking about our product development strategy. It is an over-arching development program that may include a PIP, may include a PSP, and may include a written request, but frankly, our fundamental questions remain the same. We've got scientific advice questions that we need to understand about all aspects of our development program that may not be applicable to our pediatric committees, but more so about how we can get this compound to move forward.

So what does that leave us to do? Well, there are all these different meetings that we could potentially engage in depending on where we are. And depending on what type of product we have, we may be able to get into a special
regulatory advice pathway such as PRIME in Europe or the breakthrough pathway in the U.S. And there is an opportunity for parallel advice, and I'll come to that.

But ultimately will lead to the pediatric plan application, which once agreed could go through multiple iterations of modification and go through multiple iterations of amendment. And that ultimately will generate the data that will lead to the discussion about the applicability of this therapy, then, in the pediatric population through labeling.

So what does that look like in terms of the existing timelines and how do we get to the point of ultimately getting that pediatric plan application in? Well, if you go by the procedural timelines in Europe, if we want to seek scientific advice, it's going to be about a six-month timeline. And we would suggest this before we submit a pediatric plan because sometimes they're very critical questions that we need formulation guidance. Sometimes we need modeling and
simulation guidance. Sometimes we need preclinical safety guidance.

Once we've completed that scientific advice working a party discussion through a formal procedure, we're going to go back, we're going to regroup, and then we're going to put together a pediatric plan, and we're going to submit our pediatric investigation plan. And the procedural timeline to agree on a pediatric investigation plan is 10 months.

Well, if you look at the guidelines in the U.S., the procedural requirement to agree on a pediatric study plan under PREA is seven months. It's got a 210-day review clock on it. That's assuming you do not receive an inadequate response letter that will extend your timeline to agree, and a written request will take approximately three months. But you need to understand that it is very rare that these procedures run in parallel, and in fact they often run back to back.

Just by way of anecdote, the most recent pediatric program at Novartis that was completed
through a written request took approximately 18 months to agree ultimately on a final written request. In the midst of that 18-month agreement process, we did receive agreement on our pediatric investigation plan, however, they were not aligned. It took an additional five years of multiple modifications and amendments for us to get to an aligned pediatric program, at which point we could complete our pediatric program and submit ultimately our written request.

So this is currently not very straightforward, and what we truly need is a pathway that helps us to get to some kind of global agreement at least on the scientific components that are going to underline our plans.

Why do companies want to seek this guidance early on, and why do we want to go through all of this work early on? This is data that was presented by on Regnstrom from the scientific advice office at EMA in 2017. And based on their analysis, what they see is when companies seek scientific advice -- and it is a when; it's not a
requirement. But when they do seek scientific advice and they build their development programs based on that advice that's received, they have a much higher likelihood of once an application is submitted of having a positive outcome.

So this is a critical reason why companies, who are knowledgeable about the process and know that they have questions for the complex diseases, want to engage and want to engage early so that they can understand these critical pieces that might undermine ultimately their ability to register their product.

So what do we currently have available to us in pediatrics between the global regulatory agencies? A wonderful project that was put out is the pediatric cluster, and it has been referenced. And through the pediatric cluster, which includes the FDA, the EMA, Health Canada, PMDA, and the Australian health authorities, is it facilitates the regulators' ability to speak to each other about pediatric programs that have been submitted through either the European process or the U.S.
process. And the hope is that it will enhance the
science underlying the pediatric trials and avoid
exposing children to unnecessary trials. But it's
important to note this is for the regulators only.
Companies are not engaged in the pediatric cluster.
And we might not know even that our product was
discussed in the cluster, so we don't have an
opportunity to ask specific questions.

We more recently through the cluster
process, a project called the Common Commentary
process was put in place where companies could in
fact seek a non-binding and informal comment that
came from those cluster discussions. However, this
is not a pathway, again, that allows for the direct
engagement of companies, so we don't have an avenue
to be able to really have that direct
communication.

So what avenues do we have? Well, there is
opportunity for parallel scientific advice. Again,
this is between the EMA and the FDA to exchange
views and scientific issues during program
development. Clearly, it can increase the dialogue
between agencies and sponsors because this is a
pathway that sponsors are actively engaged in
discussion. And what it's intended to do is to be
put in place for breakthrough drugs or to address
important safety issues, and it can be used for
oncology and for the pediatric population.

It's extraordinarily useful for products
that are early in their development where there's
limited precedence. Its purpose is focused on
sharing information and perspectives. It is
extraordinarily resource intensive for all parties
involved, but I would posit as a company who's been
through this process, even when we couldn't get to
a place of alignment, it probably shaved three to
four years off our development timelines because we
knew exactly what the agencies wanted. And we
believe that it's more important to have these
difficult conversations up front. So what's
desperately needed from a policy standpoint is a
greater opportunity to have these types of forums
where we can have this direct conversation with the
regulators.
Now, bear with me because the European mutual recognition procedure is about approval. I put it up here only as a fact that in Europe, there was a clear understanding that with all the member states in the European Union where there were national procedures for a single member state to approve a therapy, there was an opportunity potentially to facilitate the already agreed approval for a product and to decrease the burden and the workload amongst other member states.

So this is a pathway that's used for purposes of approval, the mutual recognition of an approval between member states. And I'm using this as an example because what is to come with the new clinical trials regulation in Europe is a similar theme, but as it relates to agreeing to the scientific content of a clinical trial application. So it's getting to the point of the plan in the agreement.

