FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF

THE PEDIATRIC SUBCOMMITTEE OF

THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

8:09 a.m

Tuesday, July 15, 2003

Room 1066
CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland 20857

ATTENDEES

CONSULTANTS: (Voting)

VICTOR SANTANA, M.D., Acting Chair
St. Jude Children's Hospital

JAMES BOYETT, PH.D.
St. Jude Children's Hospital

SUSAN COHN, M.D.
Northwestern University

NANCY KEENE, Patient Representative
(Present Morning Session Only)

HOWARD McLEOD, PHARM.D. (Present Morning Session Only)
Washington University School of Medicine

DAVID POPLACK, M.D.
Baylor College of Medicine

PATRICK C. REYNOLDS, M.D.
Los Angeles Children's Hospital

SUSAN SHURIN, M.D.
Case Western Reserve University

NAOMI WINICK, M.D.
Texas Southwestern Medical Center

SUSAN WEINER, M.D., Patient Representative
Children's Cause

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS: (Voting)

JODY PELUSI, F.N.P., PH.D.
North Arizona Hematology & Oncology Associates

GREGORY REAMAN, M.D.
Children's Hospital National Medical Center

ATTENDEES (Continued)

GUEST SPEAKERS: (Non-voting)

BARRY ANDERSON, M.D.
National Cancer Institute, NIH

LESLIE BALL, M.D. (Present Afternoon Session Only)
Office of Human Research Protection, DHHS

MALCOLM SMITH, M.D.
Cancer Treatment & Evaluation Program
National Cancer Institute, NIH

RICHARD WEINSHILBOUM, M.D. (Present Morning Session Only)
Department of Molecular Pharmacology
Mayo Clinic

INTERNATIONAL GUESTS: (Non-voting)

MARK BERNSTEIN, M.D.
Canada Pediatric Oncology Phase I Consortium
(Participated by Phone Afternoon Session Only)

JOACHIM BOOS, M.D.
University of Muenster, Germany

HUGH DAVIES, M.D.
United Kingdom Central Office for Research Ethics Committee
URSULA KERN, M.D.
Bundes Institut fur Arzneimittel und Medizinprodukte

BRUCE MORLAND, M.D.
United Kingdom Children's Cancer Group

RICCARDO RICCARDI, M.D.
Italian Pediatric Oncology Phase I Consortium

GILLES VASSAL, M.D.
French Pediatric Oncology Phase I Consortium

GUEST INDUSTRY REPRESENTATIVE: (Non-voting)

George Ohye

ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

STEVEN HIRSCHFELD, M.D.
LARRY LESKO, PH.D. (Present Morning Session Only)
MURRAY LUMPKIN, M.D. (Present Afternoon Session Only)
DAVE MAYBEE, M.D.
THOMAS H. PEREZ, M.P.H., R.PH., Executive Secretary
VICTOR RACZKOWSKI, M.D. (Present Morning Session Only)
GRANT WILLIAMS, M.D.

ALSO PRESENT:

MARK RUSSO, M.D., PH.D.

C O N T E N T S

MORNING SESSION

Pharmacogenetic Testing for
Thiopurine Methyltransferase (TPMT) Deficiency in
Patients for Whom Treatment with Purinethol
(6-mercaptopurine, 6-MP) is Being Considered

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AFTERNOON SESSION

Overcoming Challenges in Pediatric Oncology Product Development: Regulatory Oversight of Multinational Clinical Studies

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P R O C E E D I N G S

(8:09 a.m.)

DR. SANTANA: Good morning. Let's go ahead and get started.

The FDA has asked the Pediatric Oncology Subcommittee today to address two issues to give them advice on. The morning session will be dedicated to the issue of pharmacogenetic testing for patients receiving Purinethol, and in the afternoon session, we'll have a general discussion advising the FDA on how we can overcome challenges in multinational international studies.

So with that brief introduction, I want to welcome everybody and say good morning to everybody.

For the purpose of the record, we all need to introduce ourselves. If you could please, beginning with Ursula over there in the corner, state your name and your affiliation. Thank you.

DR. KERN: Ursula Kern from the Federal Institute for Drugs and Medical Devices in Germany. I'm, as a manager, responsible for our national advisory committees, among them our pediatric expert group. Thank you.

DR. DAVIES: I'm from the Central Office of Research Ethics Committees in the United Kingdom. We have the task of overseeing the research ethics committees in

the United Kingdom and their consideration of research applications.

