DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE

OF THE ONCOLOGY DRUGS ADVISORY COMMITTEE

Thursday, October 20, 2005

8:10 a.m.

Food and Drug Administration
Center for Drug Evaluation and Research
Advisory Committee Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

ODAC MEMBERS

Gregory H. Reaman, M.D.- CHAIR
Pamela J. Haylock, R.N.- [Consumer Representative]
Victoria Ferretti-Aceto-Acting Executive Secretary

CONSULTANTS AND GUESTS

Consultants

Jeffrey S. Barrett, Ph.D.
James M. Boyett, Ph.D.
Jerry Z. Finklestein, M.D.
Michael P. Link, M.D.
Charles P. Reynolds, M.D.
Victor M. Santana, M.D.
Cindy L. Schwartz, M.D.
Malcolm Smith, M.D., Ph.D.
Clinton F. Stewart, Ph.D.
Naomi J. Winick, M.D.

Patient Representative

Marilyn S. Eichner-Rockville, MD
Cathy A. O'Connell-Belchertown, MA

Industry Representative (non-voting)
Eugene Sun, M.D.

CENTER FOR DRUG EVALUATION & RESEARCH PARTICIPANTS

Richard Pazdur, M.D.
Karen Weiss, M.D.
Patricia Keegan, M.D.
Robert Justice, M.D.
Joseph Gootenberg, M.D.
Lisa Mathis, M.D.
Martin Cohen, M.D.
Jeff Summers, M.D.

NIH SPEAKER

Anne Zajicek, M.D., Pharm.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

CHAIRPERSON REAMAN: Good morning. I'd like to call to order this meeting of the Pediatric Oncology Subcommittee of the oncology Drugs Advisory Committee of the FDA--and welcome you all to this meeting that has been a bit of a hiatus in the scheduling of these meetings. And I think the real focus of today's session will be an educational and informational exchange one; on the mission and function of subcommittees in general, with a particular emphasis of the mission and function of the Pediatric Subcommittee; the reorganization of the FDA and the Office of Oncology Drug Products; regulatory and procedural issues related to post-marketing commitment studies and how they may impact pediatric drug development and clinical trials; two pieces of legislation which also impact pediatric drug development--the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act.

So I think this will be a very important

re-beginning of this committee. And I would like to start by having the committee members introduce themselves, going around the room. We can start with Dr. Sun.

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. FINKLESTEIN: I'm Jerry Finklestein. I'm a professor of Pediatrics at UCLA, and Chair of the DSMC for Phase I and II at COG. And I acknowledge the FDA audio-visual, because I'm facing all of you, and I have my own private TV screen.

[Laughter.]

DR. BOYETT: I'm sorry, Jerry, I can see it, too. So it's not only yours.

I'm James Boyett, Chair of Biostatistics at St. Jude Children's Research Hospital.

MS. HAYLOCK: I'm Pamela Haylock, oncology nurse and doctoral student, University of Texas Medical Branch in Galveston.

DR. WINICK: Naomi Winick, from the University of Texas-Southwestern Medical Center. I'm the Vice Chair for Clinical Trials for ALO, for

COG.

DR. LINK: I'm Michael Link. I'm a pediatric oncologist at Stanford.

DR. SCHWARTZ: Cindy Schwartz, I'm a professor of pediatrics at Brown, and a pediatric oncologist.

DR. BARRETT: Jeff Barrett, associate professor of pediatrics, University of Pennsylvania and Children's Hospital of Philadelphia.

MS. EICHNER: Marilyn Eichner, patient representative.

DR. FERRETTI-ACETO: Victoria Ferretti-Aceto, Executive Secretary of the Pediatric Oncology Subcommittee.

CHAIRPERSON REAMAN: I'm Greg Reaman, professor of pediatrics at George Washington University and the Children's Hospital, and chairman of the Children's Oncology Group.

MS. O'CONNELL: I'm Cathy O'Connell, patient representative.

DR. REYNOLDS: Pat Reynolds, professor of pediatrics, University of Southern California, and

head of developmental therapeutics at Children's Hospital of Los Angeles, and vice chairman for the COG.

DR. STEWART: my name is Clinton Stewart. I'm an associate member of the Department of Pharmaceutical Science at St. Jude Children's Research Hospital.

DR. SANTANA: Good morning, I'm Victor Santana. I'm a practicing pediatric oncologist at St. Jude Children's Research Hospital. And I'm chief for the solid tumor division.

DR. COHEN: I'm Martin Cohen, medical officer at FDA.

DR. KEEGAN: Trish Keegan, Director of the Division of Biologic Oncology Products at FDA.

DR. JUSTICE: Robert Justice, Acting Director, Division of Drug Oncology Products at FDA.

DR. WEISS: I'm Karen Weiss. I'm the Deputy Director of the Office of oncology Drug Products at FDA.

DR. PAZDUR: Richard Pazdur, Director of

the Office of Oncology Drug Products, FDA.

CHAIRPERSON REAMAN: I'm going to ask Dr. Ferretti-Aceto to read the conflict of interest statement.

Conflict of Interest Statement

DR. FERRETTI-ACETO: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S. C. Section 208(b)(3), a full waiver has been granted to Pamela Haylock, R.N., to participate in all official matters concerning (1) issues involved with the conduct of certain pediatric post-marketing studies for products approved for oncologic indications;

and (2) review status of studies for specific off-patent drugs for pediatric oncology for ownership of stock in a sponsor, valued from $25,001 to $50,000; and ownership of stock in a competitor valued from $5,001 to $25,000; this de minimis financial interest falls under 5 CFR part 2640.201 which is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

In addition, Victor Santana, M.D., and Tom Walsh, M.D., have been recused from participating in Neulasta (pegfilgrastim) portion of the meeting.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited industry representative, we would like to disclose that Eugene Sun, M.D., is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Sun is employed by Abbott Laboratories.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRPERSON REAMAN: Thank you. And we'll begin this morning's session with Dr. Weiss.

Opening Remarks

DR. WEISS: Good morning. And, like Dr. Reaman, I'd like to welcome everybody to this first in a little bit of time meeting of the Pediatric Subcommittee to the Oncology Drugs Advisory Committee.

I have a few just opening remarks about subcommittees in general, and this particular subcommittee.

[Slide.]

First of all, just to make it clear to people, there are a number of subcommittees to parent or standing advisory committees at the FDA.

Subcommittees, as a general kind of rule do not directly advise the FDA. They're actually advisory to the parent committee--in this case, you are advisory to ODAC, the parent committee.

Generally, subcommittees discuss and deliberate on issues and then, in turn, go back to the parent committee and provide their consensus and/or recommendations back to the parent committee, who then, in turn is the one committee that directly advises the FDA.

So in this particular case, for instance, at the next meeting of ODAC, we will probably ask Dr. Reaman, since he is a standing member of ODAC, to give a report back to ODAC on the discussions and input from this particular meeting.

Generally, subcommittees contain at least two members of the parent committee. Subcommittees, unlike the parent committees, do not have an official charter or roster, so there are no

particular standing members of subcommittees.

In general, there are a number of people who have expertise that the FDA could potentially use that are considered special government employees, and the idea is that for different meetings, we would draw upon that pool of expertise to constitute the individuals, depending on the specific topics and issues at hand.

[Slide.]

The Pediatric Subcommittee to ODAC was specifically sanctioned, if you will, under law under the Best Pharmaceuticals for Children Act--which you'll hear about in several different presentations during the day.

Under BPCA, the specific recommendations or role of the committee was to evaluate--and to the extent practicable--prioritize new and emerging therapeutic alternatives to treat pediatric cancer; to provide recommendations and guidance to ensure that children with cancer have timely access to the most promising new cancer therapeutics; and advise on ways to improve consistency in the availability

of new therapeutic agents.

And looking back over prior meetings, and even thoughts about upcoming meetings, I think that the agendas that we're thinking about or have actually already addressed probably fit the spirit of this particular subcommittee under BPCA.

[Slide.]

BPCA also goes on to talk a little bit about membership in the Pediatric Subcommittee. And it's probably not all that relevant, but it specifically says that there should not be more than 11 voting members from the Pediatric Pharmacology Advisory Committee and ODAC. As you can see, that's probably not going to be an issue; that there's not going to be more than 11 members of these other committees at any time.

And there, as necessary, individuals with expertise from the National Cancer institute; from the Children's Oncology Group and other pediatric experts or consortia; patient and patient-family community; one statistician--etcetera. And that's really the only specific guidance that there is in

the act about this particular subcommittee.

We're going to be coming back at the very end of the day to talk about issues in pediatric oncology and particular topics for discussions at this particular advisory meeting.

One thing I wanted to make clear to this group is that most likely new products that come for an approval for pediatric cancer indication would not be actually discussed before the subcommittee. They would generally got to the parent committee--to ODAC--with representation from pediatric oncologists, as relevant, to aid in the discussions and the deliberations.

And one of the main reasons for this is because, as I said in my earlier slide, subcommittees don't directly advise FDA. We have very specific to do for our government-dated timelines, for when we need to complete reviews. And so scheduling and meeting of the pediatric subcommittee to discuss a pediatric oncology application that's coming before the FDA, would necessitate then having to schedule another meeting

of the ODAC--of the parent committee--to actually give specific advice to the FDA. So, logistically, it becomes extremely difficult to do.

But we do believe that this committee is very, very relevant to advise the agency on specific issues related to pediatric cancers, as you will be discussing in the sessions to come, to help us to advise and prioritize on off-patent drugs under the BPCA process; to give us advice on development of specific pediatric cancer-type topics; possibly discuss issues such as animal models-which I know were discussed at a prior meeting; possibly ethical issues.

There are number of topics that I want you to be thinking about that might be relevant to bring to this committee in future meetings. And, as I've said, we'll come back to this at the end.

And, with that, I'd like to things over to Dr. Richard Pazdur, who will just give this committee a brief overview of the changes in CDER.

Introduction of CDER's Office of Oncology Products

DR. PAZDUR: Thank you, Karen.

I'd just like to be brief and kind of go over the restructuring of Oncology at the FDA.

[Slide.]

Over the past year or so, the considerable attention within the FDA to really look at how oncology products, both drugs, biologics, devices, etcetera, are reviewed by the FDA. And recently, there has been a coordinated effort to establish an Office of Oncology Drug Products within CDER--the Center for Drug Evaluation and Therapy [sic].

So this is the schematic picture o the Office of Oncology Drug Products--which I head. There are several portions of this, and it's listed here.

The review functions--basically looking at drugs, biologics and hematological products and imaging--are listed on these slides. And they would encompass what traditionally the FDA has done, as far as looking at products--both INDs and NDAs.

The kind of unique features of this office that are not present in other review divisions or

review offices in the FDA is an Oncology Program function that I want to talk a little bit about, and then also an RDC program.

[Slide.]

The Oncology Program is an effort by the FDA to coordinate activities within the FDA, and also to coordinate activities with external stakeholders. And let me address this on two parts.

Within the FDA there are still oncology products that are handled by CDER. These include tumor vaccines and cellular products--obviously, devices that are used by medical oncologists; pumps, infusion catheters are reviewed by the Center--CDRH. And, because of this, we felt that we needed a very consolidated consultation service and communication within the agency, which this Oncology Program will function.

Also, within CDER itself--the Center for Drug Evaluation--there are oncology-related programs that are not in this office. They would include medications such as pain medications that

are used by medical oncologists and by oncology patients, as well as anti-emetics, for example, and supportive care products. And, here again, the nature of this program is to coordinate the communications within the FDA regarding these supportive care products.

[Slide.]

The Oncology Program itself--the coordinating function here--is primarily composed of project managers. We have a staff--or will have a staff--of approximately four to five project managers. Our goal here is really to utilize the existing professional staff--M.D.s, Ph.D.s--that we have in the FDA to communicate our message. And basically the Oncology Program services to coordinate the various speaking engagements, as well as message to the external stakeholders.

We have various internal activities that I stated before. These include coordination of various policy statements within CDER and across the agency; and also external activities to our various stakeholders, which include, obviously,

practicing physicians, patients, other government agencies, and both pharmaceutical and biotechnology constituents.

[Slide.]

The Radioactive Drug Research Committee is headed--or the function within the FDA, I should say--is headed by Dr. Orhen Sulleimen, who is sitting right there. And perhaps he'd like to raise his hand. And if you have any questions, I'm sure he'd be happy to answer.

For those of you that are unfamiliar with this committee, basically it was established in 1975 to look at research activities that fall within the RDRC purview. These would include basic science research of radioactive drugs; looking at research where there are specific radiation dose limits, where there's no pharmacological effect. And, basically, the FDA looks and examines these committees, and also approves committee members.

The responsibilities are listed on this slide, and they include the review and approval of research protocols with the IRB concurrence, and to

submit various regulatory reports to the FDA.

[Slide.]

The specifics of the RDRC program within the FDA--it basically reviews the qualifications of proposed members to each institution's RDRC. It approves institutional RDRCs. It reviews their annual reports and provides technical support to FDA inspectors of the various institutional programs.

[Slide.]

And here is just a list of the activity. And you can see there's probably increasing activity--and we expect increasing activity--in this area.

[Slide.]

The other division within this office, are basically what I would call more traditional review functions, as I stated before.

The Division of Drug Oncology Products--the Acting Director is Bob Justice, who's sitting there. Bob--you want to raise your hand and say hi?

And basically this is the review, or this division has the review responsibilities of most people consider "traditional" oncology drugs. They

include older chemotherapy agents, or classical chemotherapy agents, either looking for new indications or new formulations, or newer agents such as small molecules aimed out anti-angiogenesis, or TK inhibitors.

They also have the function now of looking at the area of cancer chemo prevention. Before the office was incorporated in the FDA, many of the chemo prevention applications were dispersed throughout the various review offices and divisions. And now we have a concerted effort to have all of the chemo prevention applications coming to one division, and that would be the Division of Drug Oncology Products.

[Slide.]

The other review division is the Division of Biological Oncology Products. And Pat is there. She is waving.

And basically this division had

incorporated and moved over, basically, from CBER several years ago. They review products such as therapeutic proteins, monoclonal antibodies. Examples are here listed on the slides.

Just for clarification, tumor vaccines and cellular and gene therapy remain in CBER.

I'd like to emphasize, however: we are in close communication with CBER. We have monthly coordinating meetings. And part of the Oncology Program that I mentioned before is an effort to coordinate these activities of the remaining products that do not reside within the new office.

[Slide.]

We also have a Division of Medical Imaging and Hematological Products. The hematological products here that I'm talking about are basically applications that are not oncological. They might include, for example, iron chelating agents, products for hemophilia, benign indications rather than the malignant aspect of hematology.

This division is headed by George Mills. It also includes various imaging products such as

PET products, etcetera.

So that's kind of the office structure.

We really are in a process here--I should mention--of kind of evolution. And I do want to emphasize this. This process has begun, and we are really looking at really how we can improve both the communication with the external stakeholders that we have, as well as really to facilitate and have a common message to all stakeholders that emanate from the FDA.

Thank you very much.

CHAIRPERSON REAMAN: Maybe before going on to the next part of our program--if there are questions for either Dr. Pazdur or Dr. Weiss about mission, charge, organization of the Office of Oncology Drug Products?

[No response.]

If not, then we'll go on with the next part of this morning's program, which relates to the issue of post-marketing commitment studies; and, specifically, with the recently approved drug for a pediatric indication--Clolar, or clofarabine.

And, Dr. Martin Cohen from the FDA will present.

Accelerated Approval and Clolar (clofarabine)

Required Confirmatory Trials

FDA Presentation

DR. COHEN: Good morning. I'm Martin Cohen.

[Slide.]

And the NDA being reviewed today is No. 21-673. The study drug is clofarabine, which, structurally is cloro-fluora-Ara-A. The sponsor is Genzyme corporation.

This application was presented to ODAC on December 1, 2004. The committee recommended accelerated approval under Subpart H for acute lymphoblastic leukemia, or ALL, by a vote of nine yes and six no. Clofarabine received accelerated approval from the FDA on December 28, 2004.

And as you are aware, accelerated approval is based on a surrogate endpoint that is reasonably likely to predict clinical benefit. In the case of clofarabine, te surrogate endpoint was complete response rate, with or without platelet recovery.

[Slide.]

The indication for this NDA is that clofarabine is indicated for the treatment of

pediatric patients one to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.

As previously mentioned, clofarabine's accelerated approval was based on the induction of complete responses. Post-approval randomized trials to demonstrate increased survival, or other clinical benefit, as required by the Subpart H legislation, are the subject of today's meeting.

[Slide.]

The recommended clofarabine pediatric dose and schedule are indicated on this slide. A dose of 52 mg/m 2 is administered intravenously over one to two hours daily for five consecutive days. Clofarabine treatment cycles are repeated every two to six weeks following recovery to acceptable organ function.

[Slide.]

The pertinent clinical trials in the NDA

submission are summarized on this slide. There was one Phase II trial conducted by the sponsor in pediatric ALL that enrolled 49 patients. In addition, there was a pediatric Phase I study conducted at the M.D. Anderson Cancer Center that included 17 ALL patients.

In this presentation, I will focus on the sponsor's Phase II study. It should be noted, however, that complete response were also observed in the Phase I study.

[Slide.]

The primary objective of the Phase II study was to determine the complete response rate and the complete response rate in the absence of platelet recovery; that is the CRp.

Complete response required no circulating blasts, no extramedullary disease, an M1 bone marrow defined as having less than 5 percent lymphoblasts. There also had to be recovery of peripheral blood counts to a level of greater than or equal to 100,000 platelets/mcL, and an absolutely neutrophil count greater than or equal

to 1,000/mcL.

A complete response in the absence of platelet recover meets all the criteria of a CR, except that the peripheral blood platelet count has not recovered to 100,000/mcL.

[Slide.]

Study inclusion criteria for the Phase II ALL study included an age less than or equal to 21 years, and a presence of greater than or equal to 25 percent bone marrow blasts. Eligible ALL patients were in their second or subsequent relapse, and/or they were refractory, having failed to achieve a remission following two or more different regimens.

Patients had an ambulatory performance status, and had adequate bone marrow, liver and renal function.

[Slide.]

A total of 14 United States sites participated in the pediatric Phase II ALL study. And independent response review panel was established to confirm response to therapy for each

patient; and independent pathology review was also available.

[Slide.]

Demographics and Karnofsky Performance Status of participating patients in the Phase II acute lymphoblastic leukemia study are summarized on this slid.

A total of 49 patients were enrolled and treated. As indicated, the median age was 12, and ranged between one year and 20 years. Approximately 40 percent of patients were female; 60 percent male. Hispanic and Caucasian patients comprised the bulk of the study population.

Despite the fact that patients had relapsed and/or were refractory to two or more prior regimens, performance status was good, with 31 percent of patients having a Karnofsky Performance Status of 100, and 39 percent a Karnofsky Performance Status of 90 or 80.

[Slide.]

Therapies administered prior to entry into the clofarabine ALL study are listed on this slide.

The median number of prior induction regimens was three, with a range of two to six. A total of 15 of the 49 patients--or 31 percent--had received at least one transplant before study entry; 13 of the 49--or 27 percent--having received one prior transplant, and two of the 49--or 4 percent--having received two prior transplants.

[Slide.]

Best response to clofarabine therapy, as judged by the independent response review committee, and confirmed by FDA, is shown on this slide. There were six complete responses--or 12.2 percent; and four complete responses in the absence of platelet recovery--or 8.2 percent.

Four of the 10 responders went on to transplant, including one of the six CR patients, and three of the four CRp patients.

[Slide.]

For patients who were not transplanted, clofarabine response duration, in days, are listed on this slide. There were five patients with a complete response, and one patient with a CRp who

were not transplanted.

Response durations for non-transplanted CR patients were 43, 50, 82, 93-plus, and 160-plus days. Response duration for the non-transplanted CRp patient was 32 days.

[Slide.]

Turning now to safety, and to summarize safety: toxicity was as expected for a heavily pre-treated relapsed/refractory acute leukemia population who were receiving cytotoxic therapy. The principal toxicities were gastrointestinal--including nausea, vomiting and diarrhea. As expected, there was hematologic toxicity, accompanied by fever and febrile neutropenia. There was hepatobiliary toxicity. There were infections and renal toxicity.

Systemic inflammatory response syndrom, tumor lysis syndrom, multi-organ failure, hypotension, and left ventricular systolic dysfunction also occurred.

To summarize the efficacy results for the study population--relapsed/refractory pediatric

acute lymphoblastic leukemia patients, there were six CRs and 4 CRPs among 49 treated patients. The overall CR-plus-CRp rate was 20.4 percent.

Transplantation was performed in one CR patient and in three CRp patients. In transplanted patients, response duration and survival are determined by both clofarabine and by the transplant. The effect of clofarabine cannot be isolated.

Because clinical benefit could not be conclusively demonstrated in the submitted Phase II single-arm trial, appropriately designed randomized trials, perhaps in the less advanced patient population, will be necessary. These Phase IV commitments are the subject of the sponsor's presentation.

CHAIRPERSON REAMAN: Thank you, Dr. Cohen.

For Genzyme, Dr. Abichandani.

Genzyme Presentation

DR. ABICHANDANI: Good morning. O behalf of Genzyme, I'd like to thank you for giving us the opportunity to provide an update on our Phase IV

commitments for clofarabine.

[Slide.]

This slide shows the participants who are here with me today, and I may call upon to answer any questions that may arise.

[Slide.]

Our agenda for today is as follows: I will provide a brief introduction to relapsed leukemia and clofarabine, followed by a pre-approval clinical development highlights, our post-approval clinical development plans, risks and challenges, and summary.

[Slide.]

Great strides have been made in the treatment of acute leukemias, and currently the treatments for newly diagnosed -patients with ALL use very aggressive multi-drug regimens, and yet 21 percent of patients with ALL will have relapsed or refractory disease, making relapsed leukemia the third most common childhood cancer.

[Slide.]

This slide shows the annual incidence of

pediatric ALL using SEER data. As you can see, among the nearly 2,500 children diagnosed with pediatric ALL each year, nearly 500 children will have either relapsed or refractory disease. And just note that the patients who have second or subsequent relapse are a further subset of this population.

[Slide.]

There are many challenges in treating these children. It's a very heterogeneous population. Multi-drug resistance is common. And dose intensification with combination therapies has resulted in significant co-morbidities and organ dysfunction. Transplant is the best curative option, but it requires disease control and time to identify a donor.

[Slide.]

Clofarabine is the first drug that was specifically approved for pediatric leukemia in 20 years. The most commonly used agents were approved many years ago and, in general, development of new pediatric oncology agents has lagged behind adult

oncology drug development.

[Slide.]

Clofarabine is a second-generation purine analog. It is resistant to deamination, which make increase its intracellular triphosphate levels. In addition, the metabolites of clofarabine are not neurotoxic, unlike other agents in its class.

While the mechanism of clofarabine is not fully understood, clofarabine is converted to its triphosphate form to be active within cells. It inhibits DNA synthesis and repair. In addition, clofarabine disrupts mitochondrial integrity, leading to cytochrome release and programmed cell death.

[Slide.]

Let's move on to our preclinical development here. This slide shows the timeline, and a list of the pediatric studies, and the adults studies down here.

The first Phase I pediatric study was carried out at M.D. Anderson in 2000. This was followed by two Phase II studies, one in AML and

another one in ALL in 2002. And although we are here to talk about the pediatric development, we've also listed the adult studies that have been conducted to date.

Due to the impressive activity of clofarabine seen in pediatric patients, the sponsor at the time--Ilex--decided to accelerate its pediatric development in advance of its adult development program.

[Slide.]

Reviewing some of the key regulatory milestones for clofarabine: clofarabine received orphan drug designation in February 2002. And I apologize that your handout says 2003. It's an error on our part.

A rolling NDA submission was completed in March of 2004, and contained data on both ALL and AML patients. Following that, an efficacy update was submitted to FDA in August.

And after review of the drug evolved the questions that arose were the durability of remission, and the fact that many patients

proceeded to receiving a transplant, which could be a confounding issue.

On 1st December 2004, FA asked ODAC if clofarabine should receive accelerated approval for ALL and AML. ODAC felt that it should receive accelerated approval for ALL, but felt that the AML data was too severely confounded by patients proceeding to transplant prior to achieving complete remission.

On 28 December, FDA then granted clofarabine approval for relapsed ALL.

[Slide.]

So, to recap the basis for approval, for efficacy it was a single Phase II study of 49 patients who had second or subsequent relapse, or were refractory to re-induction. Clofarabine was used as a single agent, and the endpoint was overall response rate, which is CR plus CRp.

In addition, a safety submission was also done to support the NDA filing which contained safety information on 113 pediatric leukemic patients.

[Slide.]

FDA granted marketing approval for clofarabine for the treatment of pediatric patients

with relapsed or refractory ALL after at least two prior regimens. This approval was under the provisions of accelerated approval, and based on the induction of complete responses.

The sponsor is now required to conduct a randomized Phase III post-marketing study demonstrating clinical benefit.

[Slide.]

Let's move on now to our current clinical development plan.

This was the plan that was originally submitted to FDA after ODAC. The plan has since then been revised, but I'd like to still talk about it because it is relevant to our discussion today.

Since the treatment for ALL involves multi-drug regimen, any further development would have to incorporate clofarabine with other agents known to be active in acute leukemia.

As a first step, Genzyme would have

performed a Phase « dose escalation study of clofarabine in combination with Ara-C and L-asparaginase in refractory or relapsed ALL. As a second step, we would perform a Phase III study of Ara-C and L-asparaginase with or without clofarabine in pediatric ALL in first relapse.

This protocol was based on a Children's Oncology Group protocol AALL01P2, which had an innovative yet complicated multi-agent design.

[Slide.]

The proposed study would have taken patients at first relapse, who would have then received two non-overlapping drugs of intensive chemotherapy after which they would be either randomized to receive Ara-C or L-asparaginase, or Ara-C L-asparaginase in combination with clofarabine.

[Slide.]

FDA agreed to the Phase I/II combination study, but stated that the Phase III study does not appear to have a realistic chance of showing clinical benefit of clofarabine in children with

ALL in first relapse.

Genzyme's understanding is that the complex multi-agent design would make it difficult to isolate the clinical benefit of clofarabine. And this is a challenge that we face, because the Children's Oncology Group protocol was designed to find the best multi-agent therapy for these patients, and how do we balance that with our regulatory need to isolate and demonstrate clinical benefit with clofarabine?

[Slide.]

In addition, we ran into other problems that the clofarabine-Ara-C-L-asparaginase combination did not have wide investigator support. There were potential toxicity concerns; the combination of Ara-C and L-asparaginase is already maximally toxic, and thus they felt we may be able to effectively dose-escalate clofarabine.

Subsequently, a revised post-approval plan was submitted to FDA in March, and we met with them in April to discuss the plan, as well.

We are no longer conducting the

Clor-Ara-C-L-asparaginase study and, as a first step, we would be conducting at least Phase I/II combination studies. And the reason to do that is, at the and of the study, we'd like to choose the optimal combination going forward into our Phase III study.

The first study is a clofarabine study in combination with cyclophosphamide and etoposide, which is being conducted by Genzyme corporation. And the second study is a CLO-Ara-C combination which will be conducted in collaboration with the Children's Oncology Group.

As a second step, we would build from the Phase I/II results to design an appropriate randomized Phase III study to demonstrate clinical benefit, using one of the two combinations we've just spoken about.

[Slide.]

The patient population for the Phase III study could potentially be either patients in first relapse, or patients who are in second or subsequent relapse, or in first relapse and

refractory to re-induction.

Potential endpoints are--the first one is event-free survival, and our submission contained specifically four-month event-free survival as an endpoint. And that's one of the questions that's being posed to the Committee today.

The other endpoints are remission duration, and rate of remission, overall survival. And FDA and Genzyme will discuss the details of the Phase III study once we have data available from the Phase I/II studies.

[Slide.]

This slide shows the post-approval development timeline. In 2005, two new pediatric studies are being initiated. The first Phase I/II study has been initiated. The second CLO-Ara-C study, which is being conducted in collaboration with the Children's Oncology Group, the protocol has been finalized. WE anticipate starting up Phase III study in 2007.

In addition, there are two new adult studies in development for 2006, pending discussion

with the agency.

[Slide.]

There are some risks and challenges to our development plan. First, there are no standard chemotherapeutic options in second or subsequent relapse or refractory disease--making it very difficult for us to have a standard comparator arm.

Secondly, defining an appropriate endpoint for a Phase III study is difficult. Allogenic stem cell transplant is the only potential curative option for these children, and they deserve a chance to have it if they are candidates. However, it becomes very difficult to assess clinical benefit in the setting of a transplant.

And, finally, this is a very small patient population. There are only about 500 patients per year at first or subsequent relapse, and second or subsequent relapse are an even smaller subset of this group. There are other competing clinical trials, making it difficult to enroll a Phase III in a reasonable timeframe.

[Slide.]

In summary, in the 10 months since receiving approval, Genzyme has made progress towards meeting its post-marketing commitment. An

initial plan was proposed and required revision. One Phase I/II trial has been initiated. The second Phase II protocol has been finalized.

There are many challenges to designing an appropriate confirmatory trial in this population, but we look forward to collaborating with FDA and Children's Oncology Group to face these challenges.

That concludes our presentation, and we would be happy to take any questions.

Thank you.

Questions from the Subcommittee and Discussion

CHAIRPERSON REAMAN: Are there questions for the sponsor?

DR. FINKLESTEIN: Well, I want to congratulate you on the talk, because what you did is you pinpointed the problem we have in pediatric oncology in studying new drugs.

You also pinpointed some of the regulatory requests, which may not be appropriate for

pediatric oncology. And I mention these two statements because I really would also like to hear from my colleagues in pediatric oncology, because we've been struggling this throughout my whole career.

And then I'll come back.

CHAIRPERSON REAMAN: comments? Follow-up to Dr. Finklestein's statement?

DR. SANTANA: I think part of the problem, Jerry--part of the problem is the patient numbers; that the regulatory requirement sometimes imposes a large number of patients, like in Phase III-type randomized trials. And for populations like this, in which, unfortunately, there may be other alternative therapies--whether proven or unproven is not the issue. Other alternative therapies that we recommend to patients, that the pool becomes smaller and smaller.

So even with a consensus of all of us agreeing that x-disease should have a Phase Iii randomized trial, sometimes it takes five to seven years to get those trials. That's been the history

in pediatric oncology.

So I think the agency needs to recognize that the deadline, in terms of timeframe of our ability to get the patients and to complete the studies.

CHAIRPERSON REAMAN: I think that is a good point. I mean, numbers are certainly a consideration--and an important consideration. And I think the problem is not just related to regulatory requirements. I think there's an equally important problem on the part of pediatric oncologists who persist in actually continuing to recommend conventional therapies for multiply-relapsed patients, and multiple transplant for patients who relapse following a first transplant.

I'm not aware of any published data that lends credence to that as a continued practice. So moving that patient population to explore new agents that may actually contribute significantly to improved, event-free survival I think is hampered greatly by us.

And I think we really need to help change that, as well.

And perhaps event-free survival isn't the

perfect endpoint for these studies, particularly if we're going to be looking at patients in first relapse, who may actually, after obtaining remission or disease control, then proceed to marrow transplantation.

So--are there alternative endpoints in specific pediatric diseases which we might consider recommending to ODAC and to the FDA for specific pediatric cancers?

DR. WINICK: Just a couple specific questions.

It looks like the eligibility criteria for both the clofarabine and the Ara-C trial, and the VP 16 cycloclofarabine are identical.

DR. ABICHANDANI: We tried to make them pretty consistent, because we like to have studies at the end to be pretty comparable. We have been working with Children's Oncology Group to make sure

that the inclusion/exclusion criteria are pretty similar.

DR. WINICK: So both will be open to the same population?

DR. ABICHANDANI: Yes.

DR. WINICK: And have there already been discussions as to prioritization? Because everyone's already raised the issue: the numbers problems are significant.

DR. ABICHANDANI: Right--we have not--you know, it's really up to the physicians site to site, where they would enroll the patients. The CLO-etoposide-cyclophosphamide study has already been initiated. But the CLO-Ara-C study, the protocol is still not finalized. It's been finalized, it's not been initiated yet.

So my guess is, you know, probably patients would probably get first enrolled in the CLO-etoposide-cyclophosphamide study as it's opened up.

DR. WINICK: And the clofarabine-Ara-C trial has no--it's strictly a Phase II. There's no

dose--

DR. ABICHANDANI: There is a dose-escalation. It's 30, 40, and 50. So there are three doses there. But, in terms of, you just call it a Phase II study. But there is a dose-escalation in there.

DR. WINICK: Okay.

CHAIRPERSON REAMAN: Could I just ask: the Genzyme sponsored study will include ALL and AML patients?

DR. ABICHANDANI: The Phase I portion will have ALL and AML. But the Phase II portion will be ALL only.

CHAIRPERSON REAMAN: Because the COG study will be for both ALL and AML?

DR. ABICHANDANI: And AML.

CHAIRPERSON REAMAN: And what are your plans, then, for comparing outcome results between the two?