Now, the clinical trial regulation went into force in 2014, but it's not been fully implemented because the database necessary for countries to
share the reviews of the opinion based on the
review of the application that was handed to them
currently is not completed, so it's hoped that this
will go into effect in 2019. And this is the type
of pathway that I think companies would be very
interested in understanding if we could get to a
place of mutual-ish recognition of a plan that's
been agreed with a recognized competent health
authority.

So from my perspective, when we're thinking
about a cooperative, global regulatory pathway to
agree on a pediatric plan, utilizing what we
currently have and expanding it, refining current
pathways that we have, or creating new pathways to
help us get here would be something that I think
would help us tremendously in the pediatric cancer
environment, particularly because we know that
other pathways have been able to do this for other
life-threatening diseases. We know that these are
small populations, so we have to be thinking
innovatively.

There are extraordinarily complex treatment
paradigms that we need to be able to understand and are not so simple to discuss product by product, monotherapy by monotherapy. And because of the other questions that come along with these types of developments such assay development and other considerations related to prioritization because of the molecular targeted approach, we do need to have some consideration of alternative pathways if we're truly going to get to a more efficient global cooperative framework to agree on a pediatric plan.

So my considerations I put out there are that there is need for a pediatric dedicated parallel, true scientific advice pathway and also easier, some type of pathway we can consider. I know this is a pipe dream. I know this is a blue sky request, but mutual recognition is something that has been done, has been shown to work in Europe, and I think at the end of the day when we really want to talk about global cooperation, this may be something that we should be talking about robustly as one of the next things that needs to come from a truly transatlantic trade agreement.
So just my parting thoughts for us to move with today, we clearly are embarking on a new journey, and we have an opportunity to facilitate truly meaningful change in how we develop medicines for children with cancer. Our population, because they are small, creates an opportunity, a clear opportunity, for global collaboration avenues in innovative approaches like we've not been able to utilize in the past.

What we know from other transformative change that has been successful is it requires trust. And I think we're finally getting to the place where we're all at least sitting around the table. We have to trust that we all want to get to the same objective, and we have to do this because the children and their families are depending on us. We need to see this change be meaningful. With that, I will conclude.

(Applause.)

Clarifying Questions

DR. PAPPO: Thank you very much. We will now take questions for Dr. Vassal and Dr.
Bucci-Rechtweg. Please remember to state your name for the record before you speak.

Is it possible to put Dr. Vassal on the screen? There he is.

DR. VASSAL: Hi.

(Laughter.)

DR. PAPPO: Hello.

DR. BUCCI-RECHTWEG: Hi, Gilles.

DR. PAPPO: Questions?

DR. KOLB: Andy Kolb. That was fantastic.

Thank you for that global perspective. As you see, you gave the example of the CAR-T cells being developed in China. In those emerging markets, what kind of threat does that propose to access in the areas where we're talking about, the EU and North America? Are you inferring that Chinese companies are developing drugs for Chinese children or that traditionally North American EU companies are going to China as opposed to the FDA and the EMA for market development?

DR. BUCCI-RECHTWEG: Yes. I think it's a little bit of a mixture of both, but I would say

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the caution I want to put on here is that companies
that are EU based or U.S. based are still going to
continue to go to those regulatory agencies where
they believe that they are going to get the best
guidance for their ability to move forward with
their products.

I think the critical piece to take away from
that is that the emerging markets are clearly a
huge business opportunity for companies, so if what
we're seeing from those regulated agencies who are
becoming much more mature and are very quickly
trying to replicate what we have here in the U.S.
that you might see companies that are pivoting and
wanting to have some requirements that other
agencies may be requesting of us.

So we need to not necessarily take on
another market that might not be as mature from the
science standpoint, but we need to keep those
considerations in mind because they may be
inferring some strategic steps and the sequencing
of strategic steps.

MS. LUDWINSKI: This question is for you,
Dr. Vassal. At the ACCELERATE meeting, are you going to be involving payers or national health service representatives in going forward, or have you already?

DR. VASSAL: No. This has been one of the important messages that was discussed and advised at the last meeting, that the HDAs [ph] were not present. But I can tell that we have been trying over the last years really to have people from the HDA participating. So far it did not work, but we hope that in the near future, and especially the near next meeting, we will have people from the HDAs because we strongly believe that we need them on board as well, as well as the ethic committees really to share all the issues addressing, in addition, the topic of cost and reimbursement.

MS. LUDWINSKI: Fantastic. Thank you.

DR. PAPPO: Additional questions? Katie?

DR. JANEWAY: Those were excellent presentations, and I wholeheartedly agree with the concept of getting broad input for prioritization and alignment. I guess my question is can we
define when that's really necessary, and are there any concerns or how do we prevent such multistakeholder discussion from interfering with the pace of development?

DR. BUCCI-RECHTWOEG: Go ahead, Gilles.

DR. VASSAL: Sure. This is a very important question. The program is a meeting as a point in the development. It is not early; it is not late. Rather, it's an issue that needs to be solved. And as you saw in the full project, the reasons for having a forum are not the same. So this is why we propose that these forums are being set up when there is a real need expressed by people from industry, from academia, regulatory people as well, and parents.

