DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

THE PEDIATRIC SUBCOMMITTEE
OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

IN JOINT SESSION WITH

THE PEDIATRIC SUBCOMMITTEE
OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE
(ODAC)

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Steven Hirschfield, M.D., Ph.D.
Richard Pazdur, M.D.
Dianne Murphy, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. CHESNEY: Good morning. I think we are ready to start, and before we get into discussion I would like to just say thank you to Dr. Murphy and all of her staff at the FDA who have done such an incredible job of organizing these two days with four totally unrelated subjects, except that they all relate to pediatrics, and also to let you all know that in the "Science Section" of The New York Times today, in the middle, there is a full-page article, with a big picture of Dr. Murphy, and all addressing the use of drugs in children. So, I think that is a real tribute to her and to all of the efforts of the FDA in this regard.

We are going to start by having everybody introduce themselves, and also to remind you all that when you ask a question or make a comment, please be sure to give your name so the transcriber will know who it is and, for those of you who weren't here yesterday, the way to turn on your microphone is to push the green button. So, let's start over here, on the left-hand side. I think Dr. Murphy is the first.

DR. MURPHY: Dianne Murphy, Associate Director for Pediatrics at CDER, and I haven't read the article so I don't know if I am infamous or not.

[Laughter]

DR. PAZDUR: Richard Pazdur, Division Director, CDER.

DR. HIRSCHFIELD: Steven Hirschfield, medical officer, Division of Oncology Products. I read the article and it is very favorable.

DR. SMITH: Malcolm Smith, head of the Pediatrics Section of the Cancer Therapy Evaluation Program and pediatric oncologist.

DR. BALIS: Frank Balis. I am a senior investigator at the National Cancer Institute, Pediatric Oncology Branch.

DR. BOYETT: James Boyett, chairman of the Department of Biostatistics at St. Jude Children's Research Hospital.

DR. COHN: Susan Cohn, and I am on staff as a pediatric oncologist at Children's Memorial in Chicago.

DR. PRZEPIORKA: Donna Przepiorka, marrow transplanter, Baylor College of Medicine, Houston.

DR. WEINER: I am Susan Weiner. I am president and founder of The Children's Cause. I was a parent.

DR. REYNOLDS: I am Patrick Reynolds, Children's Hospital of Los Angeles.

DR. FRIEDMAN: Henry Friedman, Brain Tumor Center at Duke.

MS. ETTINGER: Alice Ettinger. I am a pediatric

nurse practitioner in New Brunswick, New Jersey.

DR. FINKLESTEIN: I am Jerry Finklestein. I am a pediatric oncologist in Long Beach, and also chair hematology oncology for the American Academy of Pediatrics.

DR. CHESNEY: Joan Chesney. I am in infectious diseases at the University of Tennessee, in Memphis, and also in academic programs at St. Jude.

DR. TEMPLETON-SOMERS: Karen Somers. I am the executive secretary to the Oncologic Drugs Advisory Committee, FDA.

DR. SANTANA: Victor Santana, pediatric oncologist at St. Jude Children's Research Hospital in Memphis, Tennessee.

DR. NELSON: Skip Nelson. I am a pediatric clinical care physician at the Children's Hospital in Philadelphia.

DR. GORMAN: Richard Gorman, general pediatrician in private practice in suburban Maryland.

DR. O'FALLON: Judith O'Fallon, group statistician for the North Central Cancer Treatment Group.

DR. RODVOLD: Keith Rodvold, professor of pharmacy practice, colleges of pharmacy and medicine, University of Illinois, Chicago.

DR. GELLER: Barbara Geller, professor of psychiatry, Washington University in St. Louis.

DR. DANFORD: Dave Danford. I am a pediatric oncologist at the University of Nebraska Medical Center and Creighton University in Omaha.

DR. FUCHS: Susan Fuchs, pediatric emergency medicine physician in Children's Memoria Hospital, Chicago.

DR. HUDAK: I am Mark Hudak. I am chief of Neonatology at the University of Florida at Jacksonville.

DR. FINK: Bob Fink, pediatric pulmanologist, Children's Hospital, Washington, DC.

DR. LUBAN: Naomi Luban, pediatric hematologist-oncologist, for this group mostly a hematologist, Children's Hospital, Washington, DC.

DR. SPIELBERG: Steven Spielberg, head of pediatric drug development at Johnson & Johnson, representing PhARMA.

DR. KAUFFMAN: Ralph Kauffman, pediatrician, clinical pharmacologist, Children's Mercy Hospital, Kansas City, Missouri.

DR. WARD: Bob Ward, neonatologist and professor of pediatrics, University of Utah, and chair of the American Academy of Pediatrics Committee on Drugs.

DR. CHESNEY: Thank you. Karen Templeton-Somers, our executive secretary, is going to read the conflict of interest statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that since the issues to be discussed by the subcommittee will not have a unique impact on any particular firm or product but, rather, may have widespread implications to all similar products, in accordance with 18 USC 208(b), general matters waivers have been granted to each special government employee participating in today's meeting. A copy of this waiver statement 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 guests and guest speakers, Dr. Ralph Kauffman, Dr. Steven Spielberg and Dr. Robert Ward have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kauffman would like to disclose that he has grants with Bristol-Myers Squibb and is involved in research for Bristol-Myers Squibb, Astra, Zeneca, Janssen, Merck, R.W. Johnson and Adventis, and is a scientific advisor for

Bristol-Myers Squibb, Johnson & Johnson and Purdue PhARMA.

Dr. Spielberg would like to disclose that he is an employee of Johnson & Johnson. Dr. Ward would like to disclose that he owns stock in Ascent Pediatrics and Viropharma; has grants with Wyeth-Ayerst, Novardis, Ascent Pediatrics, Adventis Pharmaceutical and Sepracor; receives consulting fees from Janssen Pharmaceutical and is a scientific advisor for McNeil Consumer Products.

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. Thank you.

DR. CHESNEY: Does anybody have anything that they haven't yet declared? Hearing none, Dr. Murphy will give us our mission for the morning.

Introduction to the Issues

DR. MURPHY: Actually, I am going to try to do a little more than that -- I try not to tell the chair what we are going to do.

[Laughter]

It is basically part of our responsibility, under the Pediatric Rule, to provide an update to this pediatric subcommittee on an annual basis.

[Slide]

As yesterday was even busier with a packed schedule, I chose this morning and I would like to take about five minutes of today's time to update the pediatric subcommittee on where we are.

[Slide]

I am leaving this up because I don't want to have slide after slide of the statistics of what has been going on because you heard some of that yesterday as far as over 150-some written requests that we have issued under the Food and Drug Modernization Act and the fact that we expect 85 percent, approximately 75-85 percent of those studies to be completed.

The other activities that have been ongoing in the meantime are rather significant and I would like to take a moment and introduce Dr. William Rodriguez. Dr. Rodriguez, would you stand up, please? He introduced himself yesterday. He has come to us as our science advisor because it has become quite clear to us, as we move into the whole area of drug development, that we have a tremendous number of questions as we go forward in how we do drug development

in children and the science gaps are significant in certain areas. Dr. Rodriguez was a professor of pediatrics at Children's Hospital in Washington for 29 years and is now professor emeritus, and we are delighted to have him join us, and you will be seeing more of him as he begins to address some of the issues that we know exist. As a matter of fact, I think Thursday is his first internal brainstorming session for us in the agency, and we will have a number of those.

The other aspects that I wanted to inform the committee about were the fact that we have a congressional report that is due January 1 on the effectiveness and efficacy, if you will, of the legislation, and we will have that report out of the Center by the end of this month and anticipate that we will be bringing that report to you next year, after it is made public, that answers the questions that we were mandated by Congress to answer about the implementation of the Modernization Act.

I said to Rosemary this is beginning to get embarrassing, and she said, what do you mean, beginning to get? -- Dr. Roberts told me it is embarrassing. We had stated last year that we thought we would have the guidance on the Pediatric Rule out by June. It is not. We are pushing very strenuously to have it out before December. The Pediatric Rule went into effect for the agency as far as

our responsibility to inform sponsors that they must have either studies in their applications or they must have a waiver or deferral from us -- that began in April of 1999. We could not require studies until this December. So we were informing them but we could not require they submit them. We can require them to have those studies as of this December. We hope to have the guidance out before that point.

One last thing for the committee to be aware -- you heard yesterday that there are continuing ethical issues that we may need to bring to you but, in particular, we will be bringing some of the issues attendant to extrapolation and the algorithms that we are developing are building upon some of the data that is coming in and experiences we have had with concentration response studies and the use of PK/PD in our development program. So, we hope in the upcoming year to be able to bring some of that information to the committee. At this point, we have had -- and this is all available as public documents on the web, the address of which the committee is very familiar with at this point -- we have had 24 products bring their studies in for an exclusivity determination, and we have 11 of those products already labeled. And, people say, "why do you say already?" I don't need to explain to this group that from the time we issue a written request to the time that the sponsor has to

develop the protocol, recruit the researchers, put the study in place, collect the data, submit it, review it and then send it in to us we have 10-12 months to review it. That is fairly phenomenal since the first request was in July of '98. So, in the last two years we have had 24 products submitted for exclusivity determination and have already been able to label 11, and we have another one and I was hoping I would be able to tell you an even dozen but it is close. So.

Now, as far as the Pediatric Rule is concerned, as I said, it went into effect April, 1999. We are requiring the studies as of December. What has happened with waivers and deferrals thus far?

[Slide]

This is an overview, and I really would tell the committee at this point that my intent this morning is not to provide you any details on these but to give you the broad-brush overview as to what is happening because, again, we can't require the studies to come in. So, in the categories of diseases where are we waiving and where are we deferring products this coming year we will provide more detail as to what is happening within some of these categories.

You can see that in cardiorenal, which leads the pack as far as written requests and/or exclusivity, we have

had two waivers -- usually this is because of a disease that would not exist in children -- and one deferral. The areas of activity under exclusivity are cardiorenal, neuropharm., metabolic, anesthetic and antivirals. So, right now it would appear that most of the studies that are being deferred are in metabolic, and as we discussed yesterday, what that means is really a spectrum of activities. It may mean that we know really what the protocol is. It may even be as developed as a Phase IV requirement. Or, it may be, as we discussed yesterday, that we think pediatric studies will be required but we are at that point that I mentioned earlier where we don't feel competent enough; there is not a level of certainty that we want to proceed in asking or demanding that these studies be done until we have additional data. So, we have a large category of deferrals at this point as we build up some of the information bases that allow us to design those studies that we are going to be requiring.

[Slide]

As I said, in antivirals are studies that have come in. So, you aren't seeing the studies that have come in. Even though they are not required, they have come in under the FDAMA. Because this process has turned out to be much more complex than I am sure any of us anticipated, in any one application that is in-house we may have a waiver, a

deferral and studies. All three things can be happening with the same product. Depending on whether that disease occurs in the entire spectrum of pediatrics, you may have some part that you are waiving; you may have another part which you are deferring because you are waiting on the information that you have on the studies that you have in-house. So, all three things may be happening in some areas.

[Slide]

This is to give you a feel for the activity. We are trying to present this in a less crowded way. We normally send you these statistics as they are up on the web and they are not particularly viewer friendly, but these slides now break out for you the various disease categories which are really our divisions, and the numbers of proposals that sponsors have sent in to us, in the left-hand column, and the number of written requests that we have issued for studies to be done in these areas. Again, this is under exclusivity. I just finished going over the rule. Exclusivity has been effective since 1997. In July of '98 we had our first written request issued.