DR. MORLAND: Bruce Morland. I'm chairman of the United Kingdom Children's Cancer Study Group, New Agents Group.

DR. BOOS: Joachim Boos from the University of Muenster and from the German Pediatric Oncology Society.

DR. VASSAL: Gilles Vassal from Institute Gustave Roussy in France and the chairman of the European Consortium for Innovative Therapies for Children with Cancer.

DR. RICCARDI: Riccardo Riccardi from the Catholic University of Rome, chairman of the Department of Pediatric Oncology, and chairman of the New Agents Group in the Italian Association for Pediatric and Hematology Oncology.

MR. OHYE: I'm George Ohye. I'm the industry representative. This is my first meeting, so Dr. Hirschfeld asked me to say a few words about an industry rep.

The Food and Drug Modernization Act that was signed by President Clinton during his administration provided for all advisory committees to have an industry rep. So you'll often see an industry rep at advisory committees. I'm a retired senior vice president of Johnson

& Johnson's Pharmaceutical Research Institute. What FDA has tried to do and industry has tried to do is get a cadre of retired pharmaceutical folks to serve as industry reps, thinking that they would be more neutral rather than representing or being paid by one company.

I'm happy to be here. I think my role is to provide an industry perspective. For example, if you have questions on how industry might develop or review protocols, I might be able to answer some questions on that. So I'm happy to be here and good morning, everyone.

DR. SHURIN: I'm Susan Shurin. I'm at Case Western Reserve University in Cleveland, and I represent the Ethics Committee of the Children's Oncology Group.

DR. WINICK: Naomi Winick. I'm from UT Southwestern in Dallas and I'm the vice chair for clinical trials for COG for ALL.

DR. POPLACK: David Poplack, Baylor College of Medicine, Texas Children's Cancer Center.

DR. McLEOD: Howard McLeod. I'm a clinical pharmacologist at Washington School of Medicine in St. Louis.

DR. WEINER: I'm Susan Weiner from the Children's Cause. I'm the patient/family representative.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

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

MS. KEENE: Nancy Keene, patient and family representative.

DR. COHN: Susan Cohn and I'm from Children's Memorial Hospital in Chicago.

DR. REYNOLDS: Pat Reynolds, Children's Hospital, Los Angeles.

DR. BOYETT: James Boyett from St. Jude Children's Research Hospital, chair of biostatistics.

DR. REAMAN: Greg Reaman, the Children's Oncology Group and the George Washington University.

DR. PELUSI: Jody Pelusi. I sit as the consumer rep and I'm an oncology nurse practitioner.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, NCI.

DR. WEINSHILBOUM: Dick Weinshilboum, clinical pharmacologist, Mayo Medical School, Mayo Clinic.

DR. LESKO: I'm Larry Lesko from the Office of Clinical Pharmacology and Biopharmaceutics in CDER, FDA.

DR. MAYBEE: Dave Maybee, FDA, Center for Biologics, representing the Office for Cell Tissue and Gene Therapy.

DR. HIRSCHFELD: Steven Hirschfeld from the FDA, and I'm in the Division of Oncology Drug Products and

the Division of Pediatric Drug Development.

DR. WILLIAMS: I'm Grant Williams. I'm the Deputy Director of the Division of Oncology Drug Products, and I'm subbing today for Dr. Pazdur who had to be out of town.

DR. SANTANA: Thank you to everyone and welcome again.

Mark Bernstein is not here this morning, but this afternoon he'll be phoned in as part of the proceedings for this afternoon.

I don't know if Dr. Hirschfeld and Dr. Williams want to address the committee as an introduction?

DR. WILLIAMS: Yes. On behalf of Dr. Pazdur and the FDA, I'd like to welcome you all. We are very appreciative to you for taking a day and what must have been quite a substantial amount of time for our overseas colleagues to share your knowledge and discussions and recommendations with us.

I wanted to also recognize Dr. Hirschfeld who has, as always, spent a great deal of time preparing for this meeting, and Tom Perez who is also making sure it comes off as it should.

So I want to thank you all and we look forward to these very important discussions.

MR. PEREZ: Good morning. The following

announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

For the topic this morning, all subcommittee participants have been screened for conflicts of interest. The reported financial interests have been evaluated, and it has been determined that the interests reported by the participants present no potential for a conflict or the appearance of such at this meeting, with the following exceptions.

Dr. Susan Cohn has been granted waivers under 18 U.S.C., section 208(b)(3) and 21 U.S.C., section 355(n)(4) for owning stock in the sponsor of Purinethol. The stock is valued between $5,001 to $25,000.