We propose in our suggestion for international pediatric forum to have a process for choosing the next forums in a way that we will contact each cooperative group to verify what are the key issues that need to be addressed. We would put on the website a possibility for anyone to make suggestion, and then this will be discussed in our
annual meeting with everyone from Europe, from U.S., including Japan, and then we implement it with FDA and the EMA.

So it's very much at the point in development when there is an expression of needs because there is an issue that can be solved or improved by such a forum. So it's not early preauthorization activity. At the moment, there are drugs already generated and they're either coming or there are many company developments [indiscernible] that we don't know how to address. This is where this forum at a given point can really help in shaping the strategy further and helping the U.S. with the decisions.

DR. JANEWAY: Thank you for that clarification. And for the record, that was Dr. Janeway from Dana Farber.

DR. PAPPO: Any additional questions? Brenda?

DR. WEIGEL: Brenda Weigel, University of Minnesota. I want to echo thank you both for a fantastic presentation. I think this really
addresses an incredibly important topic. And Dr. Vassal just addressed, the forums are really a little bit later than a fair bit of what the RACE Act is targeting as sort of that really initial forum into early-phase trials in pediatrics.

I wonder if either of you have ideas of how and what mechanism could be put in place for increased collaboration at that sort of preclinical space. I think, Dr. Vassal, you did mention there's going to be this fall this first preclinical connection, but it's that industry/academia partnership even earlier in the process and how that might look, and how we could leverage some of the platforms that are already in place with ACCELERATE and other mechanisms.

DR. BUCCI-RECHTWEBG: I'm happy first, Gilles, and then I'll punt over to you. I do you think that the existing forums -- there are existing forums that are in place, and I do think we do need to make a pivot to precompetitive space for early discovery and also early molecular target based work.
I do think that there are some existing relationships that are in place. We need to find ways that we can expand upon them, and when it comes to policy expansion, for ways to fund them. Because I think one of the critical pieces I know right now has been the fact that we can't get the appropriate funding into those spaces because there's, of course, again, not commercial drivers and individuals who are willing to invest in them.

So I think that this is one of the critical places that we need to direct our attention. What I can say from the standpoint of the work that we've done ourselves organizationally within Novartis is we can't state enough the importance of the early engagement in our truly novel innovation-based development that we're doing for pediatrics.

We can't do the work without collaboration with academia, with basic research, with platform-based development. That is what helps us to get to the point of being able to be efficient to work directly towards pediatric drug
development.

So I do think the opportunity is there. I think, Gilles, you're looking to make a pivot earlier, and I think that that's where we're going to need to focus if we're going to truly be successful in those forums being able to inform on the regulatory decisions, on what plans can be agreed to move forward.

DR. VASSAL: To the question, these forums are much meant to solve all the issues of prioritization. In my talk, I first addressed the issue of early evaluation of relevance of targets, and this early discussion, that pipeline discussion that we are proposing, is really a discussion between scientists and individual companies. And a forum is useful when there are already, for a given pathway, one or two drugs with information in the pediatric setting and many other compounds developed by other companies on the specific target.

It is echoing something that we identify through our ACCELERATE and [indiscernible] meeting
when discussing with regulatory people and members of PDCO, we understood that when any company comes with a proposal, they don't have a vision about what's going on with the other plan that has been approved before.

So the forum is at a time there is a relevant pathway or an issue in a disease, sufficient information to already discuss how to move forward and trying to figure out whether other drugs should be developed, and if yes, how. But clearly, in our forums [indiscernible], this will not solve all the issues. And what is very important is early interaction at the beginning of development of other drugs in order to regenerate the evidence of the early evaluation of these drugs in children.

Did I answer the question?

DR. WEIGEL: Yes, thank you.

DR. PAPPO: This is a question for Dr. Vassal. Is there a mechanism for updating the recommendations or the observations of the forum?

Let's say that a fourth generation ALK inhibitor
comes along and it's highly effective against ALK with neuroblastoma, but the preliminary observations said that that was not the case. Is there a way to update this or how does it work?

DR. VASSAL: This is a very important question, how were they batched [indiscernible]? We don't have a standard authority procedure saying that every 6 months or 12 months and they need to choose. It will be indicated by case. But I take your example, in the ALK or inhibition malignancy forum, the ALK inhibition -- any pediatric malignancy -- sorry -- we clearly say that there were no data with the ongoing trials and the available drugs showing real activity on neuroblastoma or without mutation.

Clearly, one of the messages was that in this neuroblastoma setting, there was a need for further development of either options, either new ALK inhibitors that would prove to be, at the preclinical level, active in neuroblastoma, and more active than the other one, or other approaches, including combinations, including
monoclonal antibody and so on.

So clearly, we paved the way for one just to say in neuroblastoma, there is a need for more research because at the moment, there is no evidence that the drugs we have are active. So we did not plan on a regulatory basis -- on a regular basis, not regulatory, a regular basis to revive this forum after 6 months, but this will be on a case-by-case situation.

DR. PAPPO: Thank you very much.

Any additional questions?

(No response.)

DR. PAPPO: Thank you very much, both, for your excellent presentations. Thank you.

DR. VASSAL: Au revoir.

(Laughter.)

DR. PAPPO: So we do not have any open public hearing speakers for this session, so we will now proceed with the charge and questions to the subcommittee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public
attendees may not participate except at the specific request of the panel. So we will go ahead and read the first question.