So, quite a few studies have been asked for in cardiorenal and neuropharm. I iterate one more time that these are voluntary. The sponsors do not have to do them, but we have some changes from last time in some of these categories in that we have had increased activity in

metabolic, endocrine and anti-inflammatory, and gastroenterology, special pathogens and oncology.

[Slide]

This slide is to lead me into the topic for this morning. In the implementation of FDAMA, it is quite clear that not only do all diseases have their own special needs and areas of development as far as the science base and as far as the clinical trials base, in the area of oncology it is -- how should I -- I am told you can't be "very" unique; you are just unique -- they are unique, and we have -- I will use the word struggled because we have to treat all diseases the same in that many a parent who has a child with a severe neurologic disease, a parent who has a child who is dying from heart disease -- these are all as serious and important to them as any disease. So, we need to do things that are consistent with an even playing field for the development of all of these areas. We found there were unique aspects that we needed to address for oncology, and to do that we really discussed it with a number of external experts.

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And, the American Academy of Pediatrics put together an invitational meeting in February of this year and invited a number of academic researchers, National Cancer Institute, PhARMA, pediatric cooperative groups,

advocacy representatives and, of course, the FDA. We discussed the issues surrounding pediatric drug development in the area of oncology, and felt that we were able to define a process and that is one of the things that we hope to accomplish this morning, to present this approach to you. There is a guidance, in contrast to the Pediatric Rule guidance, just to let you know the level of priority that was put on this. We got this guidance out in record time because we did not want this to continue without information for the researchers and the sponsors in how we were looking at the development of this area because it is different. And, that is what will be explained to you this morning.

In addition to the process, there is a new committee that has been put in place and I will ask Dr. Hirschfield to, please, come up here and explain to you the development of an additional -- let me back off; I am not allowed to say we have a new advisory committee, so an additional panel of experts which we are utilizing to advise us. Thank you.

DR. HIRSCHFIELD: Good morning. I would like to acknowledge the efforts and the support that Dr. Mack Lumpkin, our Associate Center Director, Dr. Dianne Murphy, our Associate Center Director for Pediatrics, and Dr. Richard Pazdur have provided on behalf of and in support of pediatric oncology, and none of what we are going to discuss

over the course of the day would have gone forward without their efforts.

We recognized, and you will hear several times during the course of the morning and those who go to the afternoon session on pediatric oncology, how pediatric oncology has characteristics that are different than other areas in pediatrics. The diseases are relatively rare. They are life-threatening. There is also a long history of evidence-based medicine, going back essentially fifty years. Most of the children are treated on protocols in cooperative group studies and there is a recognition that research is the standard of care for pediatric oncology. You will hear these themes again, but these themes made us examine very carefully the approaches that were taken to other pediatric diseases and ask how can we adapt the tools that we have, which are new in the history of regulatory science, to the pediatric oncology situation?

And, one of the mechanisms was to look at how we could apply the Pediatric Rule. The Pediatric Rule states that if a disease in adults is similar to a disease in children, or vice versa, there is a mandate to perform studies in the pediatric population. There is also an incentive in the sense that it is possible, if efficacy is demonstrated, to apply the adult efficacy data to the pediatric population.

Pediatric oncology has yet another difference, aside from the differences just enumerated and that is that the biology of the tumors tends to be quite different from the tumors which are seen in adults. Adults typically get tumors associated with the skin, the lining of the skin, the lining of the lungs, breast, and pediatric tumors tend to have different tissue origins. So, on the surface it looked like the Pediatric Rule would be extremely limited in its application, perhaps to some brain tumors; perhaps to some hematologic tumors. But otherwise we would have the inability to utilize what we perceive as a very important tool.

However, we decided to examine that question. So, we convened a panel of experts and supplemented what we consider our core group of experts with experts who will be coming for today to assist us in describing the characteristics of tumors, and we will be spending the afternoon asking the question how do we describe tumors? What is it we know about tumors? What are the principles that we can use to extend our knowledge of one tumor type to another tumor type?

In that regard, aside from the distinguished panel that has introduced themselves to you this morning, we will have Dr. Todd Gollup from the Whitehead Institute join us. Dr. Gollup, for those of you who happen to have read this

week's Science magazine, was featured in the "News and Views" for his work on DNA micro arrays in describing tumors.

Dr. Michelle LeBeau, of the University of Chicago, who is an authority on cytogenetics, will discuss with us this afternoon the application of cytogenetics to tumor characterization. Dr. David Parma, of the University of Arkansas, who is a world recognized expert in the histopathology of tumors; Dr. Peter Berger, of Johns Hopkins University, who is internationally recognized for his work on pediatric and adult brain tumor pathology. In addition, although he is part of our regular panel too, Dr. Frank Balis, of the National Cancer Institute, will offer his perspectives on the application of development of therapeutics.

This panel, we hope, will stretch the boundaries of what is now only known about pediatric oncology but help set a precedent for the examination of how one may extrapolate our knowledge of adult diseases to pediatric diseases, not only for the regulatory purpose but for scientific purposes that we can think of different paradigms, perhaps new paradigms in terms of combining studies in certain cases between adults and children, looking at the types of information that we would need to make not only regulatory decisions but therapeutic and

scientific decisions.

I look forward, and feel honored to be part of this day today. Thank you very much.

DR. CHESNEY: Thank you, Dr. Murphy and Dr. Hirschfield. Our first speaker this morning is Dr. Malcolm Smith, from the National Cancer Institute, and he is going to talk to us about the application of evidence based medicine to achieve progress in pediatric oncology.

The Application of Evidence-Based Medicine to Achieve Progress in Pediatric Oncology

DR. SMITH: It is a privilege to speak to you today on the application of evidence-based medicine to achieving progress in pediatric oncology.

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In many ways, I am speaking to you today on behalf of the hundreds of clinical researchers who, over the past four decades, have designed and conducted the clinical trials that have led to the progress that I will be describing, and speaking on behalf of the thousands of patients and their families who have participated in these trials.

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As an outline of what I will be speaking about, first I will give an introduction and historical perspective. Then, I will speak about the importance of

Phase III randomized clinical trials to the progress that we have achieved in treating children with cancer. I will talk about the importance of risk-adjusted therapy to developing better treatment strategies for children with cancer. I will talk about the clinical trials research infrastructure that has been essential to this progress, and I will end by talking about unmet needs and future directions. The handouts that you have, have additional details beyond the slides that I will be using today.

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First in terms of childhood cancer basic introduction, a few points: There are 8700 new cases of cancer diagnosed annually among children younger than 15; over 12,000 when you extend the age limit up to younger than 20 years of age. There are approximately 1700 children who die each year of cancer younger than 15 years of age, and over 2000 when you extend the age to up to 20 years of age, making cancer the leading cause of disease-related mortality among children over one year of age. Finally, most of the cancers of children differ from those of adults in their histology and in their biological characteristics.

[Slide]

This slide shows the distribution of cancers that occur in adults, and you will recognize prostate cancer, breast cancer, lung cancer, colorectal cancer. These are

the carcinomas that predominate in adults.

[Slide]

Whereas in children, this slide shows the distribution and approximately half of the cancers among children are divided between the leukemias, acute lymphoblastic leukemia predominating, and the brain tumors. Then, there are tumors like neuroblastoma, Wilm's tumor and retinoblastoma that have no equivalent among adults. Even the tumors that have the same name, like non-Hodgkin's lymphoma or acute lymphoblastic leukemia -- the subtypes that occur in children are often distinctive from the types that occur in adults.

[Slide]

So, in terms of childhood cancer clinical research, one basic principle is that national efforts are essential for studying the specific childhood cancers because of the limited numbers of children with individual cancer types. So, in recognition of this fact, the NCI has supported, since the 1950s, a nationwide clinical trials program specifically designed to improve the outcome for children with cancer.

[Slide]

A second basic principle is that we need to have separate studies and we need to have a separate research structure for studying the cancer in children. Again, the

cancers of children are biologically distinctive in most cases from those that occur in adults, and so the response of children to anti-cancer treatments may be qualitatively or quantitatively different from response of adult cancers.

Second, the ability of children to tolerate anti-cancer treatments may differ from that of adults. Children may be more sensitive or less sensitive to specific drugs and it may depend on age, different doses of drugs, and different schedules of drugs may need to be used.

Also, the investigators with special expertise in pediatric oncology are the ones that are really best qualified to prioritize, design and implement the clinical trials for children with cancer.

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We, in part, are still invested in our system of clinical research because of the results that have been achieved with this system. When we looked at the early 1960s, only a small minority of children were cured of their cancers. However, currently the survival rates for children with cancer approach 75 percent. The mortality rate from childhood cancer has decreased nearly 50 percent from 1973 to 1996, and this decline in mortality rate has continued in the 1990s at a rate of approximately 3 percent per year.

[Slide]

I will give two specific examples of these

improvements in outcome. The first is the example of leukemia. Mortality remained relatively constant through the 1950s and the mid-1960s. Since the mid-1960s mortality rate for leukemia has declined.

[Slide]

And, the reason for this decline is not that the incidence of leukemia has changed but, rather, that there have been significant improvements in the survival rate for children with acute lymphoblastic leukemia in particular. Cure virtually did not occur in the early 1960s but with each succeeding decade there have been incremental advances, to the point where in 1990s over 80 percent of children are surviving at 5 years from their ALL diagnosis, and most of these children are cured.

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Another example is the lymphomas as well. In the 1950s, there were little changes in mortality.

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By the mid-1960s a decline in mortality rate began, and this decline has continued into the '90s so that from a rate of over 6/million we are now below 2/million in terms of the mortality rate. Again, this has been achieved by the identification of new treatments that have improved the survival rate from less than 20 percent in the early 1960s to approaching 80 percent today.

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What have been the contributions of the NCI supported nationwide clinical trial system to improve the outcome? First, and perhaps most important, is by conducting randomized Phase III clinical trials that reliably identify superior new treatments, and I will talk about this more in a few minutes.

Second, by providing children with cancer throughout the United States and Canada with access to state-of-the-art treatment protocols that are developed by national experts, and that have multiple levels of review for scientific quality and multiple levels of review for patient safety.

Also, by providing central review of pathology and imaging, leading to nationwide improvements in diagnosis and staging, and another contribution, by supporting the research studies that have led to the identification of reliable clinical and biologic prognostic factors, and I will come back later to talk again about the importance of this.

[Slide]

First, let me emphasize the importance of randomized Phase III clinical trials. Why do we put such emphasis on this? One reason is because what is completely logical and by all accounts should work, doesn't.

Identifying new superior treatments is an empirical and not a deductive process.

One example comes from the cardiac literature. Anti-arrhythmic therapy to prevent mortality from fatal arrhythmias, and here is the logic: that elevated ventricular premature beats are associated with early death. Encainide and flecainide suppress ventricular premature beats, therefore, the application of these drugs should reduce mortality in patients with ventricular premature beats. That is absolutely perfectly logical and is absolutely perfectly wrong. The randomized clinical trials supported by the National Heart, Lung and Blood Institute demonstrated that the patients who were randomized to receive these two drugs had higher mortality rates than the patients randomized to receive placebo. We have to subject -- I am not arguing that we be illogical but, rather, that we subject our logic to the empirical testing in appropriately designed clinical trials.

[Slide]

Another reason we feel so strongly about these trials is that we need reliable answers to questions of therapy. If we were to accept a more toxic therapy as superior when it really is no better than standard therapy, this would have serious consequences for future patients. We would be treating future patients with therapy that is

more toxic and they would not be receiving any benefit from that more toxic therapy. So, we need reliable answers to questions of therapy.

The conclusions that are reached from single-arm and non-randomized clinical trials often have limited reliability, and they have limited reliability for several reasons. One is that apparent improvements that are ascribed to a new treatment in a single-arm trial are often due to patient selection. It is the patients that enter the trial and not the treatment that are different and that account for the apparent benefit for the new treatment.