DR. ABICHANDANI: We will only compare ALL, because our indication is ALL, and our post-marketing commitments are in ALL.

So the Genzyme-sponsored study--the Phase II portion--is only in ALL. Children's Oncology Group wanted to study in ALL and AML, but we will

compare the efficacy--analyze the efficacy for ALL separately.

CHAIRPERSON REAMAN: And then what are your development plans after these two Phase II studies? Do you intend to compare the results of separate studies? And how do you plan to do that? And what combination of more conventional or standard previously-approved agents effective in ALL will you combine clofarabine?

DR. ABICHANDANI: For the Phase III study?

Well, that's one of the issues. I mean, that's one of the questions to the committee today, I think also, is: potentially one could envision a Phase III study--let's say the CLO-etoposide-cyclophosphamide combination looked better, we could randomize patients to receive either CLO-etoposide-cyclophosphamide or etoposide and cyclophosphamide alone.

But again, the question is in which

population would you go in: first relapse or second relapse? The first relapse, one of the challenges we ran into was the Children's Oncology Group protocol, which was the original plan that was submitted to FDA, it had such a complex study design that they felt it would not be appropriate to study the clinical benefit of clofarabine.

The numbers are small. If you don't do a study like that, it's hard to find the patient numbers to design an appropriate trial in that population. So that sort of made us go to second or subsequent relapse then.

DR. LINK: Is there a scientific rationale or preclinical data for why you decided to combine clofarabine with cyterabine? I mean, why pursue--is there anything that underpins that? Because we didn't see that?

DR. ABICHANDANI: Actually, if you want, we can--hold on.

[Slide.]

There is some preclinical data to support the use of clofarabine and Ara-C. And there's also

clinical data--actually in adult patients, not in pediatric patients, though.

So there was nothing--it's not been studied in the pediatric population before, but we feel the data is compelling enough to study it in the pediatric patient.

DR. LINK: I'm going to ask the same question about the cytoxin and etoposide. I mean, I was aware of the cyterabine, but what--

DR. ABICHANDANI: Well, the risks of preclinical data were they had--

[Slide.]

So this is some slides just showing the CLO-Ara-C combination. So there is some preclinical data to support it. So there is some in vitro studies show that clofarabine--that the 4 Ara-C resulted in increase in Ara-CDP formation. And, as I mentioned, there is a combination study in adult patients which shows, in ALL, AML, and MDS and CML patients.

Again, it's not been studied in the pediatric population, but we feel it's compelling

enough to study in this population.

DR. LINK: [Off mike.] [Inaudible.]

DR. ABICHANDANI: Clofarabine.

DR. REYNOLDS: I'd like to ask a little bit more about your non-clinical data.

One of the approaches that the COG has taken with the NCI is doing more defined preclinical data to prioritize how one's going to approach the clinical situation. And there's a pediatric preclinical testing program, for example, which was brought up by the BCPA by Congress, and funded by the NCI to do formal evaluation of agents.

Have you considered doing a more formal preclinical testing program to decide what your real--you know, the best approach to doing your clinical trials is, rather than just doing a series of Phase I trials?

DR. ABICHANDANI: We'll call on Dr. Vasconcelles to answer that question.

DR. VASCONCELLES: Thank you, Rekha.

Yes--and maybe we can find a backup slide

for the cyclophosphamide-etoposide combination, as well--but that certainly is a component of our program. We've not reached out particularly to that program, and most of that work has been either internal, or with the group that originally synthesized clofarabine at the Southern Research Institute.

But we do have an interest and an on-going program internally to further look at potential combinations as we think about further development in acute leukemias and, more broadly, in hematologic malignancies-and even potentially in sold tumors.

So we'd be glad to have further discussions inside the context of this meeting about how we might augment that work that's ongoing at Genzyme.

[Slide.]

This slide that Rekha just put up simply provides a little bit of the rationale to support clofarabine's use in combination with cyclophosphamide and etoposide. And this is really

preclinical data, looking at work with alkylating agents, primarily in the incorporation of intracellular triphosphate modified clofarabine incorporation DNA in the setting of alkylater therapy, and some supportive additive. That's noted in the combination, which is some of the preclinical data that supports that combination.

CHAIRPERSON REAMAN: I would just echo Dr. Reynolds' comment about the existence of the preclinical testing program, and also raise the issue of: are the results--the data from preclinical evaluations in CLL directly transportable to ALL in children? And I think there are opportunities, given the robust resources of specimens that are available for the appropriate testing in the disease that's in question here--childhood ALL--that those kinds of studies cold be done.

Because I think doing a series of Phase I and Phase II studies in a very small patient population, given the difficulties that we've already mentioned, is not going to really benefit

the appropriate development of what could be a promising agent.

DR. REYNOLDS: I'd just like to add to that: this addresses Jerry's original question. I mean, we have this problem of small numbers of patients. And that's why preclinical--we would admit that there's no validated models at this point. Hopefully, at some point there will be.

But using preclinical testing to really refine what you're going to do in the clinic is probably the only way that you can do pediatric oncology studies.

CHAIRPERSON REAMAN: Victor, did you have a question?

DR. SANTANA: Yes, I want to get back to an earlier point to make clarification. I think Dr. Link kind of asked this question.

There is some pediatric data in AML, a combination of Ara-C and another nucleoside--not this particular drug. And in that model of pediatric AML, there is intracellular modulation of nucleosides generated by the combination of those

two nucleosides. But it's not this drug, it's another drug.

DR. BARRETT: Based on the background package and your presentation of the dose-escalation scheme for that first Phase I trial, the escalation for etoposide and cyclophosphamide precedes the clofarabine.

Do you think there's a likelihood that you may not get to do the dose-escalation because of the usual way that the NTD is declared?

DR. ABICHANDANI: It is a possibility.

DR. BARRETT: Is there any assurance that you can go back and study those higher doses with, perhaps, a different range with the etoposide?

DR. VASCONCELLES: There was, as you might imagine, a reasonable amount of discussion about the appropriate way to attempt to dose-escalate the clofarabine. The thinking, frankly, was that if we can't get the standard--the combination that's at least a standard combination utilized in the current approach in first relapse, then we really needed to think about the utility of moving forward

with the three-drug combination--thinking, again, about the next step of potentially comparing the three-drug combination in some fashion: either in isolation or in a more complex protocol regimen, such that if the etoposide and cyclophosphamide doses weren't equivalent, that obviously would raise questions about the comparability of the two-drug combination versus the three-drug combination.

So, that was some of the rationale that led to how we put together the dose-escalation schema. But I certainly recognize your point.

There's a lot of enthusiasm about the potential activity of clofarabine and some of the investigators involved in the study were concerned that we'd reach exactly that issue, and I think we'd have to step back and think about how to deal with that if we saw toxicity prior to being able to dose-escalate clofarabine adequately.

I will point out that in adults, the maximal tolerated dose that has been identified in Phase II studies is lower, at 40 mg/m

2. And so

there's clearly activity of the compound at that dose level.

CHAIRPERSON REAMAN: Malcolm?

DR. SMITH: Several questions. One is: are there data about the immunophenotype of the patients, in terms of responses? Is this B-precursor versus t-cell?

DR. VASCONCELLES: We've looked at that in a small-cohort study, and there's no correlation that we've yet to identify. Of course, that's something we'll continue to look at for development.

DR. SMITH: And in the preclinical data, do they support one or the other?

DR. VASCONCELLES: No.

DR. SMITH: Another question follows up on a point Dr. Cohen raised, was that the Phase IV commitment can be in an earlier stage of disease. And, you know, often in pediatric leukemia research, you know, you identify activity in the relapse setting, and then you move forward to the newly-diagnosed setting to try to see if you can

cure more patients de novo, rather than waiting for relapse.

So I wonder if that's an issue that you considered. And I'd be interested in the other members' ideas on that, as well.

DR. VASCONCELLES: It is--and it's an issue that we'd like to continue to consider--and really welcome this form to have input into that.

As Rekha reviewed in the context of her comments, I think that we recognize some of the complexities in terms of what we know about the current treatment paradigms earlier and earlier in the care of patients, and how we can satisfy our regulatory requirements, and also bring clofarabine further up in the care of patients with ALL.

DR. WINICK: This is something that we've actually discussed in great detail--not necessarily with Genzyme, but certainly among the committee members. And I'm afraid that the number of patients becomes an issue, even if you move things up earlier.

We do have a very high-risk protocol. And

one of the difficulties is that the very high risk group in pediatric ALL is fairly clearly divided between those that are Philadelphia-chromosome-positive, and those that are not.

And for those that are Philadelphia-chromosome-positive we hope to be exploring new agents along the lines of the tyrosine kinase inhibitors--not necessarily a more classic cytotoxic agent like clofarabine. Among the patients who are not Philadelphia-chromosome-positive we don't have a large enough number to do a randomized trial in a reasonable period of time.

We are still in ongoing discussions about the use of surrogate endpoints, and this gets into a much larger conversation as to whether or not a change in the slope of disappearance of minimal residual disease at a point relatively early on in therapy is an acceptable surrogate marker of response.

But I think, you know, as Dr. Smith

brought up, I think those conversations are ongoing, because the proposal, as is, describing the accrual of 30 patients with AML and 20 with ALL annually within the Children's Oncology Group, looking at patients in refractory first relapse, or second and third relapse, whereas I understand that we should be able to generate those numbers for clinical trials.

I hate to say this, but we haven't.

CHAIRPERSON REAMAN: Jerry.

DR. FINKLESTEIN: I indicated I've come this is sort of a full circle, which was my original remarks.

I agree with Greg, which is--and I'm not a transplanter--is that the transplant group in pediatric oncology has made that sort of the sine qua non in how you manage a patient in relapse. And we have to discuss that amongst our group.

I also agree with Malcolm-if I'm interpreting you correctly--which is: the regulatory issue of demanding or requesting the

Phase III study may not be appropriate in pediatric for this type of drug. And this is a new drug that received approval. And in pediatric oncology we struggled for decades on whether we even need approval for drugs. And now that we have approval, should we be looking--maybe this committee to advise the parent committee--at what is the regulatory issue, and does it really apply to pediatrics?

I think it's apparent this drug is active. I have no stock in Genzyme. I'm just looking at it, and it's active.

The next question is: where does it fit into pediatric oncology? And I agree with Malcolm, our traditional approach has been to move the drugs up earlier.

I agree that we should be looking at animal models. But I remember when L-asparaginase came in. We just plunked it in into remission-induction, and all of a sudden L-asparaginase increased our remission induction.

Well, you won't be able to do that with a

95 percent induction rate, but you may be able to plug this in in consolidation.

I don't see a Phase III study in relapsed patients ever being completed. And so therefore I ask this committee to struggle with: what is the appropriate approach for a new drug n pediatric oncology, and should we not be thinking of something innovative?

CHAIRPERSON REAMAN: Well, I think that's a good point. But I want to actually address part of your comment which related to approval. And I think there is approval, and there is approval.

And the approval of a new drug is for purposes of marketing a new agent, not necessarily for approval of its use by physicians once it's marketed for a specific indication.

But maybe the FDA could, in fact, comment on that?

DR. PAZDUR: Well, you know Jerry brought up the idea of "activity," and the approval process is not just to identify "activity" or a drug; it's to carry that a step further. For full approval of

a drug, you should have demonstrated clinical benefit of the drug.

So the approval process is not a screening process to determine whether a drug has a marginal response rate here. One has to feel comfortable that this drug will lead to clinical benefit. The whole purpose with accelerated approval program was to identify drugs early on in life-threatening diseases that appear to be better than available therapy. And in these certain situations, where we're dealing with very refractory situations, we have single-arm trials that look at therapies that are non-existent. There are no other therapies here.

So, in general, when we took a look at this accelerated approval program, the issue here is to identify agents, but then to further develop them here.

So I think the committee has to grapple with: is this all this drug is, is a 10 percent response rate in a refractory disease setting? Or should it be developed further?--you know--and how

that is going to be developed further.

If you take a look at most of the agents in adult oncology, when we entered into this program, some of the earlier agents--for example camptizor in colorectal carcinoma--had a 15 percent response rate in refractory disease patients. It went on into the first-line setting to show a survival advantage in metastatic disease.

So that's kind of the paradigm that we have been hoping for, to identify agents in a refractory disease population, and that these drugs would be further developed and become real players in the treatment of malignant diseases.

CHAIRPERSON REAMAN: Understanding that, then, I think it would be worth going back to Jerry's point--or multiple points that have been made: is this the right population to be evaluating to see if this drug, or other drugs like it, can in fact be incorporated into therapy regimens for specific diseases?

Looking at multiply relapsed patients--again, may end up giving us the same 10

to 20 percent complete remission rate, adding a known active agent.

So I'm not sure that continuing to evaluate new agents in the relapse setting, in the multiply relapsed setting is really the best way to go.

DR. ABICHANDANI: Which is why we sort of wanted to go back up to--you know, try the first relapses move up. The numbers again are small, and if we don't do it in collaboration with Children's Oncology Group, we really can't do the study.

And the study design that was out there at the time was the complex design that I showed you, or it will be some variation of that them.

And the question is, you know: how do you then isolate the benefit of clofarabine in that setting? That's our understanding of FDA's concerns with the study design.

CHAIRPERSON REAMAN: Well, I think the complex design of that first relapsed study is maybe something that has to be re-evaluated also. Because it, again, is using combinations of known

active drugs that have been proved by investigators in Europe to be effective. And it's certainly not promoting and expediting the new agent development process for childhood leukemia.

Dr. Boyett?

DR. BOYETT: A couple comments.

It seems a little late for an animal model here. I mean, you've got an active drug. I mean, you know it's active. And the animal model hasn't been validated. So I don't know that that's a point.

To Jerry: the pediatric oncology group did conduct and complete a randomized control trial in relapsed ALL patients, and it's published in the New England Journal of Medicine. In terms of moving it up, it seems to me like moving it up early, you focus on first relapse--period. Because that's an area where you can salvage patients, and I think you could, with the cooperation of the Children's Oncology Group, actually do a controlled trial in first relapse ALL and prove a point--in the context of ho pediatric oncologists manage and

treat these patients.

DR. WINICK: It's a little bit circular. I agree with everything you've said. And something Greg just alluded to: we know that the re-induction rate for patients in first relapse whose initial duration of remission was relatively short is dismal with standard agents.

It would be quite reasonable to randomize a clofarabine-VP16 cyclo induction regimen versus a cyclo-etoposide induction regimen. And in first relapse, we would probably have enough patients to do it.

The circular component of this is knowing what dose to use for the three-drug combination--hence your Phase II trials.

But I do think that that's, realistically, one of the only ways to accomplish this.

It's a little bit hard to believe that we could run successive trials looking at randomization of the three drugs versus two, and then Ara-C-clofarabine versus Ara-C alone. That's less appealing.

But I think that is a realistic view.

DR. SMITH: I would agree with comments from this side.

I think in the first relapse setting there is the opportunity to do randomized trials, and that's moving it up some--as well as the newly diagnosed setting to do randomized trials there.

You know, I think the regimen--the treat-treatment block regimen that's the first relapse study now, is not--you know, in pediatric ALL--I mean, that's about as simple as they come.

So if you can add clofarabine to one of those blocks--like Dr. Winick was saying--then potentially you have a--

[Multiple speakers. Inaudible.}

Well, I mean, you can demonstrate a CR rate improvement, or you can demonstrate an event-free survival, and some point downstream improvement.

DR. WINICK: EFS is still an issue, because of things you've already brought up. EFS becomes an issue because most of these patients will be

taken off for transplant four to six months from the beginning. And one of the things that's discussed in the manual that I'd like to hear the groups comments on is the validity of the four-month EFS; the validity of how many kids make it to transplant--realizing that that may not be the best way to go, but is the way that most of these kids go.

DR. SMITH: But the other point I was going to make was: potentially you could do these studies. But the onus gets back to the pediatric world, and not to FDA. You know, how do we re-figure out how to use this drug in ways that demonstrate that it is beneficial to use the drug in children. And that's the point Dr. Pazdur was making: "Look at this as your friend, not as your enemy."

Abut this requires the company to develop the drug in pediatric oncology. We realize there's one kid on the block here--COG--to develop this. It gives the company the impetus and the obligation to develop this drug. This should be looked at as

a positive thing.

You know, we're approving these drugs on a relatively small body of evidence, with relatively response rates here. I'm not saying that they are not important in a refractory disease population, but it is a relatively limited body of evidence that we are basing this approval on--with the anticipation that there is going to be further development in pediatric oncology.

Look at this, pediatric community, as your friend; that this drug has an impetus. Because we do have this regulation, this obligation to mandate that these studies are being done. It is, I think, the obligation of the pediatric community then to define this and work with the FDA to define what is clinical benefit here, and what are these studies.

DR. FINKLESTEIN: I like Richard's comment. Let me give you a little historical comment.

Frei, Freireich and Karon showed in the '60s that in pediatric acute lymphoblastic leukemia, if you obtain a remission you're going to increase survival--at least the duration of

survival. I mean, this is obviously fact.

And I understand that Genzyme has some marketing, legal, and so forth obligations. So my question is to Dr. Pazdur: what I'm hearing, and what I thought I'd be hearing, is that if we moved the drug up earlier in terms of Phase II studies, a real Phase III study in the classical sense may not ever be possibly feasible in this drug. And therefore, it's the regulatory issues--which was my initial statement, for Phase III agents appropriate for a new agent in pediatrics.

The next thing I'd like to comment is that I know you use medical oncology, or the adults with cancer as an example. But I also know that in Congress when they talk about progress in oncology, they talk about pediatric oncology because we're the ones with the 75 percent survival rate. We're the ones with the 95 percent remission induction rate in ALL. So our percentages are different, in terms of trying to do Phase II studies.

So I'd like to take the ball back to you, Richard--and I agree that this is our friend,

because we haven't struggled with a new drug approval in pediatrics in decades. So this is very exciting.

CHAIRPERSON REAMAN: Jim.

DR. BOYETT: You know, this brings up a good point. I mean the expertise in doing trials in pediatric oncology is in the COG or with pediatric oncologists. And there a number of examples of the FDA asking for studies to be done, or drug companies to get indication that they're absolutely out of touch with how that particular is treated and managed in this particular country--or maybe even in the world.

And so I think--friends talk to friends. And so I think the FDA could take some advice from the Children's Oncology Group, and the experts in particular diseases when they are giving companies--you know writing a letter back and saying these are trials we want you to do. There needs to be some consultation, I think, before those things are sent out to those companies.

DR. PAZDUR: Well, let me just--again, I

think we were instructed to think of this as a friend. And in all fairness, we have had conversations with all the bright people in COG regarding these studies--okay. It's not that we're just sitting behind closed doors on Rockville Pike dreaming up studies for COG to do without consultation.

CHAIRPERSON REAMAN: But you can keep dreaming of studies for us to do.

But I think if these iterative discussions led to a design where we were going to evaluate the activity of a new drug in block three of a re-induction regimen, and that was the best we could do, I'm not sure that it was the FDA, or the sponsor, that failed here. I mean, this, I think, is pediatric oncologist problem.

So we do have the expertise, and we do take pride in the fact that the results we have achieved are widely touted by Congress in justifying the continuation of the National Cancer Act. But unfortunately sometimes we take a little too much pride in what we've done. And we've done

a great job, but there's still a whole lot more that needs to be done.

And relapsed acute leukemia is the second leading cause of death from cancer in pediatrics. So there's still a lot of work there to do. And looking at a new agent in the third block of a re-induction regimen that includes every known active agent in ALL isn't good science and isn't moving therapy forward, I don't think.

Michael.

DR. LINK: So let's say we did a study where you just looked at induction, and you did your appropriate determination of dose, and you did a front-line study, randomizing with a clofarabine-containing regimen versus not. And you had an induction rate that was statistically better.

Would that be sufficient, or would you really need to look at--or is that considered a surrogate?

Because the problem is--as has been brought up--especially in the transplant world now,

with more and more patients having haploidentical transplants--everybody's going to get a transplant. So looking at event-free survival--unless you're willing to say that that's going to come out in the wash in a large study, which I'm a little bit dicey for a company to get involved with--would you accept remission-induction as being a sufficient benefit of getting more patients into remission to accept that? Because I have a feeling that once you start looking at a downstream endpoint, you're going to have to face the music of transplant.

CHAIRPERSON REAMAN: But don't we actually have to prove to you--or at least provide enough justification that that is sufficient clinical benefit?

DR. PAZDUR: I think further discussion. I'm not opposed to this, believe me. But I think we'd like to have further discussion on this.

The issue is also: if this is going to be complicated by transplant--which is a major issue here--I would feel much more comfortable if we were looking at a randomized study, where we had near

identical either complete response rates, etcetera, to a known regimen that we felt very comfortable with, and the addition of this new agent added something so you showed superiority to that, that induction rate.

And then if it were complicated by, for example transplant and we had some uncertainty as far as the duration, at least we have comfort that there was an increased number of complete response or remissions here.

So, you know, some of the problems are not only the endpoint trial design that these are running into.

CHAIRPERSON REAMAN: But I think also just to clarify: there's a feeling that these Phase IV, or post-approval commitments a Phase III study.

DR. PAZDUR: The answer to that is: no.

Basically you put--and there's many examples in adult oncology where single-arm trials that had substantial durations of response have led to full approval of drugs.

DR. BARRETT: I just wanted to get back to

your original comments, Dr. Pazdur, about the friend at the FDA.

I don't think that--you know, we should also distance ourselves from the preclinical work that was discussed earlier. It's an opportunity to backfill some of that kind of evidence. And even in the absence of a validated model, or in fact because you have activity, I think it's important that we get that kind of information. This isn't the last agent we're going to study in this population.

CHAIRPERSON REAMAN: Oh, good--I think that's especially true if you're looking at combinations. We have a limited number of patients. We can't keep doing sequential studies of adding a new agent to known combinations. We can't do it.

So--whether models are validated or not, I think it's time to look at it.

DR. REYNOLDS: That's it exactly. And, Jim, I think you misunderstood. I wasn't saying "define this agent as active in an animal model."

The issue is: there are multiple different blocks of therapy for re-induction of ALL.

And the question is: is whether you mis this in one or the other block could significantly advantage or disadvantage you. Looking for significant synergy between the agents and picking the right combination, to then ask the clinical Phase I question of whether or not that combination is tolerable is a preclinical issue, and something that should be worked out before we get to the patient.

DR. BOYETT: Yes--and I understand that. But you don't have a working model yet to do this with.

DR. REYNOLDS: Well, there are models, and some information is better than no information. The other alternative is to guess, or flip a coin as to which block you put it into. And I don't think that's the way we should do thing.

DR. BOYETT: You know, one thing I want to say is: I wasn't really defending the third block that was put up there. But what I was saying is, I

mean, I think to the people who have the expertise for knowing how these will be subsequently used, that expertise resides in pediatric oncology.

And those are the ones that are going to be using the results to treat children. And so they have to be convinced. And those are the people you have to convince, and so they have to be secure with the design of the study. And I don't know--the three block--I'm not in the STED office or the COG or anything like that. So I don't know how the investigators came up with that.

DR. WINICK: Just one quick additional comment: if transplant is going to come to pass, there's certainly an evolving literature that level of detectable disease pre-transplant has an impact on outcome.

So, again, it's still--as Mike said--probably considered a surrogate marker that if we could not only demonstrate a difference in induction rate, but a difference in the level of minimal residual disease pre-transplant, it may add some weight to the argument one way or the other.

DR. LINK: It may be a surrogate, but it's good to be in remission. I mean, you know--

[Laughter.]

--so the question is whether you accept the fact that it's better to be in remission than not.

DR. SMITH: Just in the study design, I think the comforting thing here is, you know, newly diagnosed or first relapse, you still have very effective drugs that are able to achieve remission. And even in first relapse.

DR. WINICK: [Off mike.] [Inaudible.]

DR. SMITH: Well, for the earlier, still close to 70 percent. So you have to at least acknowledge that there are active agents, and to be either ready to compare to the active agents in a head-to-head, or else to have extraordinarily good historical comparison so that you're convinced that what you're doing really is a clinical benefit so that you're convinced it's an advance.

CHAIRPERSON REAMAN: But I don't think that precludes doing what we're suggesting in moving

these agents closer up in first relapse patients. We know that there are effective regimens. They could be more effective. And so adding an agent to a known effective regimen in a randomized setting I think would be an appropriate thing to do--not to wait until the end of a bunch of, or numerous, effective combinations.

I have some questions. Are those questions that the FDA would like us to address? I think we've addressed many of them. Did you want us to do them at the end of today, or can we do it--

DR. WEISS: Actually, I have it that actually after you've had your chance to have discussions for each topic.

So I think this would be a very good time.

I think you're correct: you've actually addressed many of the same questions. So I'm glad we were actually thinking along the same lines.

But if we could actually go through--I do not have the questions on the screen, but everybody should have it in their handout. If we could maybe

just read the question for the transcript, and then make sure that we've actually addressed it, that would be very helpful.

CHAIRPERSON REAMAN: And let me also just mention that at the parent ODAC, usually questions are provided to the advisory committee by the FDA. A vote is taken. Those votes are actually then utilized as--or interpreted as--the recommendation of the advisory committee to the FDA.

AS a subcommittee, we're not being asked for a vote. We're being asked to comment and discuss about these questions. I would hope that we could develop a consensus. I suspect that for some of these we already have. But I just want to introduce that first.

But the first question is: Are the proposed patient populations--ALL, first or second relapse--and primary efficacy endpoint--four month event-free survival--feasible, and will the design permit an adequate assessment of clofarabine's clinical benefit?

DR. WEISS: Just to start, I've heard that

most people were thinking that perhaps focusing on first relapse as a population where it might be better, the ability to show benefit would be at least one thing off the bat that should be seriously considered.

CHAIRPERSON REAMAN: I think that was a comment that was made: first relapse evaluating this agent within the context of known active agents, in a randomized setting, and looking for endpoints that would include remission-induction rate and perhaps molecular and/or flow cytometric determination of minimal residual disease; and the ability to then ultimately go to transplant in a period of three months, four months.

Mike?

DR. LINK: So you've actually changed the question a little bit. So we're looking then at remission-induction rate would be a valid endpoint, as well as maybe four month event-free survival, because that's how long it takes to get you to transplant. So it would be sort of a--one of those would have to be primary, and one of them would

have to be secondary. But you could try to do both. Plus molecular.

CHAIRPERSON REAMAN: I don't think we've changed the question. I think we've answered the question by saying "no," and we're recommending perhaps an alternative methodology.

DR. WEISS: I was going to say you could certainly measure many outcomes in a trial and there are certainly ways that statisticians can talk about in terms of alpha-spending, etcetera, to preserve the overall alpha effect. And that would be something that would really require some more in-depth discussion about how best to set that hypothesis up.

DR. SMITH: Another point is that I think we've been focusing on the early relapse--first relapse, early relapse. There is a late-relapse population, as well, that doesn't go to transplant. And so in the future, that's another population that could be considered for randomized clinical trials of agents such as this.

CHAIRPERSON REAMAN: I would challenge that

it's a population of patients that don't go to transplant. I think it's an increasing population of patients that is also going to transplant--unfortunately.

But I think your point is well made: that it certainly is another population with a biologically different disease, perhaps, than early relapse patients.

As far as the second question, I believe the sponsor is looking to develop data supporting--or evaluating the potential efficacy of this agent in AML. And the question relates to: to what extent can the data generated in adult patients with relapsed or refractory AML support efficacy in pediatric patients with ALL?

We really didn't talk about that at all during our previous exchange. But, simply stated: does there need to be a separate study in children looking at the efficacy of clofarabine in AML?

DR. SANTANA: Can I take a stab at that, Greg?

I don't think they're similar animals. So

I do not think that adult relapsed/refractory AML is comparable to patients with pediatric ALL. We know the mechanism of how these drugs work. We know--ALL, it says ALL here, so I was going to ask if that was a typo.

CHAIRPERSON REAMAN: ALL. Sorry. Sorry.

DR. WEISS: No, the indication right now on the table, of course, is pediatric ALL. Of course, as everybody knows, there was discussion and initial development in pediatric AML. Many of you were at the committee discussions in December where there was a lot of deliberation. And Genzyme articulated that it was really very difficult to assess, even in an accelerated approval paradigm, the contribution of clofarabine in the AML population. So the indication was specifically limited to ALL.

We know, though, that there's going to be ongoing data, and it's going to be probably easier to get those data in adult patients because there's more of them. And we'll have that information. It's not like we're not going to look at it.

But I guess the question is sort of: what do we do with that information?

DR. PAZDUR: We know pediatric ALL and

adult AML are two different diseases. We don't need an advisory committee for that. [Laughs.]

[Laughter.]

CHAIRPERSON REAMAN: I was just responding to--

DR. PAZDUR: Even I know that. Okay.

But this has profound issues to it. If we say, well we can't do these trials in childhood ALL, however we're granting an accelerated approval in childhood ALL, and then we will fulfill that requirement with data from adults in AML.

And you could just think of these--there's a lot of ramifications and a lot of discussion that could go around this point: are children being exploited just to get a drug on the market earlier? One could take the opposite viewpoint that this is the way to expedite drugs to children.

There's debates on this issue. Does this set precedents in other diseases that we want to go

into? Because these truly are unrelated diseases here.

But it does reflect our discussions--at least internally--that we realize these are difficult areas. We are willing--you know the regulations state that these confirmatory trials should be done with due diligence. And the comment that I made at the last advisory committee, when we were discussing another pediatric drug, I just want to repeat: we're realistic that this may take years here. This is not first-line breast cancer, or first-line lung cancer, that there's thousands of people to go on clinical trials worldwide. And there's no time restriction. We have to feel that there is a development of the drug in an orderly fashion.

For us to basically be saying that we will accept adult AML data to satisfy the requirements on the part of requirements of pediatric ALL may then retard the development of the drug in pediatrics.

And I just want to bring that up, because

there are several issues here which makes this a very complicated both societal issue and philosophical issue to address.

CHAIRPERSON REAMAN: Since I totally misinterpreted this question, maybe I can just ask for some more clarification.

So this would be in general, if a drug were to receive accelerated approval for a pediatric indication, then the sponsor could meet their post approval commitment with a disease--a totally different disease in the adult population?

Is that the issue?

DR. PAZDUR: I think we would have some problems with that, but we'd like at least some discussion on that.

DR. WEISS: Maybe part of it is we just know that those data are ongoing. And actually Genzyme isn't proposing to do this--and we're not necessarily proposing to do this. We just know that we're going to be getting data in adult patients--refractory AML, maybe refractory ALL, I'm not sure--but obviously it's easier to get that

information. And, obviously, we don't want to preclude getting good quality information in pediatric patients, but that's going to be years down the road.

And, to some extent it might depend on what the information looks like--but what can or should we do with this other information that we'll be getting. It will be coming to the FDA, potentially, for, you know, an indication for adult patients. And it may be coming--likely coming--much sooner than we'll be getting these confirmatory trials for the pediatrics.

Is there anything that we should be doing, considering, thinking about in particular as that information starts to be developed and come to us?

And the answer might be "no."

CHAIRPERSON REAMAN: Victor.

DR. SANTANA: So this committee dealt with this principle very generally in prior iterations of this subcommittee in terms of looking at biologic plausibility of disease processes, and whether those biologic plausibilities could be

extrapolated from different populations--whether adults to kids, or any different population.

And I thought this committee had made their consensus at that point: that, yes, if there was biological plausibility in terms of mechanisms of action or targets, that that would be a principle that we would recommend the FDA to adopt.

Having said that, the problem is that this class of drugs is not that specific. We do know, once again, that there are the nucleosides in this general class of drugs that in AML have different levels of activity--depending on the immunophenotype. There is a particular drug that's very active in monoblastic leukemia that is not active in M2s, and in pro-myelocytics.

So, unless the adult population that has been studied reflects to that detail the pediatric population, then I think at that level we can make the extrapolation. So if you're comparing monoblastic adult to monoblastic pediatric because the biologic plausibility is there, then I think that would be something I would adhere to.

But as a general consensus that AML in pediatrics and adults is the same disease, it's really not.

DR. PAZDUR: Here again, this is an exploratory question. We wanted to get it on the table because we've been asked in other indications by the sponsors to consider this. And it's something that we wanted to have some discussion on. And I think Victor's summary of our previous discussion is right on target of the way we feel.

CHAIRPERSON REAMAN: But I think that discussion supposes that the diseases are the same diseases in the adult and the pediatric population. That's not what you're asking here, and that was the reason for my question requiring some clarification.

My understanding of the accelerated approval process--at least for those drugs approved for adult indications--is that the post-marketing commitments have to substantiate the clinical benefit in the same disease, and in the same population.

DR. PAZDUR: Or in an earlier state.

CHAIRPERSON REAMAN: Or an earlier stage. But are you--is there an opportunity, if a drug is approved in an accelerated fashion for a pediatric disease, that the sponsor's commitment for a subsequent study to develop the drug could be in a

totally different cancer? And in a different age--

DR. PAZDUR: We have not considered that as of date.