**Charge to the Subcommittee**

DR. BARONE: Please discuss transparent mechanisms for industry advocates and the academic investigator community to communicate and provide input to the FDA for purposes of eliminating unnecessary duplication of clinical trials in rare pediatric cancer populations of same in-class agents.

**Questions to the Subcommittee and Discussion**

DR. PAPPO: If there are no questions or comments concerning the wording or the questions, we will now open the questions for discussion. Malcolm?

DR. SMITH: Yes. So this is one of the more vexing challenges. At some point if we have three or four or five or six drugs in class, someone is going to say maybe we don't need to study another one. It could be a company that goes in and says we need a waiver. It could be FDA that says I
think we've done enough. We encourage you to ask for a waiver. If that process could be one that was made available to the community, that would be a way of spreading the word that, as of now, people may want to study additional drugs, but there will not be this required molecular target study.

DR. PAPPO: Ted?

DR. LAETSCH: I would just second what Malcolm said and something that Julia said before about it may be helpful to develop a list of targets that aren't relevant based on biology, like the prostate antigens and a separate list of targets that aren't relevant based on prior studies so that we can differentiate those and then perhaps seek input from the community to update those lists periodically and assess whether there are new agents that have such different activity in those particular mutations that they should be studied.

But that list may be helpful.

DR. KOLB: I think the challenge might start even earlier. Most of these concepts and these discussions with our industry partners start years
before the trial, and there are many examples where we have all spent lots of time in developing concepts of same in-class trials, not knowing which one's going to hit the clinic first. We are limited by CDAs in open conversations about these trials that are in development, and I think having a forum where we could strategize on which is the lead compound, which one are we going to develop clinically, none of us are confident enough to put our eggs in one basket because those baskets frequently vaporize without our prior knowledge.

So I do think that this is a complicated issue, as Malcolm pointed out. I think once there is initiation of the regulatory conversations, it's maybe a little easier to be transparent. I think in the early drug development when you do preclinical testing, when you're trying to prioritize agents, it's much more challenging.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel, University of Minnesota. One small word of caution as I'm sitting here thinking, to build on both what Dr.
Smith and Dr. Kolb mentioned, is that this is a really challenging problem. And we don't know when we're heading into that first pediatric trial, when there are multiple agents potentially in class, which one is actually going to have legs, which one's going to actually be the better agent. We have no necessary basis with which actually even most times to make that decision as we're moving forward.

The one word of caution is that the last thing we want to do is have any of our industry partners think that if they wait, that their regulatory requirements will be less if they're not first, i.e., they won't have to support or do the pediatric work if someone else gets to the gate first. And I think that's not what we want to do.

So I think we have to be really thoughtful of how we really do this in a competitive space with industry and really hold all our industry partners to the same bar for developing drugs for children and not make it that if you're first, you're actually almost in
a way penalized because that's absolutely not what
we want to do.

DR. PAPPO: Good point. Greg?

DR. REAMAN: I just wanted to get
clarification about moving things from the relevant
to non-relevant list based on clinical trial
experience. Just tell me again how that would
happen just so that I understand the process.

DR. LAETSCH: I don't know that I have that
process fully designed, but I would go back to the
examples of the VEGF inhibitors that were
originally at least placed on the non-relevant
list, not because we don't necessarily think
they're relevant to the biology of pediatric
cancer, but because there have been numerous
studies with low response rates.

So I just was thinking that as time evolves,
we are going to get more data on some of these
classes of agents in pediatric cancer, and some of
them hopefully will be positive, but some of them
may be negative. And in that situation, at some
point, I would imagine that, as Malcolm said, we
would feel like and the FDA would feel like it wasn't worthwhile to mandate an industry partner to study the fifth in-class of the same drug when it didn't work four times.

So I don't know how that would exactly work, whether it would be a discussion among advisory committee to the FDA to review that data periodically and update the list, but I think there would need to be a process as data becomes available, which we really don't have at the moment, to move agents that have not shown activity or classes of targets that have not shown activity off of that list.

DR. REAMAN: Because we had an earlier discussion about targets that we thought there was sufficient clinical activity demonstrating -- or clinical data to suggest that there was an activity and actually moving them back on a relevant list. So I'm assuming that things could, should work in both directions.

DR. PAPPO: Steve?

DR. DuBOIS: A couple of comments. On this
most recent topic, I think it's very much drug
dependent. So if we had said, okay, we've treated
some kids with NTRK fusions with crizotinib and saw
very little activity, and we treated some kids with
NTRK fusions with lestaurtinib and saw very little
activity. And then along came larotrectinib, and
would we really have said no -- we've ruled that
out as an attractable target of interest in
pediatrics on the basis of sort of weak TRK
inhibitors. So I think there is going to be a
little bit of nuance there I think.

Then to Brenda's point, just to agree
completely, I think we do need a little bit of
redundancy, probably not as much as we have with
some classes of agent. But at the end of the day,
we need some agents in each class to survive and to
have some dosing and safety information so that if
a drug ultimately doesn't get approved in an adult
indication, or gets approved and pulled for some
reason, that we have some data with another drug in
class because there will be patients who need to be
dosed safely with those agents.
DR. PAPPO: Malcolm?

DR. SMITH: And, Greg, I wasn't suggesting that they necessarily be considered not relevant, but just that since X number have been studied, maybe that's enough. that any others would be able to apply for waivers because of that. So I think there are two processes in which one you might use would be kind of open. But I think being able to publicize that this is what the status of this target is, is that waivers may be given -- not guaranteed but may be given -- because of the number of agents that have been studied, could be helpful.