Dr. Victor Santana has been granted a waiver under 21 U.S.C., section 355(n)(4) for owning stock in the sponsor of Purinethol. The stock is valued between $5,001 to $25,000. Because the value of the stock falls within the de minimis exception, 5 C.F.R. 2640.202(a)(2), a 208 waiver is not required.

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

With respect to FDA's invited guests, there are

reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Richard Weinshilboum would like to disclose that his employer, the Mayo Foundation, holds a patent related to the human thiopurine S-methyltransferase. The patent is nonexclusively licensed to Variagenics, Inc. Mayo received an up-front payment of cash and stock, with the stock being owned entirely by Mayo, totaling less than $100,000, and has a right to earned royalties for products sold by Variagenics. All of the stock was sold in March 2001 and to date, no earned royalties have accrued. Under Mayo's royalty sharing policy, Dr. Weinshilboum has personally received $3,188 and is entitled to share in any future payments that might be received by Mayo under this license or any third party license for this technology. Mayo is presently actively seeking additional licenses for this patent.

We would also like to note that Mr. George Ohye is participating in the meeting as an acting industry representative, acting on behalf of regulated industry.

We would like to remind the special government employees of the need to exclude themselves from discussions involving specific products or firms for which they have not been screened for conflicts of interest.

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 product they may wish to comment upon.

This afternoon we'll have another statement read concerning the different topic that will be discussed then.

I would like to point out that we have a revised presentation for Dr. Lesko that was placed on top of your handout. The one inside is the old one. The one on top is the new one. Thank you.

DR. SANTANA: Thanks, Tom.

Anybody else that wants to disclose anything now publicly?

(No response.)

DR. SANTANA: Okay, thank you. With that, then we'll hand it over to Dr. Hirschfeld to give us a brief introduction to the topics that we will try to cover today. Steve?

DR. HIRSCHFELD: Good morning, and thank you, Dr. Santana. I would like to thank my colleagues in Division of Oncology Drug Products and in the Division of Pediatric Drug Development and the Office of Pharmaceutical Sciences for what has been a very interesting and I hope

productive collaboration in establishing the agenda for this meeting and planning the particular questions and the selection of our guests.

I want to also echo a particular welcome to our guests who have traveled from so far and such great distance to come here to participate in this advisory committee hearing.

The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee has met on six previous occasions to address a variety of issues. The first meeting was in September 2001 where there was a discussion of methods that may be used to describe and link tumor types.

That was followed by discussions in April 2001 on hematologic tumors and the Pediatric Rule which was a regulation which described the imperative for doing pediatric studies if adult studies were submitted to the agency for review and the indication that existed in the adult population was also found in the pediatric population.

And there was a subsequent meeting in June 2001 which focused on solid tumors and central nervous system malignancies and the Pediatric Rule.

In November 2001, there was a meeting which discussed study designs with a particular emphasis on extrapolation of data from adult populations to pediatric

populations and on doing studies in populations of limited size, particularly some of the rare tumors that are found in pediatric oncology.

In January 2002, this committee was incorporated into law in the Best Pharmaceuticals for Children Act, section 15.

A subsequent meeting in October 2002 discussed the timing of pediatric clinical studies and the criteria for initiating studies with investigational agents, which led to the recommendations which were posted on the internet.

And in March 2003, there was a discussion of pediatric information to be included in oncology product labeling.

Today's theme is risk assessment in pediatric oncology. The first presentation will be from Dr. Victor Raczkowski who is the Director of the Office of Drug Safety and will give an FDA general perspective on risk assessment. That will be followed in the morning session by a discussion of proposed change in the product package insert for 6-mercaptopurine to include pharmacogenetic screening recommendation and in the afternoon by a discussion of regulatory and patient protection procedures and perceived barriers -- and the perceptions might well be real, we recognize, but we will discuss them -- to the

implementation of multinational studies in pediatric oncology.

To help everyone understand the issue that is being addressed this morning with regard to 6-mercaptopurine, I recognize that Drs. Lesko, Weinshilboum, and McLeod will give us details, but I wanted to offer some of the substance of the discussions that we had leading up to this particular meeting.

6-mercaptopurine was synthesized by Elion and Hitchings to inhibit cell growth and it was approved by the FDA in a matter of weeks, I might add, for treatment of acute leukemia in 1953. It has been used as a component of anti-leukemia therapy in pediatric oncology, particularly in clinical trials, for the past 50 years.