Another reason is that the improvement that we ascribe to our new intervention and the patients that we have treated with our new intervention may not be due to that but may be due to some uncontrolled factor, such as we now have better supportive care; our surgeons are better; our radiation oncologists are better at delivering radiation oncology. It may be due to those changes and not to the new treatment that we are evaluating, and randomization avoids these problems.

[Slide]

One example of the selection bias and how it can give misleading answers -- over the last decade a number of single-arm trials suggested high response rates and survival rates for high-dose chemotherapy in women with metastatic

breast cancer. At M.D. Anderson researchers looked at outcome for 1600 patients with metastatic breast cancer. All of these patients received conventional chemotherapy, standard doses of chemotherapy agents. None received high-dose chemotherapy. The patients who would have been eligible for a high-dose chemotherapy protocol had higher response rates and had higher survival than the patients who were not eligible, and the recent randomized studies comparing high-dose chemotherapy for breast cancer to conventional chemotherapy have raised questions about the true contribution of this approach to the treatment of breast cancer.

[Slide]

So, what are the Phase III trials that we support, and what are their characteristics? First, the Phase III trials that we support are large trials. They are expensive trials because of their size. They require hundreds and, in some cases, over a thousand patients to reliably identify clinically meaningful differences between treatments being compared.

In our Phase III randomized trials, patients are randomized to receive what is considered best available therapy or to receive some new treatment, and the new treatment is prioritized for evaluation based on preliminary data suggesting its potential for improving outcome, and

improving outcome could either mean better survival and, in some cases, diminished toxicity.

These trials address important questions of therapy and we don't know the answer to them. I may have my hunch a bout which arm is better, and Dr. Brown may have a different hunch about which arm is better. We truly don't know the answers to which treatment is better.

[Slide]

An important point, and Dr. Hirschfield alluded to this, in the culture of pediatric oncology research is that participation in Phase III trials is considered an appropriate standard of care for children with cancer. The rationale for this is that our standard treatments, none of them are perfect. They either don't have sufficient efficacy, or they have excessive toxicity. So, for most of our cancer types we are looking for better treatments.

Secondly, this is in the context of multiple safeguards for patient protection, including the multiple levels of scientific review and review for patient safety and, of course, is in the context of appropriate informed consent and assent.

So, given these, it is felt appropriate in most circumstances to ask families to consider participation in Phase III trials and historically most families have accepted participation.

We generally have Phase III trials available for most types of childhood cancer. There are 25 to 30 Phase III trials open at any given time for the different types of childhood cancer.

[Slide]

I will describe a couple of examples of Phase III trials that have changed standard therapy for specific types of childhood cancer.

This is an example for a pediatric acute lymphoblastic leukemia, the Children's Cancer Group-1922 trial for standard risk ALL, a population that before this trial had about a 75-80 percent 5-year event-free survival. In this case, what I will be focusing on is the comparison of which steroid is the best steroid for treating children with standard risk ALL -- is it prednisone, with half the patients on the left receiving prednisone; or is it dexamethasone, with half the patients on the right receiving dexamethasone?

There was a second randomization as well, and that question was whether the drug 6-mercaptopurine, or 6-MP, was better by the standard oral route or whether a new way of administering that drug, intravenously, was superior?

[Slide]

The results are shown here. The two lines represent patients ID and OD, patients who received

dexamethasone, and these patients had a significantly improved outcome compared to the patients in the two lower curves, the OP and the IP curves, who received prednisone, and this established a new standard therapy for children with standard risk ALL, that dexamethasone is a preferred steroid.

Before I leave this slide, as an aside, if you compare the blue and the red lines, the blue line is the patients who received the old way of delivering 6-MP, oral 6-MP. The red is below that. It doesn't look better. The IV, the new way, wasn't better. Comparing for patients who received prednisone, again, the yellow line received the old way and the light blue line received the new way. So, what we try, what is new doesn't always work but we subject it to the test. We carried forward the dexamethasone; we discarded the IV 6-MP.

[Slide]

The other example of a randomized Phase III trial that I will present to you illustrates the concept that pediatric oncology drug development is a long-term commitment, and this example is of ifosfamide and etoposide for Ewing's sarcoma, a cancer of the bone primarily in adolescents.

In the mid-1980s ifosfamide was first studied in children. It was identified, as a single agent, to have

activity for Ewing's sarcoma. By 1987, there were reports that the combination of ifosfamide and etoposide, two anti-cancer drugs together was very effective against Ewing's sarcoma. These were patients who had relapsed with their Ewing's sarcoma.

A Phase III trial was initiated that evaluated ifosfamide and etoposide for Ewing's sarcoma. This trial took a number of years to complete. By 1994 the trial closed, and by 1995 the results were available that ifosfamide and etoposide improved outcome for Ewing's sarcoma.

[Slide]

This just shows the schematic for that study, illustrating, again, that patients were randomized for what was, before this trial, the best available standard therapy, three drugs, or to those three drugs that alternated with ifosfamide and etoposide.

[Slide]

And, the benefit for the patients receiving ifosfamide and etoposide, 69 percent versus 50 percent, was 3-year event-free survival, and this, like the previous study, established a new standard of therapy for children with Ewing's sarcoma, the standard including ifosfamide and etoposide.

But identifying this new therapy required a

commitment of resources for over a decade from the initial evaluation of ifosfamide in children to the eventual demonstration that this drug actually improved outcome for children with Ewing's sarcoma, and our systems have to be able to accommodate this long-term commitment.

[Slide]

I will just note that you have in your handout other examples of recent Phase III trials that have made important findings in the treatment of children with cancer.

[Slide]

Also, in your handout you have ongoing or, in one case, soon to be initiated trials of really important questions of therapy that over the next 1-5 or perhaps longer years will answer these important questions of therapy for children with Hodgkin's disease or T-cell ALL or neuroblastoma.

[Slide]

This is what we strive for in our system of Phase III trials. This slide shows outcome for children with acute lymphoblastic leukemia treated on sequential series of clinical trials in the Children's Cancer Group from the late 1960s up through the 1990s. Each series of clinical trials involved hundred and more recently thousands of patients, going from one series of clinical trials to the next, building on what worked in the previous trials, discarding

what didn't work and having ever increasing survival rates for children with ALL. This is really what we strive for, for all of the childhood cancer types.

[Slide]

An important concept in pediatric oncology is the concept of risk-adjusted therapy, that is, classifying patients by prognosis. This slide shows a patient population for which the survival rate is approximately 70 percent, and our approach to treating this patient population and designing clinical trials for this population would be based on the 70 percent survival rate, and the risk and the types of new treatments we would evaluate would be based on this.

[Slide]

However, ifosfamide we could identify factors that allowed us to determine which patients do well with current therapy and which patients do poorly with current therapy, essentially to split that first group into two groups, a group that does poorly with the current treatments that we have and the groups that do quite well with the current treatments that we have, then this would be very helpful in terms of increasing the efficiency with which we can identify better treatments.

[Slide]

The patients who have low survival rates with

current treatments are the ones that may well benefit from novel, more aggressive therapeutic approaches that are associated with greater risk, and the patients with very good outcome with current therapy should be spared more intensive and toxic treatments and, indeed, we may focus our research efforts on minimizing acute and long-term toxicities for these patients.

[Slide]

In order to use risk-adjusted therapy, this requires that we determine reliable prognostic factors for determining which patients do well and which patients don't with current therapy. To do this requires analyzing outcome for larger numbers of patients, preferably treated in a uniform manner. Since biology is so improvement in determining prognosis for these biological prognostic factors, it requires collection and analysis of tumor tissue.

The protocol-treated patients in the Cooperative Group tumor banks have been invaluable in identifying and confirming these prognostic factors that we now use to assign treatments for children with cancer.

[Slide]

So, let me take a few minutes now to describe what this research infrastructure is that supported these Phase III trials, that supported the identification of prognostic

factors to support risk-adjusted therapy.

In terms of the scope, approximately 5000 children are entered each year onto treatment trials supported by the National Cancer Institute. The majority of these are entering Phase III trials but we also have entries onto Phase II trials to identify activity of new agents and Phase I trials to identify safe doses of new agents. For the tumor types listed here, ALL, acute myeloid leukemia, Wilms' tumor -- for some of these, most of the children diagnosed with these cancer types in the U.S. and Canada will be entered onto one of the NCI-sponsored clinical trials.

[Slide]

These trials are supported through the Cooperative Groups. Historically, these have been the Children's Cancer Group, the Pediatric Oncology Group, a group for rhabdomyosarcoma and Wilms' tumor. Together, these represent over 200 institutions throughout the U.S. and Canada, banding together to development research protocols for children with cancer, and it represents most of the institutions that treat children with cancer.

I would add that in addition to the pediatric groups here, we support the Pediatric Brain Tumor Consortium, specifically focused on developing new treatments for pediatric brain tumors; a neuroblastoma consortium for focusing on new treatments for neuroblastoma;

as well, a number of investigator-initiated projects and program projects, for example at St. Jude's Children Research Hospital.

[Slide]

In terms of the Cooperative Group structure, the four historical groups are now merged into a single entity, the Children's Oncology Group, and the decision to do this was based on improving the efficiency and developing and conducting clinical trials to identify better treatments for children with cancer.

[Slide]

An important characteristic of the clinical trials program is its multi-modality. To treat children with cancer requires specialists from many different areas and these must all be a part of the research system, including the pediatric hematologist, oncologist, the surgical subspecialist, radiation oncologist, pathologist, laboratory researchers, nurses, epidemiologist, radiologist and the clinical research associates, and others.

[Slide]

To do this work, to have 5000 children entering clinical trials each year requires a commitment to infrastructure. This infrastructure includes an operations office involved in the administration of these trials, coordinating protocol and development and distribution. It

involves the statistical center for the statistical design of protocols for data collection.

[Slide]

Of course, it requires the support of the member institutions in supporting the investigators at the institution, the clinical research associates for collecting data, and currently we provide approximately $1700 to institutions for patients entered that partially reimburses the research cost to enter patients on these clinical trials. It requires support for tissue collection so that we are able to do biology studies, and support for submitting things like radiographs and pathology specimens.

[Slide]

Then, there are the groups that actual do the science, that develop the clinical trials, the disease and discipline committees -- disease committees for all of the different tumor types, discipline committees for surgery, radiation oncology, the disciplines involved in treating children with cancer, and then individual study committees that design and implement each of the individual clinical trials.

[Slide]

In addition to this commitment to ongoing support of Phase III trials, we also recognize our responsibility to survivors of childhood cancer. Survivors are at risk for

long-term sequelae of therapy depending on their diagnosis, depending on the type of cancer that they had that could involve the heart or lungs; that could involve second cancers; impaired fertility effects among offspring, central nervous system dysfunction, and so on.

[Slide]

In part, to support research to identify these long-term effects and to identify ways to either prevent or ameliorate these, we support the Childhood Cancer Survivor Study. This is a retrospective cohort involving 13,000 5-year survivors of childhood cancer who are surveyed for their long-term health and psychosocial status.

[Slide]

The Childhood Cancer Survivor Study is currently addressing important questions for survivors, looking at the late mortality risk for survivors, looking at second cancers developing and what the risks of second cancers are, looking at pregnancy outcomes after treatment for childhood or adolescent cancer, looking for cancer in offspring of pediatric cancer patients, and following thyroid disease and survivors of childhood Hodgkin's disease, and then looking at smoking and other health-associated behaviors among survivors of childhood cancer.

[Slide]

Let me spend the last few minutes talking about

unmet needs and looking towards the future. In spite of the progress that we have achieved over the past four decades, there are still over 2000 children and adolescents who die each year from cancer in the United States.