DR. REAMAN: No, and I fully understand that waivers would be certainly appropriate in that situation. But as I mentioned earlier, our communication with sponsor about waiving a requirement is not something that we have the ability to share publicly. Sponsors can share that. So maybe that would be the mechanism, but it's not -- and that's why I was wondering about this list and how we would really affect that. But
those communications are really confidential, proprietary information, but I think encouraging sponsors to make that information available to help guide investigators and other sponsors would be very helpful.

DR. PAPPO: Donna?

MS. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer. I'm wondering, based on the strategy forums that both Dr. Caron and Dr. Vassal discussed, is there a way for the FDA to leverage those in order to reduce duplication, or is that purely European-centric at the moment?

DR. REAMAN: It has been European-centric, but I think you heard Dr. Vassal talk about expanding its scope internationally. But I think the strategy forum, I think they're very useful and very beneficial. But I just recall the experience from the last one that I was at talking about 15 clinical trials being conducted by sponsors in relapse/refractory mature B-cell non-Hodgkin's lymphoma; 15 trials that were all bought into by European investigators who were leading these
studies. But it was really kind of late in the game.

What we're really talking about here is early evaluation of potential products of interest, potential products of interest based on their molecular mechanism of action and whether they exist or don't exist on a relevant target list.

So I think we might be able to convince ACCELERATE to devote one of the four planned strategy fora that they're going to have every year on early prioritization and maybe a review. They've certainly seen the list of targets. They've weighed in on the list of targets that we've proposed. They've made additions. They've asked questions. They've recommended some deletions.

But I'm not sure that the strategy forum is -- I think what we do may inform the strategy forum, but I'm not sure that the strategy forum is going to be the best method of doing the kind of prioritization that is going to be required of us in early development of some of these products.
Again, we've tried to address this in a
disease agnostic sort of setting, recognizing that
uh, some targets are strictly associated with
specific diseases, whereas others may not be. So
it's a little bit difficult to wait for a strategy
forum that's focused on a specific disease. It's
also difficult to wait for our purposes to discuss
multiple same in-class drugs. So if we wait until
there are five or six ALK inhibitors before we have
a strategy forum to discuss which one should we
prioritize, does that mean we've waited until the
fifth one before we even evaluated the first one?
And that's another issue that I think we need to
highlight here.

There's definitely room for participation
globally in that, but as far as implementing the
mandates of this legislation, I'm not sure that the
strategy forum is going to be the right place as
it's currently constituted, and it may be that
there will be opportunities to change that. And
that's something that we'll have to talk to
ACCELERATE about.
DR. PAPPO: Toby?

DR. MacDONALD: On that note, I think on the preclinical development side, it'd be helpful if there's a mechanism in place by which a single investigator or platform could get multiple agents of the same class with which to test, so instead of going sequentially, we can do it in parallel. It's very hard. You get your one CDA, your one MTA, you test your one drug, and you publish that. And then if you compare it to another lab or European study, there's no cross-comparison or validation. So it will allow you to validate the target, and it will allow you to do head-to-head competition of the drug.

I think if there's a way that -- if I could get my hand on five drugs and test them together in the same model, in the same style, in the same dose and schedule, you could have much better prioritization of the drug that you think is working the best within that, -- it will probably be within that histology or within that pathway that you're looking at.
DR. PAPPO: Ted?

DR. LAETSCH: I should clarify. I don't mean to say that they wouldn't be relevant. I mean to say, like Malcolm said, if they've been studied multiple times, we need to sort of consider whether or not new studies are needed. And I would also echo what Steve said, that it is not just target but also agent and class. So larotrectinib is different than crizotinib, and then it's a highly specific TRK inhibitor. I'm not sure there are that many differences between the many PD-1 or PD-L1 blocking antibodies that are clinically relevant, so I think those considerations will be important.

DR. PAPPO: Julia?

DR. BENDER: Julia Glade Bender. I hope this is not a naive question, but sometimes I wonder what the pediatric ODAC role is in this, and could the pediatric ODAC itself get involved in early prioritization. I'm not sure what the nomination process is to come to a pediatric ODAC, but I wonder, in fact, if investigators could
actually nominate a target and put a call out to
see if industry wanted to come talk to us if they
had something in the pipeline.

    DR. REAMAN: Well, as you may know, the
pediatric subcommittee of ODAC has undergone a
series of evolutionary changes. We several years
ago changed to invite sponsors to come and discuss
products so that we could think about issuing
written requests early in the development timeline
rather than waiting until two or three years after
a drug was approved and then say, oh yeah, that's a
great drug; let's see if we can study it in
children.

    We could certainly do that, and I think
there's clearly a role for the pediatric
subcommittee to help advise. The only difficulty
with that is, again, when it's a specific sponsor
and if our experts that we invite as members of the
subcommittee have a relationship with one of the
sponsors that might be presenting their product,
that poses a real conflict, and we unfortunately
sometimes can't get the experts that we really
need.

So there may be mechanisms outside of a formal advisory committee where we don't have -- I mean, not that we're looking for ways to skirt conflict of interest considerations, but where we could do it in more of a workshop setting. And that was part of my thinking about these semi-annual workshops. Now, maybe we need to have them more frequently than twice a year, and that's something that we could really think about and discuss.