CHAIRPERSON REAMAN: All right. Well, that's what I just wanted to make--

DR. WEISS: And I would think that it's only--and this is not the topic of this discussion, but we've had many times this has been brought up--the whole issue of molecular targets. And if, for some reason, there's some biological rationale, that we learn years down the road when we're all a lot smarter about, potential targets, that might make some more sense to make that link.

DR. BARRETT: I guess one--I mean, I'm fascinated by the question, actually, because--[Laughs.]

DR. WEISS: I'm glad you are, because nobody else is. [Laughs.]

VOICE: [Off mike.] oh, I am, too, actually.

DR. BARRETT: I mean, if you have a population and disease that is distinct from the other, and you're basically asking: what is the evidence that his audience would like to have in order to make one a surrogate for the other? And I

think that you seldom have that information on mechanism of action that you'd like to have.

So it really boils--and I don't know that you need it to be a requirement that they absolutely point to each other. It's how predictive is that one population? Do you have a generalizability across mechanisms, across classes, that gives you the comfort to do that. But that would require a lot of data. And to think prospectively about it.

So I think it ultimately comes back to you, as the regulatory: what would you consider convincing in order to have one population, and

disease, accountable for the other.

DR. PAZDUR: This point, that he mentioned, there would have to be a plausibility between the biology of the diseases or the mechanism of action of the drug is something that we would be looking for.

Again, we put out this question as kind of an exploratory question because several people have asked it because of the problems that we've had in fulfilling pediatric commitments. We have shared a deal of the reservations that have been expressed here.

DR. VASCONCELLES: I just wanted to extend your comment and make sure I'm understanding it--and pose a scenario to have you respond to to see if I am understanding it.

And just to reiterate Dr. Weiss's comment: Genzyme is extremely committed to our plans in pediatric acute leukemia. I think many of you who have been in discussions with us since we became involved with clofarabine, I hope recognize that.

So that's really not the question.

But just to extend your thinking: we have commitments ongoing in pediatric AML, and if those look promising, those may continue beyond this

first study, which would be nice.

Is that the kind of notion that your considering? That if development were to continue broadly in a disease like pediatric and adult AML, where data was mounting with a compound, that then you might be able to start to potentially extrapolate across those populations--and to Dr. Santana's point--look closely at the kinds of patients treated, and te subtypes of patients, and then start to make inferences about the potential benefit that one might conclude across populations?

Is that--

DR. BARRETT: That is exactly what I'm basically encouraging, to go down that path; to build that bridge so that that kind of assessment can be made. Because in the absence of data, I think the answer is very easy: no, the portability of one population to the other, I think, would be a tremendous benefit if you're able to do it.

DR. PAZDUR: A difficult task.

DR. LINK: What about the toxicity? I mean, in terms of drug development, you've treated a total of 39 patients on this study. And so you'd be leaving no further sort of gathering of information about feasibility for further toxicity,

downstream things, and there's be very little impetus to but kids on a trial if there isn't a trial to put them on. So you wouldn't be getting the additional information.

DR. PAZDUR: Agree.

DR. LINK: Okay, good. So the answer was "no to the question?

DR. PAZDUR: I believe so.

[Laughter.]

It corroborates our--

DR. WEISS: If you were going to vote, I suspect it would be unanimous. Okay, thank you.

CHAIRPERSON REAMAN: All right, maybe we should break here, and instead of 15 minutes, we'll do a 10-minute break to get sort of back on schedule. Thank you.

[Off the record.]

CHAIRPERSON REAMAN: Back on the record.

We'll reconvene. And this segment of the meeting will focus on some initiatives--legislative in nature--which may be of obvious importance to pediatric drug development.

And Dr. Lisa Mathis will discuss those for us.

Thank you.

DR. MATHIS: Thanks. Good morning.

Today I'm going to overview some of the pediatric initiatives that we have at the FDA. And, really, the purpose of my talk is to set up the talks later on Kepivance and Neulasta by Drs. Gootenberg and Summers.

[Slide.]

So the two pediatric initiatives that I'm going to discuss today are the Pediatric Research Equity Act, and the Best Pharmaceuticals for Children Act. Both of these laws are intended to support and encourage drug development in the

pediatric population,

Now, today I'm going to lay very heavily on PREA--the Pediatric Research Equity Act--because that's going to be the point of discussion for the drugs later this morning. So we'll hear more about BPCA from Dr. Zajicek this afternoon--especially the off-patent process.

[Slide.]

The difference between PREA and BPCA are that the PREA studies are mandatory. And the BPCA studies are voluntary.

So why do we need both PREA and BPCA? There's actually a distinction between the scope of the studies requested under BPCA, and required under PREA.

If you look at PREA, the indication to be studied is specific to the indication that is submitted to the agency. And under BPCA, we can actually ask for both on-label and off-label indications.

I'm going to give you an example--I can't provide a lot of details because the written

requests are actually proprietary. But you can use your imagination to figure out the answer.

So if we look at Viagra, the on-label indication at the time that we issued the written request was actually erectile dysfunction. So, obviously, the sponsor received a waiver in the pediatric population.

However, under the rule at that time--which is now PREA, and I'll go into that shortly--however, we did issue a written request for this drug not for the on-label indication. And it's subsequently been approved for pulmonary hypertension in adults, as well.

[Slide.]

All right, so for PREA, it because slaw December 3, 2003. It's actually codification of the 1998 Pediatric Rule. So a lot of you are familiar with the Pediatric Rule. Thee was a lot of regulatory and legal issues with the Rule, so subsequently Congress passed a bill, and it was signed into law. So when you think about PREA--or the Pediatric Research Equity Act--you can think of

it a little bit like the Pediatric Rule. It's not exactly the same, but many of the requirements are the same.

Drugs and biologics are both affected under PREA. And, remember, under BPCA, only drugs are affected.

And PREA is not applicable to drugs with Orphan Designation.

[Slide.]

So PREA is one of two laws intended to promote the study of drugs and biologic in the pediatric patients. And this is important because studies are really needed to prevent pediatric patients from being a "study of one." When we don't have pediatric studies, we don't accrue data, and we don't base our use on scientific data. We just use our experience to do that.

A lot of times, as pediatricians, we know we have to do that, and it was a fact of life for us before a lot of this legislation. But now we have 99 new drug labels with pediatric information in them.

The studies in the pediatric population under PREA are required--but only for the indication that was studied in adults.

[Slide.]

A pediatric assessment is required for certain applications, unless waived or deferred. And there's actually a new guidance out. It was published--a draft guidance--published in September of this year, and it was included in your background packages.

[Slide.]

A pediatric assessment contains data adequate to assess the safety and effectiveness of drugs or biologic products, and data to support dosing and administration for each pediatric sub-population.

[Slide.]

An Assessment is required for applications with a new ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

[Slide.]

A full waiver is granted when: necessary studies are impossible or highly impracticable; when there's strong evidence that the drug or biologic would be ineffective or unsafe; or if the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely

to be used in a substantial number of pediatric patients.

And as you look at this slide, the talk by Genzyme for clofarabine may come to mind because, of course, the populations in pediatric oncology are indeed small. And it sometimes is highly impracticable to do studies on such small populations.

[Slide.]

When we look at "substantial number," PREA actually does not define a substantial number. The FDA has generally considered 50,000 patients to be "substantial number." But the FDA will take into consideration the nature and severity of the condition when they're making this determination. Because obviously, all drugs for pediatric oncology

patients would be waived.

[Slide.]

A partial waiver is a special waiver for a pediatric age group--specifically zero to six months, six months to six years--and it's granted when the criteria for a full waiver applies to that age group; or when reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

[Slide.]

Under Full and partial waiver, there's actually a requirement in the law that this information go into labeling. If a full or partial waiver is granted because there is evidence that a drug or biologic would be ineffective or unsafe, that information must be included in labeling.

And we haven't really used that option with oncology drugs. However we have had to use it in drugs for other indications, where maybe there's a fixed dose, and one of the doses of the medication would be too high for pediatric patients, or couldn't be adjusted based on weight.

[Slide.]

A deferral--a deferral is granted when a pediatric assessment is needed, but permits

submission of the pediatric assessment after submission of the NDA or BLA.

There are several reasons for a deferral. One is if the drug or biologic is read to be approved in the adult population, we'll accept the pediatric assessment later. And that's because we really don't want to deny adult patients the opportunity to access to medication.

Another reason is we may need additional safety data. There are times that, at the time of approval, we're not comfortable with the safety profile of the drug for use in a given indication in the pediatric population. And we may want to see several thousand adults exposed to it, so that way we may be able to identify rare adverse events.

Also, there may be other appropriate reasons for a deferral. And sometimes the sponsor comes in with reasons why they really can't do the study at that given time in the pediatric

population. And if they're able to provide us with a strong scientific rationale, we will grant the deferral.

[Slide.]

So PREA is actually not as flexible as BPCA. AS I mentioned, the indications required for pediatric studies are limited to the indication in a given submission. And assessment would be waived under PREA if the submission for the treatment of that condition in adults didn't occur in children. And some examples of this might be breast cancer or prostate cancer.

[Slide.]

Now we'll switch over to BPCA very briefly--because we did touch on it.

These two laws work together, however they're separate and have separate requirements. So it's important to keep them separate in your mind, although you have to think about them working together.

So BPCA became law January 4, 2002. It's actually renewed the authority under FDAMA for the

six months of marketing exclusivity when studies are done in response to a written request. And BPCA includes an additional mechanism for the study of off-patent drugs. And, again, you'll be hearing a lot more about this from Dr. Zajicek later this afternoon. Where we work with NCI on oncology drugs, it's a collaborative effort between NIH and FDA.

[Slide.]

So, again, we have to think about PREA and BPCA together.

[Slide.]

And, because the goal of both PREA and BPCA is to obtain information from studies about the use of medications in the pediatric population; to obtain studies for both common and rare conditions; and also to disseminate information about the safe and efficacious us of medications in children.

We like to see that dissemination occur through labeling, but there are times when the data that comes in from the study isn't sufficient for

labeling, or would perhaps mislead people about the use of the drug in the pediatric population, so there are other mechanisms for getting that information out--such as our website, or even publications.

[Slide.]

This is a compare-and-contrast slide for PREA and BPCA because, again, I think it's important to remember that we really need both of them, because they both address different pieces of drug development in the pediatric population.

Under PREA, studies are mandatory, while under BPCA they are voluntary.

Required studies under PREA are only on the drug indication that is under review, while the studies for BPCA may be off-label.

Studies under PREA are not required for orphan indications, while we can go ahead and issue a written request for orphan drugs under BPCA.

And PREA applies to both drugs and biologics, while BPCA only applies to drugs.

They both sunset October 1, 2007, so they

will be considered for renewal together.

[Slide.]

I did put in one slide, so that way you can contact our division. And I have our phone number, as well as our website and e-mail address, as well.

And that's it.

CHAIRPERSON REAMAN: Thank you.

Questions from the Subcommittee

CHAIRPERSON REAMAN: Any questions?

DR. WEISS: I just want to comment that, you know, we're going to move on to two specific product discussions, so I thought if there was any clarification people might have about PREA or BPCA--because there's oftentimes a lot of confusion about the two, or what can be requested under one piece of legislation versus the other--we have one of the experts in this area here with us now, so it's the opportunity to get that kind of clarification.

DR. FINKLESTEIN: When you said "consider for renewal," is the FDA proposing the

consideration, or are you just leaving it open--[Off mike.]-to whoever's involved, or are you mostly the initial acts?

Would you define what you mean by "consideration for renewal?

DR. MATHIS: Well, it is going to sunset. So I'm sure that Congress will be deciding whether or not they wish to renew it, or revise it--or not renew it, for that matter.

DR. WEISS: Oftentimes what happens is there's a lengthy report that the agency puts together on the progress, accomplishments, what's been the net effect of having these acts in place over the last five years. And suspect that's probably going to happen as well when the time comes nearer.

DR. MATHIS: October 1, 2006--the report goes to Congress.

CHAIRPERSON REAMAN: And I would suspect that, in addition to that report, assistance from interested groups and parties would certainly be of great benefit and help in making sure that this

doesn't sunset forever, and is renewed. And I think we'd certainly be more than willing and able to do that.

DR. WEISS: My understanding is that organizations such as the American Academy of Pediatrics have been very heavily involved in providing information as Congress deliberates on the renewal of these acts.

DR. MATHIS: Yes, the AAP was actually very instrumental in passing the BPCA, as well as PREA.

CHAIRPERSON REAMAN: So, no questions for Dr. Mathis?

Thank you very much, it was a great presentation.

DR. MATHIS: Thank you.

CHAIRPERSON REAMAN: So I think next we're going to discuss two agents, both from the same sponsor--from Amgen. And we'll begin with Neulasta.

Pediatric Post-Marketing Commitments

Neulasta (pegfilgrastim)

FDA Presentation

DR. SUMMERS: Good morning.

Amgen's pegfilgrastim--marketed as Neulasta--is a recombinant granulocyte stimulating

factor that is effective in decreasing the instance of infection in patients with malignancies receiving myelosuppressive anti-cancer drugs.

My name is Jeff Summers. I'm a review officer for the Division of Biologic Oncology Products. And today I will briefly highlight the basis for the approval of Neulasta, and briefly touch on ceratin aspects of the label affecting pediatric use.

[Slide.]

Both Neulasta and Neupogen function as granulocyte colony stimulating factors. Neulasta is a pegylated version of Neupogen. Neupogen is a non-glycosylated No-terminal methionine modified human recombinant granulocyte colony stimulating factor protein.

[Slide.]

Granulocyte colony stimulating factors control the proliferation of committed progenitor

cells and influence their maturation into mature neutrophils. They stimulate the release of neutrophils from bone marrow storage pools, and reduce their maturation time. And they act to increase the phagocytic activity of mature neutrophils.

In patients receiving cytotoxic chemotherapy, G-CSFs can accelerate neutrophil recovery, leading to a reduction in the duration of the neutropenic phase.

[Slide.]

The two studies submitted for Neulasta approval included two randomized, double-blind, non-inferiority studies. Study 1 used 100 microgram/kg dose, while Study 2 employed a 6 milligram fixed dose. Both studies were conducted in high-risk stage II of State III and IV breast cancer patients that were greater than 18 years of age, and receiving Docetaxel and Doxorubicin chemotherapy.

The endpoint of the studies was the duration of severe neutropenia comparing Neulasta

to Neupogen.

[Slide.]

This table depicts that both studies met their primary goals of demonstrating that the mean days of severe neutropenia in Neulasta-treated patients did not exceed that of Neupogen-treated patients by more than one day in cycle one of chemotherapy, based on a 95 percent confidence interval.

[Slide.]

In addition, the duration of severe neutropenia in cycles 1 through 4, the depth of ANC nadir in cycles 1 through 4, the rates of febrile neutropenia, and the time to ANC recovery by cycle and across all cycles was similar for both Neulasta and Neupogen.

[Slide.]

Based on the results of these studies, Neulasta was approved for use to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer

drugs associated with a clinically significant incidence of febrile neutropenia.

[Slide.]

The following limited pediatric information can be found in the "Precautions" section under the "pediatric use" of the Neulasta package insert. "The safety and effectiveness of Neulasta in pediatric patients have not been established. The 6 mg fixed dose single-use syringe formulation should not be used in infants, children, and adolescents smaller than 45 kg."

Of particular note here is the availability of only a 6 milligram fixed-dose, single-use syringe. This essentially precludes the use of pegfilgrastim in certain pediatric age groups outside of the context of a clinical trial.

[Slide.]

However, Neupogen is specifically labeled for pediatric use, and contains the following important pediatric components: Neupogen is indicated for use in children and infants with severe chronic neutropenia; the studies used to

support the registration of Neupogen included patients with neuroblastoma; and the formulation of Neupogen allows for dosing on a mcg/kg basis, from any vial, using any type of syringes, versus the six-milligram, fixed-dose syringe.

[Slide.]

One of the key statements in the Pediatric Research Equity Act reads: "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretaries may conclude that the pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."

[Slide.]

In order to begin to extrapolate the pharmacodynamic effects of Neulasta from adults to children, an understanding of the pharmacokinetics in adults and children is required.

Some important aspects of Neulasta

pharmacokinetics in adults include: the pegylation of Neupogen--filgrastim--greatly reduces the glomerular filtration rate, essentially removing renal excretion as a means of elimination for Neulasta.

Peak Neulasta concentration for subcutaneous administration occurs approximately 30 to 70 hours after dosing.

The volume of distribution at steady state approximates that of plasma volume or the central compartment.

And elimination is primarily via neutrophil-mediated clearance receptor mechanism. Based on this receptor clearances mechanism, the pharmacokinetics of pegfilgrastim are non-linear, and it's dependent upon the clinical situation.

The half-life of the drug is variable, depending on the clinical setting. In the most-myelosuppressive chemotherapy therapy, Neulasta has a half-life of approximately 33 hours, compared to 3.37 hours for Neupogen. But, once again, this is also depending on the intensity or

the severity of the myelosuppressive regimen.

[Slide.]

The only remarkable safety signal generated from the controlled clinical studies of Neulasta in 932 subjects to date is essentially moderate to mild bone or musculoskeletal pain. However, voluntary spontaneous reporting of adverse events suggest a rare incidence of splenic rupture, allergic reactions, and the precipitation of crises events in sickle cell anemia patients.

[Slide.]

The major FDA thoughts regarding the pediatric Neulasta post-marketing commitment trial at the time the commitment was made were: is there any reason to expect the efficacy or activity to be different in a pediatric population? Would the demonstration of a similar pharmacodynamic in a small number of pediatric patients treated with one chemotherapy regimen be sufficient to predict efficacy across the broad array of cytotoxic regimens? Will establishing the pharmacokinetics in pediatric age groups likely to be treated with

pegfilgrastim ensure the safe use in pediatric patients? Could there be different or more pronounced end-organ effects in patients of pediatric age groups compared to adult patients treated with pegfilgrastim? And is the approved form likely to be useful in the younger pediatric age groups?

[Slide.]

Based on these considerations and discussions amongst Amgen and the FDA, Amgen agreed to submit results from an ongoing study evaluating the pharmacokinetics, safety and efficacy of pegfilgrastim in pediatric sarcoma patients receiving a single dose per cycle of Neulasta as an adjunct to VAdriaC/phosphamide etoposide chemotherapy; to discuss the appropriateness of an expanded access study to make Neulasta available to children between study closure and approval of an indication for pediatric use; and to develop a pediatric dosage formulation based upon data obtained from the pediatric study.

Amgen will now discuss their

post-marketing commitment.

Amgen Presentation

DR. DREILING: Good morning, everyone. My name is Lyndah Dreiling, and I'm a hematologist/oncologist by training. And my role at Amgen is to oversee the Neulasta development activities.

Before getting started, Amgen would like to express our gratitude to the meeting organizers. We believe that a once-per-cycle injection of a growth-factor support will provide the same benefit for children as it does for adults; including increased compliance and potentially better clinical outcomes.

[Slide.]

For adults, Neulasta was approved in early 2002, with an indication that was very similar to that of Neupogen: specifically, that is, to decrease the incidence of febrile neutropenia in patients with non-myeloid malignancies who are undergoing myelosuppressive chemotherapy.

To date, approximately 4,000

patients--adults--have received Neulasta in clinical studies. An additional 500,000 patients have received commercial Neulasta since registration.

[Slide.]

The pediatric development program began in 1999, and that was about the same time as the ongoing Phase II trials in adults.

This program had two primary goals. The first was to identify a safe and efficacious dose for children, and then to introduce a dosage form that would cover all ages and weights.

This is important because, as Dr. Summers pointed out, the currently-available dosage form is as a pre-filled syringe designed to deliver a fixed six-milligram dose. This covers all of the adult population, but is inconvenient for use in pediatrics.

Both of these goals seem pretty simple and straightforward, but we've experienced a number of challenges in trying to complete them.

[Slide.]

Some of those challenges are common to all of pediatric oncology drug development. And we'll start with the fact that in children, cancer is not

a prevalent disease. And although this is very fortunate for children, it does limit the number of patients that can actually enter protocols.

To the credit of researchers in this field, the majority of children actually do enter clinical studies, and these studies are generally open at referral centers or centers of excellence. And these are limited not only in number but in location. Often this requires the patients and their families to travel long distances in order to participate in those trials.

As we're often reminded, children are not just little adults, and they do metabolize some drugs differently. That means that pharmacokinetic data is very valuable in pediatric studies, but is also demanding--especially if a lot of intensive monitoring is required, or frequent blood samples.

[Slide.]

Some of the challenges we've experienced

have been specific to pegfilgrastim. And we'll start out with the fact that filgrastim--the parent compound of the pegylated pegfilgrastim--is actually available and widely used in the pediatric population. And it is incorporated into regimens and trials where myelosuppressive therapies are used. And generally these therapeutic protocols are designed with endpoints to evaluate old drugs in new fashions, or potentially new drugs--all with the promise of potentially better efficacy.

These are very attractive trials to clinicians and to patients--and appropriately so. But these trials compete with our supportive care protocols.

In designing the pegfilgrastim study, it was ideal to identify a tumor that would occur across all age groups, in an incidence that would allow a reasonable timeframe to enroll a protocol, and would have as its treatment a myelosuppressive regimen that would be the standard of care--or at least an acceptable standard of care--at that time and for the foreseeable future.

These criteria are challenges in pediatrics. As you know, tumors seem to cluster in one age group and not another. And because of the

incidence, sometimes these studies can take four to six years to enroll. And often chemotherapy may change during that time.

[Slide.]

We were--along with the pediatric community and the FDA--able to identify such a tumor, and that tumor is sarcoma.

The protocol actually allows all sarcomas to be enrolled--however, predominantly the diagnosis enrolled to the ongoing study is Ewing's sarcoma.

You see in the magenta bars of this histogram, the incidence of all sarcomas. And you can see that it does cluster in the older age groups. But there is enough incidence to enroll a protocol over approximately two to three years.

You see in the blue bars the incidence of Ewing's sarcoma--again, a little higher in the older age groups, and less frequent in the youngest

age groups. And this will help with some of the challenges we're going to show you at the end of the presentation.

[Slide.]

In the ongoing sarcoma study, the primary objective is dose selection. It's based on a clinical hypothesis that at the identified dose, pegfilgrastim will provide absolute neutrophil count recovery, and a safety profile similar to that of filgrastim.

Parameters measured include: ANC recovery--defined as two ANCs of 500 after nadir before day 21; the duration of severe neutropenia, and the rates of febrile neutropenia. We're also collecting pharmacokinetics in the study.

[Slide.]

This is the study schema.

So, eligible patients, scheduled to receive VAdriaC/IE are randomized to either pegfilgrastim or filgrastim in a six-to-one ratio. Daily ANC and PK samples are collected in Cycles 1 and 3, and patients are followed for a total of

four cycles.

[Slide.]

Dose selection for each age group is done independently. And you see up here the protocol-defined age groups. This is from infants to pre-schoolers; adolescents and teenagers.

For each age group there are seven total patients; six pegfilgrastim and one filgrastim, and an entire dose cohort would include 21 patients.

So how is dose selection in the protocol? Well, the algorithm requires two successive dose cohorts demonstrate ANC recovery. So let me show you a couple of possible efficacy scenarios.

[Slide.]

In the first dose cohort, five or greater patients recover their counts by day 21. And this is five of the six pegfilgrastim -treated patients. And in the second example, less than five recover.

So if we turn to the first example, a second confirmatory cohort would be done at the same dose. And if at least five patients recover their counts, dose selection can be made.

In the second example, a second cohort is started at a 50 percent escalated dose. And if at least five of those patients recover their counts,

a confirmatory cohort can be done at that same escalated dose. And if, again, at least five of the pegfilgrastim-treated patients recover their counts, dose selection can be made.

[Slide.]

100 æg/kg was the initial selected dose for the sarcoma study. And this was based on the rationale that pharmacokinetics and the mechanism of action in pediatrics and adults is expected to be similar. And this is due to--as was shown in a previous presentation--neutrophil-mediated clearance.

Additionally, this is a safe and effective dose in adults. And, finally, the commonly-used dose of filgrastim is the same in children as it is in adults.

[Slide.]

So where are we in completion of the study?

Well, asked 50 sites to participate. Fifteen agreed, and we have initiated all of those sites.

Despite the difficulties we've had, we've been able to enroll and treat all of the 100 æg/kg cohort in all age groups.

We started a second confirmatory cohort. And in the older age group, we've completed enrollment and treatment. As it turns out, all of these patients weighed more than 45 kilograms. And so this information is essentially contained in the current label.

We need another four patients in each of the two younger cohorts, with at least three demonstrating ANC recovery, in order to select a dose. We need six patients.

[Slide.]

When we talked to our investigators about how to get where we want to be from where we are, they cite he same obstacles as we've just discussed: filgrastim is available and it's used in protocols. And these therapeutic protocols have a

higher priority than do our supportive care trials. This is appropriate. We need to remember that for children, cancer is largely a curable disease. And our time and valuable resources should be spent in improving survival. However these studies do complete with our trials.

And we've already talked about the low incidence in the youngest age groups of sarcoma. And this is going to make it hard to rapidly find these patients.

And, finally, some of the families that were offered the protocol declined due to the demands of monitoring of the protocol.

[Slide.]

So--what are we doing to improve at the moment? Well, we've stayed in very close contact with the pediatric community. And we've looked at ways to increase enrollment. And, as it turns out, we probably have a window of opportunity.

Competing trials have completed their enrollment, and while COG is analyzing their data and designing an additional trial for sarcoma

patients, we have the opportunity to open our trial at their sites and accrue those patients that would not otherwise enter a trial.

Our protocol is currently under review with the rhabdo and Ewing's group to do exactly that. We believe that this will expedite enrollment and complete the study.

[Slide.]

So, to this point, we've shared our experiences--both positive and negative, and we have some lessons learned.

So in order to not compete with therapeutic protocols, whenever possible, we'd like to add our questions onto those protocols. We believe it wouldn't dilute the therapeutic questions being asked.

We need to work very closely--or continue to working very closely--with the FDA and with the pediatric community to do this. And in this way, we can design the most efficient studies possible. WE can also use our early experience in those protocols to inform protocol decisions, and maybe

modifications directed at removing barriers to enrollment.

One such example would be to ask ourselves whether or not, in the ongoing sarcoma trial, we need daily ANCs in a confirmatory dose cohort.

[Slide.]

In summary, we are striving to complete this study. We believe that pediatric patients, like adult patients, will benefit from the availability of pegfilgrastim, to increase compliance, decrease febrile neutropenia, and improve overall outcomes.

We've made significant progress, and continue to take actions to complete the study--but we need your help. That's why we look forward to the discussion today, and input from both the FDA and the subcommittee on ways to expedite not only completion of this study, but in all pediatric oncology drug development.

Thank you very much.

CHAIRPERSON REAMAN: Thank you.

Questions from the Subcommittee and Discussion

CHAIRPERSON REAMAN: Maybe, before going on to the next presentations, if there are specific questions for Dr. Dreiling about this study--the

trial--from the committee?

Michael?

DR. LINK: Just a quick question: are you going to use this same chemotherapy protocol for rhabdo? Because that really isn't the standard therapy for rhabdomyosarcoma. And so I'm wondering if you would allow using the standard therapy in rhabdomyosarcoma. That's where most of the one to five-year-old sarcoma patients are going to be?

DR. DREILING: It's a good question.

When we first designed the study, I think it was more of a standard across a number of sarcomas. Clearly now it is the Ewing standard.

We had discussions with COG about actually superimposing this on the rhabdo study. And although the chemotherapy was a little bit different, we pursued that avenue--to exhaustion--and decided that the best way to complete the study was with the ongoing design, and

on moving with the plan that we have.

DR. LINK: Just a couple comments. Number one, the rhabdo study that you wanted to sort of get onto has actually finished its gruel--so that it would be a free-for-all in terms of those patients until a new study is open.

And, second of all, that current therapy is not going to be used for rhabdomyosarcoma patients--mostly because of the anthracyclines in young patients. So if you want the one to five-year age group, and want to do a robust study, I'd recommend you re-negotiate.

DR. DREILING: Thank you.

CHAIRPERSON REAMAN: Clinton?

DR. STEWART: Yes--I have a question--and this may be just real obvious, and maybe I just missed this. But could you perhaps explain again what the rationale was for the three age groups?

DR. DREILING: Yes. Remember that this protocol was designed in 1999, before the ICH guidelines around age groups. And we believe that it was essentially designed to kind of catch the

small, medium and large patients, because the medication is weight-based.

In looking back, it would be much more reasonable to have included an age of zero to two, and then maybe three to 11, and then the 12 to 21.

DR. STEWART: Can I follow on with that?

CHAIRPERSON REAMAN: Go ahead.

DR. STEWART: But I'm not even clear why you would even have ages. I mean, are you speculating that there's a difference in the way the different age groups of children handle the drug? Are you speculating that there's a difference in toxicity based on age?

I'm not sure what, again, the rationale for the age divisions are. That's what I'm not getting.

DR. DREILING: We wanted to be sure that there wasn't a difference--in essentially the youngest age groups. I think that probably--and certainly you can speak more to this--but the very youngest age groups are going to be hard to evaluate in this setting anyway. Because as I

understand it, they're not really dosed by BSA, they're dosed per kilogram. And doses are reduced, and metabolism of those agents is not uniform over the whole period of that age.

And so they may actually receive higher doses of chemotherapy, have lower nadirs, and longer recoveries.

DR. STEWART: So this is more a function of the chemotherapy, not the pegfilgrastim. Because, obviously the pegfilgrastim is a neutrophil mediated clearance--which has nothing to do with age. You're worried more about the chemotherapy effect.

DR. DREILING: Correct.

CHAIRPERSON REAMAN: So to follow on that: why weren't the strata actually defined rather than on age, but on the dose of chemotherapy administered--if that was the concern?

And I also have a question about the age-range "zero to two years of age," because where we see the greatest variability, unpredictability, because of developmental factors that may impact

pharmacokinetic parameters would be in the first year of life. So "zero to two years of age" doesn't really make a great deal of sense.

DR. DREILING: And at the time, we did work very closely with COG--which I think was POG actually at that time-and had a lot of input in trying to design what would be the right age groups.

CHAIRPERSON REAMAN: Can I just--for clarification: how intensive were the blood draws and the specimen procurement? You said daily CBCs--but as far as the PK studies?

DR. DREILING: it was a daily sample--once; once per day, along with the CBCs, the PKs.

CHAIRPERSON REAMAN: For how many days?

DR. DREILING: Starting day four, until day 21.

CHAIRPERSON REAMAN: And can you explain the concept of "competition," with therapeutic trials? I don't understand how supportive care studies "compete."

DR. DREILING: I think the point that we're

trying to express there is that COG did start sarcoma studies subsequent to ours, and I think that those have been pretty large studies. And they've been able to complete those studies in less period of time than we've actually been open with our studies.

And I think that that's because they're answering important questions. And probably clinicians and families alike, given the choice, enter those protocols, as oppose to a protocol that answers a question about pegfilgrastim.

CHAIRPERSON REAMAN: But the COG does its studies at over 200 sites, not at 15, or 40--or whatever the currently expanded number is.

So I'm not sure that "competition"--because these patients were on--I assume the ones who were on this trial may have been on--

VOICE: [Off mike.] [Inaudible.]

CHAIRPERSON REAMAN: Not allowed?

DR. DREILING: Not allowed. Yes.

VOICE: [Off mike.] [Inaudible.]

DR. DREILING: Yes--so that was our challenge.

DR. WINICK: A couple of comments--first,

given that it's a randomized trial comparing the pegylated product to the non-pegylated product, should the chemotherapy regimen--given that it will cause myelosuppression--matter?

I mean, it would seem--Clinton's comment about rhabdomyosarcoma, and I'm sure Pat's going to make a comment about neuroblastoma--since you have an internal comparison, if you want to gather younger children, you need a different histology. And I'm not sure why the regimen would have a bearing on outcome--would be comment number one.

Comment number two: I don't know why you'd need daily blood counts--especially if you have a better endpoint; if you actually believe you can reduce the incidence of fever and neutropenia.

And then comment number three would be that it would seem as though you could--and I'm not suggesting you start from the beginning--but given that in most pediatric protocols the same

combination is given more than once throughout the course of treatment, that you could actually use each child as their own control. And if you have--I'm making this up--but if you have VAdriaC-administered cycles 1 and 5, and you have VPCyclo-administered cycles 2 and 4, that the child could receive one product with one VADRIAC, the other with the other.

And if you're worried about a cumulative myelosuppressive effect--which I'm not sure is a horrible concern in pediatrics--but if you are, then what you could randomize is the order in which kids begin. So half the kids would get VAdriaC number one with the pegylated produce, half would get VAdriaC number one with the native.

But the advantage of having each child receive both is that, number one, you may be able to compare; and, number two, one of the things you described is the hesitancy of parents to consent, because one involves one shot, and one may involve 10. But this way all children benefit--assuming--I'm reaching here--that it's a

benefit, and that the peg's okay. This way all kids have a benefit with at least half of the cycles.