Some of the children who are cured with our current treatments experience diminished quality of life because of long-term effects of their cancer diagnosis and treatment, and our current therapies for many cancers are near-maximal intensity and we need new treatment strategies to improve outcome for these children.

[Slide]

This shows the distribution of cancer mortality in children younger than 20. About a third of the deaths result from leukemia, about a fourth from brain tumor. Endocrine is actually neuroblastoma, and so on. We need better treatments, new treatment approaches in each of these different cancer types.

[Slide]

The handout has some of the different approaches that we are trying for some of these different diagnoses. What I will focus on in these last few minutes is that we are moving towards a new era in treating cancer both in adults and children, and an era in which our treatments are molecularly targeted and the treatments are based on specific molecular characteristics of the cancer. The

treatments that we have had to date have been, in large measure, are non-specific treatments that harm normal cells and cancer cells as well. These treatments, in principle, will be more specific for processes required for tumor cell survival and growth but, as I mentioned early in the talk, what is perfectly logical and makes perfect sense may not be true and, of course, we will have to evaluate rigorously whether these new treatments actually do work for children with chancer.

[Slide]

There are a number of opportunities for molecularly targeted therapies. The example that I will focus on is for Philadelphia chromosome positive ALL, but there are also opportunities using monoclonal antibodies and opportunities using growth factor receptor inhibitors.

[Slide]

This example -- Philadelphia positive ALL, is ALL that develops because of a fusion protein resulting from chromosomal translocation. This has very poor outcome with our treatments, 20 or 30 percent event-free survival.

This fusion protein that causes the leukemia has an enzyme activity that is absolutely essential for the leukemogenic effect of the translocation, and we now have a drug, STI571, that is an inhibitor of this critical enzyme activity. This drug inhibits the proliferation of the

leukemia cells and induces them to undergo apoptosis or cell death.

[Slide]

This schematically illustrates the genetic change in the Philadelphia chromosome positive ALL with the 922 translocation leading to the leukemogenic fusion protein that produces a Ph positive ALL. Over, on the right, is what happens when STI571 inhibits the activity of the fusion protein and causes the leukemia cells to die, resulting in restored normal hematopoiesis.

[Slide]

Phase I trials have been completed in adults with chronic myeloid leukemia. High levels of anti-leukemia activity were observed. Pediatric Phase I trials are ongoing and will be completed shortly. And, we are working with the Cooperative Groups to develop a pilot study for newly diagnosed patients to incorporate STI571 with conventional drugs to treat these patients with a type of ALL that currently, with current therapy, has such a poor prognosis.

[Slide]

In closing, let me first emphasize that the public health of children has been improved by the long-term sustained NIH support of this ongoing infrastructure for conducting clinical research for children with cancer. As a

result of this long-term sustained NIH support, superior new treatments have been identified, identified based on definitive and reliable evidence, and these new treatments, and superior treatments, have been made widely available to children with cancer throughout the United States and Canada.

[Slide]

The second point I would emphasize is that progress in the past as well as progress in the future depends on collaboration and cooperation among the pediatric cancer researchers and healthcare professionals throughout the country working together. It depends on the families and their advocates participating in these trials. It depends on the National Cancer Institute recognizing that this is a priority area. It depends on the academic and pharmaceutical developers of new cancer treatments and on the FDA and its regulations. And, it depends on third-party payers supporting the clinical care costs for treating children with cancer, and then all of these groups working together, so that the most promising therapeutic approaches are expeditiously evaluated with the ultimate objective of continuing to see improvements in outcome for children with cancer.

I thank you and I would be glad to address any questions that you have. Thanks.

DR. CHESNEY: Thank you very, very much, Dr. Smith. That was an exceptionally complete and informative overview. Let me just ask Dr. Hirschfield, should we accept questions now or wait until after the break? Now? Are there any questions? Yes, Dr. Fink?

DR. FINK: Apropos yesterday's discussion, your data on Ewing's sarcoma showed a p value of less than 0.00005. Was there a data and safety monitoring board in place that could have led to earlier termination of that study and let more children receive the optimal therapy?

DR. SMITH: Yes, for all of our trials we have data and safety monitoring committees. The Children's Cancer Group, the Pediatric Oncology Group have data and safety monitoring committees that are looking at the interim results from our Phase III trials, and the protocols are written with guidelines for what the monitoring boundaries should be for these trials.

I wasn't a member of the data monitoring committee for that trial so I don't know the specifics for that trial, I can remember in the past few years a number of trials that have closed either for one arm being superior to the other arm or closed because there was no chance that a difference could emerge related to the question being addressed. We have described our data monitoring committee system in the Journal of Clinical Oncology and I would be glad to provide

you with that reference.

DR. KRAILO: Mark Krailo, from the Children's Oncology Group. There was a data monitoring safety board for that study. We met three times while the trial was ongoing, and the differences in the therapies emerged later on in this trial. So, they emerged after the study had completed all its accrual.

DR. CHESNEY: Are there any other questions for Dr. Smith?

[No response]

Thank you again. As Dr. Smith pointed out, the role of families as advocates for children is so important in all studies but particularly in oncology studies, and we are very fortunate this morning to have Dr. Susan Weiner, from the Children's Cause, who will speak to us on lessons and challenges of participation in clinical trials, a family perspective.

Lessons and Challenges of Participation in Clinical Trials -- a Family Perspective

DR. WEINER: Thank you, Dr. Chesney and Dr. Santana, for giving me an opportunity to speak this morning, and we are grateful -- I figure in my next life I will use Power Point but, somehow, in my generation it hasn't quite caught on -- we are specially grateful in the parent community for the increased attention that the FDA has been

paying to pediatric cancer under the leadership of Drs. Pazdur and Hirschfield.

As some of you know, I was the parent of a child with a brain tumor who was diagnosed in infancy and died just short of his fourteenth birthday. Since then I have worked as a patient advocate in the brain tumor community and in the pediatric cancer advocacy community, building programs to serve patients and counseling hundreds of families who are trying to make rational decisions about treatment and care in an irrational situation. I have founded the Children's Cause to devote more time to strengthening the pediatric cancer community through education and advocacy.

The experience of children and families who struggle with the diagnosis of childhood cancer is different from that of other pediatric diseases and disabilities. When I watched my son years ago in a special education class interact with his class mates disabled as a result of a variety of other diseases, I realized the uniqueness of his experience and that of our family. While they lived the slow course of chronic illness and developmental disabilities, we were living with an internal anti-personnel bomb. The uniqueness of the pediatric cancer experience lies not in its threat of its incidence or as a public health menace but, rather, in its uniquely destructive force

on children and families.

The uniqueness of pediatric cancer, of course, is inherent also in its diversity, namely that it represents many orphan diseases, often of embryonic origin. Families affected by childhood cancer share a common goal with the pediatric oncology research community. We want new treatments that are less toxic, that can destroy disease and spare healthy tissue with laser-like precision. Despite extraordinary gains in the treatment of some childhood cancers, many other childhood cancers, most notably solid tumors and, of course, brain tumors, have not enjoyed the same degree of improvement. We are still a long way from achieving our goal.

Our question as parents and patient advocates now is what will it take to ensure that pediatric oncology researchers can have rapid access to new agents so that our children with cancer can receive what so many people call the best possible treatment? During the 1990s, FDA and Congress, urged on primarily by the American Academy of Pediatrics, created initiatives to generate pediatric information on new and improved oncology drugs for purposes of labeling, as well as to increase industry financed pediatric research.

For children with cancer, both the Pediatric Rule and the pediatric exclusivity provision of FDAMA have had

disappointing results. While it has been successful for other diseases, the interpretation of FDAMA has resulted in relatively little pharmaceutical investment for our children. Now FDA's emphasis for labeling for pediatric oncology drugs, by enforcing the Pediatric Rule, leaves a series of questions about whether this enforcement will slow and alter the course of pediatric cancer research, questions which I hope we will discuss later today.

First, how can strict requirements for labeling possibly keep pace with rapid advances and knowledge about gene expression and molecular targeting?

Will the enforcement of the rule, in effect, redirect the strategy of the cooperative groups that have been responsible for the successes in children cancer treatment from consensus development and layers of review in clinical trials using available drugs off-label that pediatric oncology researchers believe are the most promising approaches?

Finally, why should research priorities in pediatric oncology now be shaped by a regulatory requirement that places first those diseases that may be judged the same or similar in adults as in children?

As parents and patient advocates, we want clinical research studies in children with cancer to be determined by the medical need to answer the most important research

questions and, of course, by the most promising scientific opportunities, and not by ill-fitting regulatory requirements.

Neither FDAMA nor the Pediatric Rule offer successful solutions to achieving the goals we all share for children with cancer. We seem to have strayed from our point. We have not yet struck the right balance between incentives and enforcement in pediatric oncology research. We should use industry's desire for exclusivity to encourage them to invest in pediatric oncology research and, at the same time, expect conforming to academic standards and strict cooperation with the cooperative groups. From the FDA, while we depend on your watchfulness, there needs to be a more flexible approach to regulation in pediatric cancer, and when it is time to re-authorize FDAMA we may need to craft special provisions appropriate to pediatric cancer research.

If rapid advancements in basic science are to translate into effective treatments for our children in the foreseeable future, a new interactive paradigm is needed whereby each constituency involved in pediatric oncology research will need to show more flexibility, a greater commitment of resources and a continuing awareness of the uniqueness of our diseases. Thank you.

DR. CHESNEY: Thank you very much for articulating

the issues so clearly. Are there questions for Dr. Weiner?

DR. HIRSCHFIELD: I would like to ask if there are any perspectives you would like to share with regard to family participation in the process?

DR. WEINER: Could you be a little bit more specific?

DR. HIRSCHFIELD: We have all stated that research is the standard of care, and it is a different paradigm when a child has cancer than going to the local pediatrician and getting whatever the standard of care may be for that particular community. It is a process where one has to sign consent forms, be made aware of protocols, and learn a new vocabulary, and I would like to know if you would make some comments with regard to these aspects which are different than families have when they are treated typically for other illnesses.

DR. WEINER: There are two things that I think are operating now. One is that there is a great reliance on the wisdom and the necessity of referral to centers of excellence to be treated. And, when families line up in a pediatric neuro-oncology setting, there is an important kind of bonding that takes place initially. There is an enormous need to assimilate a great deal of information under very, very dire circumstances. I believe that parents are helped these days by the web, by the free and open availability of

medical information from reliable sources such as the NCI and the FDA.

As every pediatric nurse knows, there is an initial phase of sort of being deaf, dumb and blind at the beginning and it is during that period where consent typically has to be signed over a period of days or understanding what needs to be done, and we are very much dependent on the good will and directness of the medical team. Does that answer your question, Dr. Hirschfield? No?

DR. HIRSCHFIELD: Well, you have not only had your own experience but the experience of talking to hundreds of other families, and I wanted our colleagues to be able to have a little better understanding of the impact of having the diagnosis of a child with cancer on not just the type of care but on the lives of the families.

DR. WEINER: Well, it is a life-altering situation and many families are, of cost, cast in disarray. The siblings are oftentimes neglected, and work is sometimes entirely neglected. There is a sense of unreality about being in a hospital and not being in a hospital at the same time. That is, while the hospital environment is a menacing phase, one relinquishes the care to strangers on the one hand. On the other hand, being out of the hospital means that life should appear normal which, of course, it is never again since a diagnosis of life-threatening illness means

that there is always imminent danger.

Does that do it? Let me try again?

DR. HIRSCHFIELD: I think you have shared some important information. Would you just elaborate a little bit more on what types of supports and what types of crises are faced, and where do people turn when they face these crises? Is it to the medical system? Is it to each other? Or, what are the responses and what are the resources available?