The current product package insert states in the indications and usage section that mercaptopurine is indicated for remission induction and maintenance therapy of acute lymphatic leukemia. And the product package insert uses the terms lymphatic, lymphocytic, and lymphoblastic to refer to the same set of diseases.

There is a caution at the head of the product package insert, which states that mercaptopurine is a potent drug. It should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is knowledgeable in assessing

response to chemotherapy.

In the warnings section of the product label, there is a notation -- and I won't read every word of this -- but that there are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase who may be unusually sensitive to the myelosuppressive effects of mercaptopurine, and a note that substantial dose reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. There are references in the product label which amplify some of the comments which are made in that section.

The dosage section states that 6-mercaptopurine is administered orally. The dosage which will be tolerated and be effective varies from patient to patient and therefore careful titration is necessary to obtain the optimum therapeutic effect without incurring excessive, unintended toxicity. And once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient.

The estimated number of affected patients with thiopurine methyltransferase deficiency and acute lymphoblastic leukemia is based on two sets of data. One is the estimate of how many children in the United States have acute lymphoblastic leukemia, which if one takes

figures from the National Cancer Institute surveillance epidemiology response program, there are somewhat over 3,000 children in the United States who are diagnosed with leukemia and approximately 2,400 have acute lymphoblastic leukemia.

Based on a frequency of 0.3 percent, or approximately 1 in 300, of the homozygous deficiency and assuming proportionate representation in the leukemic population, as in the populations previously studied to derive this figure, an estimated 8 children in the United States per year would be affected as homozygous.

Based on the frequency of an estimated 10 percent heterozygous deficiency and with similar assumptions as above, an estimate 240 children per year would be affected who would be heterozygous.

The question of dose adjustment should be based on data, and the data on dose adjustment in the literature, both in the United States and primarily in the United Kingdom, are that for homozygous patients, the data are somewhat limited and variable. There are a number of suggestions which are made in individual case reports. And for the heterozygous reduction, there are one or two retrospective studies but no data exist from a cooperative group prospective clinical trial on what dosing regimen is appropriate to use.

And questions regarding the assessment of 6-mercaptopurine metabolism. Again, these are just questions that were being raised in our internal discussions. How does one correlate the highly variable absorption of the oral drug to serum levels, the rapid metabolism in the blood, and the product label states that the half-life is approximately 20 minutes in children, and the red cell test for 6-thioguanine nucleotides which uses living red blood cells, but it may not represent the true tissue levels.

And some of the questions regarding genetic testing are which mutant alleles are captured by which tests. Will different tests have different results? And should testing procedures receive formal FDA approval?

Our decisions are based on evidence, and the applicability of extrapolation from published reports should be borne in mind. For instance, can toxicity seen with intravenous preparations of 6-mercaptopurine be applicable to oral preparations? Can complications of patients that have received one type of therapy, for instance, intracranial radiation or particular combinations and sequences of chemotherapy, since there are a variety of regimens available to treat acute lymphoblastic leukemia, be considered to represent patients that have not received that particular therapy?

We want to be clear that not at issue is the

rationale for pharmacogenetic testing in general nor the rationale for individualization of dosing to minimize risk. What we are focused on is for this product and for the indicated patient population, what should our recommendation be.

This afternoon we'll discuss international cooperation, and at the recent meeting of the American Association of Cancer Research, the president of the association, Dr. Susan Band Horowitz said, "To proceed, science must cross boundaries." Pediatric oncology is a set of diseases with about 13,000 new cases per year in the United States. To complete studies in a timely manner and to effectively use limited resources, international cooperation is necessary. The FDA is issuing written requests for pediatric oncology studies with time limits to improve access to investigational drugs and stimulate clinical research.

For international studies to proceed in a timely manner, regulatory requirements must be consistent. Regulatory requirements that pertain to study initiation and study monitoring have been perceived as barriers. And we should note that pediatric oncology studies may or may not be intended for registration of a marketing claim, but are most often initiated to define optimum therapy for a particular population.

So what we are seeking are recommendations on how to achieve consistency and minimize barriers in multinational international studies in pediatric oncology.

Thank you. And I will now introduce Dr. Victor Raczkowski who is a pediatrician himself and has had a number of positions within the Food and Drug Administration and will now comment on risk assessment.