DR. REYNOLDS: Yes, I would agree that neuroblastoma, there are some opportunities within the COG neuroblastoma committee you may want to explore that would address a younger age group.

But if this is going to be used in that younger age group, what are your plans for providing a dosing form other than this six-milligram syringe?

DR. DREILING: And I'm going to ask Bob Charnes to actually answer that question for us.

DR. CHARNES: Right now, obviously, we need to make sure that we have the right dose. And so everything that we have is ongoing and is not finalized.

We have started the pharmaceutical development of alternate dosage forms. The key element here is that we will make multiple dosage forms available so that we will be able to dose across the entire weight range, from 4 kilograms to

45 kilograms.

Until we have additional data, I think it's premature to comment on the specific type of--

DR. REYNOLDS: But you do have that ongoing.

DR. CHARNES: Yes, we do.

CHAIRPERSON REAMAN: Thanks very much.

DR. DREILING: Thank you.

CHAIRPERSON REAMAN: So maybe we will go on to a discussion of another Amgen product. And first, Dr. Gootenberg from the FDA, to discuss palifermin.

DR. WEISS: Dr. Reaman, while we're getting ready, just two quick comments that the previous presentations illustrated: one, in terms of just the frequency of drawing blood work, it's not clear to me, as a reminder that these studies were put into place a number of years ago, but one doesn't want to certainly miss the nadir and the recovery of the dosing. I would agree that perhaps daily dosing in a pegylated form of a molecule seems perhaps excessive. But there's always an

issue. And we've learned in hindsight sometimes that data were not collected prospectively, and when it's really to look at things like neutrophil recovery, you know you can't just go back and collect that afterwards.

The other issue, in terms of formulations: in the biologicals, as opposed to--most biologicals are parenterally administered agents. They're not solid tablet formulations. So the issue of a solid to a liquid, which comes up a lot in many of the small molecule products, is not relevant here. However, this issue about the appropriate concentration and dose formation is very relevant. And clearly, for a lot of the adult administration there are these single-use syringes that are just, you know, one squirt in the syringe--which makes things very easy. But with pediatrics, as has been mentioned, there oftentimes needs to be multiple configurations of the material to account for--particularly because many of these do not contain preservatives and are for like single-use only. They tend to be fairly expensive. There's a

real concern about pooling, or multiple dipping into a vial which doesn't contain preservatives, which could cause a lot of problems.

And so those are just issues in the biological world that clearly need to e considered under the sort of rubric of "formulations.

CHAIRPERSON REAMAN: Thank you. And I think you make a good point.

And I think you also make a good point about the daily CBCs, and not wanting to miss the nadir. But one might also not be able to miss the nadir with alternate day CBCs, rather than daily CBCs.

So there are some alternative approaches.

Kepivance (palifermin)

FDA Presentation

DR. GOOTENBERG: Thank you, Greg.

Amgen's palifermin, marketed as Kepivance, is a recombinant human keratinocyte growth factor that is effective in reducing the incidence and duration of severe mucositis associated with hematopoietic stem cell transplant for hematologic

malignancies.

I'm Joe Gootenberg, team leader in the Division of Biological Oncology Drug Products in CDER's Office of oncology Drug Products. And today I will be presenting the basis for approval of Kepivance, and certain aspects relating to pediatrics.

[Slide.]

Kepivance is recombinant human keratinocyte growth factor manufactured by Amgen in E. coli. It's 140-amino acid protein, with a molecular weight of around 16,000. And it differs from the endogenous KGF by deletion of the first 23 amino acids.

Now, the endogenous human KGF is a member of the fibroblast growth factor family that binds to a unique KGF receptor and stimulates proliferation of epithelial cells.

[Slide.]

This KGF receptor is expressed almost uniquely on epithelial cells. And so it's found in many tissues in the body, including the GI

tract--for example on the tongue, the buccal mucosa, salivary glands, and on the GI epithelium--and also the skin.

Very importantly, cells of the hematopoietic lineage--such as granulocytes precursors and progenitors--do not express the KGF receptor.

[Slide.]

Kepivance acts to reduce chemotherapy and radiotherapy-induced injury to epithelium by, number one, increasing the epithelial thickness; and, number two, enhancing the speed of recovery of epithelium after these injuries.

[Slide.]

The major study that supported the approval of Kepivance was a randomized placebo-controlled trial that compared Kepivance to placebo in patients with hematologic malignancies who were undergoing autologous hematopoietic stem cell transplant. This population was chosen based on the distribution of the KGF receptor which, as was previously mentioned, is not expressed on cells

of the hematopoietic lineage.

The primary endpoint was the duration of severe oral mucositis.

212 patients were randomized one-to-one to Kepivance versus placebo.

[Slide.]

The subjects were primarily patients with lymphomas and leukemias, and ranged in age form 18 to 69 years old.

They received a uniform preparative regimen of TBI/VP-16/Cytoxen, and post transplant G-CSF--Neupogen--along with an infusion of autologous peripheral blood progenitor cell stem cells.

[Slide.]

This is an outline of the study treatment, with TBI, chemotherapy, the autologous stem cell infusion, and then the period of GCSF until the white count reached the threshold.

It's important to note--and this is sometimes confusing--the "Ks" on this side over here, stand for Kepivance, and the "Ps" stand for

"placebo"--not palifermin.

But what's important to note is that the drug was administered at two separate occasions during the treatment. The palifermin dose was 60 æg/kg/day for three days prior to starting the preparative regimen, and then the same dose 60 æg/kg/day for three days after the infusion of the peripheral blood stem cells.

[Slide.]

This slide summarizes the results of the trial. Oral mucositis was graded by the World Health Organization mucositis scale, as outlined on the top.

In this scale, grades "3" and "4" represent severe oral mucositis.

In the bottom table you can see that the primary endpoint, which was duration of severe oral mucositis, was reduced from a mean of 10.4 days in the placebo group, to a mean of 3.7 days in the group receiving Kepivance.

The secondary endpoint of the incidence of grade 4, the most severe mucositis--mucositis that,

to the extent that oral alimentation is not possible, these are kids who end up on IV hyperalimentation--was reduced from about 62 percent in the placebo group, to about 20 percent in the group receiving Kepivance.

Other secondary endpoints were all consistent with these findings.

[Slide.]

Based on this study, Kepivance received regular approval for an indication--here--to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy that requires hematopoietic stem cell support.

The indication goes on to state that the safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies.

At present, the indication for Kepivance is restricted to hematologic malignancies because of concerns that, as a result of tumor-cell stimulation, KGF-receptor-expressing

epithelial-derived tumors--in other words, carcinomas--could possibly be protected from the cytotoxic effects of chemotherapy and radiotherapy.

In addition, currently there is inadequate data regarding second tumors in patients receiving Kepivance. And, as will be discussed, the issue of so-called "tumor protection" in KGF-receptor-expressing tumors--in other words, carcinomas--would be less of a factor in designing pediatric of Kepivance for reasons known to all the members of the committee.

[Slide.]

In addition, the label reflects the fact that no pediatric trials have been conducted--no results are available--using the Kepivance licensed dose and schedule. Therefore, language has been included in both the "special populations" section regarding the PK, and in the "pediatric use" sections, noting the lack of data.

[Slide.]

In act, PK data are available only in adults. The mechanism of elimination of Kepivance

is really not entirely known. But, like the Neulasta and Neupogen, it's possibly receptor binding and subsequent internalization. However, what is known is that the terminal half-life is 4.5 hours; that with the three daily doses used in the trial there was no accumulation of the drug; and also that really there is insignificant renal clearance, so that with renal impairment, there's really no influence on the PK. And this has been added to the label.

[Slide.]

Safety, of course in an important consideration.

The Kepivance Transplant Safety pool included 650 patients, all adults, who were enrolled in a number of clinical trials. This was 409 patients who received Kepivance, and 241 who received placebo.

Importantly, most of the adverse events were attributable to the underlying malignancy, the cytotoxic chemotherapy or the total body irradiation, and occurred at similar rates in

patients receiving Kepivance and those receiving placebo

In fact, most of the Kepivance-related adverse events were consistent with the known pharmacologic action of Kepivance on skin and oral epithelium; for example, skin rashes, pruritis, erythema, edema; mouth and tongue thickness or swelling or discoloration; and taste disorders.

[Slide.]

Now we all know that safe use of Kepivance in children is predicated on being able to determine a safe dose and schedule. Therefore, the major focus of a pediatric trial conducted to satisfy the requirements of PREA should be safety evaluation.

In addition, in order to allow some extrapolation, the pharmacokinetics of Kepivance should be studied in the pediatric age groups likely to be treated with Kepivance.

Finally, the pharmacodynamic effect--in this case reduction in all mucositis--should be evaluated.

[Slide.]

In order to fulfill these goals, the FDA feels that a trial should utilize an anti-cancer

regimen with a high incidence of severe mucositis. And, to increase the ability to characterize the Kepivance-related adverse events, there should be a randomized, placebo-controlled trial that enrolls patients with a uniform underlying disease, uniform clinical status and uniform treatment.

[Slide.]

Because of the high levels of baseline toxicity associated allogeneic hematopoietic stem cell transplant regimens which could confound the detection and analysis of Kepivance-related toxicity, that type of therapy should probably be avoided in a PREA trial.

In addition, tumor stimulation cancers of epithelial origin, which are of such concern in adult oncology patients with carcinoma is the major family of tumors studied, is less of an issue in pediatric malignancies, because cancers of epithelial origins which carry the possibility of

expressing KGF receptors are, as we all know, rare in children.

[Slide.]

In response to FDA's PREA request, this is now one of the trials that was originally proposed by Amgen. This was, in fact, a Children's Oncology Group-proposed trial to conduct a study in children with stages 1 and 2 B-cell NHL who were receiving a highly oral mucositis inducing methotrexate regimen. It was going to include children from ages three to 16; a multi-center dose escalation study; placebo controlled.

Unfortunately for the drug development, but fortunately for children, advances in the treatment of pediatric NHL--specifically the demonstration that much less toxic therapy is as effective as the therapy that was proposed, have made this particular trial infeasible. And, as the next speaker, Amgen's representative, will discuss their current approach to propose trials to satisfy the requirements of PREA.

Thank you.

DR. FINKLESTEIN: Joe, I don't understand the previous slide--why you wanted to avoid hematopoietic stem cell transplant regimens.

CHAIRPERSON REAMAN: Allogeneic.

DR. GOOTENBERG: I can go back here.

It's GVH--GVH, the mucositis is caused by the toxicity associated with allogeneic transplants--which is not found so much with autologous transplants. That's why, in the original trail that was conducted for licensure, basically an autologous transplant milieu was chosen.

CHAIRPERSON REAMAN: Why don't we wait and have the discussion and questions after the sponsor's presentation.

DR. WEISS: And actually that's a very good question that we wrestled with a lot. It was relevant for another one of the adult approvals. But--agree, we should get to that when we finish the presentations. But save that question.

DR. GOOTENBERG: And I actually wanted to sort of break the mystery. Dr. Weiss is going to

have specific questions--right?--regarding both the Neulasta and the Kepivance pediatric trials. And you've covered a lot of them in your previous discussion.

CHAIRPERSON REAMAN: Thanks, Joe.

Dr. Berger?

Amgen Presentation

DR. BERGER: Good morning. My name is Dietmar Berger. I'm a hematologist and oncologist, and I oversee the Amgen global clinical development program for palifermin.

I appreciate the opportunity to discuss the pediatric program for our recombinant human keratinocyte growth factor with your today. And as discussed by Dr. Gootenberg, we have developed palifermin in adults for the indication of chemotherapy and radiotherapy-induced epithelial injury in a hematopoietic transplant setting.

After high-doses chemotherapy and total body irradiation, the majority of adult patients develop severe mucositis with painful oral mouth sores. Patients show decreased ability to eat, to

drink, or swallow, to speak--and will frequently require parenteral feeding and pain medication, and they may develop infection.

Palifermin has been safe and effective in adult patients with hematological neoplasms in this setting, and it has been approved--as discussed--by the FDA in December 2004.

In children undergoing myelotoxic therapy with hematopoietic transplantation, the same clinical picture of severe oral mucositis is seen.

Palifermin might provide a major benefit to pediatric patients--to children--as well, with hematological neoplasms undergoing transplant. And we have developed a study program to establish safety and efficacy of palifermin in children.

With this presentation I want to introduce you to the details of this pediatric development program

[Slide.]

For palifermin we began development of the pediatric study program during the pre-registration phase. And let me emphasize here that palifermin

is first in class epithelial growth factor--and you heard about this--and a new molecular entity.

With this new type of biologic, a careful clinical development program needs to strongly focus on safety aspects of the drug. Initial discussions of pediatric development of palifermin with the FDA took place in September 2000 during the end of Phase II meeting. At that time it was agreed that efficacy and safety of palifermin should be established in the adult population prior to embarking on studies in children. Further adult studies, including a pivotal Phase III trial in patients with hematological neoplasms--as discussed--were conducted between 2001 and 2003.

In September 2003, a pre-licensing meeting--the pre-BLA--meeting was held, and the pediatric Phase I and II study design, focusing on safety, efficacy and pharmacokinetics of palifermin was developed.

In June 2004, the adult BLA was submitted, and the same Phase I/II study was included as a post-marketing commitment.

[Slide.]

Let me provide further details of the original Phase I/II study proposal.

This was a Phase I/II study, planned to be conducted with the Children's Oncology Group, in patients with B-cell non-Hodgkin's lymphoma receiving combination chemotherapy.

Patients between three and 16 yeas of age were to be included, and palifermin was to be applied intravenously for three consecutive days before chemotherapy.

In the Phase I part of this study, eight to 16 patients were to be enrolled. This first part of the study focused on a dose escalation, with four dose cohorts, and the safety and pharmacokinetics objectives.

In the Phase II part, 100 patents were to be enroled in a randomized fashion, with 50 patients each in the palifermin and placebo groups. The focus of the second part was efficacy and safety.

[Slide.]

In September 2004, the adult BLA was approved, and we worked together with the Children's Oncology Group to implement this post-marketing commitment.

In March 2005, however--as discussed--and the therapy for children with B-cell non-Hodgkin's

lymphoma changed on the basis of new data. The new transplant-induction regimen shows comparable efficacy with decreased toxicity; specifically, it is inducing a lower degree of mucositis, limiting feasibility of the initial study protocol.

Consequently, we had to develop a new approach to the development of palifermin in the pediatric transplant setting.

We submitted a revised study proposal in June 2005, specifically for the Phase I dose finding and pharmacokinetics questions. Further specifications of this revised approach were discussed with FDA again in September 2005, and we received further guidance on this approach.

So let me provide you now with details of this revised proposal for the palifermin pediatric

development program.

[Slide.]

We are now planning for two separate studies: a Phase I and a Phase II.

We are working with both the Pediatric Blood and Marrow Transplant Consortium, as well as with the Children's Oncology Group. Patients between one and 16 years of age will be included, with three age groups in the Phase I study.

The Phase I will again focus on dose findings, safety and pharmacokinetics. And the Phase II study will answer different questions in a randomized, placebo-controlled fashion.

In the first part, safety of palifermin will be assessed in a homogeneous pediatric transplant population at the doses established in Phase I. And we will focus on the younger age group.

The second part of the Phase II study will generate efficacy and safety information in a broader population.

[Slide.]

So if we look at the Phase I trial specifically, here we will work closely with individual sites of the Pediatric Blood and Marrow

Transplant Consortium, focusing on the key objectives of dose finding, safety and pharmacokinetics. And we plan for patients with acute leukemias requiring total body irradiation and high-dose chemotherapy with allogeneic hematopoietic stem cell transplantation to be included in this dose-finding study.

There will be 36 to 72 patients in three age groups, with the cohorts from one through two, three to 11, and 12 to 16 years.

Dose escalation decisions will be made for each individual age group.

With this population, recruitment into the youngest age group might be limited. If this is the case, we will later on include patients with neuroblastoma in this youngest age group as a contingency plan at this time.

We will use a conventional dose escalation, with four dose cohorts. And palifermin

will be given for thee consecutive days before and after chemotherapy--very similar to the pivotal study in the adult population.

[Slide.]

The Phase II study design is currently under discussion with the Children's Oncology Group. The objective of the first part of this study will be to establish safety in a homogeneous population. And this population should be homogenous with regard to disease type and transplant procedure.

We will include 60 to 80 patients, focusing on the younger age group. And, as discussed by Dr. Gootenberg, this evaluation of safety will require an autologous transplant setting--this is the guidance we've received--for example, in a neuroblastoma population.

[Slide.]

The second part of the Phase II study proposal is also currently under further discussion with the Children's Oncology Group. This part will then focus on efficacy and safety of palifermin in

a broader patient population.

We are planning to include roughly 200 patients between one and 16 years, with hematological malignancies or neuroblastoma, undergoing either allogeneic or autologous hematopoietic stem cell transplantation--obviously, with the right types of stratification, etcetera.

Incidence and duration of severe oral mucositis, as well as acute and long-term safety, will be the key endpoints for the second part of the Phase II study.

[Slide.]

In the framework of the palifermin pediatric development program we encountered various challenges which are common to the majority of drugs in pediatric oncology, and which are very comparable ro pegfilgrastim--to what Dr. Dreiling has told you before. These include, of course, the small patent population--which is even smaller than in the transplant setting--and the inclusion of all pediatric patients in existing cooperative group studies.

We also encountered specific questions for palifermin: firstly, the change in standard therapy with B-cell non-Hodgkin's lymphoma required to

redesign the pediatric development program for palifermin,

Secondly, palifermin is a supportive care agent, and although oral mucositis is a severe condition in children undergoing myelotoxic therapy and hematopoietic transplantation, competing trials with therapeutic agents may limit the available population if patients cannot be included into these trials at the same time. So one solution would obviously be to overlay on ongoing studies.

Thirdly, establishment of long-term safety of palifermin in children requires extended follow-up periods.

[Slide.]

So please let me conclude: palifermin has demonstrated a positive benefit-risk profile in adult patients with hematological malignancies receiving myelotoxic therapy and hematopoietic stem cell transplantation. However, severe mucositis is

still and unmet medical need in the pediatric transplant population, where children undergoing hematopoietic stem cell transplantation frequently show severe oral mucositis requiring parenteral nutrition and opioid analgesics, and some cases, even ICU treatment.

This is why we have developed a clinical study program for palifermin in children. And this program has presented with different challenges.

But as the sponsor of Kepivance, we share the goal with you of making this drug available to children as quickly as possible, if it can be shown, of course, to be safe and effective.

We appreciate the opportunity to present today, and of course we look forward to further discussion. Thank you.

Questions from the Subcommittee and Discussion

CHAIRPERSON REAMAN: With respect to the safety evaluation: was there anything in the toxicity profile in the adult experience that would require the elimination of patients who are at risk for developing graft versus host disease from that

population? And why are we evaluating safety in only young children in the autologous transplant setting?

DR. BERGER: Let me answer the different parts.

We do not have any reason to believe that there would be a difference between the pediatric safety or the adult safety--between these two populations. We have, though, a limited data set. In the adult population, we have a study which is an investigator-initiated study, with 100 patients, which did not show any effect of palifermin on the incidence, duration or severity of GVHD in this population.

On the basis of that data set, we have also received the approval for the adult population for the autologous and allogeneic transplantation.

CHAIRPERSON REAMAN: And another question related to toxicity: how strong is the theoretical possibility of induction of epithelial malignancies as second cancers? And although epithelial malignancies are not a concern in pediatrics as

primary cancers, they may be as second tumors. And what would be the anticipated time course? And is that going to be part of the safety evaluation?

DR. BERGER: Yes--it absolutely will be part of the safety evaluation.

We have different data sets to draw upon to answer this question.

We do, of course, have various preclinical data where, with hematological malignancies there has been no stimulation with KGF. We have also done further clinical studies to look whether there's a stimulation also in the solid-tumor arena. And at very high doses, you see stimulation of individual in vitro experiments. We never saw anything in the in vivo setting.

And then we have the empirical data set in the adult population, of course, where we have 650 patients--which have also been introduced by Dr. Gootenberg--where we have a two-to-one, basically, frequency with palifermin and controls. And there was no difference in long-term survival, and also no difference in secondary malignancies in this

whole population.

So we are taking this question very seriously. We are following the adult patients for life for this question. We have so far not seen any difference in secondary malignancy or in changes in progression-free survival or overall survival of the primary malignancies. And we will also follow the children in the pediatric development program very intensively for this question.

CHAIRPERSON REAMAN: But I think the issue in the pediatric population is not so much one of tumor protection as it is of new tumor induction.

DR. BERGER: Yes.

CHAIRPERSON REAMAN: So the time course I suspect would be very, very different, and would require much longer follow-up.

So, again, I'm not sure how long you propose following children treated with palifermin, from the standpoint of induction of second cancer. I mean, this could take years--decades.

DR. BERGER: In the adult population, we

have committed to a follow-up registry, with a total of 4,000 patients--2,000 palifermin-treated, and 2,000 untreated. This follow-up will be done through the CIBMTR registry, and there will be a follow-up of 10 years for every individual patient.

DR. REYNOLDS: I think this a ver interesting agent to consider in high-risk neuroblastoma, as you are considering.

What are your non-clinical data that the KGF receptor is not expressed in neuroblastoma?

DR. BERGER: We're currently obtaining that data set, together with an investigator at St. Jude. And that data will be available at the end of this year.

CHAIRPERSON REAMAN: Dr. Link?

DR. LINK: So I just presume that this is going to qualify as a study where the pathophysiology in adults and children is considered to be the same--of the underlying problem, the mucositis. But the efficacy is sort of--I mean, it's sort of a no-brainer: like, if it's safe, it should work in children just as well

as it works in adults.

DR. BERGER: That is our expectation, yes.

DR. LINK: Good. So you're really looking at the safety study.

So I'm not sure why you would pick neuroblastoma, for example, which is going to eliminate the possibility of looking at the older--you know, in other words, your range is very confined. And I know they do get severe mucositis. But if you want severe mucositis, we've got lots of things.

So if you just used acute leukemia with an allo transplant, you'd have your study done probably as effectively as possible. You could stratify a little bit about according to preparative regimen--although there's not that much difference, because most of them get TBI-containing regimens, and they all get severe mucositis.

DR. BERGER: Yes.

DR. LINK: And I just don't--and, you know, why don't you make it as easy as possible instead of having to design several phases of your trial,

exploring groups which are very limited in terms of --and plus, you've already seemed to--there's less worry about the tumor itself expressing the receptor, when you've already sort of confirmed that in hematologic malignancies.

So I'm just wondering why you're sort of making that--the second phase--more complicated than it need be. And I think you'll have your answer.

We're already running a trial in COG with another mucositis-preventing agent, which--you know, you could sort of substitute this agent in there, and probably get the study launched pretty quickly.

CHAIRPERSON REAMAN: Well, that was actually a recommendation from part of the pediatric community to Amgen: to look in that identical patient population.

Clinton?

DR. STEWART: Yes, I had a couple questions.

In the adult trials, has there been any

relationship between the concentration of Kepivance--palifermin--and the toxicities that have been observed?

DR. BERGER: Not to my knowledge--no.

DR. STEWART: Okay. And from the first presentation, I think what was shown was that there was no effective renal failure on elimination. But the suggestion was there is really not much known about the way the drug is eliminated.

Do you know much more about the way the drug is eliminated?

DR. BERGER: No, that's very true: we have limited data on elimination. There is discussion about the possible receptor-mediated elimination mechanism. But we do not have final data about that.

DR. STEWART: Okay--so this sort of leads me into--you know, everybody seems to be talking about how limited the data sets are in pediatric oncology, and yet everybody starts dividing them down further and further and further.

So I still don't understand--I'm sort of

beating a dead horse here, but I still don't understand the rationale of further subdividing the groups, if there's no real basis or rationale for subdividing them.

I'm sorry I keep harping on that. But I still don't understand that, and I wonder if you could maybe get into the reasoning for that--or maybe anybody else could?

DR. BERGER: You mean, now, the subdivision in age group specifically?

This is, I have to say, has been developed in let's say close consultation with FDA, as well--and then with different parts of different cooperative groups.

I think there is a rationale to talk about the younger age groups. We've been told that very often the younger age group--the one to two-year-olds--may react differently as the older children.

Of course, we are not the experts in that field. And I have to say we have to take guidance in that area. And we are happy about the

opportunity to discuss this here.

DR. WEISS: Can I ask Dr. Dinndorf to comment, as well, on that issue? Would that be okay?

CHAIRPERSON REAMAN: Sure.

DR. WEISS: Thank you.

DR. DINNDORF: because I was the person who was assessing the safety data in the adult studies.

Because most of the toxicity that you are going to see in evaluating the safety of these trials is not related to the treatment. I'm sorry--is not related to the palifermin, it's related to the preparative regimen--it's more difficult to pick out the specific palifermin toxicity when you have more background noise from the procedure.

And there's more background noise in allogeneic transplant than autologous transplant. I mean, that's the reason why they chose to do the adult studies in the autologous hematological setting

That's the reason--I want to see data on a

group of patients where I can control for the background toxicity better. And when I look at that data set, it's going to be easier for me to do in an autologous group of patients treated with the same preparative regimen.

CHAIRPERSON REAMAN: But we heard that there are no toxicities that are specifically related to, or could be confounded by--

DR. DINNDORF: But that's what I'm looking for, though--

CHAIRPERSON REAMAN: --GVH. I mean--

DR. DINNDORF: Well--no. GVH--the major toxicities of palifermin are skin and oral mucositis, are--a major manifestation of GVH is skin rash--albeit, I admit, later than in the period that you'd expect to see it. But it overlaps.

DR. LINK: Yes, but it's a randomized trial, right?

DR. SANTANA: Exactly. I don't understand that comparison.

DR. DINNDORF: It's--

DR. SANTANA: First of all, where is this drug going to be used? It's going to be used in patients that have really bad mucositis--whether

you get an autologous transplant or you get an allogeneic transplant, you get bad mucositis. And the patients are randomized. So you're controlling for the two major impact factors, and you won't know the answer.

It may very well be true that patients in an allogeneic setting have greater toxicity related to this agent. But you want to know that, in a controlled fashion.

So whether it's autologous or allogeneic, you're going to get the answer of toxicity differences between the placebo and the drug. It may be higher in one patient population--if it's autologous, or it may be lower in the other population. We don't know.

DR. WINICK: In the time course--you know, you've said it quietly--but the time course really is drastically different. I mean, mucositis normally resolves as counts recover. Count

recovery--and I'm not a transplanter--but count recovery often heralds the initiation of graft verus host disease.

So not only is it randomized, but the overlapping effect should really be minimal.

CHAIRPERSON REAMAN: Pat, did you--sir, this comment actually really relates to both these products, and what we don't know about differences in terms of end-organ responsiveness from normal tissues.

We have a bit more concern, for instance, in the pegfilgrastim situation that marrow responsiveness to the exogenous growth factor may actually be somewhat different.

We don't have that information or that signal yet for palifermin--for the Kepivance. But that's based, really, on fairly little information.

So, in the even that there's a small signal, it will be much more difficult to pick it out in a very noisy background. And so what we're attempting to do is--hopefully--maximize our ability to detect even small signals that might of

clinical significance, that may actually differ in the younger children--in children--and across what age range would be difficult to know--based on biological differences in their responsiveness to the exogenous growth factors that we're administering.

So what we're trying to do is maximize what information we can get from really small data sets, by trying to control, to the extent possible, the confounding factors.

Skin toxicity may, in fact, not be the only toxicity. And there may be differences in the toxicity profiles between children and adults. And in order to pick up those other signals, we're going to try and keep this tighter.

DR. LINK: Wouldn't your approach, then, to be a bigger trial? So, in other words, if you're looking for smaller differences, so you just want a bigger trial.

By confining it to a very small group of patients, in a very particular, confined age range--let's say--I can tell you--let's say

10--year-olds have a higher rate--you're not going to see any 10-year-olds with neuroblastoma--or not very many of them.

So I would say: do the opposite. I would broaden the trial and do it in leukemia, because it's going to cover all age ranges, and it's going to give you a bigger n. And if there's a difference in a randomized trial--it's at least, in my poor understanding of statistics, and you can correct me if I'm wrong here--but bigger n usually is what you guys are happy about.

[Laughter.]

So you'll have a chance to pick it up.

DR. KEEGAN: Yes, I suppose that's a possibility that we could look at, even when you talk about "bigger n's" in pediatric oncology, it doesn't begin to approach the "n's" I think about.

So I'm not sure what the trade-offs are.

Jim?

DR. BOYETT: You know, if you think of allogeneic as a higher noise background than autologous, you stratify. And you design your

study around knowing what kind of effects you might see in those different strata.

So--a randomized trial. You've got your control. You stratify for those things, and you design it around that.

But, I agree--open it up. I mean, ALL, we have lots of mucositis.

DR. LINK: See, I learned something.

[Laughter.]

DR. WINICK: Just to be difficult--

[Laughter.]

--the data are very impressive, that mucositis is ameliorated by this product. It's already on the market. What is the likelihood that if the trial takes--I'm not supporting this--but what is the likelihood that the trial will take too long, and this will already have become--sort of "on the street"--standard of care?

DR. WEISS: I think that tends to happen fairly commonly with pediatrics. And that's--I mean, some of it is the issue about just the necessary delay in pediatric development because it

almost always lags behind for these types of therapies, the adult development.

I don't know to what extent. I suspect that, with the first molecule we discussed--the pegfilgrastim--there is an extensive--and the indication doesn't actually preclude its use in pediatric patients. And we specifically write labels that do not have age restrictions, and say "It's only indicated for adult patients." That wouldn't be--we don't think that would be appropriate.

But, nevertheless, the whole idea is: knowing that these are going to be widely used and might have an incredible benefit in pediatric oncology patients, to try to generate the data that you want to have. And, I mean, I think that's why discussions are very useful.

To the extent that we can get good quality data in a more rapid fashion, so much the better for the pediatric oncology community that are going to be using these to help provide better recommendations for safe use of them.

CHAIRPERSON REAMAN: But if it takes too long to generate those data, then they're really of no benefit to the patient population--or to the

agency.

So, you know, I think this is a very beneficial discussion. And if there are opportunities to try and compromise to rapidly obtain data that may not be the cleanest and quietest data, that might be necessary. I think it would really be of benefit.

We're already--as was mentioned--we have an ongoing randomized study of another agent looking at mucositis--which is being jeopardized because of the availability of this agent on the market.

So I think the concerns are really very real.

DR. PAZDUR: We hear you. We'll have some internal discussions on this with the sponsor.

CHAIRPERSON REAMAN: Malcolm?

DR. SMITH: Could you comment on what the adult dose is? And what the dose-response curve is

around the dose that you're using?

DR. BERGER: Mm-hmm. Yes.

The adult dose that we're using--60 æg/kg--given six times total: three times before, three times after the toxicity. We have done dose finding studies in healthy volunteers, for example, which span a wide dose range, up to 250 down to a few micrograms.

The doses we want to start here--the dose escalation--we want to do four doses. We want to start at 20 æg/kg. This is the dose where we have seen the first biological effects in our healthy-volunteer studies. And we were planning to go up in 40, 60, and then 80 micrograms. And 80 micrograms is where we've seen the DLTs in adults--the dose-limiting toxicities.

DR. SMITH: And those DLTs were--?

DR. BERGER: Those DLTs were in line with the pharmacological activity of palifermin, which were skin rash, erythema, and then the oral toxicities that Dr. Gootenberg described, like the thickening of the tongue, the coating, white film,

etcetera.

Transient--let me that there were transient increases is amylase and lipase, which did never show any clinical sequella. And these are the three DLT's that we've seen.

DR. SMITH: Okay--well, depending on the severity of those toxicities, to do four dose levels, if speed is of any merit here--to do four dose levels is really going to take a long time.

And so, to the extent that you do want to get to your definitive studies quickly, you know, it seems like you could pick a couple of dose levels and get this done, and then be ready for the efficacy trial.

DR. BERGER: Yes--and we had discussed that previously, and I feel that's a very good suggestion. Yes.

CHAIRPERSON REAMAN: Also, just as far as your longer-term development plan--at least in the adults and in what has been discussed so far about pediatrics, which may change--it appears that the agent is going to be evaluated in the transplant

setting, whether it's autologous or allogeneic transplant. But there are certainly indications--or potential indications--in the pediatric experience with multi-agent chemotherapy regimens that cause mucositis.

The schedule that's being evaluated are three doses prior to transplant, three doses after. Do you have plans for looking at other schedules of administration? And is that going to require additional safety evaluation? And where are you in thinking about that.

DR. BERGER: What we are currently thinking about is evaluating palifermin in settings where you have sever oral mucositis. Severe oral mucositis is, as you say, seen outside of pure transplant settings.

I think we have to distinguish between hematological neoplasms, where we do not see KGF-receptor expression, and then solid tumors--or carcinomas, quite frankly--where you have a much higher hurdle with regard to pharmacovigilence and safety, etcetera.