DR. WEINER: Well, there are many pediatric groups that have formed support groups and produce information materials but that typically is not accessible at the time of diagnosis. That usually comes after consent is signed and after the first treatment decision is made. It is often most accessible at the point of occurrence.

But with the Internet there are increasing resources that are out there. There are chat rooms, and for whatever they are worth, they represent a community. There is no substitute for the experience of one parent with another, and it is very important for children's hospitals and medical settings to offer that opportunity.

Finally, I think, you know, in terms of management of the sort you are referring to, it is very important to ameliorate -- it is difficult for me to describe the degree of distress. It is very important to have an intermediary

between the pediatric oncologist and the family -- not a research nurse, a nurse practitioner.

I guess I would like to leave this part of the conversation with something that I have recently called the "parents' double-bind," the parents of children with cancer. That really amounts to a situation in which the diagnosis of cancer as a life-threatening disease really violates the first principle of being a parent, that is, you have failed to protect your child from disease and imminent death. However, in order to ameliorate that diagnosis you have to relinquish your role as parent and fail to protect your child from harmful and sometimes toxic treatments at the hands of strangers. So, in that situation you can't maintain your role as a parent either originally or through treatment, and it is an understanding of that kind of paradox that is very important and really is unique to participating in clinical trials.

DR. CHESNEY: We do have some other questions for you, Dr. Weiner, if you would like to stay at the microphone. Dr. Santana?

DR. SANTANA: Susan, you made a comment that has been resonating in my brain for a little while, and I would like you to help me by giving examples or sharing your thoughts further, and it is this concern that you have that with new regulatory issues coming from the FDA as regards

pediatrics whether we will have to redirect the model of cooperative group research and how this potentially could impact it. Could you elaborate on that?

DR. WEINER: Well, Jim Boyett and were sort of talking about this a bit yesterday. It would seem perhaps unfortunate if there were studies -- let me start over again, there is a paucity of subjects available in pediatric oncology research. They are a valuable commodity and prioritization of approaches is something that is, as you know, critical towards progress. Dr. Smith described how long it takes to come up with a Phase III standard of care. It would be, I believe, unfortunate if these resources through the cooperative groups were to be used to establish similarity equivalence of disease rather than really taking account of scientific opportunity that perhaps looked more promising for new treatments. That is the context.

DR. CHESNEY: Dr. Kauffman?

DR. KAUFFMAN: I wanted to follow it up to try to understand better if you have any specific suggestions how changes in FDAMA might -- if it is renewed and if it is possible to make changes. In our discussions last February, as I recall, the issue came up that maybe FDAMA is not an appropriate vehicle to accomplish what we want to accomplish, and there are some inherent characteristics of the current law that make that so.

One is that many of the drugs that need to be studied in kids, usually in combination, no longer have exclusivity to which to attach the benefits of FDAMA. So, FDAMA is irrelevant to those drugs.

Secondarily, of the new drugs, new agents, they don't have the market size where FDAMA has had the most impact -- they just don't have the market size to bring FDAMA into play. So, what do you see as concrete changes in the law that might help with the oncology agents for children?

DR. WEINER: Well, you know, I am not an attorney and not someone who really is experienced in crafting the concept-precise proposals that you are aiming at, however, one suggestion that came up in discussion yesterday afternoon might be the point that the six months of exclusivity is more valuable -- you know, somehow or other, the older the drug, the closer it is to going off patent, the more likely it is that those six months are likely to be valuable. So, in some sense, FDAMA might take account of the kind of history or newness of the drug, and how that could be crafted I am not prepared to say right now, but the phrase "sliding scale" has been used a lot but the exact dimensions of that remain to be seen.

DR. CHESNEY: Dr. Nelson, you had a question?

DR. NELSON: Thank you, and thank you for your

remarks. When you started talking about the double-bind it began to address the area I was interested in asking about, which is specifically the consent process.

One of the things that is explored in the process of looking at informed consent is the ability of an individual to distinguish research from standard of care but, yet, we are in the process of conflicting that distinction by saying that the standard of care is to participate in research. So, I am just interested in hearing your reflections about how at some time in the process a parent becomes aware of the research components, and what suggestions you might have or directions for looking at the quality of the information and the quality of the decision that a parent makes to enroll in that kind of a process.

DR. WEINER: This is, of course, the heart of the matter. As those of us who are in the pediatric oncology community really know in our heart of hearts, parents do not make that distinction. It is in some sense unthinkable and many of us can report instances in which the most sophisticated parents and family members will say, after a course of treatment and after having signed consent, that their child was not part of a research study. I think that that is evidence for the kind of power of the need to believe that one is treating one's child, one is subjecting

one's child to harmful intrusions for the purpose of their getting better.

There may be other ways around that. The consent form, and as many of you have reviewed dozens of these -- the consent form language is always contorted in a way that makes it difficult. That can always be tinkered with. Sometimes, particularly for example in Phase I trials, it is useful to have the investigator and the physician care-taker roles distinguished between people. I think there is no easy solution but those are some of the strategies.

DR. CHESNEY: Dr. Murphy?

DR. MURPHY: Susan, you were at our February meeting so you know that many of these issues were brought up and we thought that we left that meeting with a way to resolve many of these issues. And, Dr. Pazdur is, you know, going to be presenting the guidance outcomes for the group here and the approach, and after he speaks and presents the process to the group I think it would be helpful for us to hear where you still think there are issues, particularly as relates to the selection of products to be driven by science, because that is the very concern we have, that FDAMA be driven by science and not because there is a lot of money to be made off of a block-buster product.

And, the second issue is flexibility and that is one of the goals of this approach, to provide flexibility

for the development of pediatric oncology products while not making it a complete free for all. By that, I mean that every group ends up with administering things in a regulatory way and in a different way.

So, I would just like to say I would like you, after we hear Dr. Pazdur, to point out to us where you think this approach does not address those two issues in particular because I think one of the concerns we have at FDA is, as Dr. Smith has clearly articulated this morning, that there has been a lot of success in this field because of the cooperative groups and the standard of care, and we don't want unintended results here where FDAMA drives the process in a different direction. So, we don't want to disrupt something that is working. I guess that is one of our concerns, we keep moving in this area. So, again, those two issues, the flexibility and why this process won't help that and why this process won't help the science approach, would be questions I would ask you to come back and tell us. Okay? Thank you.

DR. CHESNEY: Our next speaker is Dr. Richard Pazdur, who is Director of the Division of Oncology Drug Products at the FDA, and he will speak on the FDA initiatives in pediatric oncology -- adaptation of the general case to special circumstances.

FDA Initiatives in Pediatric Oncology

Adaptation of the General Case to Special Circumstances

DR. PAZDUR: Good morning. I somehow feel like a fish out of water. I am not a pediatrician and I was thinking back on my pediatric experience and, I am ashamed to say, it has been about 25 years ago that I treated a pediatric patient. So, if I make any major faux pas in the science and medicine of pediatrics, please forgive me.

[Slide]

I came to the agency about a year ago. In fact, the last week in September will be my one-year anniversary as far as starting at the FDA. My former job was as a clinical professor at M.D. Anderson Cancer Center where I was very involved with Phase I, Phase II and Phase III drug development in colorectal carcinoma, a quite different disease than one would see in pediatrics. Nevertheless, in my experience in interacting with my colleagues in pediatrics at M.D. Anderson and in the greater Houston area, I was always aware of a particular angst or a particular distress that the pediatric oncologist had when we talked about clinical trials, especially when the adult medical oncologist had a wide array of new agents that they were studying. There was somewhat of an uncomfortable feeling among the pediatric oncologists that they simply were not getting those good drugs right away. In other words, they were somewhat relegated almost to a second-class citizen --

let's see how these drugs work in the adults and they maybe we will consider developing them in pediatrics.

When I got to the agency, it was clear from Dianne's presentation and working with the pediatricians in our oncology group that the implementation of the FDAMA incentive program was simply not working in oncology, and I kind of stepped back because I was new and that always gives you a fresh perspective -- right? -- and I said, well, why isn't this working? And, I said, really, you have to have a whole plan of basically developing a drug in pediatric oncology.

When one takes a look at the applications that come into our division of medical drugs, where are sponsors developing drugs? They are developing drugs in the big markets for oncology drugs -- breast cancer, prostate cancer, colorectal cancer, lung cancer. Very few approaches or very few applications are coming in for indications where we would even think of extrapolating from an adult indication to a pediatric indication. It is very hard to make that bridge between developing a drug in colon cancer and saying, well, we now have to exert the Pediatric Rule for development of this drug in pediatrics.

So, there are some very unique characteristics about the whole field of pediatric oncology that I thought needed revision. The difficulty in extrapolating adult

indications to the pediatric population in oncology is one that we will discuss this afternoon, and it is a very difficult decision and perhaps, as science progresses and we learn more about the biology of the diseases, we will have a greater flexibility in applying this rule.

But, as I stated before, the major disease categories that we receive applications for are in the common adult malignancies which makes the application of the Pediatric Rule very difficult. Nevertheless, we know that pediatrics has very special characteristics both in the pediatric community in general and in the oncology community, and we must be cognizant of these special characteristics as we develop any plan in developing pediatric oncology drugs. And what are those special characteristics?

Number one, as has been stated repeatedly, it is the standard of care for patients, children, to participate in pediatric protocols. I wish I could say that about adult malignancies. In essence, with adults it is just the opposite. It is the exceptional patient that participates in a clinical protocol.

Secondly, and most important, it is the relationship that the academic and the practicing pediatric oncologist has with the NCI and the Pediatric Oncology Group structure that must be protected, and that was part of a

whole development plan that we have initiated, that we do not disrupt this relationship because it has worked; it has turned pediatrics really into a very successful model of producing curative therapies in our generation.

So, in any implementation of any plan, I want to make it quite clear we are not attempting to exert a regulatory hammer on a near-perfect relationship that exists between the cooperative group structure, investigators and the NCI. The scientific agenda must be established by the physicians that are doing the trials, those that are involved in the cooperative groups. We are here as a facilitator to get those drugs, to use "regulatory pressure" via FDAMA regulations, to act as a funnel to get those new agents into the pediatric structure. It is not our decision of what drugs should be studied. That should be left up to the experts in pediatrics.

[Slide]

This is the Food and Drug Modernization Act of 1997, and this is what we call the incentive program. Some people call it the carrot in contrast to the stick, which is the rule, and it is a provision for a 6-month extension to the existing marketing exclusivity or patent protection of the entire line, and it can be granted to an entire product line of an active moiety for providing new pediatric information that will benefit public health. The

submissions must come in response to an FDA written request, and I will go over this in a little more detail.

[Slide]

This slide provides you the Pediatric Rule, which I think you all have been briefed on as far as the membership of this committee yesterday. In this rule, this is what we kind of refer to as the stick or a mandate, and it provides that a product under review must provide pediatric information if the indication under review is a disease found in children. If a disease is not found in children a waiver may be granted. And, this is one of the major problems that we have with the application of the Pediatric Rule, that we issue far more many waivers than we implement this rule simply because many of the diseases, or I should say most of the applications and products are being developed in common adult malignancies that do not have this ability to extrapolate into pediatric indications.

[Slide]

Most people or many people have difficulty in comparing the FDAMA incentive versus the Pediatric Rule, and what I have attempted to do in this slide is to provide you a listing or a comparison of FDAMA versus the Pediatric Rule. FDAMA is a voluntary program. It applies to the entire product line, the incentive does. There is no restriction on eligible pediatric diseases. It only applies

when there is an underlying patent or exclusivity protection. Obviously, you need something to extend. Biologicals and some other products are excluded and orphan drugs are included.