DR. SANTANA: Thank you, Steve. Can I ask you a regulatory question? Either you or Victor may answer this in his presentation. But the current warning section for Purinethol in the package insert that describes the issue of TPMT deficiency, when was that inserted and under what review was that inserted? Can you clarify that for me?

DR. HIRSCHFELD: I can't give you the precise date, but it was within the last 5 years. It was more than a year ago, that I can attest to. And it's part of an ongoing dialogue between pharmaceutical sponsors and the FDA to maintain currency in product labeling. In this case, the pharmaceutical sponsor was GlaxoSmithKline, and if I may, I will just ask Dr. Peter Ho from GlaxoSmithKline if he has a further comment on that particular question.

DR. SANTANA: The question is when did this get inserted into the warning label and under what review process was it inserted. That's the question.

DR. HIRSCHFELD: That's all right, Dr. Ho. I didn't mean to put on the spot. I thought if you had some additional information you wished to add, we'd give you the opportunity.

DR. SANTANA: Thanks, Steve.

DR. LESKO: Steve, can I add to that? In the label, there are two references that are related to that statement. One is from 1991 and one is from 1993.

DR. RACZKOWSKI: Good morning. My name is Victor Raczkowski and I'm the Director of the Office of Drug Safety. Dr. Hirschfeld asked me to address two large issues in risk assessment in the postmarketing and pre-approval arena, as well as risk management. So my talk will be focused on broad conceptual issues.

CDER assures that safe and effective drugs are available to the American people, and here I would just like to note that there are three components to the CDER mission statement. One is the safety of drugs. One is the efficacy, and the third is access to drugs or drug availability.

Now, the mission of the Office of Drug Safety, we evaluate drug risks and we promote the safe use of drugs by the American people. Traditionally the Office of Drug Safety has been primarily concerned with evaluating postmarketing signals generated through the Adverse Event

Reporting System, but more recently, the Office of Drug Safety is getting increasingly involved in pre-approval risk management plans and assessment of drugs because the evaluation of safety is a continuum throughout a product's life cycle. And in addition, instead of just relying on a spontaneous adverse event reporting system, which has limitations that I'll get into, the Office of Drug Safety uses a number of databases in order to better address and assess drug risks.

Now, all medical products, when they're approved, are required to be safe, but safety does not mean the absence of risk. I don't think I need to emphasize to this group that a safe product is one that has reasonable risks given the magnitude of the benefit expected and the alternatives available. For example, if there is a great benefit, such as improvement in survival, then the risks that may be acceptable are generally greater for those sorts of drugs than if the benefit is less. Or similarly, if a drug has therapeutic alternatives which are safer, then the risks that would be acceptable with that drug would be less.

What I'd like to do is talk about postmarketing surveillance and some of the issues associated with this. I think that this group knows the issues of clinical trials. Clinical trials are generally of limited size,

limited duration, and oftentimes safety signals are not completely evaluated in the premarketing arena because of some of these limitations. But postmarketing surveillance also has limitations, and traditionally, as I said, we've used the Adverse Event Reporting System, but this is a passive system and it's best probably for evaluating signals or detecting signals.

Now, the traditional role of the FDA has been in risk management to approve a drug, and labeling it would be the primary risk management tool that would be used. However, product labeling has variable effectiveness in terms of its comprehension, in terms of its adherence by either physicians, other health care providers, or patients. And more is needed in some cases because there are sometimes unacceptable levels of morbidity and mortality due to errors, poor quality, and those sorts of things.

So what there is a need for is a systematic approach to improving safety and to reducing errors. Risk management encompasses the assessment of the risk, either control or prevention or mitigation of that risk, communication of that risk to all affected parties, including health care providers, as well as patients, and then evaluation of the effectiveness of any risk management intervention.

Now, FDA also has a role in larger risk management systems. Traditionally the main interaction that FDA has had has been with industry in terms of drug approval, but in order for risk management interventions to be successful, there needs to be broad stakeholder involvement. These include patients or consumers, health care professionals, pharmacists, insurers, HMOs, the industry, and government agencies such as the FDA and others.

Now, in the Office of Drug Safety, we evaluate, as I said before, primarily postmarketing risks associated with drugs. The reviewing divisions in the Office of New Drugs continue to evaluate clinical trial data even after a drug has been approved. We also use drug utilization databases. My main focus in terms of risk assessment will be on these first two items, the Adverse Event Reporting System and the drug utilization databases. Again, I will not go deeply into discussion of clinical trials or use of other epidemiological tools such as cohort studies or case-control studies.