For the hematological neoplasm setting, we are specifically thinking about multi-cycle chemotherapy, or more chemotherapy-induced

mucositis, instead of like induction and radio or chemotherapy for transplant induced.

The biology of the mucositis is not different, but we need to do the studies. And, as you say, we're thinking about an application of palifermin in these settings only prior to the chemotherapy, not pre- and post.

DR. SANTANA: I did read the package, and if I missed this point, please correct me. I can stand corrected. That's okay.

So--there are no adult trials with, like, head and neck cancers, where they're getting combined chemotherapy and radiation, or--

DR. BERGER: Oh, there are.

DR. SANTANA: --and, if so--because--like Mike and Greg have been saying, you know, we could fill up the room with other pediatric patients that get horrendous mucositis that are not being transplanted.

DR. BERGER: Yes.

I just wanted to make this distinction between hematological neoplasms, and then solid tumors. And--yes, of course, radio-chemotherapy of head and neck cancer is one of the key other settings where you do see a lot of mucositis; high

degrees of severe oral mucositis, grade three and four, in up to 80 percent of the patients that are treated. And we are currently conducting studies in this setting, with an intensive focus also on the pharmacovigilence part.

DR. FINKLESTEIN: Would you describe the dose you're using? I think that's what people are asking. I mean, it's one thing for the dosage pre- and post-transplant. What's your concept, in terms of treating patients who, say, have high-dose chemotherapy or radiation?

DR. SANTANA: And then also schedule, which I think is what Greg was trying to get at earlier.

DR. BERGER: We're currently thinking about oral mucositis in three large "pockets"--let me say that. There's the heme transplant single toxicity,

where we want to give palifermin pre- and post. Then there's the chemotherapy-induced mucositis, where we're thinking about a pre-dosing, and an effective dose should, for example, be 120 æg/kg as a single dose. And this is a dose we are currently assessing in our clinical study.

And then if you go to the radio-chemotherapy setting in head and neck cancer, you have the more chronic toxicity, and you have radiation from Monday through Friday. So what we're thinking about is applying palifermin after the toxicity, or Friday and Saturday would be a possibility. And then the dose per week should be between 120 and 180 æg/kg, in either a single dose applied, or in two doses applied.

CHAIRPERSON REAMAN: Just another potential recommendation: you're looking at KGF-receptor expression in neuroblastoma. The solid tumors that will be of interest in pediatrics are not epithelial malignancies.

But I would encourage you, early, to look at rhabdo's, Ewing and other sarcomas to make sure

that this isn't something that holds up further development.

DR. BERGER: And that's where, definitely, the pediatric population presents a unique opportunity also to study these settings.

CHAIRPERSON REAMAN: Any additional questions? Comments?

DR. WEISS: I think most people have touched upon the specific questions that we already asked. But maybe if we could just take a minute to re-look at those questions, and see if anybody has any other additional comments--both at the FDA, as well as the panel?

DR. LINK: Greg, is this--the two separate, or do you want the comments on the other one, as well?

CHAIRPERSON REAMAN: Well, I think--my question was whether or not there were specific comments, or specific questions for the speaker.

But I think going to the questions that the agency has asked us, I wold probably take them separately.

I think we've discussed some general issues that certainly encompass both of these products and similar products, but maybe we ought

to discuss them separately--unless people think otherwise?

[No response.]

Hearing no objection, then, the first question is, then: please comment on Amgen's ongoing study in patients with sarcoma treated with VAdriaC alternating with iphosphamide-etoposide.

Will this study allow for extrapolation of activity and safety findings across all age groups and to different pediatric cancers?

Any comments, other than what we have, I think, already discussed?

Malcolm?

DR. SMITH: You know, the point's been made that it's hard to get the younger patients who are receiving GCSF onto this regimen. And, would neuroblastoma patients, rhabdo patients all have different chemotherapy, but all is myelosuppressive, and those would have been

opportunities--and still could be opportunities--to get that experience in the younger patients.

CHAIRPERSON REAMAN: And I think the other important point to make is that the issue of competition also could, I think, be adequately addressed with the approach raised by Dr. Winick, where patients actually serve as their own controls.

And, you know, if there are alternating cycles of therapy, then stratify or randomize the sequence in which cycles are begun.

But I think there are enormous opportunities for doing these studies of supportive care--which are absolutely critical within the context, and not competing with therapeutic trials.

And, unfortunately--at least speaking for myself on behalf of the Children's Oncology Group--it wasn't until rather late that we were even aware of the interest in looking at these agents in pediatric malignancies.

CHAIRPERSON REAMAN: Michael?

DR. LINK: I don't this is our purview, but

are there plans to use this pegfilgrastim in chronic neutropenia? Like Costman's neutropenia? Because that would be another group of patients--small group, but--

DR. WEISS: I would ask Amgen.

DR. LINK: [Overlapping speakers.] [Inaudible.]--huge beneficiaries. It's sort of a lifetime commitment.

DR. KEEGAN: The issue of using the patient as their own control--I'd like to know about differences in the need for dose reduction in these myelosuppressive regimens in children, as compared to adults.

In adults, that wouldn't really serve because of the frequency with which there's a dose modification after the first cycle in trials of myelosuppressive regimens of adults.

Does that not occur in children?

DR. WINICK: I think we are nicer than we actually are. And in most of the solid tumor regimens, there is no indication for dose reduction based on myelosuppression alone.

DR. KEEGAN: And there are data to support that the degree of myelosuppression and the duration of it is not different? Based on the

cycle number?

DR. WINICK: For the most part, it is not. But again, I think that you can randomize the start so that you would account for that.

CHAIRPERSON REAMAN: I think that's certainly a concern if we were looking at cycles 10 and 12. But if we're just looking at the first cycle of therapy, or the first two cycles of therapy.

For most of the solid tumors that we treat, that's not a major problem. And I think there would be ways of actually demonstrating, or obtaining those data, in order to convince you of that fact.

Do you want to make a comment about the non-malignant--

DR. DOMSEY: I think, as you know, Amgen provides, currently Filgrastim--four patients with their ESCN.

Once we've established the dose--we've established the efficacy--as with other indications, we'd be happy to engage--and have had some informal discussions with some folks in the ESCN registry of what possible steps we could take. But we still have to get through the first steps of

establishing safety and efficacy.

CHAIRPERSON REAMAN: Any other comments on question number 1?

[No response.]

We can go to the second question, related to palifermin: "Please comment on the suitability and feasibility of the proposed pediatric program; specifically: need for dose escalation, need for collection of pharmacokinetic data; choice of patient population--homogeneous versus heterogeneous with regard to underlying disease; source of stem cells; cytotoxic regimen; source of stem cells--"--again. [Laughs.]

And I think we have touched on all of these. But are there additional points that we should raise--that anyone wishes to raise--at this

time?

Malcolm?

DR. SMITH: You know, in terms of getting the PK and correlating and minimizing the dose escalation--and there may be ways to just pick a couple of doses, do the PK, assure yourself that you're in the right range, and then just proceed with your efficacy testing.

And often, in a situation like this where we're not extraordinarily concerned about toxicity, and we build that dose escalation into the efficacy trial as the first cohort of patients in a safety study, and that can cut out some time, in terms of developing two studies, as opposed to just building that into the first study.

DR. WEISS: One question that's a little bit relevant to both, but we can sort of--here is: I think when Jeff Summers brought up his slide with the PREA, and said the PREA directs us to basically get the information in all the relevant populations where a product is likely to be used. And it's not just unique for pediatric cancer, but we struggle a

lot with getting the data in the very youngest of children, where there may be some differences. And we'll hear a little bit more about that from Dr. Barrett's presentation, I think, this afternoon--about trying to collect really good data in the very young; the zero to one-year-olds; sort of the one to two-year-old populations.

But a question is: to what extent can one extrapolate--particularly if we're talking about, I think, the Kepivance data from somewhat older patients down to the younger patients.

With the pegfilgrastim there was some concern perhaps about maybe marrow responsiveness in some, you know, more exuberant leukocyte responsiveness in the very young children, perhaps compared to some of the older ones.

But would we expect much differences across the ages with respect to palifermin?

DR. LINK: I don't think you'd know. But the infants are the worst, in terms of--especially the very young, like neonates.

The reason I suggested--actually, I should

have--the reason I suggested doing a study of chronic neutropenia is because there are newborns--or there are very close to newborns. And you may not be able to get the data from many other places, and that's the population where you maybe actually get the data on the very youngest children--who are probably going to have the most differences--this is about the pegfilgrastim--but are going to have the most differences in terms of how they handle the drug.

DR. BARRETT: One of the advantages in having the benefit of adult data--particularly pharmacokinetic data--is that we're not entirely naive in terms of when to sample and how to sample.

I don't think you can go into this with the expectation that all of these age sub-populations are going to be the same.

You may use that as a working hypothesis to test differences in the pharmacokinetics. So that's perfectly relevant, and we'll talk that in more detail later.

But, you know, you can guide the

measurement of these moieties with a lot of common sense, based on the knowledge of the adult data. So I think there is a path forward into doing this in the least intrusive manner.

CHAIRPERSON REAMAN: And I would also echo the special considerations for the infant population. But I guess I would have some reservation about whether or not Kussman's patients are actually going to contribute to--I mean, if we wait for Kussman's patients, they're really not going to contribute much to our--well, safety--but the numbers of those patients are even less than the numbers that we, painfully, have to deal with as it is.

So that would be my only reservation.

DR. WEISS: I think you have some very good advice, particularly with the palifermin. That was a very exuberant discussion--and obviously things that we wrestled with in the agency regarding, you know, the choice of a transplant for teasing out both good and bad effects of a particular

investigational agent.

So I think we'll just have to--as Dr. Pazdur said--do some more discussions internally about the merits of the different approaches.

Open Public Hearing

CHAIRPERSON REAMAN: Okay.

At this point, we will move on to the open public hearing session of the meeting. I'm advised that we only have one speaker at this point. But before inviting that speaker to address the committee, I need to read an advisory with respect to particular matters at these meetings.

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, FDA believes that it is important to understand the context of an individual's presentation.

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

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

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Having said that, I will invite the one scheduled speaker, Sadhana Dhruvakumar, to address the committee.

MS. DHRUVAKUMAR: I wanted to start by saying that I don't have any financial relationships with any of the sponsors of the products being discussed here.

And while it's coming up, I just wanted to say the subject of my talk is animal use in drug

development; and specifically in cancer drug development. And it seems that it's particularly important to preclinical models in this field due to--as many people discussed--the limited patient populations, and the difficult of recruiting in trials. So you want to be really clear at the preclinical stage that you have something that's worth going forward with. So I'm really happy to be addressing that topic.

I also wanted to say: I hear several times "preclinical models" being used almost synonymously with "animal models." And that may have been true in the past, but I hope that will not be true in the future.

[Slide.]

A quick introduction to PETA. PETA just celebrated its 25th anniversary. We're a non-profit with 850,000 members worldwide, growing very quickly.

We address many different areas in which animals are used to their detriment. But when it comes to animal use in experimentation, we take a

very scientific and serious approach.

[Slide.]

So, to take a quick look at animal experimentation and the problems with it: most of the animal tests and most of the models in use are decades old tests that would not necessarily be validated if they were created today.

The biggest problem, of course, is that they're not reliably predictive of human responses, especially when you consider different patient populations. At a time when we're at the level of pharmacogenetics and thinking about how different people vary in their response--and especially, for example, thinking that we have to consider different races, male versus female patients, and also the question of whether you can extrapolate between adults and children--the thought of extrapolating from different species, with all those different factors as well, to humans seems really very crude and inconsistent.

When you use animals as disease models, quite often the disease models have a superficial

similarity, but so many other differences that really confound what you're looking at, and they're not necessary good models of the actual human disease.

We think that looking at animals in laboratory conditions may be simpler, but those conditions have laboratory confinement, stress, the food you choose to give them, etcetera, are all other variables which can confound your experiments, as well. And all this leads to a kind of a lack of reproducibility and reliability of animal tests, especially compared to in vitro alternatives.

Of course, animal tests are more expensive, time consumable, and not really fitting with the high throughput environment of pharmaceutical drug development now.

And the main thing is that now that we have tools to study humans directly, that is obviously more efficient than trying to work everything out in animals and see whether you can make that leap.

[Slide.]

This I just put forward, it's just an example of, you know, the problems with animal

testing. I'm sure you've all seen data like this, where, for example, even the mouse and the rat don't show a lot of concordance. When you look at this an across various different species, you really have no idea--it would be total guess work to say what would happen in humans for any given chemical.

[Slide.]

The problems with using this animal research for humans is that not only might we miss drugs which would been boons to human health--for example, penicillin, which is toxic to guinea pigs--we also will miss problems where animal studies will not detect safety issues in humans; for example, where Vioxx was actually protective of cardiovascular health in the animal trials and, of course, has been found to have a very different effect in humans.

So what are the alternatives?

[Slide.]

In terms of human-based development, looking at human biology, we can do target discovery through genomics and proteomics profiling of human tissues, looking at disease versus normal; different stages of cancer development and tumor

development; epidemiology.

In terms of safety and efficacy testing, obviously in vitro technologies, using tissue cultures, experimental medicine, and micro-dosing trials using these very early stage biomarkers with genomics, proteomics and imaging biomarkesr--which I'll discuss a little bit more later; and also predictive toxicology, computer based modeling simulation and that type of thing.

[Slide.]

The advantages of these technologies are numerous. Basically faster, cheaper, more reliable, reproducible, relevant. So basically, across the board, they're better.

The only way in which, compared to animal models, they're worse is that there's not a whole

animal. And that is really the reason that people cling to animal tests is that they want the security of knowing what happens in a whole system.

But I would say that, when you're looking at a whole system that is a whole different species, you really don't know what you're getting. You don't understand the relevance. And we would be better able to predict safety by breaking it down, understanding the mechanisms, and putting together a battery of in vitro tests where we really understand what's going on, instead of black-box animal testing.

[Slide.]

[Slide.]

So I just want to introduce that through the ICCVAM Authorization Act, Congress has mandated that every Federal agency "shall promote and encourage the development and use of alternatives to animal tests." So this really is a mandate that the FDA must follow. And the interagency coordinating committee on the validation of alternative methods is an interagency committee

that the FDA's a part of, which works on these issues.

I think the FDA is recognizing the problems with animal testing, and the need to move forward. And the Critical Path Initiative--which I hope you're familiar with--is an example of a way that this can move forward.

The Critical Path Initiative is a report by the FDA--the report itself mentions that 92 percent of drugs that pass preclinical testing---which is currently almost animal testing right now--now failed during clinical trials. And that number has gone up.

So what we're doing right now is really not very good, it's not very predictive. So we really need to change the paradigm of what's happening.

And I just want to mention at this point: you know, some people see this as being weighing animals against humans. And it's really not. Because if we just cling to animal testing blindly, we're really hurting humans, if we could be using

systems that are more predictive of human safety.

So what we really need to do is modernize the development path. A lot of these animal tests are just old, leftover tests. And we need to update to some of these newer technologies that are out there but are not being incorporated appropriately into the pharmaceutical development process.

The Critical Path Initiative also says a couple of things about animal models' having limited predictive value and failing to predict safety problems.

So--to get more specific about cancer drugs: some of the problems with animal testing for cancer therapies, more specifically, is that animal tumors are inherently different from human tumors. They grow more quickly. They regress spontaneously. They're usually of different types than human tumors--and I'm sure you all know this. And there's also a variety of specie-specific mechanisms in the genesis of these tumors; for example, saccharine, which I'm sure you're all

familiar with, having been thought to be a human carcinogen for so long when they discovered it was really only a rat-specific mechanism that made it look like a carcinogen.

Metabolism in the liver is very significantly divergent between species. And this, of course, impacts the response to both cancer-causing chemicals as well as chemotherapeutic drugs. So you really don't know what metabolites are running around in animals versus what you're really going to see in the humans.

The induction of cancer in experimental animals is high unnatural--usually chemical or radiation poisoning, transplantation of tumors, transgenic or mutation--things like that. And they're not really relevant to the way that a tumor progresses--the way that cancer progresses in people, which a combination of genetic risks, environmental factors, and over long periods of time. And there's not enough focus on understanding these things in humans. And when you

study these cancers that you've created in animals, you're not really learning anything that's relevant to that.

And just as a specific example, even when you make the exact mutation, if you create Rb-defective mice, the mice don't develop retinoblastoma. You can't just recreate diseases in animals.

And just also the example of cancer and smoking. You may be aware that animals that inhale tobacco smoke, or are exposed to tobacco derivatives, just do not develop cancer. It just highlights, again, the fact that animals and humans are very different when it comes to cancer. And people can hide behind that, but we really need to get beyond using these animal models.

Just a couple of quotes that relate to the history of this, and the track record.

[Slide.]

And there were many quotes I could have chosen from, denigrating these animal models. But these quotes--for example: the NCI's screening program of plan species, "several of the plans

proved effective and safe enough in the chosen animal model to justify clinical trials in humans--"--but "--none of these drugs was found useful for therapy because of too high toxicity or ineffectivity." "That means that despite 25 years of intensive research and positive results in animal models, not a single anti-tumor drug emerge from this work. AS a consequence, the NCI now uses human cancer cell lines for the screening of cytotoxics."

And also from Richard Kausner, who is the former Director of the National Cancer Institute--this is when he was the Director: "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades, and it simply didn't work in humans."

And people were discussing the ALL mouse model earlier--the fact that it doesn't work; that it's unvalidated. And there was a comment that, "Well, we should still look at it because some information is better than no information." And I

would submit that some information that is misleading is actually worse, because you could end up pursuing false avenues. You take time and resources to do these animal studies, and you end up perhaps missing something that could have worked in humans, or vice-versa.

So we really need to take those same resources in using unvalidated animal models, and put them towards developing better models, rather than letting these unvalidated models get entrenched and waste a lot of time and money--which is cancer patients' lives.

What are the alternatives--in cancer research specifically?

[Slide.]

Most of the advances in basic research have come from clinical research studying cancer patients. And nowadays we have so many more technologies where we can study them directly, using things like gene expression profiling that helps to detect the mechanisms already discussed, as well as sometimes people really don't understand

that in order to profile patients into groups that help make better prognoses for how their disease will progress. And, obviously cell and tissue culture models--which are also used in testing drug candidates.

When it comes to testing these cancer drug candidates, I wanted to mention biochips. I don't know if you're familiar with this technology. It's quite new. Basically, these are microfluidic circuits lined with human cells. And one version of this--the Hurel--has been getting a lot of press lately. It's a very new and innovative technology. And the originator of the Hurel actually has a version that incorporates human uterine or colon tumor cells, as well healthy cells from various organs, which helps to test for drugs that selectively kill the tumor cells, and his vision of this going forward is that you can actually create these biochips with a patient's own cells, which will help you get towards personalized medicine.

And actually, they're looking for development partners right now as they're entering

their validation stage. So if any companies are out there who are interested in that, you should contact them.

In terms of in silico prediction, there's a lot of companies out there that do in silico prediction. There's one, Physiomics, that specifically focuses on cancer drugs.

And also, when you go to early exploratory studies in humans, we're talking about getting to earlier surrogate endpoints. And things like PET scans can detect glucose uptake, which is a surrogate endpoint which is necessary for tumor growth, much earlier than other kinds of endpoints. So you can get to these very early surrogate endpoints using this.

[Slide.]

I want to talk about Gleevac as just an example of kind of tying together a lot of things we've talked about. And, obviously, it's a great example of a targeted therapy, where you understand the human biology, the mechanism , and you address it specifically.

In terms of its research, obviously the basic genetic defect was discovered through analyzing patients. You never would have found

this in an animal model, because you really needed to understand what was going on in the specific patients.

In terms of discovery, the chemical was first tested on cancer cells in culture, and also regular cells in culture, and that was where the excitement over its specific effect was generated.

And when it comes to the testing of this drug, Novartis almost did not pursue it, partly because it was toxic to dogs. This is another example of if you rely on these animal tests too much, you could miss something that would really benefit humans. But however, when they did microdosing studies in humans, the PET scans showed that glucose uptake stopped as early as one day after the first dose, so they could see how effective it was.

[Slide.]

Just to wrap up by talking a little bit

more generally about PETA's priorities, as we work with the FDA--and we have been meeting with various centers at the FDA; meeting with the Pharm Tox people at CDER tomorrow.

We are addressing endpoints like phototoxicity, skin irritation; these ADME tests, whether they can be replaced with microdosing; carcinogenicity--it's kind of the flip-side of what you're talking about, but it's obviously a lot of drugs are tested for carcinogenicity, and for the same reasons, that animals are different when it comes to humans, for cancer these tests are highly unpredictive. And acute toxicity is something else we're looking at.

[Slide.]

So--I'm not going to go over this slide, but I just wanted to quickly just note that there's been a lot of recent attacks on the two-year rodent cancer bioassay, and it's something we really hope can be replaced--or there at least can be an effort to replace it very soon.

[Slide.]

When you think about barriers to change, these are the things that we work against. These new modern technologies should be included and

updated, and we really need to move toward things that are more predictive. And these are some of the reasons that we can't.

The FDA has no real established structure for keeping up to date on these evolving preclinical research technologies. They pretty much react to whatever is submitted to them, which is usually the older tests. As the newer tests come in, there's really no way to look at them, validate them. There's really no time to do that. And so we end up just stuck with the same old tests, which have not been working. There really needs to be some way to overcome that.

When they do look at the non-animal tests, in general regulators also compare them to the animal tests, which hasn't really been working very well anyway. We really need to compare them to human results, as well as validate the animal tests against the human results.

And usually these in vitro tests are held up to unreasonably high standards because animal testing is just presumed to be somewhat relevant or valid in and of itself, even if the test itself has never been shown to predict human results. But the in vitro tests have to be perfect before they can

be used.

And generally, emotional reasons: inertia, conservatism, and lack of urgency in that kind of issue is something we need to overcome.

[Slide.]

So, lastly, I just wanted to talk about what can be done.

The guidances that the FDA puts out have a lot of these animal tests imbedded in them. They need to incorporated the validated non-animal technologies out there, and delete the corresponding animal tests when it is less predictive.

There needs to be more effort towards funding and developing these non-animal technologies--

CHAIRPERSON REAMAN: Ms. Dhruvakumar, I'm just going to interrupt. I'm going to give you one minute to sum up and close.

MS. DHRUVAKUMAR: This is my last slide.

CHAIRPERSON REAMAN: Thank you.

MS. DHRUVAKUMAR: And there should be more discussion of these things; FDA workshops, meetings, and opportunities to really familiarize the FDA reviewers with the new technologies.

And, of course, we would like to participate. As the animal protection, we have a lot of scientists, and we would like to help make this transition that will really benefit humans as much as animals.

Thank you.

CHAIRPERSON REAMAN: Thank you.

DR. FINKLESTEIN: I respect the respect the speaker for her enthusiasm. On the other hand, I have had an opportunity to work with the FDA pretty closely in this last seven and eight years. And I find them very flexible. I find them very intelligent. And I don't think they've put on

blinkers to close their eyes to any new developments--at least the way I've seen it in the last seven to eight years.

MS. EICHNER: I just wanted to point out, from a parent's point of view--as you heard to do, clofarabine is the first drug to be approved for childhood cancer in the past 20 years. So, the drugs that were approved in the '60s and the '70s are still prevalent today. They were the drugs that happened to--they're the same drugs. They haven't changed--and save my child's life.

So I am in favor of animal studies. And I hope that they continue. I'm also in favor of exploring other avenues of research. But I did want to make that point clear.

CHAIRPERSON REAMAN: Thank you very much.

MS. DHRUVAKUMAR: Thank you.

CHAIRPERSON REAMAN: If there are no other comments, we will break for lunch, and resume at 1:15.

[Luncheon break.]

A F T E R N O O N P R O C E E D I N G S

CHAIRPERSON REAMAN: Back on the record.

I think we can call the afternoon session to order, and start with a discussion of the Best Pharmaceuticals for Children Act--BPCA. And Ann Zajicek, from the National Institute of Child Health and Human Development will present, and lead that discussion.

Ann?

The Best Pharmaceuticals for Children Act (BPCA)

DR. ZAJICEK: Good afternoon. Nice to see you all. I used to work at the FDA, so it's nice to see familiar FDA faces. And when we sort of started this effort with the Children's Oncology Group and the Pediatric Subcommittee a couple of years ago--this was the first time we talked about these drugs--and now the projects are ongoing. So things have been going well.

So I want to talk about the Best Pharmaceuticals for Children Act--the BPCA.

[Slide.]

This is a law that was enacted in 2002,

and the six-month exclusivity provision of it is scheduled to sunset, according to the Act, in 2007. It's a very long act--I think it's like 27 pages or so. It, in part, continues the exclusivity provision of FDAMA. And the main purpose is to acquire more information about pediatric drug therapy--and, specifically, pediatric labeling.

[Slide.]

So just to summarize--as Dr. Mathis had this morning--for pediatric labeling, the Pediatric Research Equity Act should cover drugs pre-approval. For on-patent drugs there is a section of the Best Pharmaceuticals for Children Act which continues the exclusivity provisions of FDAMA, as well as supporting some on-patent studies that are directed by the pharmaceutical industry.

But its main purpose is to fund off-patent drug studies.

[Slide.]

The way the law is written, there's a specific section dealing fairly extensively with pediatric oncology. And there's one section that

talks about, for pediatric oncology: methods of prioritizing new drugs for study; assuring timely access to new treatments for patients and to develop some sort of preclinical models of pediatric cancers.

[Slide.]

Now the way this act works is that the FDA provides to the NIH--and, very specifically, the NICHD--a list of all off-patent drugs which lack pediatric labeling. And this is an ongoing process. It happens yearly.

The list usually is around 200 drugs--170, somewhere in there. And it's the responsibility of the NICHD to prioritize these drugs. And the law very specifically mentions some factors to be considered in prioritizing drugs. So, in order to take the 169 drugs and come up with 10 drugs, or 15 drugs--or some smaller list, where there's a focused question about exactly what should be studied.

And so in considering drugs for prioritization, we are asked to consider the

availability of safety-efficacy data. So, in other words, if there seems to be sufficient data in the literature, there's no point in reinventing the wheel by doing the studies again, if it can be gotten in some sort of data base, or by the literature.

"Are additional data needed?" "Will new studies produce health benefits?" And I'd like you to think about that health benefits issue, because well be coming back to that. Because that is sort of the crux of the matter here, is: exactly how do you define a "health benefit?"

And there are also issues of formulation. As you know, a lot of these compounds come in tablets and capsules, and not suspensions or solutions. And this is a major problem for children who could not possible swallow a tablet or a capsule.

So we send this list of drugs to experts in pediatric practice and research, as well as advocacy groups, in order to get their input into what they consider to be drugs that require more

study.

And then we develop, prioritize and publish an annual list in the Federal Register. And this ends up, again, being--starting from 170 drugs and culling this down to some more reasonable number a year, usually 10 drugs or so.

[Slide.]

So, again, the FDA provides us a list of all the off-patent drugs lacking pediatric labeling. We request input from the IC's--the institutes and centers--other Federal agencies, including the FDA and the CDC; experts in pediatric therapeutics, as well as advocacy groups, as I mentioned.

The NICHD then convenes an annual prioritization meeting of experts. And there are sort of two sets of experts; there are experts in fields--for example pulmonology, infectious disease, and so on--as well as experts in pediatric clinical pharmacology. This meeting this year is taking place November 8th and 9th. If you're interested in coming, give me a call. I'll be glad

to invite you.

And then based on this meeting--again, once this list of drugs is culled down to a smaller list---this list is published, according to the Act, in the Federal Register.

[Slide.]

Now, because the Act treats pediatric oncology somewhat differently from the other pediatric areas, I'm requesting input from this group--and we've requested input from the Children's Oncology Group--for drugs to be studied. And we'll talk about those drugs in a bit.

[Slide.]

These are drugs that have been prioritized so far. This was the first list--drugs: azithromycin, baclofen, bumetanide, dopamine, dobutamine, furosemide, heparin, lithium, lorazepam, rifampin, sodium nitroprusside, and spironolactone were listed initially. And we'll gt to what happened to those later.

[Slide.]

The August 2003 list included

ampicillin/subactam, diazoxide, isoflurane, lindane, meropenem, metoclopramide, pip/tazobactam, and promethazine.

What you may be noticing with these drugs is these are all off-patent, they're all old drugs. So these are not new drugs on-patent.

So part of the question is--as we go on--have some of these drugs sort of outlived their utility, and therefore we should not spend time studying them?

[Slide.]

The list from February 2004 included ampicillin, ketamine, vincristine, actinomycin-D--and, again those drugs were submitted to us by the Children's Oncology Group--as well as metolazone.

[Slide.]

Last year's list included ivermectin, hydrocortisone valerate--ointment and cream, hydrochlorothiazide, theambutol, griseofulvin, methadone, and hydroxychloroquine.

[Slide.]

Now, what happens to these drugs is that now that we've gotten this prioritize list that gets published in the Federal Register, that list

goes back to the Food and Drug Administration. And the FDA is responsible for writing a Written Request. And the Written Request is simply a letter to the holder of the NDA, or the abbreviated NDA, saying that we would like studies to be done--in this patient population, this number of patients, these kinds of studies; this is what we're interested in. So, it's a three-page letter or something like that, going to the NDA holder.

And for the off-patent drugs, the companies have 30 days to accept or decline. And if they do not respond, it's assumed that they have declined, and then the Written Request gets referred to the NIH, to the NICHD, for a contract.

[Slide.]

Now, the NIH has three methods of funding: there are contracts, cooperative agreements, and grants. And probably everyone in the room is probably most familiar with the grant process,

where you can put together an RO1, and investigator-initiated grant. It gets reviewed, it gets a priority score, and then gets funded or not funded. But there the onus for the work is primarily on the grantee.

And the cooperative agreement is more of a partnership between the NIH and the awardee of the cooperative agreement.

A contract is different. It's a legally binding agreement between the contract awardee and the NICHD for very specific deliverables, The BPCA specifically stated that these projects should be done under a contract mechanism, although it's not completely clear that the writers of the law meant "contract." It may just have been that they were more familiar with the contracting process.

The good thing about the contracting process from our point of view is that we need very specific things in these projects in order to get labeling. We need to have certain studies done, in a certain way, with a certain number of patients. And so, for our purposes, probably the contract

method is probably the best way.

[Slide.]

So the way this mechanism works at the NIH is, again, the Written Request is referred to us. The medical officer--who would be me, and others--put together a request for contract, which is an internal document, which then goes to the contracts management branch, who puts together a fairly extensive document called the "RFP," to the "Request for Proposal."

This gets published in a sort of odd location that the government uses for its contracts, called "Federal Business Opportunities." And we're trying to get the word out that that is where these are published. These are not in the NIH Guide. They're published in a very specific place because this is how the government requests contract business, is through www.FedBizOpps.gov.

So that's where--we're trying not to hide this in plain sight, but that is where these are all published: in FedBizOpps.

[Slide.]

The proposals--you typically have a 90-day timeline. The proposals are then peer reviewed--similar to a grant mechanism. There's a

special emphasis panel that's convened, consisting of people that are experts in the disease area or the drug area, statisticians and so on, who give the proposal a score. And then a contract or contracts are awarded.

[Slide.]

And, again, this is the location of where we post these. So I would--if you would like to take a look at these, everything that we've published so far should be on this website. And, again, it's www.FedBizOpps.gov.

[Slide.]

Post-award, the way the things that we're in the process of going, is that the study is performed. These are all done under an IND--and "Investigational New Drug Application." The project officer, or the medical officer at the NIH, is responsible for overseeing these projects, is the holder of the IND. So I, for example, am the

holder of the IND for the nitroprusside project.

In the future, the data will be analyzed. The results will be submitted to us. And the data will be published on our website. The results will be submitted to the FDA, placed on the public docket, and then negotiations will go on for labeling.

[Slide.]

So--where are we in this process?

[Slide.]

These are Written Requests that have been issued by the FDA so far. There are two Written Requests that were issued for lorazepam. It was felt that there were two main indications for lorazepam that needed to be studied. So there was a Written Request issued for lorazepam for sedation of children in the intensive care unit on ventilators, and one for children receiving lorazepam in the emergency room for status epilepticus.

There was a Written Request issued by the FDA for nitroprusside for blood pressure reduction

in the operating room and in the ICU; two Written Requests for azithromycin--one for the IV form for treatment of ureaplasma urealyticum pneumonia, and prevention of BPD; and, for the oral formulation for prevention and treatment of chlamydia pneumonia.

One for baclofen--now, baclofen's an interesting case. When this was initially prioritized it was off patent, but then it went on-patent because of a new formulation. So--we'll get to that in a minute. But, anyway, it has been both on and off-patent.

A Written Request was issued for lithium, for the treatment of acute mania in children with bipolar disease.

[Slide.]

Lindane for treatment of scabies; rifampin for treatment of methicillin-resistant staph aureus, endocarditis, and CNS shunt infections; meropenem for abdominal infections in neonates; vincristine and actinomycin-D for children with pediatric malignancies.