In contrast to the FDAMA, the 1998 Pediatric Rule has the following characteristics, and these include that it is mandatory if the disease is found in adults and children, it must be studied in children. It only applies to the product and the indication under the review rather than to the entire product line, and it only applies if the pediatric disease is similar to the adult disease. It applies to biologics, and orphan products are excluded.

[Slide]

This gives you an indication of how pediatric exclusivity comes into being the actual process of how the FDA works with this. A proposed pediatric study request is usually generated. Who can generate this pediatric study request? Virtually anyone. It could be a cooperative group; it could be an academic; it could be a commercial sponsor; it could be any other interested third party. A written request is then generated from the FDA. This written request is very important because it has the exact specifics that must be followed, and these specifics must be followed to the detail to allow granting of the eventual exclusivity.

So, in response to a proposed pediatric study request, a written request is generated from the FDA. A sponsor, if they are willing to do it -- remember, this program is voluntary -- submits study reports after completing the required studies and then the FDA determines, as it would in any review of an application, the scientific validity of the material that is submitted to determine whether it meets the specifics of the written request that is generated from the FDA. Because we have had a paucity of proposed pediatric study requests, we have taken the initiative to generate some written requests on our own from the Division level of Oncology Drug Products recently.

[Slide]

Let me give you the idea or the concept of this pediatric plan that we are asking you to consider here and to comment on. As I stated before, if somebody is developing a drug in an adult indication, such as breast cancer or such as prostate cancer, it is going to be hard to say where do I go with this drug in pediatrics. It requires really, if you take a step backward, a whole plan to develop this drug.

One has to take a look at the dose in pediatrics, the toxicities in children that might be unique. What pediatric disease do you study it in? Well, there might be some diseases that may be applicable if you know a specific,

for example, genetic mutation such as in the STI drug that Dr. Smith referred to. However, for the vast majority of cases we are dealing in an area where we don't know what pediatric disease this may work into. So, therefore, you would need some type of screening Phase II study to determine the eventual activity of the drug, if it does have activity.

This is a very risky process and we are aware of this, and this whole plan that we are devising is some way of sharing the risk of developing an entire oncology drug for pediatrics with the sponsor. So, the following provisions have been made: An overview, dosing and pharmacokinetics in the Phase I one study must be done. We need this information obviously to proceed further. What is the dose of the drug? What are the toxicities?

Then, Phase II or pilot studies in a range of potential indications can be performed, and these are usually stipulated in the letter or there is some flexibility and here, again, we would encourage strongly sponsors or people that have received a written request to discuss what Phase II studies they want to do with the pediatric academic/cooperative group community. Pediatric patients are an important national resources. We do not want them to be used as a commodity. They should be used i the best -- and I shouldn't even use the word "used" but

they should participate in the best designed scientific studies, designed to ask the most important questions.

Here, again, this plan is to introduce either old agents that have not bee studies, and by old agents I mean approved drugs in oncology, or new molecular entities that have not been approved yet by the FDA. It is important to note that this development plan is not a supplemental NDA since efficacy does not necessarily need to be demonstrated. Obviously, we would want efficacy to be demonstrated if the drug is active and for us to label this drug as well as to approve this drug for a pediatric indication if warranted. This applies to both new agents and approved agents that have not been adequately investigated in pediatric oncology.

[Slide]

Let's take a look at the first stage of development, and this correlates basically with a classical Phase I study in medical oncology or pediatric oncology. Phase I studies would be done to determine the dose, the pharmacokinetics and the toxicities -- pretty straightforward. Roughly, about 25 patients would be planned to be entered, and here again we have some flexibility. Obviously, nobody knows a priori, before starting the study, exactly how many patients would be entered on a Phase I study. So, there would be a range here and some flexibility.

The important point here is if unacceptable toxicity occurs the development would stop and an exclusivity extension would be granted -- pretty generous, right? The reason behind this is we look at this as an exceptional situation. We feel that there would be very, very, very, very, very few drugs that would go to Phase I in pediatrics and would be stopped because of unacceptable toxicity. Nevertheless, if somebody makes a good faith effort in developing this drug and proceeding with a development plan to a point where they can no longer proceed, then we believe that this has been a good faith effort and, therefore, they should be rewarded by the granting of exclusivity. We view this as a very generous concession, in a sense, but we realize this is an important aspect to promote and act as a funnel of getting new drugs to the pediatric oncology community.

The most important aspect, rather than concentrating on an exception, is where we believe most of the drugs will go, and that is if the toxicity is acceptable, and here, again, that is a decision that will be made by the pediatric, academic and cooperative group community, the development of this drug should proceed to a second stage and this is the vast majority of cases, and let's go on to that second stage.

[Slide]

Here, again, it is rather general because we cannot dictate specific situations to a general plan such as this, what we are looking for in our Phase II studies is what is the activity of this new molecular agent or an existing approved agent in pediatric malignancies? So, we would propose that Phase II studies would be done and here, again, it would depend on what disease one is studying. If it was a very refractory situation one could take a look at single agents. Perhaps we would take a look at window studies, perhaps at add-on studies or pilot studies of various combinations to demonstrate an agent's characteristic and contribution to the following -- efficacy, perhaps using surrogate endpoints such as response rates, such as time to progression, and this would also provide justification for further development to examine clinical benefit.

[Slide]

Possible outcomes after the Phase II portion -- well, if efficacy is demonstrated on the basis of a surrogate endpoint, this may lead to a concept known as accelerated approval or subpart (h), and for those of you who are unfamiliar with this FDA provision, it allows us to approve drugs on the basis of a surrogate endpoint such as response rate, such as time to progression, with an approval for marketing with a commitment that a clinical benefit such

as a survival benefit or a palliative benefit in terms of symptoms be subsequently studied in a Phase IV commitment. But, anyway, if efficacy is demonstrated there is a possibility for accelerated approval, allowing for full marketing of the drug.

If there is no beneficial effect that is observed, then the development is halted and stopped. The drug simply doesn't work. Here, again, a good faith effort has been made in the development of this drug and even if the Phase II studies are what we would call negative in that they have not shown anti-tumor activity in a particular disease to warrant further development, exclusivity would be granted on this attempt to provide further information.

We would hope the latter or the third portion is the most common one, and that is if results are promising but not sufficient to support approval a commitment to further development would be made. As stated here, in all three cases granting of exclusivity extension can be made. It is important. We are interested in good quality data. The granting of exclusivity on "negative" data whether it be a negative Phase I study with prohibitive toxicity or with negative clinical results does not mean that we are accepting poor quality data, studies that are poorly conducted. We are interested in working with the cooperative groups to guarantee the best scientific

integrity of the studies, and we will be looking quite closely at how these studies are performed in our review process.

[Slide]

The results of the completion of a pediatric development plan are listed here. The results are summarized in a study report and submitted to the FDA where a determination based on meeting the proposal is finalized. Upon review, if the conditions of the initial written request are met, regardless of outcome, a 6-month exclusivity extension may be granted. We are looking for well designed, well executed studies where negative results can qualify as long as these studies are well designed and well executed. Our intent is a prospective plan to produce and to really introduce new information of importance to the pediatric oncology community.

In the year I have been here, although as I have stated before I am not a pediatrician, because of Dianne's influence and because of Steve's influence, it has been on our radar screen to make pediatric oncology an important element at the FDA. Not only have we written this plan up in a guidance, which is on our web site and I would encourage all of you that are interested to view that guidance, but also we have taken an active recruitment posture as far as recruiting two additional pediatric

oncologists to our review staff. We have 20 medical oncologists, three of which are pediatric oncologists, really to underscore our commitment to the pediatric oncology community in developing drugs.

There is only a certain amount that the FDA can do. We do not make legislation. We can simply implement what has been done, and this is an attempt basically to introduce new agents into the existing structure. To reiterate once more, we believe that the relationship between the investigators, between the cooperative groups and the NCI is an important one. We are here as a facilitator, working with the regulations that we have at hand -- again, we do not make laws; we interpret them and execute them. But, this is an attempt to funnel new agents, to funnel drugs that have not been properly studied to the people who we think can study them, can give us the answers that will lead to important information.

Although I am presenting it, this work has been done by many people. Dianne has been actively involved with it. Steve Hirschfield has been actively involved with it, as well as the entire pediatric team that Dianne oversees. So, I am open for questions but really I would like to deflect the entire questions not only to myself but Dianne and Steve also since they have been active participants in this program. Thank you.

DR. CHESNEY: Thank you very much, Dr. Pazdur. That was extremely clear and helpful, I believe, to all of us. I am wondering, Dr. Weiner, would you like to respond first to Dr. Murphy's request or wait? Okay. Yes, questions for Dr. Pazdur? Dr. Finklestein has the first one.

DR. FINKLESTEIN: I would like to make a comment, a comment that I also made at the February meeting and have made subsequently. I am probably the senior pediatric oncologist in this room, and for most of my career the FDA was "we" and "they." But, in February I concluded that it is "we" and "we," and since then I have absolutely watched what has happened at the FDA and I am convinced that it is "we" and "we." The tone that I hope we will adopt for the rest of the meeting today will accept the fact that we really are all on the same side of the fence.

Now, since the February meeting, in the spring, with Greg Reaman, who is sitting right opposite me, who has the same hairdo so you can recognize him --

[Laughter]

-- co-chaired a meeting, and in that meeting was a group that came from the FDA, the NCI, PhARMA, the cooperative groups and the public, and the pediatric oncologists. All the participating parties were in the same room, with one goal in mind, that is, to advance the therapy

for children with cancer. So, I am convinced that the FDA will not direct, but I am convinced that the FDA will work with us in advancing the care of children with cancer. Research is the standard of care.

Now, my colleagues in pediatric oncology I know will absolutely agree with the next statement, we spend a lot of time in the multi-disciplinary approach to children with cancer. This was alluded to by Malcolm. So, consent forms are important to us. All of us as psychologists, social workers, psychiatrists, people who spend time with our children, with the siblings, with the families, we recognize that when a child is diagnosed with cancer we change the family's life forever.

So, I look at what we are doing today as just another tool in working with this community which I mentioned, which Greg co-chaired, to advance therapy with cancer. I don't think one aspect is going to direct the other. I think we will all work together. So, I don't consider FDAMA a threat. I look forward to finding out, as Rich Pazdur pointed out, how we can use the rule, the exclusivity, the interpretation to help children with cancer, and if you can't do it completely in the FDA, and I don't think you can, we will do it through the NCI; we will do it through the cooperative groups; we will do it through the public. I think working together we will get the job

done. Thank you.

DR. CHESNEY: Thank you very much. Dr. Friedman?

DR. FRIEDMAN: Richard, one question, for a drug that clearly is now in the Phase II or better stage for adults where a drug company has a clear indication that there is going to be a marketable agent that will produce financial gain, the plan you have outlined seems quite reasonable. For a drug that is in very early stages of adult evaluation, Phase I potentially, where they are not sure there will be any financial gain to the organization at all, the real time where pediatric oncologists say, "gee, we'd love to get this drug; it's in the lab, we'd like to get access to it in the lab; we'd like to get access to it in the clinic," there, where a company has less strong conviction that the drug will ever produce financial gain for them, I don't see that there is the same incentive for them to expand to pediatrics with that and get an increase in exclusivity which may never be of any meaning to them. How do we deal with that issue?

DR. PAZDUR: I think that potentially is a problem because, obviously, exclusivity has to be attached to a patent, in a sense, or something that is in existence. We have been making efforts to basically promote this when we meet with companies in all of our meetings, whether it be end of Phase I meetings or IND meetings, to encourage them

to participate in this.