But in addition, the agency also has agreements to evaluate safety signals through cooperative agreement programs, the CERTs program, which is the Centers for Education and Research on Therapeutics, and through other collaborations such as with the VA system.

Now, the Adverse Event Reporting System. I think it's important to understand its strengths, that it is a signal detection system in the postmarketing arena. And it's a computerized database which arose roughly in about 1997. However, it has adverse event reports going back for over 20 or 30 years.

Now, the adverse event reports are submitted by sponsors when they become aware of an adverse event, and this is mandatory once the event is detected. However, health care providers and consumers give voluntary reports. For example, if you look at the back of the Physicians' Desk Reference, you'll see that there's a MedWatch report where any physician or health care provider or patient could report an adverse event to the FDA, and that is voluntary. These adverse event reports also include medication error reports.

Now, some of the strengths of AERS are that it can identify uncommon adverse events and can identify adverse events in special populations, and it provides information on real-world use of drugs. Again, clinical trials are typically of limited size and the number of patients can limit the ability to detect adverse events. Clinical trials, in a sense, are very ideal conditions of use where patients are on protocols and that may differ from the real-world use, the types of monitoring, the

careful administration of drug, and so forth.

Now, a major limitation of AERS -- and I think this is important for folks to understand -- is that it does not provide rates of adverse events and there's limited information in case reports. For example, since it is a voluntary reporting system, we do not know the number of adverse events associated with a drug because of under-reporting. That represents a small selection of the totality or the universe of adverse events associated with the drug. Oftentimes the case reports that come into the Adverse Event Reporting System have limited information. This again is somewhat different than in clinical trials where there are case report forms and so forth and there's often extensive information captured about patients.

So to get around some of these limitations, we have a number of data resource procurements, including the IMS Health Database, and this allows us to estimate things like the number of prescriptions that are being used, particularly for out-patient information, demographic information about patients, information about the providers, the subspecialty and those sorts of things.

But as I said, the IMS is primarily an out-patient database. So we have access to several other databases, including Premier, which provides in-patient information; AdvancePCS, which is longitudinal out-patient

information; and the CHCA, which is the Child Health Corporation of America, which provides some pediatric in-patient information.

So from these databases we can assess not only adverse events, but we have an idea of the denominator, the number of patients who were exposed to the drug, to allow us to, therefore, calculate rates in a more real-world setting than in clinical trials.

I'm going to switch gears now and talk briefly about risk management in some broad outlines.

One definition of risk management that comes from a concept paper that the agency recently produced in March of this year -- and there was a public meeting in April on it -- is that risk management is a continuing process throughout a product's life cycle, so not just during development, but it continues into the postmarketing phase, and it's on a continuum. The goal largely is to optimize the benefit-risk profile. So there are two ways to do that. One is to decrease the risks associated with the drug or to optimize the benefits.

Any risk management plan should have clear, specified rules and objectives and should have an evaluation of the effectiveness of the program. Again, previously FDA has relied very heavily on labeling. However, there are a number of studies that show that

labeling is of variable effectiveness in terms of physician compliance with the labeling or those sorts of things.

So one of the major risk management tools, of course, is education and outreach and things that go beyond the professional labeling or the package insert. So there are health care professional letters and other public notices. Many of you may receive them periodically from the industry.

There can be training programs and continuing education credits that are provided to health care providers for completing them to learn about specific issues or risks and how to recognize, manage, and prevent or mitigate them.

There is also patient-oriented labeling which include medication guides and patient package inserts.

So education is a major addition to the use of merely professional labeling.

However, risk management can go much further than just professional labeling. There can be systems that guide prescribing, dispensing, and the use of the drug. Many of you may have seen these such as patient agreements or informed consent before a drug is administered to a patient. An example of this may be if you look at the Accutane labeling, patients or whoever is taking Accutane needs to check off that they understand some of the risks

associated with the use of that drug because it's a teratogen.

And there needs to be enrollment of one or more stakeholders in a special program in some of these cases.

There are practitioner certification programs such as the drug is only administered to certified professionals or practitioners, and there are special conditions of dispensing that can be utilized such as special packaging, limiting supply of a drug, and checking mechanisms to assure appropriate prescribing.