[Slide.]

And these are the ones that have been declined by industry. And you'll see that this

list is exactly the same as the other list--except that lindane was accepted by industry. So all of the Written Requests that have been written have been declined. So the two for lorazepam, nitroprusside, the two for azithromycin; baclofen has been rejected twice, both on and off-patent. And rifampin--the Written Requests there have been rejected as well.

[Slide.]

Also meropenem, vincristine and actinomycin-D.

[Slide.]

And, again, the Foundation for the NIH could theoretically pay for on-patent Written Requests that had been declined by industry.

The ones that have been declined and referred to us so far include: morphine, baclofen--again. Bupropion, sevelamer, zonisamide, hydroxyurea--and two recently: dexrazoxane and

eletriptan.

[Slide.]

Contracts and interagency agreements have been awarded for some of these projects. There was a contract awarded for lorazepam for sedation in ventilated patients. This went to Case Western University, and Jeff Blummer, in particular; Lorazepam for status epilepticus to Jim Chamberlain at Children's National Medical Center.

Two contracts were awarded for nitroprusside: one to Stanford, and one to Duke. And, most recently, a contract was awarded for lithium also, to Case Western.

[Slide.]

Inter-agency agreements have been funded, as well. There was concern about ketamine producing Olney's lesions--central nervous system lesions, and apoptosis. I guess this may be a concern for a lot of sedating agents. But we have funded some preclinical toxicology studies for Ketamine.

We have funded vincristine and actinomycin-D projects through the National Cancer institute; and hydroxyurea, for an ongoing project

in the Heart, Lung and Blood Institute.

[Slide.]

Contract negotiations are currently ongoing for the RFPs for azithromycin for ureaplasma. An RFP has been published for chlamydia. Contract negotiations are ongoing for baclofen. And the RFP submission date for, meropenem, I believe, was Monday. So we'll be having negotiations and peer review for the meropenem project, as well.

[Slide.]

We also funded a data coordinating center. It was necessary because of the number of studies and the amount of data that would be coming in, to have an organization to coordinate patient enrollment; coordinate and monitor data collection; report adverse events and other data to our Data Safety Monitoring Board; and to analyze and organize results into a supplemental NDA--or

whichever formal is decided on--for FDA. And this contract awarded to Premier Research in Philadelphia.

[Slide.]

I next wanted to talk about what was in the written requests for vincristine and actinomycin-D. Dr. Barrett will be talking specifically about those projects. But I just wanted to let you know exactly what the FDA had in mind, regulatory-wise about these projects.

The Written Requests were similar for both. They both proposed two studies. Study 1, a prospective PK study in patients zero to 16 years of age. The diagnosis was proposed to be Wilms' tumor rhabdomyosarcoma, as well as other tumors in children. They proposed a number of at least 100 patients, especially if sampling was done in a sparse-sampling way, as opposed to a dense sampling. And the endpoints of the study were to be the relationship of pharmacokinetic parameters to body size and composition; cancer type and severity; age, gender; and other concomitant

medications.

[Slide.]

Study 2 was an analysis of data bases and ongoing clinical trials to evaluate safety and efficacy endpoints in this same population of patients with Wilms' tumor, rhabdomyosarcoma, or other tumors. And the endpoints would be event-free survival. And toxicity endpoints for actinomycin-D that were of special concern included thrombocytopenia, and especially hepatotoxicity; and for vincristine, neurotoxicity. And, again, Dr. Barrett will discuss those projects.

[Slide.]

These are drugs proposed by the Children's Oncology Group this year. There were three drugs: doxorubicin--which is on-patent. So that will go through another process. And the two drugs that were off-patent included daunorubicin and methotrexate.

And I think the concerns from the Children's Oncology Group included--for daunorubicin as well as doxorubicin--the

relationship of obesity to efficacy, safety and PK parameters. And for methotrexate, safety--in particular, neurotoxicity--as well as efficacy of two different treatment regimens.

[Slide.]

Now, the next few slides have an enormous number of drugs on them, and I'm not going to read all of them. And this is more for your perusal in the next week or two, to sort of think about it.

These are the drugs that are off-patent this year. And the question is: in your mind, do you feel that there's any benefit in studying any of these drugs? And, again, there are about 200 of them. So I'm not going to read through all of them.

But there are numerous numbers of anti-infective drugs. Again, you'll notice these are not new antibiotics. These are old antibiotics that have been around for a while. Although, as I understand it, because of drug resistence, it may be that just because they're old doesn't mean that they're bad. It may mean that they're being used

again, after resistence has occurred with newer agents.

[Slide.]

And more of them.[Slide.]

And still more.

[Slides.]

Again, some of the question here, again, has to do with the health benefit--as I mentioned before. If you feel that there is literature, or if you know about literature for any of these drugs, that would be submittable, we could certainly--we'd be interested in discussing that, too.

[Slides.]

But, again, long lists of the anti-infective drugs.

[Slide.]

I guess I should mention also: for some of these antibiotics, we had had them on the priority list in past years. And what sort of came up was that there was sort of this offset of the sheer numbers of patients receiving these

antibiotics--meaning that there were huge numbers of patients receiving them, but yet that they seemed fairly safe, and that people felt comfortable dosing them. So there didn't seem to really be a question. There didn't seem to be any toxicity that was burning in anyone's mind.

But, anyway--more antibiotics.

[Slide.]

These are the anti-neoplastics. And I'll just mention these: decarbazine, 6MP, bleomycin, cisplatin, cyclophosphamide, actinomycin-D--if there's another question that hasn't been answered--daunorubicin, and so on.

So, again, if there's any question in your mind in the next several weeks that you feel that there would be a purpose in studying any of these drugs, we'd certainly be most interested in hearing about it.

[Slide.]

Now, the other question is about supportive care. These are drugs that are off-patent. These are sedation drugs: lorazepam,

oxazepam, chloral hydrate, pentobarbital.

[Slide.]

Drugs for pain management that are off-patent at the moment: hydromorphone, ketamine, methadone--so, again, not necessarily the anti-neoplastic agents, but these supportive care drugs we would also be very interesting in supporting studies if it's felt to be important.

[Slide.]

And these are some miscellaneous drugs that didn't really fit into any other categories.

[Slide.]

So the questions we have--and, again, these are sort of things to think about. I'm not expecting an answer in the next 10 minutes--but to think of exactly how to go about prioritizing these drugs, and what sort of prioritization process should be used for deciding which drugs should be studied. And most of the crux of this question has to do with the health benefit: how do you define a "health benefit?" Number of patients? Lack of other drugs to treat the disease? Severity of the

disease?

[Slide.]

And the second question is, specifically: are there any of these drugs that you feel would deserve another study? Or any kind of study? Anti-neoplastics, supportive care medicines, anti-emetics. I think metoclopramide was the only one currently that's off-patent that's an anti-emetic. But, again, this on-patent, off-patent thing is sort of fluid. So just because it's off-patent this week doesn't mean that it won't be on-patent next week, and vice-versa.

Anti-infectives, analgesics, and other drugs. So these are some food for thought for us. And we would appreciate, again, any input that you have. Again, if you want to give us an answer today, you have my e-mail, feel free to contact us. Because we're very interested in any input you could offer.

[Slide.]

So, in summary--again, this is a work in progress. It's an act that's only three years old.

It's a good partnership with the FDA. And it's our responsibility--the NIH responsibility--to prioritize the list. We have ongoing discussions with the FDA about input on the Written Request. And it's our responsibility to sponsor clinical trials in children that will provide improvement in pediatric therapeutics.

Thank you.

CHAIRPERSON REAMAN: Thanks, Anne.

Any questions that relate to the Act or the program?

Victor?

DR. SANTANA: Anne, does it allow to study combinations of drugs? Or does it have to be a single drug, alone? I'm thinking of the example--I'll give you an example--the issue that we always wrestle with supportive care, with anti-emetics; using steroids with another drug. And then the combined toxicity of those.

DR. ZAJICEK: It's my understand--correct me if I'm wrong--that we could study a combination. However, the label that would result from it would

be labeled as, "When drug X was combined with drug Y, these were the results." So it would have to be--for example, with the lorazepam for sedation project, the question there is: if you have patients on a background of fentanyl, then the label would have to state, you know: "The patient was treated with lorazepam with a background of fentanyl--"--and required this kind of dose. So it would have to be--is that correct?

DR. MATHIS: Yes, we would label it as "adjunct therapy" if it was used in combination, and had to be used in combination for efficacy. Or sometimes what we do--like if there is a background of fentanyl, what we might do is more clearly describe in the label exactly what the study was, and what the other medication was that the patient was on.

But most of the time if it's a combination, then it has to be labeled as "adjunct therapy."

DR. DOMSEY: There's also a logistical issue, which I think Anne also--and we--have had to

deal with, is that in the early part of this process for the off-patent, where you have to issue these letters to the innovators, you have to issue a letter to an innovator. So if you have a combination, if you've got two companies involved, you have to issue letters for both.

With the vincristine and actinomycin, for example, we recognize that in the clinical setting they're used quite frequently together. And nevertheless here, in this case, this wasn't so much an issue, because there was an interest, in terms of the safety and efficacy in different age groups with respect to each by itself. But even if there weren't, I think we would have still had to find some way to issue a Written Request to two sets of innovators to get around that.

DR. SANTANA: That doesn't both me too much, because the history that I just heard is that the industry's not very interested.

DR. MATHIS: I think at other times, too, one of the ways to get around that, really, is when we're writing the Written Request, we identify the

drug that we're really interested in, and then we'll say, you know, "in adjunct therapy to standard of care medication for this." So sometimes we won't specify exactly what the other drug is. But all the experts in the field know what that drug is, and use it in the studies.

And when the studies are submitted to NIH, they would, of course, evaluate it to make sure the right adjunct therapy was being used, as well.

DR. REYNOLDS: There's a drug that's not on your list that's actually an anti-neoplastic that I'd like to bring up for a couple of reasons, and that's 13-cis-retinoic acid. It's off-patent.

First of all, there's some real questions about pharmacology and formulation that need to be studied, that even though there was an efficacy study by the CCG, there are still unanswered questions. In fact there's a COG study that's about to amend--a protocol--to answer those. But no one's doing it formally.

There's no labeling for it except in Italy; it's labeled as an indication for

neuroblastoma in Italy. If it were labeled in the U.S., then children in Japan could actually get it--possibly--because they can't right now, because there's no acting in Japan, and the Japanese government won't even look at anything that doesn't have an indication here.

So there's lots of reasons to study labeling on this.

But the second issue is relative to the fact that the dermatological population is different than the pediatric neuroblastoma population in a lot of ways. And one of that is the risks for having teratogenicity. There's an onerous program in place now by the people that are dealing with this--the various generics--and it takes a lot of effort to deal with this, for a pediatric oncologist.

And it's not clear to me why, since most drugs that pediatric oncologists are teratogenic--and they don't have to register the patients or themselves on a website--why this drug should be any different. And I've had a lot of discussion

with the agency by e-mail on behalf of the neuroblastoma community on this, and we haven't been able to resolve this issue.

So I wondered: is this the forum to resolve this issue? Or is there another way? Because it's not an individual sponsor now. It's a generic issue.

DR. ZAJICEK: Well, if it's off patent it would sort of be under BPCA globally. Umm--why don't we--we'll have some conversations about this.

DR. REYNOLDS: I'll send you an e-mail.

DR. MATHIS: If I could just follow up, too.

The drug is currently approved and indicated for a different disease. I mean, it's for a dermatologic indication. So, if the drug were to be studied for another indication, I don't know what the requirements would be for--you know, right now there is limited distribution; you have to have pregnancy tests. I'm not sure how that would change, or if it would change.

But, taking the drug off-label and asking

for different requirements--that probably isn't something very realistic. However, NIH could look at it and consider studies for an oncologic indication. And that may have different ramifications as far as what's required for the patient to get the drug.

DR. WEISS: What I would suggest, though, is--and we'll have more time, I think, after the next presentation, to have just more discussion on the issue of other drugs to think about. And I think that if the committee thinks that cis-retinoic acid would be one to strongly consider, what we could do at a future meeting--and we'll have time at the end to also discuss future topics--is to think about what--you know, if we wanted to have a more in-depth discussion, for instance, on that particular molecule, and how might it best be studied to provide health benefits--to think about bringing in some of the other experts, and other groups that actually deal with this drug, including like the risk management programs.

I mean, we might want to have a little bit more comprehensive--because of the unique aspects of this particular drug compared to some of the

other things.

So I think it's a really good thought, and one might want to think about--you know, if we want to further discuss this--because there's only precious few drugs that get to the list, and even precious few smaller numbers of oncologic drugs, because the list is, you know, encompassing all of pediatric disease--and that this is one that people think is a really important one.

Again, we'd want to then think about how to develop the right questions, and get the right input in a future meeting to address, in a comprehensive way. Because we'll have our best shot to study it in a sort of prospective plan.

CHAIRPERSON REAMAN: I think that's an excellent suggestion. And, actually to begin the program, we really were focusing on the most widely used drugs that would have the greatest impact on the largest portion of the pediatric oncology

population.

But maybe before going on and discussing general issues related to BPCA--was that your question, Jerry?

DR. FINKLESTEIN: This is more global--but it includes the FDA and your agency, which is anywhere between 14 and 25 percent of children today are obese. How are you attacking that, in terms of your drug evaluations.

CHAIRPERSON REAMAN: That was actually one o the reasons that we are looking at vincristine, actinomycin-D, doxorubicin, daunorubicin, were specifically for those issues, looking at a variety of factors and parameters that might relate to PK issues.

So--that's a perfect segue, I guess, into Jeff's--and age being just as important, actually, as obesity, because of issues that we were talking about earlier today.

So--Jeff, go ahead.

Actinomycin-D/Vincristine in Pediatric Oncology Trials

DR. BARRETT: I'd like to thank Dr. Weiss and the rest of the committee for inviting me here today to give you an update on progress that we've

made through the Children's Oncology Group on studying actinomycin and vincristine really in response to the RFP that Anne discussed in the previous presentation.

[Slide.]

What I want to do is just give you a very little, brief introduction on the clinical setting for these two agents in pediatric oncology; again, spend a little bit of time talking about the "missingness" of certain data--which is really behind the reason why the RFP exists; and not just the fact that it exists, but the impact of that missing data on pharmacotherapy with these agents.

I'll talk a little bit about the objectives and goals of the project itself; and I will spend some time describing the individual projects that are consumed within our efforts.

And then we'll focus on the project plan update and where we are with this effort.

[Slide.]

So, just a little bit of background--we're here because there were issues with the dosing of these two agents; and specifically three active protocols for pediatric rhabdomyosarcoma were suspended after four chemotherapy-associated deaths

from venous occlusive disease.

No subsequent evaluation as to the cause of these effects were correlated between the toxicity and drug exposure. And this is primarily a factor related to the lack of pharmacokinetic knowledge of actinomycin-D. But because it's obviously a critical agent, it continues to be used, and the clinical evaluation is obviously vital in terms of replacing our lack of knowledge.

So just a little bit of review of the historical timelines.

[Slide.]

In June of 2004, the NIH did request that COG respond to an RFP, which we did on July 21, 2004; provided a letter of intent with four project proposals. This is really in response to the RFP.

The full proposal was submitted on August 11th, and the award was made on the first of October.

We've been having monthly meetings with the NIH and various components of the core project leadership on a monthly basis. And just keeping track of the project and moving this effort forward.

On the 31st [of March] we presented some of the initial results at the COG meeting to NIH and NCI, and gathered some requirements for a simulation plan--which is really what we're hoping will guide the prospective trial.

And then here we are today, providing some update to FDA on this topic.

[Slide.]

A little bit about the history. Of course, both of these agents have been studied f or a long time. And what you see here is just a little bit of the timeline of the most interesting studies: the National Wilms' tumor 4 and 5 studies, along with the International rhabdomyosarcoma 4 and 5 studies.

So three things come to mind when you look at this table: one, they span several decades. The pediatric indications vary. The n's with some of

these studies are substantial. The treatment groups as well as the dosing paradigms change from study to study.

So, because there hasn't been the kind of pharmacokinetic characterization, the issue of exposure response has really not been elucidated with these agents--separately or together, for that matter. So this really drives home the problem.

But also one of the things that's embedded in this--and I'll talk at length about it--is: the data handling practices, and the mechanisms used to collect that information vary dramatically over this time window. And that, in fact, will dictate the progress that we've been able to make in some areas of piecing together the historical data.

[Slide.]

Just an example, maybe, of some of the dosing paradigm that is provided in the various protocols--you'll see there is some guidance on

both of these agents in terms of dosing on either a body-surface area or weight-based regimen. What is true, specifically in the case of actinomycin is that there's no data to base this on. So, historically the dosing has been guided empirically.

There are several complicated dosing paradigms to handle backing off based on toxicity, or dosing in special populations--for example, renal impairment. But, there again, there's no quantitative data that supports those adjustments. So this has provided some of the impetus for the Written Requests.

[Slide.]

Again, there hasn't been any historical analytical mechanism to support the quantification of actinomycin-D, so the kinetics are largely unknown. Likewise, the pharmacodynamic--any correlation of exposure--is unknown.

Because the historical datas were collected in the manner that they were, even associating dose to the toxicity profile has really

not been well characterized--qualitative, at best.

So this is true for vincristine, as well--although there is quite a lot of pharmacokinetic data--particularly in adults. And this is not really well defined in pediatric populations. So the exposure response with respect to toxicity is not well defined. And another area of interest, of course, is the pharmacogenomic potential here. This continues to be an agent that we struggle with in terms of managing individual patient care. And there is plenty of evidence on the pharmacogenetic side that we could possibly be able to explore these relationships. So this was another part of the proposal that we integrated into our efforts. Likewise, the dose-limiting versus manageable toxicities are really unclear here.

So, one of the things you saw very clearly in Anne's presentation was the request to consider age and size dependencies, special populations, and guidance on drug interactions.

[Slide.]

So this is an overview of the four projects that we had submitted in response to that request--the first being to conduct a retrospective

analysis of the historical data from these four pivotal studies in which these agents were co-administered.

The second was to develop a dosing and pharmacokinetic sampling procedure for both of these agents using a single-lumen central venous catheter. What remains to be an obstacle in terms of the conduct of these studies in this population is, in fact the need to request that parents allow us to put in a peripheral catheter to sample from. So one of the things we had hoped to do was to put together a procedure by which we could actually dose and sample from the central venous catheter. This, we thought, would both improve enrollment, and also give us some flexibility in terms of a sampling.

The third project was to look to define PK/PD relationships based on actinomycin and vincristine response characteristics--

physiologically or mechanistic-based when possible--but to simulate these relationships prior to conducting the actual prospective clinical trial, which would be what we would do in project 4, and that would be similar to what was requested by FDA.

Again there was some incentive to look specifically at studying children three years of age or less. There is some evidence that this age group potentially has more adverse events associated with the dosing of these two agents.

Again, I would say that this is really qualitative. But we certainly recognize the need to get that data in this very young population, as well.

[Slide.]

So one of the things that's obvious with these four projects is that they are highly interrelated, and the overall success definitely depends on communication and project management. So the retrospective study and the catheter study really have been the primary projects to kick

things off. And Dr. Jeffrey Skalnik, who's here with us today, has been leading Project 2, which is the catheter study and the clinical trial concept. And with Project 1, Richard Ablens, in conjunction with COG statisticians have been assembling a lot of the data which has been quite an effort with the historical studies. And I have led the modeling and simulation piece.

But one of the things I'd hoped to illustrate with this figure is that we really need both the retrospective analysis and the catheter study in order to get to the ultimate clinical trial here.

Now, I'll give you a little bit more specific detail on the individual projects.

[Slide.]

So, with this historical data analysis, we wanted to specifically look for--to put together the dosing constructs from those four studies; to correlate the dosing with the efficacy--particularly in children less than three; correlate dosing data from Aim 1 with toxicity in

children less than three; and, finally, analyze the combined data set with quad analysis to provide background data for the trial simulation.

So, simply put: we need to look at dose versus the frequency, grade, severity, time course of adverse events. One of the things that's painfully obvious is that these studies were not collected with the level of granularity that we would like to have. So one of the things that I will already foreshadow--the questions to come--would be: we simply can't do that in the prospective study.

We would like to maximize the utility from this data, but also ensure that the data that we collect from the prospective study is rich and informative.

[Slide.]

A little bit about the specific methods here. There's no magic to what we're going to do here. We simply need to get the data in a form that we can do basic univariate and multivariate analysis, and we'll use a combination of

case-cohort and cohort analysis in order to build these kinds of relationships.

[Slide.]

With respect to Project 2, which would be the catheter experiments, we want to look at the recovery of actinomycin and vincristine in common catheter configurations would be utilize via central venous line; to assess the in vitro equivalence utilized for sampling procedures; develop a specific procedure for dosing and sampling to ensure robust sampling; and, finally, to validate the procedure with an actual clinical test prior to introduction into a larger prospective trial.

[Slide.]

So these studies have been ongoing, and, in fact, we're doing a lot of work related to preclinical characterization. Again, both of these agents historical--in fact, actinomycin, most of the work was done in the '50s, in terms of its clinical development and evolution. So there's good reason why there are no actinomycin assays.

This is a very difficult molecule to quantify. So we don't know very basic things, like the protein binding, like the metabolism. We're doing those studies in addition to what we committed to in the grant. So there's been a number of studies conducted to see if this will turn over the CIPP before 50 enzymes. We have done protein-binding experiments, in addition to developing assay methodology.

I'm going to show you next where we are with all of this effort, but a lot of work has gone into this preclinical characterization to take away some of the uncertainty in the dose exposure relationships. But what you see here is kind of the progression of those kinds of experiments that are heavily dependent on developing methodologies and the commitment to doing the in vivo validation prior to introducing this to a broad number of patients.

[Slide.]

With the modeling--here again, you know, because of the lack of assay methodology we had

heard very little for actinomycin-D. The sum total of the historical experience was a paper published in 1971 in the Journal of Clinical Pharmacology and Therapeutics in three adult patients with tritiated compound in which they tracked radioactivity. And that was really the sum total prior to 2004.

Recently, the UK group--Children's Cancer Group in the UK--has published their own assay methodology and actually studied three subjects in their analytical paper. So we did have the benefit of that. And, more recently, inherited even more data from that group.

But prior to that there was very little information. So we ended up using a physiologically-based pharmacokinetic model developed in the dog to frame the basis of predictions in children. Now, I'll show you how that's constructed in a little bit. But what I could tell you is, based on the preliminary data, this is highly predictive. So--the public comments notwithstanding, I can definitely advocate the use of some of these preclinical animal models

to guide us here. It's definitely been a help in our case.

So, the second aim of this was to incorporate the dose and toxicity data from the Project 1 into the models that we develop on the pharmacokinetic side to derive initial relationships for exposure response; conduct a pilot study in pediatric patients to both verify the sampling procedure and then gain some more knowledge about the inter-subject variability to refine the model.

And, finally, we would like to do trial simulation--both from the standpoint of verifying the historical data--the exposure and toxicity relationships--and also to guide us, both in terms of the dose, the regimen and the timing of therapy study--the prospective study.

So, more or less to articulate what I just said: we're putting information in from a variety of sources, both preclinical data developed in animals, as well as data obtained from preliminary pilot studies to build this family of models.

We've done a lot of this work already--which I'll show you next. But it's clearly with the idea of guiding the prospective study.

[Slide.]

And, finally, we seek to develop and finalize a clinical protocol based on Project 1, and the clinical trial simulation results from Project 3. We're obviously going to evaluate the actinomycin of interest and dose response relationships with a mixed-effects modeling approach. And that specifically implies that we're going to do sparse sampling. And one of the other reasons to develop these models a priori is that we don't have to go down the path of doing a lot of extensive sampling. We have a pretty good idea of the time course, even of actinomycin right now, so we don't have to be in a situation when we're collecting data for the first time.

Again, we're going to look specifically to identify the sources of variation in that dose exposure relationship, but hopefully really derive relationships around those predictors of response.

And ultimately we would like to propose dosing guidance based on clinical utility that's suitable for labeling changes.

[Slide.]

I apologize if you can't see this in a whole lot of detail, but let me walk you through a little bit of it.

We have continued to generate project plans here to keep track of this effort. So, on the top, you'll see Project 1, which is associated with this data mining effort--particularly on the data base creation and data assembly side. The project plan currently goes through April of 2006, although we're going to obviously extend this.

The project plan allows us to both keep track of the interdependencies of these projects, and also continue to revise this and identify those areas where we're poor performing. So it's what every drug company use, obviously. But it's also giving us a handle on our success with this effort, and making sure that we stay on track.

It's in your handouts, and I can provide a

more blown-up copy if you're having trouble looking at this.

But we have made significant progress on this effort, and I'll go over the milestones next.

[Slide.]

So let me tell you first what we've achieved, and then I'll show you.

We have developed an analytical method that measures actinomycin and vincristine simultaneously. This method has been validated to FDA standards, and has been published.

We have developed a procedure for dosing and sampling from a central venous catheter, and we are awaiting clinical validation of this procedure right now.

We have initiated a pilot pharmacokinetic study with three of the eight patients enrolled. We have developed physiologically-based pharmacokinetic models for both actinomycin and vincristine, and scaled these to project pediatric exposures. And these seem to project very nicely to what we've obtained in children.

We have refined these models, based on the data in children. And these are suitable now for clinical trial simulation and application--which is

ongoing.

We have finished a clinical atrial simulation plan that is being circulated right now for additional comments. And we do have a draft clinical protocol that's been circulated to NIH and select COG phase 1 sites. And we will continue to expand this as we get comments.

[Slide.]

So let me review these by project. So we have an initial data base on the Wilms' tumor side. This is still fraught with errors and inconsistencies. This continues to be an issue, and we're moving toward resolution. The other issue is that some of the data on the IRS side needs to be entered for the first time. So that is ongoing.

The statistical analysis plan has been finalized, but this is really the rate-limiting step for our effort overall.

[Slide.]

As I mentioned, we have validated this analytical method for actinomycin and vincristine that uses LCMS technology. We continue to refine this analytical method, with a like limit of detection of less than .1 nanograms/mL for

both--and I'll take you through a little bit more of that.

So both analytes use an internal standard. WE have excellent linearity in terms of assays. Again, the limit of detection for actinomycin is .1, and vincristine .2--or did I have that backwards, Jeff? Anyway--so it's already very good, and suitable for the pediatric clinical trial. But we are continuing to improve this method.

[Slide.]

And this shows you basically how the method performs from two patients who are participating in our pilot study so far. So, again, for the first time you're getting to see what these drugs look like in the target

population.

One of the issues with actinomycin, in particular, is that the drug actually hangs around for a very long time. That terminal phase concentration 24, 48 hours out may indeed be pharmacologically relevant. This is something we hope to tease out of the historical data, because we obviously will not choose to sample patients when it's inconvenient, and try and pick data points that are going to be meaningful--which is, again, so important to actually get the toxicity data together.

[Slide.]

Likewise, there's been a number of experiments that were conducted in order to develop this procedure, which ultimately uses a pull-push methodology to, in fact, clean the catheter prior to sampling. So this gives you an idea of the performance--I mean, we studied a variety of factors here; different agents to clear the catheter, changes in pH, flash volume, etcetera.

This information has been summarized and

is available in an abstract and will be published soon. I have a reference list at the end that I'd be happy to provide some of the source data, as well, if you're interested.

But, in any event, the in vitro results are extremely encouraging and suggest that we should, in fact, be able to move this in the clinic and utilize this in actual patient trials.

[Slide.]

AS for the modeling effort, we started with the model that was developed by Bob Dedrick when he was at the NIH, and have refined this. This is data that was generated with actinomycin and vincristine separately, in the beagle. These are flow-limited PDBK models, and we have scaled them using human physiologic parameters; assumed a moderate amount of variation; and then just projected out what the exposures would be--not just in the plasma, but in the target tissues that we think are associated with toxicities.

Now, again, these are just the results of some of the simulations. We are able to do this

kind of scaling, not just sin the adult but in the pediatric patient, by using allometric expressions. Now, of course, we don't have the actual observed data in these target tissues, but the plasma levels compare very nicely.

So, as a first check we know that this model seems to be suitable to project pediatric exposures. Now, initially we had this just from the two subjects that are in pilot study, but recently the UK group has shared with us data in 31 pediatric patients with actinomycin-D. So this has dramatically improved the modeling effort here. We can really kind of get a good estimate of the variability in the pharmacokinetics of actinomycin, and are now able to use these models to project the various dosing has been done historically, relative to the likely plasma levels that we obtained in those patients.

[Slide.]

This just shows you some of the actual observed data from the UK group. Again we have now, I think, a clear picture of what the exposure

to actinomycin is following IV administration. We took the originally physiologically-based model and have lumped this into a compartmental model to be used in the trial simulation. And, again, we got pretty precise estimates of both volume and clearance in order to make these projections. So this is suitable for the next round of simulations.

[Slide.]

We have completed a simulation plan. I have, in fact, provided this--an earlier draft of this--to FDA reviewers at some point, just for some feedback. So it's certainly nothing we want to keep secret, and we're soliciting input from other colleagues who have expertise in this area.

So some of the scenarios we'd like to consider--we, of course, would like to take a look at the historical trials as kind of a validation that the model is performing as we would expect. We certainly want to explore dosing modifications that have been employed in the past in infants; considered body surface area versus body weight dosing.

With many oncology agents, as you know, there's a switch that happens somewhat arbitrarily at different time points. In some instances, this

actually occurs at different times with the same drug in different indications. So this is not something we have a good handle on overall, but we can use this tool to, in fact, explore it with actinomycin.

There also may be an issue of dose capping that is used with this agent in a variety of variety of other locations outside the U.S. And certainly the most relevant point with the simulations would be to explore study design constraints and sampling considerations to look for adverse event rates that we would like to--or expect to get from a prospective study, as well as clinical response. So these are the simulations that are ongoing right now.

[Slide.]

I don't mean to do too much in the way of statistics, but I want to basically explain a concept that will be relevant when we start showing

more of these results.

So, in the classic pharmacokinetic sense, we develop relationships around an individual's kinetic behavior. And the error that we can't explain in that individual would be this epsilon--or residual--term here. But that one patient is part of a population of subjects. So this inter-individual variability in clearance exists, that we know, within a study. And we'll characterize that by looking at, perhaps, the mean and the variance term around a particular study.

But the other reality is: we do several studies--we do many studies--with these agents, so there is some uncertainty about the mean and the variance. And as you've seen with the historical data here, we also have a sense that maybe the toxicity response is different.

So these simulations are not just of the ilk to look at the variation across subjects within a study, we're looking at the variation across studies; looking at the uncertainty in these pharmacokinetic characteristics across studies.

So how does this really pan out into clinical reality?

[Slide.]

Well, you know, we know that there's discrepancy across studies that may be due to population, dosing, treatment differences or differences across regimens and exposure. Correlation with toxicity is obviously difficult to assess with conventional means--which is, again, leading us to the standpoint of modeling.

On the pharmacometric side of things, we do have techniques in place to look at the model prediction error and the root mean squared against the population means. So we can really identify those design characteristics which will give us a minimal bias, and high precision.

The whole sum total of all of this is that we should be pretty confident, prior to doing that study, that we're going to get good data. I mean, that's what I'm hoping to drive this to.

[Slide.]

We do have a draft of the clinical

protocol. Again, I'm really hoping that we get some additional feedback. Right now it looks more like a COG protocol template, but we are starting to put the results of the simulations, and the data from the historical trials in there now.

It will be in keeping with what the FDA requested us to do, but we simply need to get further down the path with actually recruiting sites to participate in the trial.

[Slide.]

So, as far as critical activities go: we need to complete this pilot study and the in vivo validation of the sampling procedure. We're opening this up beyond the Children's Hospital of Philadelphia to recruit additional sites so that we can get this done in a short term.

A critical factor is, of course, the completion of the data entry and assembly from the historical toxicity data; and likewise to correlate the toxicity with the dosing metrics so we can complete the key trial simulation scenarios.

[Slide.]

And these are really--the next steps would be the actual revision and finalization of the clinical protocol; investigator solicitation and

education; data collection strategy and data management plan for the prospective trial; and then statistical analysis plan for the prospective study. And we're also considering a label exercise based on the trial simulation output, just so we consider the kinds of labeling statements we would be able to make from this prospective trial.

[Slide.]

And this is a list of the references that have already come out of this work.

And if there's any questions, I'd be happy to answer them.

Questions from the Subcommittee and Discussion

DR. SANTANA: Jeff--so explain a logistical issue to me: this future trial is a layover to other therapeutic studies that COG will do for Wilms' and for rhabdo? So this will be like a layered-over objective?

DR. BARRETT: Yes.

DR. SANTANA: Okay. Thank you.

The other question I had is: you know, we heard this morning a little bit about when we do these studies that are either PK-guided in terms of data collection, that sometimes we have problems convincing parents and patients to participate,

because it provides some burden.