I would hope also that there may be some competition even within the cooperative groups -- not competition within the cooperative groups but if multiple agents are coming forth obviously there is a limited number of patients to be entered on these protocols, and perhaps this would provide an incentive for the companies to come to the pediatric groups earlier on in the course of the drug development process.

DR. FRIEDMAN: Let me follow it up with one more question that may reflect my ignorance of the regulations, but if you have a company with a reasonable portfolio of agents that are out there that are being evaluated, some of which are clearly being sold and yet there are clearly, in the developmental side of that organization, drugs that we are interested in accessing to pediatric oncology, why cannot we use a carrot that says we will give you exclusivity for one of your agents because we clearly see the profit that will come to you from that but, in return, we want to access for the pediatric oncology community compounds A, B and C which may or may not ever make the financial gain for your organization? Why does it have to be linked to the single drug we want in pediatrics? Why not give them a financial carrot, and the bigger the drug the more one can ask from that organization?

DR. PAZDUR: Well, we don't make laws. That is one of the problems.

DR. MURPHY: Actually, just to address that question first, that was discussed. There have been various mechanisms that have been discussed, and that is called the "wild card" exclusivity which a company would be able to apply to any of their products. I can tell you that it has been discussed. I can tell you that in looking at the economic impact of what we are doing already, it is very costly, and that is without the wild card. In other words, the FDAMA activity, as it is right now and I can't say any more than that, this is costing us, and it is one of the things that will be discussed in the FDAMA assessment by Congress -- how much is the cost to the taxpayer and to society to develop these products for children? I am a pediatrician. I think it is long overdue. The Academy thinks it is long overdue. Many people who take care of children think it is long overdue. I just want to put forth that we have been doing the math on this and this is an expensive program and people are going to have to make a cut.

So, I just want to say, first of all, that alternative approaches have been discussed. They are even more expensive. Now, that doesn't rule them out, and people may look at that again in the re-authorization of the

legislation. That may be looked at again.

I know we have emphasized how often you can't extrapolate or where the diseases aren't the same, but where a product is in-house and the disease is the same and it is early on, you could use the rule if exclusivity were not going to be applicable for some reason.

DR. CHESNEY: I think Dr. Balis has a question.

DR. BALIS: In twenty years I have probably treated two patients with colon cancer and there are reports of it occurring in kids. So, if a company comes to the FDA with an application for colon cancer you could theoretically say that it should be studied in children since it occurs, but that literally probably would take centuries to do. What is the cut-off that you have in terms of incidence of diseases to apply the rule?

DR. MURPHY: We have two criteria for the rule. One is a meaningful therapeutic benefit and the other is substantial use. You can qualify under either. You do not need both. So, the substantial use is 50,000 population, however, there are populations which do not meet that substantial use but may meet the meaningful therapeutic benefit. In other words, it would provide a meaningful therapeutic benefit to have the information that we need to dose it and to know what the safety is for that population, and then the rule would allow us to require those studies.

DR. HIRSCHFIELD: We haven't come to that situation, and if we ever get a block-buster drug in colon cancer, of which there really none right now, then we potentially could face that. We have looked at ball park ideas of several hundred cases which would sort of be a threshold.

I would just like to reiterate something that Jerry Finklestein said to answer Henry Friedman's question, and that is the working together approach because we are very excited about having colleagues who are pediatric oncologists and industry, and many of them took time out of their schedules to be here today with us in the audience, and we think by having advocates in the companies, as well as inquiries from the NCI, as well as inquiries from the cooperative groups and the investigators, as well as inquiries from the parents and the patient advocacy groups, as well as receiving letters of invitation from us to participate that we hope that that combination would be sufficiently persuasive that these new drugs could be made available.

DR. PAZDUR: The other point I want to mention is I think we have to have some integrity and credibility here in the application of these rules. To try to extrapolate and say that colorectal carcinoma or breast cancer or lung cancer is a pediatric disease I think would produce a lot of

problems with our sponsors. Okay? And, although we might like to exert a heavy hand, there are situations that I think for the sake of continued really good faith effort in promoting this, we should look at this in a very objective fashion.

DR. CHESNEY: Dr. Reynolds, did you have a question?

DR. REYNOLDS: Yes, thank you. Within the Children's Cancer Group, strategy group for neuroblastoma as well as the new approaches to neuroblastoma therapy consortium, as well as we think probably within the Children's Oncology Group as this is formed, we have a stated commitment to do development of agents based upon good preclinical data, and we have relied for the most part upon large numbers of cell lines available in vitro to determine activity for most agents, and that has served us well. One of the frustrating components of this has been in getting access to new agents as they are being developed within the pharmaceutical companies, and I know there is discussion of using this sort of preclinical modeling to develop priority schemes within the Children's Oncology Group beyond just neuroblastoma that would address some of the questions such as Susan has addressed, and that is, what is driving what we are going to do within the testing here. Is it the need to test an agent for exclusivity or is it the

science? And, since there are limited numbers of patients, good preclinical models are extremely important in developing the prioritization of doing Phase I studies.

You mentioned facilitation with the FDA. Can the FDA facilitate getting these agents early on into the laboratories of investigators studying pediatric cancer so we might see if they have some promise and warrant further testing in children rather than just adults?

DR. HIRSCHFIELD: A good point, an interesting strategy. Our grip is essentially when something is made available for clinical use, and for the most part that is where our responsibilities and our mission lie. In terms of making agents available for laboratory studies, we don't have any regulatory authority.

DR. REYNOLDS: Have you had problems obtaining these agents? Because my experience in the academic world has usually been that companies have given the agents out for preclinical studies. We, for example, have wanted to study any farnesyl transferase inhibitor in neuroblastoma and I don't know of anyone who has been able to do such in vitro, certainly not in my laboratory.

DR. PAZDUR: Here, again, I would like to reiterate that the decision of what drug should be studied by a specific cooperative group is not an FDA decision. Obviously, it is that group's decision and it should be made

on your scientific assessment, whether it be on preclinical assessments or on perceived clinical potential of the drug.

DR. REYNOLDS: True, but we are not getting access to these, nor is industry even returning phone calls or letters requesting access to these agents. So, if there could be some facilitation through the cooperative group and the NCI by FDA for getting agents in for preclinical testing I think we would all benefit, including the companies.

DR. PAZDUR: We heard that, and we will make it a point in our discussion with the companies when we meet with them on preclinical matters.

DR. CHESNEY: Dr. Spielberg?

DR. SPIELBERG: I think we are all struggling with a lot of issues here. On the other hand, I think a perspective that Dr. Finklestein put forth is absolutely unique. Probably in no other area of pediatric therapeutics right now do we have the opportunity to make such changes as we do here. The presentations this morning had better science than almost any other therapeutic area that this group has dealt with but even more important is what Dr. Finklestein emphasized. We have here representatives from the best pediatric clinical organization for doing investigation anywhere in any therapeutic area. There really is a network. Other groups talk about networks; there really is a network.

Even more important, we have the cognate of COG if you will within industry of pediatric oncologists now within the industry who have been trained mostly from the same kinds of programs. The issues of early access apply really throughout all therapeutic areas, but often there are no advocates within industry within whom the pediatricians who are taking care of the patients can actually interact. Our best hope, I believe, for those early interactions and for solving the issues of exclusivity and coming up with other novel ideas is the fact that we have real advocates within the industry, coming from the same programs, dealing with the same patients, trained under the same circumstances, who recognize these issues.

Having spent 25 years on the other side in pediatric clinical pharmacology, I had the same frustrations in all sorts of different therapeutic areas of calling a company blindly and ending up with no one to talk to, and being turned down repeatedly. The whole issue of early access, of working out these programs, of trying to get advocacy within companies is having, if you will, plants within companies, and we have the unique opportunity here because we have a large number of pediatric oncologists within companies who can act as advocates, and many of whom are here today and are active participants in that process. In no other therapeutic area do we really have that same

kind of opportunity.

So, the issues of early access is in knowing whom to call. You know, it is the old ghost-buster story. The issue here is that we have ghost busters now lined up in multiple different companies. Is it always going to work? Of course not. If it works with a couple of compounds that the COG needs to get into early evaluation and preclinical models, that is where it is going to happen. It is going to come from personal contacts and interpersonal contacts.

If we need advocacy to solve the kinds of things that Dr. Murphy was talking about, either modifications of FDAMA or wild card approach because of the nature of things -- for example, we are already doing very well with all of the ancillary drugs that are used in oncology that keep children alive, the antibiotics, the things that relieve pain, the things that relieve nausea -- those all work pretty well under FDAMA right now. There may be a way of saying, okay, if you are working on compounds that are used in oncology, somehow or another working out some mechanism as those compounds get more benefit because you are also working on a compound which is a very orphan drug that you are introducing to actually attack the tumor -- there may be creative ways of doing this, but the way that we are going to do it is exactly what Dr. Finklestein described at the beginning, the fact that there is incredible good will

within the agency right now, as well as pediatric oncologists within the agency, pediatric oncologists in industry and pediatric oncologists out there actually doing the studies and treating the kids.

So, I think while, indeed, the cup is still half empty and we have a long way to go, I feel it is more than half full because we have all these people here today, and all these people are listening and they are listening to Dr. Weiner's concerns; they are listening to the concerns of the oncologists. It is not going to be simple, but the bottom line is if it is important and it needs to be done, it will be done in the context of all these people working together.

DR. CHESNEY: Thank you, Dr. Spielberg. Dr. Nelson?

DR. NELSON: In listening to this, I guess in the form of a comment I am going to ask a question about FDAMA and see if there is an angle on this early access that might be viable. My understanding of FDAMA is a company needs to respond to a written request. The written request is shaped by the notion of what might be in the interests of pediatric patients and in the public health. It strikes me that cooperation at the level of the formation of the written request from the standpoint of preclinical modeling of what drugs ought to be in the pipeline, and the like, that at the written request level one could focus those to compounds

that the oncology community truly wants to use. So, it would then be driven by science and by the priorities of COG within the formation of the written request.

A couple of concerns though, since the motivation to use the rule instead of FDAMA is at potentially sunsets, unless it gets approved which is where I think some of the warnings about expense come in and the political process, if a written request is issued before it sun sets but, yet, there hasn't been a response I don't know what the situation would be in terms of allowing that exclusivity to still exist. I am also not clear about the impact of the exclusion of biologicals and how that is defined in terms of some of the new agents that are trying to do antibody-mediated sort of attacks at receptors and that sort of thing, and whether that is a loophole in the application of FDAMA.

DR. MURPHY: Let me try to address first the preclinical part. FDAMA is very clear on that issue. We have to ask for clinical studies and they actually routinely are pharmacokinetic studies. Even though they are done in human beings, they are not considered in that category but for FDAMA they are because of the recognition that for pediatric development dose-finding, extrapolation, all those issues are relevant. So, FDAMA requires us to ask for clinical studies.

However, when we issue a written request, and we have done this, where we think there is critical information, preclinical information that needs to be developed, we have included it in the written request as an informative process that we will be looking for this, but it cannot be an element of meeting the terms of the written request. Does that make any sense?

DR. NELSON: It makes sense, but I guess somehow you need to decide who to write that letter to and about what if part of the process of cooperation is at that level, not at the level of asking the company to do the clinical studies but at the level of deciding which compound to focus a written request to -- if that is where the cooperation takes place.

DR. MURPHY: Right, that is what we are trying to construct with this approach, that we work with the cooperative groups in issuing written requests that are targeting those priority products because of all the issues that you have heard brought forth today. That is a real concern to us. You know, we really want to maintain -- we think our goal is a public health goal here and to maintain that public health goal we need to have a cooperative approach to developing the products for which we would issue written requests, and that is what this structure is supposed to assist in doing.