And if one goes even further, then there are actually restricted access systems that can be used in risk management. These are basically designed to enforce compliance with program elements. These may require registration or enrollment of physicians or pharmacists or patients. They may include documentation of safe use conditions such as lab tests before a drug is prescribed. An example of this last point may, for example, be thalidomide. I'm sorry. Clozapine is probably a better example where with thalidomide, patients need to document that they've had a negative pregnancy test before taking the drug, and with clozapine, which is an antipsychotic drug, patients need to get a blood test to evaluate their white counts. So these sorts of things are called "no blood, no drug" sorts of programs.

Finally, of course, if none of these interventions are effective, then there can be the suspension of marketing either with or without application withdrawal.

So as the committee deliberates today, I think it's important to consider some of the following things about selecting and developing tools for managing risks. First is obtaining stakeholder input, and by stakeholders, that means anybody such as health care providers, patients, et cetera in terms of their feasibility and acceptance. Look for consistency with existing or accepted tools that are used, and is there evidence that these tools actually work, that there has been past success of monitoring or use of these tools in the same or related areas. And finally, to assess the variability, validity, and reproducibility of any intervention that is undertaken.

I would also encourage the committee to consider risk management plan evaluation. Oftentimes the agency has implemented labeling changes, for example, and just assumed then that these interventions were being utilized by health care professionals or patients. But as I mentioned before, there's a fair amount of evidence that this is of variable effectiveness. So in order to assess the effectiveness of a program and its tools, ideally one would do some pretesting before implementation of the risk

management plan and then assess the effectiveness periodically after implementation.

The goal here really is to ensure that any efforts are expended on effective interventions and that these changes can then be used to guide adjustments to the risk management programs.

Finally, on the same line, of course, if one is evaluating a risk management plan or program, one needs to have outcome measures or metrics. These can be used to measure changes in the absolute levels of patient health outcomes or a particular adverse event, surrogates of health outcomes. They can be process measures to evaluate whether patients are being appropriately counseled, for example, or not. Or one can use behavioral components such as assessing patients' or health care providers' comprehension, knowledge, and attitudes.

So what I've tried to provide is a very broad overview for consideration of two major areas in my talk. One, again, was risk assessment and the second was on risk management. And I'd be happy to entertain any questions that people may have.

DR. SANTANA: Thank you, Victor.

Any immediate questions? We're going to have a period of discussion for which certainly, I'm sure, Victor will be available. Dr. Reynolds.

DR. REYNOLDS: Since you mentioned Accutane and since this is a pediatric oncology committee, I wonder if you could comment on the insistence that we get negative pregnancy testing on these patients that are most often 2 years old in the use of Accutane in the pediatric oncology community, which has put a burden on people that is really probably not necessary, and if there is some way to change that.

DR. RACZKOWSKI: Well, that's a good point. Accutane is approved for its dermatological indications and as of yet, it does not have a pediatric or oncology indication. So that is considered to be an off-label use at this point and is, as you know, under study. So there are some limitations in our ability to -- since acne is largely an adolescent or later type of condition, the labeling reflects the realities of the indication that it has been approved for. So I guess I would say it's difficult to make labeling changes for an unapproved use.

DR. SANTANA: Can you give me an idea of what the universe is from the agency perspective in terms of how many times or how frequently do label changes occur because there are issues that you have identified in your risk management program for a particular product? Is it a frequent occurrence that this happens? Is it occasional? It happens infrequently? What's the sense of how this

program works in identifying issues?

DR. RACZKOWSKI: I would simply say that in postmarketing, it's very, very common for labeling changes to occur even addition of black boxes or new contraindications, new warnings, new precautions because again, when a drug is approved, the entire safety profile of a drug is not completely understood. So there's this ongoing vigilance to monitor the safety of the drugs.

DR. SANTANA: Jody?

DR. PELUSI: I just want to kind of follow up on that as well. In terms of your educational piece, trying to get the updated information out, I think that's a very valuable source because many of us may have read the package insert once and not necessarily do it on a regular basis. So that whole issue of education from consumers to providers becomes a very important piece that we can't lose sight of.

DR. SANTANA: If there are no other questions or comments, we'll proceed with the morning session. I think we have three speakers lined up, and I'll ask Dr. Lesko to go ahead and give us his presentation.

Thank you, Victor.

DR. LESKO: Well, good morning, everyone. Again, let me add my thanks to Steve's and welcome you to the advisory committee today. I look forward to your

advice and comments on the particular topic that I'll be introducing today.

What I'm going to do is introduce the topic and frame it in some broad terms and turn it over to three of our guest speakers to make presentations from different perspectives.