And I was just curious that on one of your--the things I read, that there was sampling that was very extended: six, eight hours; 24 and 96 hours. And I was just thinking of the kids with Wilms' and rhabdos who come in and a vincristine/actinomycin shot, and then they want to go home. You're not going to see them for another week.

So how feasible and practical is that going to be in the context of the discussion we had earlier this morning/

DR. BARRETT: Well, THIS IS PART of the reason to do the pilot was to, in fact, determine whether or not we need that data at all.

So one of the things that's still ongoing

right now--or will be in earnest and more detail--will be to look at limiting sampling schemes so that we collected the most informative data. And what we will likely propose is that we have several randomized schemes. So when a patient is enrolled in the trial, they'll be randomized to a certain sampling scheme.

So perhaps--and I don't know this is the case yet; we need to do the simulation--we will have some patients in which we will request them to stay around for 24 hours, and other that we won't. So it will not be a burden across the board. One of the things that this procedure does allow us is the ability to characterize the meaningful data, but not by collecting by fixed sampling times in every subject. So there will be flexibility in that.

But it may very well be that we need to collect data. In fact, what I could tell you is: I don't think it's been the duration of sampling that was the impediment to enrollment. The addition of the peripheral catheter was the biggest reason that

parents just did not want to burden their children with a trial.

DR. SANTANA: Thank you.

DR. SMITH: Could you comment on your sampling procedures, and how you see those being applicable--not just to vincristine and actinomycin, but to our Phase I studies, for example, and what we would need to do to use those methods?

DR. BARRETT: Yep--absolutely.

So we've worked with the nursing staff extensively to make sure that the combination of the hardware and the procedure can easily be reproduced. And it's been really a tribute to some of the work that Jeff has done over in our own ward to make sure that we didn't propose something that was so outlandish that it wouldn't be portable.

But as far as the generalizability of this, this is likely a procedure that could extend to many agents. So we would certainly be willing to use this procedure in a variety of other settings.

What I could tell us is that there's

nothing that we have put forward that is likely to be a barrier in terms of collecting this data. And the difference, in terms of the efficiency of the procedure, does seem to vary by agent. So I don't know that you can necessarily generalize and extend it to the others, but we do have a mechanism now to test common agents that we would like to actually do routinely this way.

DR. SMITH: So, before you use this method with a new agent, you would want to do the studies to test whether the method actually worked.

DR. BARRETT: Absolutely. Absolutely.

And that's what's ongoing right now. We will be able to compare the peripheral sampling versus the common central venous sampling in actual patients to verify this.

The recovery data is extremely encouraging, but until we actually do that in vivo validation, we're not going to move forward with it.

DR. WEISS: I was just a little curious: towards your last slide you talked about some label

simulations. And, of course, that always perks up the FDA because that's a lot of what we do is, you know, labeling.

So can you explain a little bit about kind of how you were thinking that would work, and what kinds of scenarios?

DR. BARRETT: I mean, I had done this when I was in industry before, too, so I know kind of the hoops that you will have to go through would be: what do you expect that labeling to be like post-this study. So some of the characteristics we would obviously like to explore would be: do you expect there to be any differences based on the age, or body weight, or body surface area.

So, basically while--or before--we're doing these simulations, we would craft language depending on the outcome of that. We'll obviously look very closely to the simulation and decide what would be the way we would phrase this? Are we going to talk about hard and defined age categories? Are we going to speak about differences in clearances? Or exposure

differences?

I mean part of the issue with this agent is: if, in fact, we do see a difference in exposure relative to the grade, severity or time course of the various toxicities of interest, we would, of course, drive the labeling to those statements, and not speak in pharmacokinetic terms. But, you know, we have to do the simulations before we actually get that far.

But what we're trying to do is get our clinical community comfortable with actually writing it that way, and not actually summarizing the data in tabular form that's less informative to giving dosing guidance. So what I'm hoping we can do is go further down the path to writing language that gives dosing guidance, instead of summarizing what happened in this trial.

Anne, was that your expectation, too, as far as what we would do?

DR. ZAJICEK: Yes.

DR. SANTANA: One last question if I may, Greg.

So, you know, the current studies, when some of these issues of toxicity occurred, was to modify the dose for those younger patients--with

the caveat that if their weight or age changed during the therapeutic interval, that you would potentially increase the dose.

So are there plans, in your studies, to kind of give us guidance on that, too, based on modeling or actual data?

DR. BARRETT: Absolutely.

DR. SANTANA: So you'll study patients when they switch over to a different age group or weight?

DR. BARRETT: Right, we're going--I mean, obviously because there's going to be a longitudinal window that we capture this data from, these changes will matter-of-factly occur. This why, again, I keep driving us to the simulation, because we should be able to get some idea of this from the historical data, and plan for it in terms of capturing it.

I think that's the main thing that we're

hoping to utilize is, too, is to ensure that we capture the appropriate data from the prospective study to do the kinds of investigations you're asking.

DR. STEWART: I just want to make sure I'm clear on your answer to Victor's question. So what you're saying is: in the same patient you'll be performing pharmacokinetic studies longitudinally as they age. So you have built into the protocol to study them, let's say just for example, at six months, 12 months, 18 months and 24 months--assuming they're still getting the drug.

DR. BARRETT: Yep.

DR. DOMSEY: Just a quick--maybe this is, at this point, somewhat historical, but it seems to me one major point is that you've developed a method for a simultaneous measurement of both vincristine and actinomycin. In the earlier part of your presentation you discussed limitations of the previous data in terms of the ability to measure each sort of on its own.

So I guess my question is: was the major

issue before this that it's difficult to measure one in the presence of the other? Or are there simply technical limitations, just for each in isolation of the other? Because the major point here, now, is that you can measure both. You have a simultaneously measure.

DR. BARRETT: There was no analytical method for actinomycin at all. Vincristine has been measured in the past. But the issue for us was: you would like to not have to have two samples. It's obviously more cumbersome to have to manage the sample handling. And just from an efficiency standpoint, as well as the collection standpoint, is better for a single common sample.

DR. DOMSEY: And from a clinical standpoint, they're used pretty much together, so--

CHAIRPERSON REAMAN: I think that was the other big driver, was that rarely are they administered sequentially, or a day later. So it would really preclude doing an assay of just one.

So, based on the fact that they're used together so commonly in so many diseases, I think

that's what really drove this.

DR. WEISS: So, one last question.

You know, you've commented, I think, a little bit on the historical data set being a challenge. And I'm just wondering if you can just give some sense about whether or not you'd actually been able to plow your way enough through that, or are you still in the stages of trying to put it into some kind of data bases that you can try to utilize?

DR. BARRETT: Right. One of the issues is, you know, a lot of this data lacks the granularity we'd like to have. So the events occur over dosing windows where we know that there was a certainty frequency of dose, and we actually know what dosing changes occurred. But we don't have the specific timing of what it occurred. We know the severity--and it's captured maybe across subjects in some data sets, and not down to the level of the patient in others--although that data may be there in the road map.

So what we're really wrestling with is:

how much of that data do you actually use from the electronic form, versus just putting that aside and going specifically to the road map and try to reassemble it from scratch? That's what's going on now.

Because I have seen different cuts of the data, and you know, we know that it's fraught with inaccuracies at the current stage.

CHAIRPERSON REAMAN: So maybe we can address the questions that we were asked to address by the agency, related to these studies, which Dr. Barrett has described on the approach to the generation of safety and efficacy and pharmacokinetic information on these two drugs, and are there suggestions about additional data that should be collected. And then we could actually then talk about other drugs--other parameters.

[No response.]

Well, I guess this was a very rough thought out proposal. WE can offer no suggestions--

[Laughter.]

--which is very unusual for this group, or the people sitting around this table--some of whom

I know very well--

[Laughter.]

--that they can't make some comments.

DR. WINICK: You alluded to his in your presentation, but looking at vincristine alone, you alluded to the fact that there are dose caps that may or may not have been logically derived.

Can you elaborate on that?

DR. BARRETT: I believe this is with actinomycin, as well, that there are dose caps--

DR. WINICK: Correct.

DR. BARRETT: --so one of the things we wanted to use the historical data from was: what happened if we applied dose caps? Okay, so if you know the dose toxicity relationship, and you imposed dose capping in this prospective study, would you reduce the frequency of adverse events? Or toxicity based on that?

I mean, that's what I guess I was getting at is: you know, you have a--we have a procedure

that has fallen out of all of these protocols in terms of making adjustments. So we can look at the historical data to see what occurred during those trials. But I think the interest wold be: you know, well, what would happen if we, in fact, did a trial in which we fixed--we ensured that dose capping occurred at different times? Did it improve toxicity if we had increased the number of patients in the trial? Were you able to conclude, specifically, that dose capping had a clinical benefit?

DR. LINK: We have dose capping, and the question is whether it was the right thing to do.

DR. BARRETT: Yes. So I guess what I'm saying is: we want to take that information and basically--well, you're wondering if it made a difference.

DR. LINK: No, no--we're wondering--it would be an efficacy problem, rather than a--

DR. BARRETT: Oh, okay. So you're talking about efficacy versus toxicity.

DR. WINICK: [Off mike.] [Inaudible.]

DR. SCHWARTZ: Well, I didn't actually publish it. I got it to the abstract form. [Laughs.] But, anyway--because we had looked at

some of the patients at Hopkins with ALL, in terms of--just for induction with vincristine--as to how much drug they actually got. And I think we did load advance per meter squared looking at the caps--and found an efficacy difference in terms of induction, and actually long-term survival, I believe. I can't remember right now--by the vincristine dose.

And took some of that into the Hodgkin's committee now, where we just arbitrarily changed the cap to 2.8. And I'd love to see what that meant--or to get the actual pharmacokinetics on something like that some day.

DR. WINICK: When I reviewed this for the--we wrote an article for ALL--there was a symposium held at St. Jude in 1963? '57? '63?

DR. SANTANA: I wasn't born yet.

[Laughter.]

DR. WINICK: I actually was, but I wasn't

invited.

CHAIRPERSON REAMAN: An oversight, to be sure.

[Laughter.]

DR. WINICK: An oversight. [Laughs.] I doubt if I was out of diapers.

But there was a fairly arbitrary decision made, because the single-agent response data in ALL to vincristine was so overwhelmingly good that no dose greater than 2 mg was necessary, because everyone responded anyway; why risk the peripheral neuropathy?

And then what Cindy brought to light, and what other people have subsequently challenged is: is it conceivable that one of the reasons that adolescents do less well is because their dose is capped, and they're getting a relative under-dose when compared to, you know, a three-year-old who gets one milligram, and then a 17-year-old who gets two.

DR. BARRETT: I tend to focus on the toxicity all the time, but we do have event-free

survival as a response.

DR. WINICK: Okay.

DR. BARRETT: It's already built into this. So, we will definitely pursue that question.

DR. LINK: Actually, Vince deVido proposed this a long time ago with MOP. The original MOP guidelines had no cap dose. And that's one of the reasons that this has come up again is, you know, why are we capping it?

DR. WEISS: Can I ask a question? You have said you focused a lot on the toxicity, and this bears to maybe some topics for future discussions.

But are there questions--or do you have questions--about how to assess the neurotoxicity? Are there concerns about the methodological ways to assess, particularly in certain age groups? Is that an issue that bears some question? Is that something that's a discussion topic?

DR. BARRETT: It absolutely is a discussion topic, particularly when we're proposing the prospective study.

I mean, one of the problems with the with

the historical data is that methods changed, of course. And, you know, you're trying to decide how to, in fact, interpret that data when you pull it together.

So it's absolutely an issue.

DR. WINICK: Not only is it difficult to assess peripheral neuropathy in little kids versus older children, but it's cumulative--very hard to know if it's a reflection of the single-dose or multiple doses.

There have to be some host polymorphisms that reflect on the toxicity. And then the other major issue is: if it would be true that the difference between--and I'm being intentionally melodramatic here--the difference between life and death is the vincristine dose; and if the down side to the higher dose is foot-drop, that's quite different than when you're talking about anthracycline, where the down-side to the higher dose may be death from sepsis and mucositis, or death from cardiac disease.

So it is an enormous issue, both in how to

reliably assess it, and then how to weigh the relative risk-benefit.

And one of the people that's, I think, been very helpful to us--not dealing with the ethical component of this, or the weighing component, but just with how to quantify toxicity--has been Frank Bayliss. He wrote a modification of the CTC-3 grading system for peripheral neuropathies that makes it much more readily applicable to toddlers and to young kids.

So at least on the ALL side, we've incorporated his modification in the RDE system so that the toxicities will be scored in that way.

The other thing that comes up all the time--and I don't have enough knowledge to evaluate it--is whether or not we should be requiring tests like the--I don't even know what the title is--the alternating PEG test or something? You're nodding--can you help me? [Laughs.]

CHAIRPERSON REAMAN: They're tests of coordination, basically--the alternating PEG.

But I don't think we actually, in clinical

practice, usually look for these things and evaluate them. And we wait 'til the child comes in and can't walk on their toes, or they can't open their eyes. And then we say, "Oh, yes. Neurotoxicity." But we don't evaluate.

And I think because of the very fact that we don't consider this a life-threatening or even necessarily a life-altering toxicity. Because it is reversible.

DR. WEISS: What about the other drug that's been under discussion, though: the actinomycin-D, and the potential hepatic toxicity? I mean, do we have the same issues--is it in the same vein? That it's something one can monitor and potentially reverse?

Obviously, it could be potentially, I guess, more serious.

VOICE: [Off mike.] His opening slide--

CHAIRPERSON REAMAN: But it is something that can be monitored. I mean, it's not predictable, but the laboratory abnormalities have a very consistent pattern. So I think it could be

monitored, and I think it is actually regularly monitored for.

DR. FINKLESTEIN: Greg, I have a question, really for Michael.

Hepatotoxicity in actinomycin-D historically has come in waves. This is true.

So there was a period of time, for two to three years, that we saw a lot of hepatotoxicity across the country, and we contacted the Federal government, and we thought it had something to do with formulation. And then it disappeared for awhile. And then it came back in another wave. And then it disappeared for awhile.

My question to Michael is--since he's the sarcoma king, and has been using actinomycin-D for a long time--whether this impression I have still holds, or is there now a consistent toxicity that we attribute to actinomycin-D?

DR. LINK: Well, you're asking the wrong person. But I do remember the days when it was a little browner than before, and we went to the FDA because there was an increased incidence--when Dan

published those papers about the hepatotoxicity, it was felt to be a formulation and, actually, activity level of the drug, as opposed to--but I don't know if anybody's thought about it since whenever we published those in Lancet. That was years ago.

CHAIRPERSON REAMAN: But there were also changes made in how the drug was administered, and the schedule. And subsequent to that there have been changes made again--and the combination that actinomycin was given with.

So, you know, there may be some influence related to lots, production, activity. But I think there are other issues that certainly require some investigation, also.

I want to just make a comment about the capping--and if this is something that we're going to be capping the doses, if we're going to be able to look at whether there is an impact on toxicity.

It concerns me that we are sort of empirically capping, uncapping, recapping, creating new caps in different diseases. And we really

ought to think about this across all of the diseases in which we utilize vincristine, if this is going to be an opportunity to really look at toxicity and efficacy.

So I don't know how that might best be accomplished, but if there mathematical models that could be used to do something a little bit better than just picking a level out of a hat.

DR. BARRETT: I think the issue would be--you know, we know that the capping occurred in the four historical studies. So it would be to correlate--can we correlate, in fact, the capping to outcomes, both on the event-free survival side, or the toxicity side?

And then would be: if we impose capping rules in a simulated prospective study, does that make a difference? Now, you know, this why, when we talk about modeling the uncertainty, it's so important to do that correctly. Because, you know, of we're propagating the error by having something non-predictive, that doesn't serve the purpose either.

But I think the issue is, in the prospective study, if we can show with a simulation that there was nothing to be gained by capping,

then we shouldn't do it.

CHAIRPERSON REAMAN: But I'm not sure that we're looking at the right population in the retrospective. Because there certainly aren't too patients with Wilms' tumor in whom the dose of vincristine is capped at two milligrams--maybe some in the rhabdo study.

So that's kind of my concern.

DR. LINK: If the way it was administered is totally different. So in Wilms' tumor, they get 12 weeks in a row. And we talked about the cumulative effect. And in rhabdo what happened is it was given every three weeks. And then there was some of the mouse modeling, which showed that vincristine was a very effective dose in a xenograft, and it sort of changed the whole--and I think it was IRS4, where they started giving these blocks of weekly vincristine.

So--you know, good luck on trolling

through these retrospectively, because it's not only--in different periods, they got different schedules.

DR. SCHWARTZ: Yes, I was going to ask that, as far as whether you're going to look at it in terms of not just the dose one time, but whether it's weekly, or every three weeks--and also in terms of are you going to be analyzing mgs per kid, mgs per meter-squared, body mass index or some of those things that might give us perspective?

DR. BARRETT: The first goal was to look at--we have to derive dosing metrics for getting exactly what you're talking about: you know, not just the frequency of dosing, but this cumulative dose. And there's many ways of quantifying that.

But we're going to develop these indices of dosing that we'll try and correlate. And, as you point out, we don't know, a priori, what the correlation will be. So we're really operating from a vacuum of knowledge at this time.

VOICE: [Off mike.] [Inaudible.]

CHAIRPERSON REAMAN: I knew if we waited

long enough we would have some suggestions and recommendations. So you didn't disappoint me.

[Laughter.]

So maybe we can then go to the next question, which is really, I think, not necessarily a question, but an opportunity to discuss broader issues, areas, for further expansion of the BPCA process: Are there additional off-patent drugs--therapeutic classes of drugs--that we think there are opportunities for investigating and providing future health benefits?

DR. WEISS: Before we start--I was last night reading the transcripts from this subcommittee meeting exactly two years ago in October of 2003. And I know many of the same people were here at that meeting. It was very interesting, because there was discussion--that's when actinomycin and vincristine kind of rose to the top of the pile as ones that might be good to study, for a number of good reasons. Which is why it's been, I think, very comforting to hear the update from Dr. Barrett on what the progress has

been, which has been quite impressive.

But there was a discussion then about a number of other chemotherapeutic agents that were mentioned--as well as some brief touching on supportive care and other types of therapies, including cis-retinoic acid. Dr. Reynolds, I think you brought it up two years ago. [Laughs.]. So it's good to know you're consistent.

But so--would like to open it up because, you know, obviously actinomycin and vincristine are now on their way--well on their way in study. And are there other things now that one should seriously consider for potential inclusion on that priority list?

DR. PAZDUR: Kind of an alternative question here--if I may pose it: are there other questions in pediatric oncology that need answering, that you could answer via this mechanism, by selecting drugs here also? Because I think when we just focus on drugs, we're looking at methotrexate--drugs that have been around for a long time--and you're scratching your head here.

But what questions really could be answered about these kind of ancient drugs here?

But the real question is: what are the questions that need to be answered? And could this be a mechanism that we answer these questions vis-a-vis older drugs that are on the market? In other words, we're not slaves to the drugs. We should be proposing the questions that we want answered, and probably using that mechanism in that way.

DR. SANTANA: I'll take you up on that.

I think there was a brief mention this morning of the issue of obesity, and how to dose patients who are obese.

DR. PAZDUR: I really like that idea.

DR. SANTANA: And there's like 10 drugs that I'd like to see studied in that regard, because I think it's a major issue.

I can't think of how to do the study today, but I think as a general concept--I think we discussed that briefly this morning--that would be an impetus for another discussion in a meeting--

DR. PAZDUR: And as I sit here as an adult medical oncologist--this is not a pediatric problem. [Laughs.] it is a pediatric problem, but

it goes beyond pediatrics, obviously. [Laughs.]

DR. LINK: Well, there was just a Lancet paper that addressed it in a breast cancer trial. So we're very attuned to that.

DR. FINKLESTEIN: Greg, I think, in terms of obesity, this is a pediatric problem. If you take steroids--which we use by the carload in oncology--then you add on asthma for steroids, and all the rheumatoligsts that use steroids--if we could create some kind of mechanism to analyze just steroids in the 9 to 25 percent kids that are obese, we will do a service for the children of the United States.

DR. ZAJICEK: What specifically did you have in mind? Like PK?

DR. FINKLESTEIN: Dosing. Dosing. Dosing and PK.

DR. ZAJICEK: Okay--dose response?

DR. FINKLESTEIN: Dosing and PKS. For

example: some of us can talk about caps, some of us cap steroids, prednisone, say at 60 mg/m

2. Then you have a group that says, "Hey, you shouldn't cap it." Some think it's too high, some think it's too low. We can go on and on and on.

But certainly we don't have an idea of the mech--and I've looked at this. The pharmacology has not really been done for steroids in obese children. WE use it in pediatrics across the board.

CHAIRPERSON REAMAN: Good point.

Mike?

DR. LINK: I don't know if this is the same kind of thing, but in anthracyclines--in addition to the obesity issue--it's method of administration. And we have all kinds of arguments about giving it as a continuous infusion is safer or it's not safer. It causes more mucositis--I think most of us think that. But in terms of the cardiac toxicity--hmm?

DR. WINICK: [Off mike.] I thought [inaudible] actually addressed it.

DR. LINK: Yes. He's overturning what we thought.

So I think that that's exactly the point,

because not everybody agrees with his data. So I think that we need to--[laughs]--so I think that would be something that we need to address. Because that's one of the major long-term toxicities. It's a big drug that we use in pediatrics. And boy, if there's one that you'd like to avoid delayed effects of, that would be one of my favorites.

DR. DOMSEY: So there's no longer a consensus that a 24 to 36 hour continuous infusion is associated with less cardiac risk than shorter--

DR. LINK: I was never aware that there was a consensus.

DR. DOMSEY: Well, I'm just trying--

DR. LINK: The original thing was that Bob Benjamin studies--early on--that if you give it weekly instead of once every three weeks at a third the dose, there's less cardiac toxicity. And I think that that was sort of extrapolated. But I think that there are data from Steve--which I've

heard in an abstract. I haven't seen the publication--which indicates that it may be--it's published? Well, okay. I didn't read everything.

But it's actually worse. So, we don't know the truth, but there are certainly conflicting data.

DR. WINICK: Worse in children. And I don't know this, but clearly the mechanism of anthracycline-induced cardiac toxicity is different in the developing heart than in the established heart.

So, this is a beautiful example where adult data not only are not applicable, but shouldn't be applied to pediatrics.

DR. SCHWARTZ: And it was also, though, with different dosing. I mean, it wasn't the sarcoma-type dosing, it was the ALL-type dosing that they used. So it may not be for each dose.

I also wonder about--we've alluded to it--but looking at infants and young children in general, because we tend to either do nothing to modify their dose, or we modify it across the board

in a specific way. And yet it may be very drug-dependent, that certain ones that are hepatically metabolized, you may need to modify in one way, whereas if it's renal it may need to be another way.

And I've never seen anyone look at it that way. I mean, we just sort of say, "Oh, they're small. Cut it in half." Or change it to "per kilo."

DR. PAZDUR: I'm kind of trying to challenge you here to think beyond the box here, you know.

CHAIRPERSON REAMAN: I think that's an excellent--I mean, there are no formal investigations of the PK of any drug in the infant population. And all of the recommendations--many of which I've actually written in the Pizzo and Poplack chapter--are purely empiric, and derived exactly as you suggest. If it's a hepatically metabolized drug, then reduce it by 30 percent in the first three months of life. Why? I don't know--it sounds good.

But I think evaluation of pharmacokinetics--and if we're going to talk about looking at things in discrete age groups, rather

than the age groups that we saw examples of this morning, I think this is a population of patients where we could really learn something.

Look from zero to one month; one to three. Every drug that we use.

Clinton?

DR. STEWART: Yes, I echo: that's very, very important, Greg.

But one of the things that I would probably say is--just from my experience of studying one drug--topotecan--for 10 years--and we did very extensive pharmacokinetics for that one drug. We've studied one child less than one month in that 10 years. That child had very different pharmacokinetics. But that's the full extent of our experience in 10 years.

So, I guess my point is: it's very, very difficult to get that kind of information--even when you're very intentional about going after it.

CHAIRPERSON REAMAN: But I think in multiple institutions, those opportunities would probably be greater. So, you know, I'm not suggesting that it's easy. And that's why all of the recommendations have been empiric for 20 years.

But I think there are opportunities to

network and do this.

DR. STEWART: And just real quick--by the way, that one child had very different pharmacokinetics than all the rest of the population.

CHAIRPERSON REAMAN: All the more reason to do this.

DR. SANTANA: I want to follow up on the anthracycline issue, because I think we had some discussion.

I think if we do go down that route, I'd like to see a discussion about the tools--how to measure the toxicity. Because a lot of the controversy in this area is what tools you use to define early toxicity so you can potentially intervene.

And so if we go down this route, I would encourage us to have a discussion about that in the future, also.

DR. WEISS: Are you thinking specifically of cardiac toxicity, or--

DR. SANTANA: Everything is on the table.

CHAIRPERSON REAMAN: Well, if we go down that same route, in addition to the tools, I think we also have to look at all of the

cardio-protective effective--dexrazoxane and its sort of empiric use, and empiric use with different schedules of administration.

So I think that's another thing that ought to be evaluated.

DR. SCHWARTZ: And I hate to say this, but also the tools have to then get reported back, because even if we know how to do them--[laughs]--we need the data back.

DR. LINK: But even--you know, different people have different ideas of what giving an IV push is. So, in other words, the pharmacokinetics of giving doxorubicin--I think UCSF studied

this over like--real bolus infusion, versus giving it over 15 minutes, which is sort of many people's idea of "push," it's very different in terms of peak levels--which may have a lot to do with the toxicity subsequently.

VOICE: [Off mike.] Or over one hour.

DR. LINK: Or over one hour--yes.

DR. PAZDUR: I'm kind of pushing you in another direction here. You're kind of talking about conventional studies here: PK, PD, toxicity issues. And what I'm trying to ask you is: are there questions--big questions--that need to be answered?

You know, sitting here as an adult oncologist, I'd like to know--you know, you have a great deal of success, but you also have some children that don't respond to these therapies. Are there pharmacogenomic issues that need to be looked at? And you could use this mechanism--because these are older drugs--to get seed money to study those issues.

I'd hate to have this just look at, you

know, peripheral issues. And I'm not saying that these are not important issues. But there are big questions.

And, here again: rather than thinking of a drug--because, here again we list these as "drug questions." Think of the questions that you want answered in the field to use this mechanism to do studies.

Am I making myself clear here? Because that's a different perspective than just saying, "Oh, we have an anthracycline. I'd like to know better how to study cardiac toxicity." That's an important question, but there are bigger questions, I think, that need to be answered, that may actually push the drug development further in pediatric oncology.

CHAIRPERSON REAMAN: Perhaps. But I--

DR. PAZDUR: I'm throwing that out as a possibility.

CHAIRPERSON REAMAN: No, no, no. I'm glad you threw it out. And it wasn't because, certainly, pharmacogenetics wasn't considered to be

important.

But I think we will still have these same nagging questions which, you know, may not be very intriguing--even if we have pharmacogenetic data.

DR. PAZDUR: But, here again--

CHAIRPERSON REAMAN: So, I--we hear you. If this is really an opportunity, we are very interested in host differences that may explain differences in outcome, responsiveness, and risk for toxicity.

DR. PAZDUR: And I think you could use this mechanism--

CHAIRPERSON REAMAN: Absolutely--

DR. PAZDUR: --and clearly. You know, here again, you're asking questions about a specific drug that you use--actinomycin, vincristine, etcetera--by why aren't patients responding? That might be an issue here--to these regimens--which may be an alternative question, and utilize other areas in science.

So it doesn't necessarily have to be the drug that is the focus. The drug could be the

mechanism to answer the question, in other words.

DR. SANTANA: I'm confused. That's not--please correct me. You know I can always stand corrected, and I take it very well--but I thought that's what PREA and BCPA is all about. I thought the impetus was safety, and providing information that would help us put something in the label so that people that were using it used it in a better way.

[Overlapping speakers.] [Inaudible.]

DR. PAZDUR: Well, in general it is.

[Overlapping speakers.] [Inaudible.]

CHAIRPERSON REAMAN: --identify the specific polymorphism that--

DR. PAZDUR: Yes, but, in general it is. But you could use--

CHAIRPERSON REAMAN: That gave an increase in--

DR. PAZDUR: --but you could use that in that fashion. I'm just trying to think beyond the box here, and a bigger question that we could utilize this mechanism.

Yes, you are 100 percent here, Victor. But can we look to expand this, in a sense? And still be in compliance.

DR. ZAJICEK: Now, we've been having this conversation--and the Europeans are having the same conversation--about how to go about prioritizing things.

So rather than picking, you know--berry-picking drugs this year, we thought we'd have some discussions about diseases. So, in this case: pediatric oncology, or supportive care, and so on.

So what the Europeans have started doing--and what we're going to have some conversations about--is maybe thinking about inflammation. Like you were saying--so let's talk about steroids. What are the issues with steroids? Infectious disease--that kind of thing--rather than picking out the drugs.

One example is the issue of hypertension. Now, when I trained--and I did my residency from '95 to '98--there was no primary pediatric

hypertension. It was all secondary. I mean, that was just the party line.

And now the kids have eaten themselves into primary hypertension and, you know, metabolic syndrome and all these other problems

So we a workshop several months ago to talk about pediatric hypertension, because the peculiar thing about it is that--you know, I see patients every couple of weeks over at Bethesda Naval Hospital--so, you know, there's a plan for, you know, a kid with otitis--single dose amoxicillin,

double dose amoxicillin, augmentin. You know, there's a scheme for it.

Asthma--you know--

CHAIRPERSON REAMAN: [Off mike.] [Inaudible.]

DR. ZAJICEK: Exactly. There you go--very nice. Asthma--you know, you have albuterol you know what to do.

With hypertension, nobody knows what to do because we're dealing with something that didn't really exist until about eight or 10 years ago or

something. So it's sort of peculiar.

So if we're berry-picking the drugs that are on the list, for example--so the diuretics are on the list. So does that mean that we should study the diuretics in hypertension? But that would give the indication that the NIH is supporting, you know, a diuretic for hypertension.

So should be thinking, well--you know, is there some other game plan, you know--other than just betty-picking the drugs. Should we be coming up with some sort of trial design where we'd be thinking about, you know, other sorts of drugs that may be on or off-patent or something else?

So just thinking about the disease states.

The thing that's sort of odd about the hypertension cases, that it all has to do with obesity. So if you take away the obesity, essentially they're not hypertensive anymore which, again, complicates it.

But, anyway, you know, thinking about the disease, rather than cherry-picking the drugs might be a way to go, as well.

DR. DOMSEY: One question I had actually for Anne--and maybe Lisa--Anne, in one of your slides, the implication is for the specific

off-patent BPCA process, that once the data is gathered and analyzed--whatever was outlined in the contract and the Written Requests that then that would be submitted for labeling, etcetera.

From the presentation we just heard--and, potentially, as things move along--there may be information that's gathered as you go along, before everything's completed, but that there may be data that you gather as you go along that may, in and of itself, represent an advancement over what's currently in labeling for some of these older drugs.

So I wonder, sort of internally, from our side, with NIH and FDA, whether we should be flexible in terms of considering adding some of the information to the labeling as you go along, as

opposed to simply waiting for x years until all the components of the contract or the request are completed before you do that.

For example, here you already have the methodology for the simultaneous measurement of both. Now, maybe that by itself you can discuss whether or not that's worth evaluating.

But, you know, sooner rather than later, there may be some data generated say from the retrospective review of the data base that you have already, and it's not clear that you would need to wait until you complete the prospective study to have additional information added.

So I didn't know whether that was during the whole formulation of the Act, or in the discussions, whether that's ever come up, even with other drugs--I don't know, other non-cancer drugs.

DR. ZAJICEK: To be honest with you, we have not had that conversation, but I think it's a really good idea. Because it would make a lot of sense to get what we have, instead of waiting for the five or six years it's going to take for the

trials to be completed. I think it's a really good idea.

DR. MATHIS: I think it's a great idea, too. And I think it really opens the door for us to think creatively again.

Because one of the problems that we're finding now with BPCA is that we really haven't added into the Act a provision for the sponsor accepting the data into their labeling without them paying a user fee. So now we're taking sponsors who didn't want to do the studies in the first place, and asking them to pay hundreds of thousands of dollars to incorporate that information into their labeling. So it's something that we're grappling with at this point in time.

And the question is: if we have the opportunity to make that information publicly available via a website, via publications--are there alternate forms of communication that we can use until we sort out the problems with labeling?

And that would also give us an opportunity to use information as it becomes available, rather

than waiting for the prolonged labeling negotiations to occur and finalize.

So I think that's a great idea.

DR. WEISS: Just getting back to the question that we had asked--even though it was focused more on the drug as opposed to sort of the disease or mechanistic, which I agree is another way of looking at it. And as Rick and I were saying, they're not necessarily mutually exclusive.

But taking that, and then looking back at the discussion two years ago where there was a vigorous discussion about other potential drugs or situations that might be worth studying, what I had pulled out from reading that is: in addition to retinoids that came out as a potential area of interest, there was a mention of 6-thio-guanine. There was also discussion about cisplatinin, but a lot of discussion back and forth about the difficulties in actually measuring cisplatinin. There's probably some very technical difficulties.