DR. NELSON: Right. I guess just one brief question, in facilitating getting certain compounds into the preclinical testing -- I mean, I would think if you were a company with a certain compound, if you heard rumors that there was an interest in developing a written request on that compound and that a certain physician wants to do preclinical modeling, I think it would be in your best interest to send that compound to that person. So, doesn't that begin to make some of these connections in the pre-written request phase that are being asked for?

DR. MURPHY: Yes, it appears to make good sense. One would hope it would work that way. What we are trying to say is that we have certain constraints within which we have to work. We wish to develop the science and have them putting in these -- I won't use the word requests but the recognition of certain preclinical areas that we think are important and, again, doing that in this context, the oncology context with the process that you have heard outlined today.

The question you had about sunset, I try never to answer this question because I am always saying something incorrect legally, but my understanding is that if we have issued a written request for a product that is on the market prior to the sunset, they can bring in the studies after the sunset and it would still be able to gain that exclusivity.

Now, I have been very open about this, that I am hoping Congress will not have this exclusivity sunset because I think it is the engine that is driving product development for children and also the science in many areas.

DR. CHESNEY: Dr. Boyett, do you have a question?

DR. BOYETT: Yes, I have a question for Richard. Throughout your presentation you alluded to the need to have well designed studies, and I think most of us agree that our clinical trials should be based on sound statistical science with a design that specifically addresses the study objective. If your study comes from the cooperative groups, I don't have real concern because I know the design at a very high standard will address the study objective. I don't know how the FDA can provide assurance that these studies will be well designed if they don't come through such a mechanism because, as I understand it, the FDA is not authorized to critique a study design.

DR. HIRSCHFIELD: Yes, I will address that. We critique study designs all the time --

[Laughter]

-- the question maybe is do people listen to us?

[Laughter]

But when a study comes in, there are some circumstances where we review the study design in detail. For a new IND, study designs are reviewed in detail. When

someone submits a study design which they say is for a pivotal study for registration, we review that in detail. There are a number of other protocols that fall in between where we do not typically send out our comments. We look at them but, unless we are requested, we don't send out comments.

In terms of the pediatric written requests and pediatric studies in general, we look at the studies in great detail, and when we say great detail it means at least -- at least two physicians reviewing the protocol plus at least two statisticians reviewing the protocol and, if need be, we also have biopharmaceutical consultation and toxicity consultation.

DR. BOYETT: If I could just follow up, I would hope that you would provide comments, especially for these that are going to argue for exclusivity for their drug. We have had the experience in Memphis, just this past year, of an investigator coming to us with a "FDA approved" trial for our scientific review committee to approve, and the study design was absolutely inadequate for addressing the study question.

DR. PAZDUR: It is difficult to comment on a specific example. You know, we do not approve protocols; we let them proceed, in a sense. So, you know, this concept of does the FDA approve a protocol -- no, technically they are

allowed to proceed and depending on what level of risk we are looking at, different protocols obviously undergo different levels of review. Some are even exempt from FDA review if they are using commercially available drugs in safe doses, and recognized routes, without a commercial intent, or commercial intent on claim. So, in a sense, it really depends on what the protocol is.

I think in this situation where we are talking about pediatric oncology and the fact that these are being done with a commercial intent by the sponsor in terms of exclusivity, obtaining exclusivity, these would be looked at quite closely.

DR. MURPHY: Could I just say one more thing? I think that we are often accused of many dastardly deeds, but one of the things in the process, as has been pointed out, is that we allow a protocol to proceed, and we have a mechanism called a "hold" mechanism. We have very strict guidance and regulations as to how we can put a protocol on hold, and we have an entire activity surrounding a reporting mechanism and when we put a protocol on hold. I guess I can say we could argue probably for a long time about how a poorly designed protocol is a safety issue but, in general, we cannot put a protocol on hold unless it is a safety issue or clearly has to be put on hold for concerns that we can articulate and can justify. Having a design that we don't

agree with -- usually it is not within our power to put the protocol on hold unless it crosses a certain threshold. Basically, as I say, it is just totally clear that it will never be able to achieve the ends that it is intended to. One could argue that that is a safety issue but, in general, what I am trying to say is that the areas in which we can tell an investigator that they absolutely cannot proceed are limited compared to the number of protocols which are not designed the way we would like them to be designed, but may still achieve the ends that researcher feels that they could achieve. So, there is a huge spectrum in there, as you can imagine.

DR. PAZDUR: Here, again, I think there is this basic misconception, that is, we do not approve these protocols. This is not like NCIC that has a vested interest in these protocols. These are allowed basically to proceed rather than a formal approval process.

DR. SPIELBERG: I would like to make one quick comment though because I think it is important that people understand the FDAMA process as opposed to most typical protocols. The written requests really provide industry a great deal of specificity, down to the number of patients, the endpoints to be evaluated, the duration of the trials, in much greater specificity than is typical for the average drug study where the sponsor says, "oh, I'd like to study X

indication," and then design a protocol which is then submitted to the agency for review. In setting up the written request a great deal of specificity, including the indication, the precise number of patients, the precise nature of the study -- because at the end of the day, provision of exclusivity is dependent on the agency reviewing step by step the written request against the material.

So, in fact, the agency really has a great deal more control over the nature of the studies done under FDAMA than under typical studies, and one would certainly hope that in areas where there is difficulty designing studies the input comes from the subspecialists, etc. to make sure that that negotiation which goes on with the FDA results in a protocol that truly is going to get the information the kids need and I think that process has worked extremely well.

DR. PAZDUR: One of the other features, we meet with sponsors on a continuous basis, going over these protocols and for important protocols such as this that we are looking for implementation in this program, we would probably meet with the sponsors and go over them.

DR. MURPHY: I guess one of the confusions here is that maybe we are talking about two different activities when we talk about the hold issue and we talk about the

general procedure. What Steve is addressing is the written request process which is very different. The process for drug development for children under FDAMA is very different than the routine process because FDA does have tremendous amount of authority in what they ask for in their written requests, and that is why it is very important that we have expert input and cooperative effort.

I would also like to say that for any serious or life-threatening disease we will meet with the sponsors early on in the development of the product. Again, this is not FDAMA; this is just in general but particularly when you look at the Pediatric Rule. There are many aspects of this and it clearly tells us for all pediatric drug development that we will meet with the sponsors and talk about their pediatric plan for serious and life-threatening diseases at the end of Phase I, and for other non-serious or life-threatening diseases at the end of Phase II. That is in our regulations.

So, we are meeting with our sponsors. But, again, it comes back to what I said the first time, it is advising but what we would want them to do, what we will do, and where we will come out in the end are sometimes not always the same. However, under the rule, again, we can require studies and we would work with the sponsor in developing what those studies are, but that is a different process than

the exclusivity process.

DR. HIRSCHFIELD: And, our written request template says that the trial designs should have the input of pediatric oncologists, and all the studies should be at facilities which are specialized in the treatment of children with cancer. So, that is a condition generically of the written request.

DR. CHESNEY: We don't have anybody scheduled for the open public hearing, and we have three people who have been patiently waiting to ask their questions here, and we want to give Dr. Weiner a chance also. So, my thinking is that we allow these three people to ask their questions, and any comments from Dr. Weiner, and plan our break at 10:45. Dr. Friedman?

DR. FRIEDMAN: I think it was covered.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: I would like to make a comment and then ask a question of Dr. Spielberg. As an outsider, it seems to me that both the Oncology Group and the Food and Drug Administration have worked very hard to try to fine-tune FDAMA and the Pediatric Rule to move children's studies further on. But one of the things I have learned sitting on this committee is that the FDA is restricted because it doesn't make laws; it only interprets laws that are presently on the books.

There is also the question about early clinical access for people to drugs that are in development by pharmaceutical companies, and I would like to posit to you, before I ask the question of Dr. Spielberg, that you are still intervening in the process way too late, and this is not under the aegis of the Food and Drug Administration but may be something that the group that sits across the table from me would strive for.

It strikes me the chemical moieties need to be studied for pediatric cancers rather than being studied strictly for adult cancers and then being adopted for pediatric cancers, and my question to Dr. Spielberg is in the development of new oncologic agents, are there panels in the early testing of clinical moieties before clinical trials are even considered, specifically designed for the biology that we know about pediatric cancers? Because this is one of the few areas where we have enough biological information to do early tests on those types of agents?

DR. SPIELBERG: I am really not the person to ask in terms of the biology. I think the generic question though is in the screening processes that normally go on within companies or, for that matter, at NCI, do we have enough validated models preclinically that will suggest a pediatric applicability of a given compound early enough so that that compound -- for example, there may be a situation

where it doesn't work in any of the adult preclinical models but might give hits in the pediatric model. You know, take the tumor type that is atypical for pediatrics and is there a unique pediatric disease? The real question is how predictive are the models, and are they currently being included in the general screens, and I have to defer that to the oncologists.

DR. GORMAN: I would like to just follow that up because I realize that is a very specific question to ask somebody with very general knowledge, but there are three programs, as far as I understand it, that now allow -- or that our government has tried to make available to children drugs. One is the Pediatric Rule, the second is FDAMA and the third is the orphan drug program. All three were, hopefully, designed to test or promote the development of pharmaceutical agents in small populations, and one of those should be tinkered with, in whatever legal way things get tinkered with, to allow for us to reach back because in this particular area there is enough biological -- I realize there is a long way from testing chemical moieties until they become clinical agents, but there needs to be a reaching back far enough downstream that you are not left in the position of using drugs that show promise for big diseases and then have the development of agents specifically for the biological of your diseases.

DR. SPIELBERG: I would point out comfortably as well that FDAMA can be applied to orphan drugs so that if you do have an orphan -- if you have any kind of exclusivity, including orphan drug exclusivity, you can get an additional six months.

DR. CHESNEY: Dr. Smith, were you going to respond?

DR. SMITH: I was just going to echo Dr. Spielberg's comment that there is a real question about what the validity of the preclinical screens are, both in the adult models where they are applied by drug companies but how effective they are, and in pediatric cancers as well.

We, at the NCI, do recognize this is a priority area and researchers in the Children's Oncology Group recognize this is a priority area, and we are working together to try to development a pilot program that would facilitate the screening of new agents, and to do it in a rapid way so that the information is actually useful in considering the prioritization of agents. But, we have to do this recognizing that the systems for the preclinical screens as of this time aren't validated as to whether they really are predictive, and what shows as promising in a preclinical screen isn't truly validated as being an agent that is going to work for a particular type of cancer.

DR. GORMAN: Being relatively a newcomer to this,

with only 12 years of interest in this particular area, it strikes me that these same screens do predict for the pharmaceutical companies a pathway on which to go down, which agents show initial promise, and then more from there forward. And, in the restructuring of these laws, perhaps a financial incentive for the companies that is meaningful would allow that process to develop much more rapidly.

DR. SMITH: And, we think as well that the use of NCI funds for researchers to study new molecular targets and new agents is an appropriate avenue to pursue as well.

DR. CHESNEY: Dr. Fink?

DR. FINK: My comments were essentially the same as Dr. Gorman's, and I think if NCI is already doing it, obviously getting these preclinical screens into the hands of the pharmaceutical industry is one of the answers to the availability question, and it clearly falls outside, I think, the Pediatric Rule of FDAMA because these are really orphan diseases and the Pediatric Rule isn't going to apply to most of them in terms of numbers.

DR. CHESNEY: One more question, and then Dr. Weiner and then our break.

DR. COHN: Yes, I was just wondering in terms of the Pediatric Rule, if someone could just clarify, if you have a class of drugs that is not necessarily tumor specific but pathway specific, for example, the anti-antigenic agents