DR. PAPPO: If there are no additional questions or comments, I'll try to summarize some of the salient points of this discussion. Anybody else have -- we still have one more question to go through.

So regarding the most recent question, the possible role of pediatric ODAC in early prioritization of agents, there could be a possibility of incorporating that in the future. Just be careful of the conflict of interest that you might have if you invite a specific sponsor
that has a relationship with a drug company.

There were a couple of discussions regarding the development -- a process for new agents for multiple drugs in the same class and how that could be done. And the overall strategy would be to try to develop a forum or some kind of process to make available to the community to help strategize which should be the lead compound. On the other hand, we don't want to wait for multiple compounds to be available until all of them have been developed. And if the first compound in its class is available and it's the only one that is currently ready for prime time, I think that should be evaluated.

Is that a fair statement, Greg?

DR. REAMAN: Yes.

DR. PAPPO: Okay. I think that's it. A lot of it was just back and forth. Any other things that I left?

(Laughter.)

DR. PAPPO: There were a lot of clarifying questions that Greg was able to answer that I don't think I should be summarizing, but if you wanted me
to -- I didn't write it down.

Anything else I left out. Ted? You're okay with your priority lists and all the agents and all that stuff? Okay. Let's go to the last question.

DR. BARONE: Please comment on process development aimed at enhancing international collaboration between clinical trial networks to facilitate global cancer drug development for children in light of currently nonaligned regulatory requirements.

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

PK?

DR. MORROW: Just as a follow-on to the discussion about the common commentary and the pediatric clusters, would there be a mechanism for which companies would be able to receive guidance that is not drug specific but rather target specific? That is saying if one has a specific target or disease state globally harmonized, what type of appropriate endpoints or backbones could be
utilized?

DR. REAMAN: That's certainly possible, although usually the cluster calls use, to develop an agenda, applications that have come either to the agency or to the EMA, applications, or study plans, or proposed pediatric study requests, or the EMA, their pediatric investigation plans or PIPs. But this sounds like not PIP or PDSP specific questions, a bit more general questions.

The cluster calls are organized by the Office of Pediatric Therapeutics. I think they would be open to facilitating collaboration and coordination. And again, they're monthly, and we block off three hours, so some of these discussions might take more than just the 20 or 30 minutes because sometimes we have a lot. But I think there may be a mechanism for doing that.

There may also be a way of accomplishing this through workshops, but that may be a little bit more difficult to get international colleagues and representation. And it clearly would be difficult to get people from the EMA to travel here
because we can't reimburse for that. And the same
when we go there, we're not reimbursed. And there
may actually be a mechanism that we could set up
outside of the cluster calls, just within the
Oncology Center of Excellence because there are
adult agent and clinical trial cluster calls as
well with multiple regulatory agencies.

So we could have a pediatric-specific one
that really was not necessarily product focused but
may be target or pathway focused. And it may
involve or maybe could involve more than one
company even, as well as regulators. So yes, we
could certainly look into ways that we could
accommodate something like that.

DR. PAPPO: I have a question for Greg. Is
it realistic to think that it will be possible to
harmonize the EMA and the FDA for a single
application and be able to get all of the
requirements for the two agencies, or that's not
realistic?

DR. REAMAN: In your lifetime or in mine?

(Laughter.)
DR. REAMAN: I mean, harmonized is a difficult word because harmonization I think really requires legislative changes that lead to regulatory procedures and processes. And I don't think we're in the right place to truly influence legislation.

Having said that, I think there are ways that -- and we have, actually with the early part of PIP requirements and written request requirements, been able to harmonize and agree on a single international study or one study that's being done in the U.S. and another study that's being done in Europe. And the results of those studies would satisfy both regulatory agencies' requirements.

So there are ways to do it, but there's no single way to do it all the time. And it really is more a question of coordination rather than harmonization, I think, which to me means something very different that is not necessarily immediately achievable.

DR. PAPPO: Thank you. Elizabeth?
DR. RAETZ: Elizabeth Raetz. This is a question for Dr. Reaman, and forgive me if this might be naive as well. Have there been any thoughts about harmonization of strategies for trial design? Because you may have a number of different agents that have promise in a certain class, but sometimes there is disagreement about how to study them, whether there would be combinations or common platforms that are agreed upon globally.

Has there been any thought about also working on those sorts of issues?

DR. REAMAN: There have been. And again, not as part of what we're talking about here with implementation. But it's not uncommon that we get proposed pediatric study requests for evaluation of a new drug in a particular disease or diseases with a backbone. And it's a backbone that is not used in the U.S. but is used in Europe. I won't mention the diseases because you can maybe then figure out what I'm talking about.

So we have tried to work with the EMA and
work with sponsors to accommodate both, and
sometimes it's getting feedback from the company
that there are enough of U.S. investigators that
would be willing to enroll patients even though
it's not the quotes/unquotes "standard of care,"
for lack of a better word, in this country and vice
versa. And sometimes there are major changes to
study design that are required to accommodate both
backbones, and maybe even to the point of a
randomized study looking at both with the new
agent.

DR. PAPPO: Steve?

DR. DuBOIS: Steve DuBois. Most or all of
what we've talked about today has centered around
drugs that are being evaluated in adults and then
making their way to children, and that will get us
only so far. At a certain point, the hope of
course is that for some of these targets that are
truly pediatric specific, that there will be drugs
developed, which really the first in-human study is
a first in-child study. And I suspect that those
would probably have to be international in scope,
or at least the broader development plan would have to be international in scope.