But platinin also came out as a potential issue in the setting of obesity as well. And so I

just was going to put those things on the table, as whether or not there was, again, more interest in sort of dredging up a couple of these older drugs, where there might be important questions.

And then, finally, just to go back to the issue that add had kind of ended with, which is: in addition to the chemotherapeutic drugs, are there classes where--again, people don't normally think that as maybe the important thing to study in the setting of pediatric cancer, because you're really thinking about cancer drugs that will improve--you know, ways to improve the safety or improve the efficacy--but there are also, again, a whole vast area of supportive care that are not limited just to pediatric cancer, but you know all those anti-infectives that are out there that might be able to be studied, perhaps in an oncology setting as well as maybe in other disease settings like, you know, HIV--which is becoming, again, an issue. Are there some common themes with immunocompromise, where if you get information across different settings, or in one setting perhaps, and use it to

extrapolate that data to another setting, in addition to the anti-infectives again--you know, the anti-emetics and other types of supportive care.

Are there areas there that we should be thinking about? And not necessarily that what you say here is the be-all-and-end-all, but to give us some thoughts about where there are gaps--you know, from your experience, your clinical experience--what you would like to have more information about that might help you in terms of using these drugs, that we can then go back and see what we have, what are other things, what are things maybe that are on-patent that might have taken precedence and make these drugs just no longer very useful in the armamentarium.

But, I guess that's the kind of--I'd like to see if there is any additional thoughts on those couple topics.

CHAIRPERSON REAMAN: Certainly a very fertile area to explore. And neoplastics aren't the only drugs that we use in pediatric oncology.

And I guess part of it relates to the process of prioritizing what drugs are going to be evaluated. And obviously there are multiple

constituencies with whom you have to relate. And everyone has their pet projects.

But there may be--and I don't know how broad the group is who makes the final decisions. But if there are anti-infectives, or drugs that are used for pain control, then there may be opportunities for pediatric oncologists.

And I don't know how open the forum is for making the discussion. So, I guess I will just stop there, and ask the question.

But I think if there's an opportunity to broaden it, then I think creating or exploiting those opportunities would be, certainly, of interest to pediatric oncology.

DR. WEISS: I might ask either Anne or Lisa, that have been involved in some of those discussions, those yearly prioritization meetings, to maybe comment about, you know--I guess it's sort of the issue of leveraging, given the precious

resources. You know, if there's an important drug to study that maybe has utility across different disease categories, not just the run of the mill garden variety infections but, you know, in immunocompromised, and trying to hook up various types of cooperative groups that will be doing those studies.

But, again, it's more leveraging types of resources. What are the--because I haven't been involved in those discussions either, in terms of prioritization.

DR. ZAJICEK: Well, the group consists of again, you know, sort of a two-tiered group of people; so, specialists in different therapeutic areas, and then pediatric clinical pharmacologists. So they've been broad, and the selection of drugs has been all over the map. So it hasn't concentrated anything in particular on, you know, only infectious diseases or, this year, only anti-emetics the next year.

So it's been very broad.

And they all have different aspects of

what the question is. So a therapeutic question, a pharmacokinetic question, and then bringing in the label also, what's already in the label, not duplicating what's in the label, taking into consideration that if it's for a new indication that would require more extensive kinds of studies than if it's just a safety, PK kind of study using extrapolation.

But there are really no limits on anything you could propose. So we're wide open. And we're very interested, again, in getting input from your group.

CHAIRPERSON REAMAN: I guess it's not so much a question of proposing, it's really more an issue of: what all is on the potential menu that could be actually selected as opportunities that would have sort of cross-specialty interests and actually give NIH the biggest bang for its buck, maybe.

DR. ZAJICEK: So, the drugs that I have on your slides at the ones that I picked out that seemed to have applicability to oncology. There

were other drugs--other classes--that--you know, like the radionuclides. There are a hundred of those. And, you know, there are lots of other choices.

But I picked the ones for your group that I thought would be applicable.

As I mentioned, a couple of years ago, when I and George Giacoia put the prioritization meeting together, I decided I would go through and pick out the drugs--just, you know, to cull down that 169 drugs down to something more management--to, you know, 30 or something like that.

I went through the AAP practice guidelines, because I couldn't figure out where to start. So I figured, okay, well I'll go with the sheer numbers. So I looked through the treatment guidelines for otitis, the treatment guidelines for pyelonephritis--that kind of thing. And so I picked out those drugs.

And it was an interesting conversation because, again, there was that sort of the

health-benefit offset of the sheer numbers of patients getting the drugs--okay, amoxicillin. You know, every child in the United States has gotten this drug 15 times. So just by sheer numbers--huge numbers of patients' getting it.

On the other hand, people feel very comfortable dosing it. It's not a toxic drug for the most part, unless you have an allergic reaction to it. You can pretty much dose all over the map and still get a fairly good efficacy if you're treating something that it's sensitive to.

So picking out--that did not work too well that year, because I think the infectious disease people felt that, "I use this drug all the time. I don't see that there's any major question about it."

So, on the other hand, things like azithromycin now--there were questions about, you know, in the neonatal population, the neonatologists are very interested in a lot of these drugs because a fair number of the drugs have labeling now for let's say, you know, six months

and up. They're still lacking labeling for the neonatal population. So that's where the idea of the azithromycin for ureaplasma, and the use of azithromycin for chlamydia.

Now, the offset of this problem is a feasibility issue, because even though it may be a scientifically interesting question, it is very hard to recruit a neonatal population. You know, you've got one patient in 10 years for topotecan. So it might be a little less difficult, but it's still very hard to recruit for these kinds of studies.

So the scientific interest, the medical interest, the feasibility, I guess, is where a lot of these things come up to be problems, is that you just can't do the study. It may be interesting but, you know, there are a lot of others factors involved--you know, numbers of patients, practice changes, you know a lot of adult--ob/gyns are treating a lot of women that may be exposed to chlamydia with azithromycin off the bat, and so it's producing the number of patients with

chlamydia. So, it's multifactorial.

So I think feasibility ends up being a big problem for some of the projects that would be interesting, but feasiblely difficult.

DR. BARRETT: On a very broad note, one of the things we were interested in is some of the diversity in dosing guidance that's provided in the various compendiums. And we've done an observational look at just how much diversity there is. And it varies dramatically.

That led us to kind of looking at our own institution, what would be the standard of care with certain agents relative to what would be available both in the compendiums and in the label if it is a drug that, in fact, has that information in the label.

There, again, what we put in place in an on-line system to look at drug utilization, where we can actually marry this up with diagnosis, but also to look at those time-dependent changes, and can we correlate when they occurred. Was there something that happened in the best practice that

necessitated that migration in best practice.

So what we'd ultimately like--you brought up the idea of prioritization. So I think one level of interest would be: could we marry up those places where we see this discrepancy or this change in maybe practice, with those agents where there is little information either on the pharmacokinetic side, or on the side of actual patient management, to kind of guide this process.

DR. MATHIS: I think the other thing that I'd like to point out is when we look at limited resources, and you think, well, we don't want to have 10 oncology drugs on the list--NIH is actually very open to suggestions for additional drugs on the priority list.

And the truth is that the FDA can issue as many Written Requests as NIH provides us drugs on the priority list. And we're frequently working on five or six different off-patent Written Requests at a given time, all for different indications. We have a division that is--you know, that's our top priority--one of our top priorities.

So, while there are limited resources, I don't think anybody would complain about having more than one oncology drug, or more than one drug

for supportive care.

And as Dr. Pazdur mentioned, you know if you step back and look at the big picture, your primary question is: how do you cure childhood cancers? The secondary question is: how do you make the kids comfortable while we're doing that? What are our pain control drugs that we have? So then you can look at the world of pain-control drugs and figure out which ones need to be studied. And that crosses over to other indications as well. Cancer kids are not the only children with pain.

So I think that there are many different approaches that you can take, and many ways to really satisfy more than just one patient population.

DR. REYNOLDS: I'm glad to hear that, because a couple years ago when we discussed this, I understood was, well, there was going to be two oncology drugs, and that was it. There was limited

resources. That was--well, this is off-line discussion.

And I think that one of the things we ought to look at--and this is first of all oncology drugs, if you study them, you might have a greater impact than if you study amoxicillin. Amoxicillin's used a lot more. But if you use it a little bit less or a little bit more, you might not change anything. Whereas if you change the dose of a drug that's known to improve survival, it might change a lot.

The second issue is that I think some of these studies may not require a lot of resources, and just might require a little bit of resources--and the agency behind them to get the labeling change put in.

And so why not have several of them? Why limit it in number? And I'd love hearing that.

DR. MATHIS: Just, again, not to beat a dead horse, but--you know, we actually learn things over time.

We learned from our first priority list

that it's very difficult if you have a lot of drugs for neonatal diseases that aren't firmly defined, and that don't have good endpoints to follow, you're not going to be able to study those 12 drugs that you put on your priority list.

We've also learned over time that while we want to make sure that drugs that affect a large number of patients are studied, we also want to make sure that those patients with serious and life-threatening diseases that only occur in a small fraction of the patient population, that they also benefit from this process.

So I think we're less fixated on specific numbers at this point in time, simply because of our experience. We've learned a lot over the last couple of years about how to prioritize drugs, and which drugs we want studied.

MS. HAYLOCK: A point that you made that I just wanted to go back to, and that's the neonatal population.

I have several colleagues who are neonatal nurse practitioners, and they do a lot of primary

care. And from what they tell me, there's almost no neonatal--or medications used in neonates that are approved, or clinical trials and whatnot--but particularly in the area of pain and symptom management.

So I think--I only notice morphine on the list here. And clearly we know there's different mechanisms of pain that do not respond to morphine, which I think would apply in neonates or children, as well.

So I think a better exploration of just the pain and symptom management medications that we have that would cut across not just cancer, but all the other things that happen to neonates. However, I think the children pain issue is a little bit better--toddler on up. But I think the neonates is still a huge under-addressed issue.

DR. ZAJICEK: Agreed. George Giacoia, who's in our branch, is a neonatologist. And he's put together the Neonatal Initiative, which are a series of phone calls and meetings to discuss various issues in neonatology pain, cardiovascular

disease, pulmonary disease, and so on and so on.

There was a huge meeting--what?--a year ago February, in Baltimore. It was so interesting. It was a two-day meeting with everyone that had been involved with this initiative. And you couldn't get these people to stop talking. I mean it was so interesting. They were so happy to be discussing these issues about how to go about defining pediatric pain; how to go about studying it and so on. Very nice initiative.

Now, speaking of morphine--we're supporting--it's been a little complicated. You know, you think that neonates have pain and so it should be treated. And adults get morphine, and so we should give them morphine.

Well, there was a study--the Neo Pain Study. Are you familiar with this? It was published a few months ago, and they were talking about actually bad outcomes in children that had received morphine--so actually sponsoring--I didn't put that on the list, but--a project looking at receptors--morphine receptors, and sort of

preclinical issues in using morphine before we go on to doing a morphine Written Request, or doing the study that was put in the Written Request.

But--yes, your point is well taken about the neonates.

MS. HAYLOCK: One other thing: I live in a fairly rural area, and I'm aware of a lot of families who have made very painful and hard decisions about not getting treatment because--I'm in Taxes so, you know, it's 300 miles from anywhere--because of access issues.

So I was thinking in terms of drug delivery, or medication delivery, of different ways or different avenues to deliver a lot of the very complex regimens that children require--but doing it closer to home; so somehow figuring out delivery systems, or regimens that would actually increase access to care for children who are unable to physically or economically or whatever get themselves to one of your centers that focuses on children.

DR. WINICK: I'm certainly not advocating

denying access, but it's a little bit frightening, because the issue isn't really the delivery of therapy; it's access to the center when they're febrile and neutropenic, or dehydrated.

And so it would frighten me to be able to deliver the therapy in a situation where the family can't get to help if they need it.

MS. HAYLOCK: [Off mike.] I'm an adult [inaudible] so I can't speak to it a lot. But there are a lot of, especially, supportive care things that can be done in less sophisticated settings than a comprehensive cancer center; certainly thing--I mean, they have home-care nurses; they have various things that can be done in community-based settings that don't require the complex systems that you all have.

But I think those things are not often considered, in terms of the protocols that are established. So I'm just sort of putting in a bid for those kinds of things to be added into consideration of regimens.

And the other one I wanted to mention,

too, is--that I haven't really heard talked about much--is the whole issue of the long-term sequella for the kids.

I know that most of--or a lot of--the centers have long-term follow-up for peds, but there's a certain point where they don't get long-term follow-up. And I know CDC is considering adding into the SEAR data some long-term data bases. But that also hasn't been done, and because of the changes in protocols, that it's very hard to get to the long-term sequella.

But, still, we're having kids and adults live longer--decades longer--after cancer treatment, and they'll end up 10 or 15 to 20 years from now not having really any idea of what late effects they might end up with, or long-term sequella.

DR. WEISS: Greg, can I say this--that's a very good segue into actually the very last topic. And I know everybody's probably tired and post-prandial.

And I had actually just wanted to open

up--I have one slide that just has some potential topics for future discussions--the long-term sequella, I had actually thought about but forgot to put that on my list. So that's a very good one to put back on there.

I was just going to ask you: we were supposed to have had a break like, you know, a half hour ago. And I don't know whether or not--but there's one last topic.

And so if you want to move through--yeah I can put that up there, and we can shoot through that. Probably some administrative things that we're forgetting also that you were talking to. Yeah, I didn't know if you needed--I know there was an open public hearing schedule.

Open Public Hearing

CHAIRPERSON REAMAN: We were told that there was no one signed up. So--

DR. PAZDUR: Is there anybody here, though? If we could just ask the question, "Is there anybody here for the open public hearing."

CHAIRPERSON REAMAN: Is there anybody here

for the open public hearing?

DR. PAZDUR: That would like to speak.

CHAIRPERSON REAMAN: That would like to speak?

[No response.]

If you can keep your remarks under five minutes.

[No response.]

Hearing no one who's--I'm sorry, I missed that.

And I also missed the break because I think the discussions were actually--

DR. WEISS: Well, if you'd like, I mean--there's like these--you know, carbohydrates there. I'm happy to just put this up, if people want to like grab a carb and carb-load. And I could--and to think about just the last topic at sort of all at the same time, just to finish up. If that would work I'd be happy to do that.

CHAIRPERSON REAMAN: Well, let's do that, then. We can forget about the carb-load, I think.

DR. WEISS: Okay.

CHAIRPERSON REAMAN: Unless people really must have the carbs. But some of them really must avoid them, so--

[Laughter.]

DR. WEISS: As we're talking about obesity--okay.

VOICE: [Off mike.] [Inaudible.]

CHAIRPERSON REAMAN: No-break approach--right. Well, we're not going to 11 o'clock at night, either.

Topics for Future Meetings

DR. WEISS: All right.

[Slide.]

Well, this is the last slide. And so--one slide, even though it could be like many, many slides and a list.

I just thought that at this committee, in addition to just talking about potential topics--drugs, or questions that might be appropriate to be adding to the off-patent list for prioritization, a broader issue is this particular subcommittee and potentially topics to take to

future meetings of this committee.

And I had, just to stimulate discussion, not to cut off anything, there are some things that certainly were somewhat holdovers from prior meetings, and actually were, again, addressed at this meeting--which I think was very good--issue of daunomycin, or the anthracyclines, in particular as it relates to obesity. And Dr. Santana mentioned also, are there metrics for measuring not only the pharmacokinetics in obesity, but also issues related to safety assessments and measures for that as a topic for--in fact, actually that was going to be, you know from the agenda, actually on this particular meeting. In retrospect it's probably good it wasn't because we would have been running out of time. But there were some logistical issues of why we couldn't bring it to this meeting. So that could be, certainly, a very ripe topic for future meetings.

And daunomycin and methotrexate were both drugs that have actually been added to the priority list. Of course, that means really the agency is

going to be looking into Written Requests, and through the process that Anne Zajicek already mentioned about going through--you know, offering this first to the holders of the actual, the NDAs or the generic products. And then if those are rejected--which probably be the case--to refer it to the foundation for further study.

So those are areas that we might need some input into measurements, not only on the pharmacokinetics but other issues and other things to measure with those drugs.

There's also--again, what we talked about already--to maybe further the process of other things to add to the priority list.

The whole issue of neurotoxicity. There are, of course, you know, brain tumors which have very significant toxicity. And this is a topic that is actually going to be discussed perhaps at a future workshop--not specifically limited to pediatrics, but issues in brain tumors in general, and how to assess outcomes. Because there are very unique issues to pediatric patients who develop

brain tumors, pending that open workshop, that might be a very relevant topic again to take to subcommittee, perhaps supplemented with additional individuals who specialize in brain tumors. I know all of you have experience, but there may be some additional people to include on that.

Neurotoxicity--we touched upon that a little bit the vincristine, and with some methotrexate, it's come up before with that issue.

Drug shortages is a topic that I know people, it's near and dear to many people, and we could go through sort of what--you know, it's not necessarily an FDA issue, per se, it's a manufacturing issue. But it does come up quite a bit.

Long-term follow-up is a topic that was mentioned. I know there are other topics that I've had discussions with various people in the past.

So this is just thrown open in the last few minutes, to ask people for their thoughts about other topics that we should consider in further meetings of this particular subcommittee.

And all sit down and we can talk from the seat there.

CHAIRPERSON REAMAN: Cathy?

MS. O'CONNELL: I know that we all hope children will be cured of cancer--but as a patient advocate, I happen to have lost my daughter to neuroblastoma, and have several friends who lost their children, too.

I think end-of-life care is a topic that needs to be discussed, and pain control. I know there's been some studies done with it, but I don't think that, especially--I can only speak for neuroblastoma--but it's difficult with pain control at the end of life for a lot of children. And I'd really like to see that discussed, and see if there's some other drugs that can be identified, or maybe a protocol that can be used.

CHAIRPERSON REAMAN: Pat?

DR. REYNOLDS: A couple of topics: one is--in your handouts you gave us the form that basically is the Request to Waiver form. And I'm not sure that the check boxes on there are totally

consistent with out discussion--at least in one area.

So I'd really like us all to review that checklist form, and make sure that we agree that the check boxes as consistent with our previous meetings on that.

In particular, one area, which small-cell lung cancer, was listed on there. And, actually, we had agreed that that wouldn't necessarily granted a blanket waiver because of its possible relationship to neuroblastoma. So that's one topic.

The second is, is that there's something that there's something we're wrestling with in neuroblastoma, and I think it's probably true for other diseases, as well. And I'm sure it's not just a pediatric problem, but it's more of a pediatric problem since there are so many adults they can ask questions in. And that is: if you have agents that stabilize disease but don't cause tumor shrinkage, how do you study them? And, in particular, in a setting where, if you've got some

known disease--and neuroblastoma's a classic example where you've got MRBG-positive disease, and you have a drug that probably stabilizes the disease, and will prolong at least the symptom-free--they're pretty non-toxic drugs that form this category--symptom-free period without a lot of pain and suffering.

How do you study it? Because you can't do a randomized trial. You can't randomize them to this drug versus nothing. It just doesn't work.

So we're actually talking about that in COG next week, in the neuroblastoma development of therapeutics meeting, and trying to come up with some trial design. But since there's drug companies interested in registration trials in this category, I think that we really need to have some input from the agency.

CHAIRPERSON REAMAN: The issue that was raised by Pamela earlier about delivery. You know, as pediatric oncologists, we really don't think about it. And I think what has made pediatric oncology unique is that most children--all

children, essentially--are cared for in centers. The concept and the definition of "centers" is changing. It's not 10 to 20 anymore; it's 200, and maybe 300.

But I think we do have an opportunity to look at delivery systems which are not as difficult for families, particularly in rural settings. And then coupled with the issue of palliative care, or end-or-life care, that, I think, is a particular area where delivery outside of the center concept is particularly important.

DR. WEISS: And just to comment--I mean, I think those are great topics. And obviously if we're going to develop that in a future meeting we'd want to bring in individuals with expertise in various types of delivery systems--probably some of the people that deal a lot more with the--you know, pain control, and issues in supportive care. And so that's good. It just that it gives us thoughts about how we will develop an agenda, and what kinds of additional expertise we'd want to bring to the discussion.

CHAIRPERSON REAMAN: And I think Pat introduced the concept of study design and endpoints in one disease. I think it's not limited

to one disease. I mean, it's a particularly difficult issue in neuroblastoma, but I think--is survival, overall survival, event-free survival--are they the only endpoints? Is it appropriate--just as in some adult cancers--to look at time-to-progression as a reasonable endpoint for studies that may be important for pediatric cancers?

And then the whole issue--and I don't understand enough, myself, about the orphan drug indication, and what we keep talking about--the relative rarity of childhood cancer. I mean, are there opportunities for drugs to receive orphan drug status? Is that an opportunity or is that a hindrance to development? And I don't really know.

I mean, my gut reaction is that once you receive orphan-drug status, you go nowhere, except that you always have orphan-drug status.

But I think having some educational

opportunity about that, and how that might be utilized, I think would be helpful also.

DR. BARRETT: I'd like to see a topic on preclinical predictors of clinical outcome, more or less--you know, we had the topic earlier about the review of some preclinical models, validated or not, and some discussion on the extent to which they gave us some comfort as we went down the drug development pathway--specifically for pediatric oncologic indications.

DR. SMITH: I had one question about that. Were you thinking primarily of predicting toxicity? Or predicting activity? Or both?

DR. BARRETT: Actually, I was thinking mostly of activity, but I think it could be both.

DR. SMITH: Okay.

The other--the topic that I had is one that we discussed before. And I know NICHD is sponsoring something on this, for formulations.

You know all of our--I think of all of the agents that are coming into Phase I trial in pediatrics, you know, most of them now are oral.

They're administered every day. And we're having to round-off, to degrees that make dose escalation hard, because the error in just dosing, based on rounding-off can be 20 to 30 percent.

So, it is an issue of getting a drug early--relatively early--into children, and particularly the younger children, and having accurate dosing and ways of reliably getting the drug in.

DR. REYNOLDS: If I could just echo that, I think there are some opportunities in some of the older drugs--not too many, but a couple of them--to stimulate some formulation development. They'll never occur because they're generic drugs now--but that would allow us to learn how to better deliver some of these agents in the pediatric setting.

DR. ZAJICEK: We are having a workshop--I'm missing the date. I don't remember--Lisa, do you remember off hand the date? The formulation meeting?

Anyway, I'll send around an e-mail with the date--because we're having a workshop to

discuss exactly this: what are the problems with changing something from a tablet to a solution and a suspension--that kind of thing.

So I will let you know.

DR. FINKLESTEIN: Greg, I have a round-off question.

If we're rounding off 10 to 20 percent, I'd like to ask my colleagues in the FDA: what are the Federal guidelines when a drug is released, in terms of what is the percentage variability that is allowed in the concentration of the drug when it's released to the public? In other words, when you reformulate it, six months from now is it 100 percent? Or do you allow a 10 percent variability? Or do you allow a 20 percent variability?

So what's the Federal guideline for round-off?

DR. STEWART: Whenever they do different formulations they allow as much as 20 percent--in terms--

DR. FINKLESTEIN: Well, this was a loaded question, because obviously if--and I learned that

just recently--if you allow up to 10--not you, it's not you--but if it happens that one allows 10 to 20 percent when the drug is released, and then we're allowing 10 to 20 percent, we're lucky we have the survival rate we have.

CHAIRPERSON REAMAN: And we actually may not want other formulations then, if that's the case.

DR. PAZDUR: That's a chemistry issue and manufacturing issue, and we'll be happy, Jerry, to get back to you. I don't know that specifics. This is a different group of people that work on that, and I don't want to really give out any impression that I may have.

CHAIRPERSON REAMAN: But I think--I think it does--I mean, it would probably be worthwhile just having someone comment on it.

DR. PAZDUR: Talk about the formulation, etcetera.

CHAIRPERSON REAMAN: Exactly.

Cindy?

DR. SCHWARTZ: I guess I have a question

going back maybe toward the morning--and I don't know if this is within the realm of this--but I wonder, in the context of pediatric trials, where we have so few numbers of patients, whether there should be some attention to how new drugs are brought up in terms of study design. I mean, we're not in a situation where we can potentially run 10 Phase II trials with sufficient numbers to get some estimate of efficacy, and then bring it to a Phase III trial.

And is there a way to have a better grasp over which direction we're going, in terms of the long term that we want to bring it to a Phase III presumably, so that we're not wasting our resources, or that we're really bring to bear--just listening to the pharmaceutical companies that design things, and then it doesn't work because we change our plans?

It seems that we need--

DR. PAZDUR: Well, here again, these are issues--

DR. SCHWARTZ: --a unique design plan.

DR. PAZDUR: These are issues of design and endpoints. And, as you know, in adult diseases the office--and before that, over the past couple of

years have been partnering with AASCO and AACR to take a look at specific diseases: lung cancer, prostate cancer, colon cancer--to look at endpoints and trial designs in specific disease settings.

I would be not opposed, and I would encourage, this same activity to proceed in pediatric oncology. The way we've done this, basically, is organize a workshop with those parties however--for the pediatric group it could be with COG, and with other pediatric entities--to explore specific issues. And I think these are issues. And we're facing, you know, the dilemmas, as you point out--you know, the same type of trial that one may want to do in first-line breast cancer, where you have thousands of women afflicted with this disease, are not the same type of trial that one might be able to do in a rare pediatric tumor. So we have to come to terms with that--both in perhaps the endpoints that we look at, as well

as the design of these trials.

So I would be more than open to really exploring that as kind of a joint effort as we go forward in adult diseases in these various diseases, to have several pediatric workshops in this area.

CHAIRPERSON REAMAN: Well, we would definitely take you up on that. And that was actually one of the items that I was hoping we could have discussed. Because I know there was a workshop on endpoints for clinical trials in leukemia that the FDA had in--

DR. PAZDUR: We're always in this dilemma of do we--because we have a limited period of time for any workshop--do we want to include pediatrics in that workshop, versus have a separate workshop. And, you know, there's pros and cons with this because, obviously, there are different players, there's a different natural history of the disease, there's different therapeutic options that are available. And once you start getting a vast array of questions in a limited period of time, you might

lose focus.

But we have no problem, basically, of looking more--and having specific pediatric focused workshops in these areas. We're in the present organizing a brain-tumor workshop which we have included pediatrics in, in contrast to perhaps a lengthy discussion that we had in leukemia.

But, here again, we could revisit this whole area, and I'm very open to developing the resources, or having the resources to look at these areas.

CHAIRPERSON REAMAN: But my understanding with the leukemia was that there were--

DR. PAZDUR: Yes, there was a pediatric--

CHAIRPERSON REAMAN: --pediatric focus. So we don't know what the endpoint of those--

DR. PAZDUR: Yes, and--

CHAIRPERSON REAMAN: --discussion about endpoints was.

So, you know, we are the people who would be doing trials, designing trials--

DR. PAZDUR: We're waiting for some of that

information to be coming back to us. And, here again, that might be an excellent point to bring back to that committee.

But here again, I think that is a cogent question to ask: as we move forward with these diseases--and some might--obviously when we're talking about endpoints for lung cancer it's not germane to this group. But in areas where there are pediatric components, is it appropriate to have that in the general workshop? Would you rather have a focus looking specifically at the disease from a pediatric perspective, since there are unique issues here that have to be taken into consideration: success of the therapies that you have available, etcetera.

DR. FINKLESTEIN: Greg? Cindy's question is very important--

CHAIRPERSON REAMAN: Actually, Pat had his hand up first, so I would like to recognize him.

DR. REYNOLDS: Well, thank you. I'll be brief.

I think related to these topics and some

of the others is something we touched on in one of the previous meetings, and that's how we might do international trials of some sort; and how, from the regulatory standpoints--which will be considerable burdens or hurdles, if you will to get around--how we might, at least in select populations internationally, get together a trial to increase our numbers and to hit our endpoints a little faster.

DR. PAZDUR: And, here again, these are not necessarily regulatory FDA or EMEA hurdles. Remember, for most of the applications that we receive now from pharmaceutical companies, it's the rare exception that the study is only done in the United States. Most of these trials are large international trials that are being done.

CHAIRPERSON REAMAN: Yes, these have, in large part, been OHRP hurdles.

DR. REYNOLDS: That's a regulatory hurdle.

CHAIRPERSON REAMAN: Right. So--we have to be careful when we say "regulatory," it's not always aimed at the FDA.

But I think just to answer your question about pediatric-focused workshops, I would say, in general: yes, if they are diseases that are

primarily pediatric, or impact the pediatric population, then I think--

DR. PAZDUR: And we could come back--even if we've had workshops, we could come back and refocus some more attention in pediatrics.

CHAIRPERSON REAMAN: Well, I think that would be very good.

DR. PAZDUR: Because there are, you know, obvious unique issues. And having gone through numerous of these workshops already, you know there's only so much information that can exchange hands during a particular meeting here. And, obviously, if you have more adult people at the table, then those issues--adult oncology people, I'm talking about--[laughs]--those issues tend to get more of a focus than the pediatric oncology issues.

CHAIRPERSON REAMAN: Jerry?

DR. FINKLESTEIN: Cindy's question is very

important. About seven years ago Dr. Pazdur, Dr. Herschfeld--and I don't know if Malcolm was at that meeting or not--but we had this meeting which actually ended up--this whole committee is probably generated in part from that committee, which was the question: how do we get drugs into pediatric cancer earlier?

And this was about seven years ago. What we're seeing now is seven years of deliberations.

And, therefore, I would suggest that having a focused meeting to see if, indeed, we've changed anything in the past seven years would be appropriate. But it would have to be a pediatric meeting.

DR. WINICK: I think it's also important, though, to make sure that we don't duplicate efforts, and to add to what's already being done.

Dr. Lehman's paid for, so he's fully cognizant of a retreat that was held relatively recently for members of the ALL, AML and development of therapeutics committees, because we do consider new drug development, at least in

pediatric leukemias to be at something of a crisis.

You know, it's been very difficult to enroll patients on studies because of all the issues that came up during the clofarabine discussion: endpoints, transplant, limited numbers of patients. Dr. Lehman talked about the sort of the ad nauseam use of standard agents to re-induce children with ALL.

And I think that that workshop was successful. We didn't have a great deal of drug company representation at the workshop. We certainly didn't have FDA representation. And if there's a way to add to an ongoing discussion, to make sure that there are practical endpoints and decisions about study design, and decisions about prioritization, I think it would be marvelous.

CHAIRPERSON REAMAN: So, have we given you enough agenda items--

DR. WEISS: I think we have topics.

CHAIRPERSON REAMAN: --for future meetings?

DR. WEISS: Yes, I think we're good for the

next several years, frankly.

[Laughter.]

So that's very good. Thank you very much for that.

CHAIRPERSON REAMAN: And do we have some idea as to when the next meeting might be?

DR. PAZDUR: [Off mike.]The first quarter, '06.

DR. WEISS: So--yes. Stay tuned. But we'll be back to working on that, and to seeing what's a good topic.

Obviously, for this kind of meeting it's a little bit more difficult, in some ways, to plan because it's not built around a particular drug application coming before the committee. And so, in one it's good, because we have a lot of freedom to do what we want. On the other hand, it's a little bit difficult sometimes to try to figure out what topics, and what types of expertise to pull together.

And I just want to say I very much appreciate the very vigorous discussion that

everybody had at this committee. It was really very gratifying to hear, and to listen to all of your contributions.

CHAIRPERSON REAMAN: DR. PAZDUR: Well-

DR. PAZDUR: Well, let me end it on a light note. When I'm always asked about when--from a drug company, "When am I going to get the answers to my application?" The answer is: "Soon." Okay? [Laughs.]

CHAIRPERSON REAMAN: I like that answer.

But, having been at both kinds of meetings, I think--well, I shouldn't say this is more interesting. It really depends on the--

DR. PAZDUR: [Overlapping speakers.] [Inaudible.]

CHAIRPERSON REAMAN: --and perspective, of course.

But I think--I appreciate the FDA actually organizing this meeting. We would be very happy to work with you, of course, in organizing the next and subsequent meetings.

But I think there were a number of very

good issues that were brought forward; a lot of very important information exchange. And I look forward to the future.

DR. PAZDUR: And, in conclusion, I would just like to thank Karen for really spending a lot of time on this meeting--as you know. Because Karen is a pediatric oncologist. We are going to have a greater focus, since this is now at the office level in pediatric oncology, and I kind of tasked her with this being one of her major responsibilities.

But also, the other pediatric oncologists that we've had in the division. I think we are blessed in the fact that we have Ramzi, Steve, Pat, Dr. Summers--various pediatric oncologists--Steve Herschfeld--to work with us. And I'm sure I'm missing some--Joe Gootenberg. I'm sorry, Joe. Dave--okay--Dave. But many--so to speak.

DR. WEISS: Thank you very much, everybody.

[Whereupon, at 3:55 p.m., the meeting adjourned.]

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