So how aligned are the regulations in terms of conducting a first in-human study in a child?

DR. REAMAN: I'm not sure that I know the answer to that. I know that it's not out of the question as far as the FDA's position. I'm not a hundred percent sure what the EMA's position is on that. And you're absolutely right. This piece of legislation is not going to solve all of the challenges with drug development for children with cancer, and the most promising agents that we'll hopefully be able to see developed are not ones that are repurposed for pediatric indications, but ones that are developed specifically for pediatric indications. And this legislation really has nothing to do with them.

Having said that, I think -- and the other non-alignment of our regulatory processes is that the pediatric investigation plans require consideration of the development of a product through its continuum, so not just early dose
finding and signal seeking, but real efficacy
studies, comparative efficacy studies if necessary.
So it may be that the earliest phase studies might
be done here, which would actually inform the
pediatric investigation plan, and that the more
definitive studies could be designed so that they
meet the regulatory requirements of both the EMA
and the FDA. That's how I would possibly see
things happening.

DR. PAPPO: Julia?

DR. BENDER: I just wanted to -- and this
probably goes back to PREA and some of the points
that Brenda was making about multiple drugs in
class and things that are going on in Europe and
going on here. And I wonder if the incentive to be
the first one out is sufficient for the extra
amount of burden it may put on the first one, and
whether in fact incentives should be graduated
not based on positive results but rather based on
how many studies or how much work it took to get
there.

DR. REAMAN: Well, just to clarify, there
are no incentives associated with PREA. PREA is a
mandatory requirement to do studies. The only
incentives are associated with BPCA and the written
request mechanism. But I understand Dr. Weigel's
point, and I would hope -- or I would suspect,
maybe incorrectly, that if a drug were truly of
interest to a sponsor, that being first in class
wouldn't be jeopardized by considering that they
may have to study this in the pediatric population.

Our intent is clearly not to jeopardize
cancer drug development. I don't think that's the
intent of this language. It's certainly our
interpretation of the law. But I don't think that
companies are going to wait to submit the
applications just because they might be able to
escape, if you will, the requirement for a
pediatric investigation. But that might be a
question that's better addressed to our industry
representative.

DR. MORROW: I think I would concur that
there's a strong desire to be first in class, so I
agree.
DR. PAPPO: One more?

DR. BENDER: Even if in the end, they don't get the indication but they did all the appropriate pediatric testing, is there an incentive through the BPCA for that, a voucher or something like that?

DR. REAMAN: They could submit a PPSR, and we could maybe issue a written request. So a written request, describe in pretty vivid detail or extensive detail the studies that are required. And the studies don't have to be positive. It doesn't have to lead to an indication. Generally, we hope that it leads to information that could inform labeling with respect to toxicities, PK doses. But there are new guidelines or guidances that are preventing us from including even some of that information in labeling.

But the studies don't have to be positive, but if they are conducted and data are submitted within the timelines, and they meet the requirements of the written requests, then they could get exclusivity without a pediatric
indication, sure.

DR. CASAK: Just to clarify, sponsors need to submit the pediatric plan at the end of phase 2. In order to develop their own track for the indication they're looking, they need to submit a pediatric plan. So they are not going to wait for somebody else to submit theirs.

DR. BENDER: My only point is that we're trying to move the timeline earlier, so they may not know yet. So they're making an early investment -- if they make an early investment and that drug doesn't go all the way through, is there an incentive?

DR. REAMAN: You mean that drug doesn't go all the way through for their planned adult indication? There is no -- no, there's no incentive. No, there's no incentive.

DR. PAPPO: Raj?

DR. MODY: Rajen Mody, University of Michigan. I just wanted to follow up on Steve's point. We do have an example of an active agent in pediatric, dinutuximab, which received FDA -- if my
memory serves me correct -- in March 2015 an EMA approval in August 2015, so a rather short succession, so when you have an active agent. Even though I would say that there are some lessons in that, when we are considering for approval for FDA and EMA, it's important to look at what therapy patients receive previously, and the backbones are not the same. Even though there are differences, the EMA and FDA were able to grant approval in a very rather short succession.

DR. PAPPO: Good point. Nita?

DR. SEIBEL: So in some of the presentations, it was mentioned how the cooperative groups have done international trials but they haven't involved IND agents. So that's how they've been able to be done. So it seems like really industry has to sponsor the trial if it's going to be done internationally. But my question is, have you had any discussions on would it be feasible to do an international trial that isn't industry sponsored but more through the clinical trials network? The main problems obviously are
regulatory from the IND standpoint or they have to be companion trials.

DR. REAMAN: I don't think we've had any specific discussions with companies. I suspect that we will as they now may be required to do studies that previously they knew they were just going to be automatically waived because they were developing the drug for an adult cancer indication. Now I think -- and they may well have to consider that the study would be international in scope, so their sponsorship of it, even though it's conducted through a cooperative group here and a cooperative group in other countries, and their requirement to supply the investigational drug I think would still exist.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel, University of Minnesota. Just building on Nita's comment -- and I think it speaks to some of the joint communications internationally between pediatric oncologists -- for non-industry sponsored international trials, the real work is to have, in
the current regulatory environment, parallel trials and matching the data collection, matching the eligibility, matching all of that. And that really gets down to the collaboration among colleagues. And I think that's very doable, but that is also the buy-in of our industry partners to say it's really two parallel trials and then merging of data sets.

So it is possible and certainly doable, and we certainly have experienced doing it, but that's the only way with the current IND system, as Dr. Seibel points out. So I think there are ways to do it. It speaks again to that international collaboration, international communication that needs to occur and the academic industry partnership around that to be clear of what the options are.

DR. PAPPO: Any additional questions or comments? Greg?

DR. REAMAN: I would just question the regulatory buy-in. Parallel studies and merged data sets aren't always the optimal way to go. In
the adult setting, there are many international studies, and a single data set is clearly preferable. And I think that is something that in an industry-sponsored study that's conducted internationally would be required and would be certainly preferred if there was really a plan to license or get an approval for a pediatric indication.

DR. PAPPO: Malcolm?

DR. SMITH: And I will just add to what Brenda and Greg said, that we are working out ways so that we conduct a single trial. There's an NCI sponsor on this side of the Atlantic and there's a company sponsor on the other side of the Atlantic, but it's a single trial with a single database. So that's a model that I hope would be satisfactory. So it's all complicated, but we're working out the procedures to do that.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: The two main topics that I was
able to get out of the discussion -- because most
of the questions were addressed to you, and you
gave an exceptional answer to all of them.

(Laughter.)

DR. REAMAN: So you can repeat them back.

(Laughter.)

DR. PAPPO: Not really. They were not
related to the -- anyway, one was if there was any
kind of guidance for companies for a target, what
should endpoints and what should be the backbone.
And I think that the answer to that is that some of
this is addressed in the cluster calls and there
are some workshops.

Then the most recent discussion was
regarding international collaboration and trials
that include an IND drug. And although there's not
a specific mechanism right now, there are parallel
trials that are being conducted at the same time in
Europe and the U.S. in which the data is merged;
although Malcolm mentioned that there is currently
an initiative to try to come up with a mechanism to
actually conduct those trials internationally.
Is that correct? Is that fair?

(Nods of affirmation.)

DR. PAPPO: Any additional things I missed other than all this stuff that you were kind enough to answer to everybody?

(No response.)

DR. PAPPO: Now, Dr. Reaman, on top of everything else, is going to provide the closing comments.

**Closing Comments - Gregory Reaman**

DR. REAMAN: Well, I just want to say thank you to all of you for participating in this. This meets and is the end of our statutory requirements for open public meetings, so for that I can congratulate you. But it clearly does not mark the end of the work that you have to do, that we have to do, and that industry sponsors have to do in implementing this. It's not easy. It's not going to be easy. And I think we've said, I've said during the day a few times, that this is really going to take collaboration and multistakeholder collaboration.
We see the statutory requirements to the agency on the creation of the molecular target lists maybe a little bit differently than they were intended because we I think prioritize the potential public health benefits of children a little bit higher than regulatory certainty. But at the same time, we don't want to make that prioritization of the public health of children at the expense of regulatory certainty.

We've tried to do this by defining molecular targets as broadly as possible and keeping the required evidence base as indiscriminate as possible. But I think we are clearly committed, to the concept of designating levels or grades of relevance so that we can provide a little bit more information to industry in their regulatory planning.

I think we're definitely committed to the concept of successfully and responsibly and effectively implementing Title V of FDARA in such a way that we don't jeopardize cancer drug development in general, and that we don't deprive
access to promising therapies by adults.

This is going to require continued to work. We're committed to engaging outside experts for advice. We clearly don't have all of the expertise and mechanism to define evidence bases for defining relevance. We don't have all the information that's required for decision-making with respect to how we implement these lists and decide whether or not we're going to need studies.

I think we did accomplish today, and I thank you for that, a list of relevant targets, a list of targets that will lead to waivers. And I think the concept of automatic waivers as we move from indication-based to mechanism of action or molecular mechanism of action-based triggers for PREAW has changed our concept and needs to change industry's concept of automatic waivers.

The list will be updated with some of the comments that we heard today. VEGF receptors will come off the automatic waiver list and go back to the relevant list, and we'll add the PTEN, KIT. RET is actually already there. We'll add
mutational burden, CCND1 and 2, STAT2, and we'll expand the MLL and ETS fusions. And the BRD4 NTM1 and BRD3 NTM1 I thought were on there; they're not. They'll be added also.

I think the other message is that we really need more industry academic investigator collaboration in the nonclinical or preclinical space. I would hope that we could emulate the European experience with the ITCC P4. And if ACCELERATE is willing to expand internationally, I would hope that the P4 platform could do the same.

We will work to our best capacity with ACCELERATE in priority setting, priority setting within the drugs that are available given the patient populations that we have to enroll on studies, as well as in the multiple in-class products. But I think we're going to need also another mechanism for coordination and collaboration internationally with early-phase evaluation of studies that hopefully will actually inform global development plans.

So again, thank you all for the discussion
and the input, but just to make it clear that your job's not done today because --

(Laughter.)

DR. REAMAN: -- we have until 2020 to actually successfully implement this. And we have started outlining a guidance for how we're going to implement this with which we will respectfully request some input as well, so thank you again.

Adjournment

DR. PAPPO: Thank you, Greg.

We will now adjourn the meeting. Panel members, please remember to drop off your name badge at the table, actually leave it over here, so that it can be recycled, and thank you very much.

(Whereupon, at 4:10 p.m., the meeting was adjourned.)