Let me start by saying that the agency's broad goals for pediatric therapeutics include identifying opportunities to improve the quality of therapeutics related to the use of already-marketed drugs as well as new drugs, to update product labels where new data is relevant to the safe and effective use of the drug, and to place information in product labels as a mechanism to disseminate important information about the drug's use.

Now, these goals are entirely consistent with label regulations. This is part of the label regulations from the C.F.R. that evidence is available to support the safety and effectiveness of the drug only in a selected subgroup of the larger population with a disease, and that subgroup can be defined by many different intrinsic or extrinsic factors. The labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug. I've underlined that part of the label that I wanted to highlight.

Turning now to pharmacogenetics, pharmacogenetics in many ways can be thought of as an intrinsic factor. The genetic makeup of an individual can increase or decrease blood levels of a drug and subsequent clinical responses in a way similar to, say, drug interactions or a disease state the patient might have. But pharmacogenetics can be thought of as the study of genetically determined variability in drug metabolism and responses to drugs which can include either adverse events or desired effects. And variability in a dose-response relationship occurs because of variations in DNA such as polymorphisms in a single gene, which we'll be talking about today, or a limited set of multiple gene sequences that subsequently influence enzyme or receptor activity.

Now, integrating pharmacogenetics into therapeutics is an agency-wide initiative. This is one of the five major planks in the platform that Dr. McClellan has for the agency, and as he stated in the Washington Drug Letter following an FDA Science Board meeting, new therapies will be developed along with genetic or phenotypic tests that can be used to identify appropriate populations and detect patients who might need different doses or are prone to certain toxic effects. This reflects the potential that he and others in the agency feel that pharmacogenetics can bring to therapeutics.

I wanted to show you an example of what that means in terms of actual labeling. This is an example of a drug that was approved in the earlier part of this year, atomoxetine, and it was approved for the treatment of pediatric attention deficit disorder. It's not a TPMT substrate, but rather it's a 2D6 substrate. I'm using this as an example to illustrate the various ways in which information about pharmacogenetics can be incorporated into the label. The evidence to support a priori testing of 2D6 for atomoxetine was not strong enough to recommend that in the label, but in the spirit of truth in labeling, we did include information that was factual and was evident from the trials that were done on the drug.

CDER, in turn, has focused on both new and approved drugs in terms of integrating pharmacogenetics into therapeutics. This is a quote from Dr. Woodcock at a presentation she made to the FDA Science Board where she focused primarily on genetic contributions to variability and toxicity and primarily differences in metabolism that are related to pharmacogenetics. This is, as you're probably aware, one of the most mature areas of pharmacogenetics in terms of translating it into patient care.

So now we turn to 6-MP and childhood ALL. As you all know, ALL is a life-threatening disease and 6-MP,

in turn, can cause life-threatening toxicities. In many ways it can be thought of as a drug with a narrow therapeutic index. Dose titration, as the label indicates, defined by dosing size, duration, and intensity of therapeutics, is a major determinant of long-term event-free survival, as well as myelosuppression. It's well known that 6-MP is metabolized to pharmacologically active thiopurine nucleotides by the enzyme we're talking about today, TPMT, and TPMT activity shows a well-defined trimodal variation in the general population.

This is some prescription use of 6-MP from the IMS database, and you can see the use of 6-MP in oncology as well as the use of 6-MP in off-label indications such as in the GI, and the other bar shows all of the prescriptions for 6-MP. We're focusing primarily on the approved indication for ALL.

What about the polymorphism of TPMT? Well, it's well documented in terms of a causal link between the polymorphism and TPMT and the clinical effects, including toxicity. In your background package, there were about 8 to 10 references from the literature, and much of the current literature over the last 10 years has provided evidence in terms of clinical utility of the test and in terms of various recommendations for dose adjustments.

Genotypes with reduced, which is 10 percent of

the population, or no activity, which is the 1 in 300, are at a substantially increased risk of myelosuppression and secondary cancer based on the literature from the past 10 years.

More recently, pharmacogenetic tests have become available for TPMT genotype and phenotype. They're feasible. They're relatively easy in terms of technology related to DNA analyses, and these tests are fairly robust in predicting and identifying patients who are of a certain genotype and they can be used to guide optimal dosing.

Pharmacogenetic tests you'll hear more about from Dr. Weinshilboum, but the TPMT genotype can predict no or very low enzyme activity. There are three major alleles in TPMT, the *2, *3A, and *3C, that identify almost all, but not quite, those individuals with no or very low activity. In turn, those patients experience excess accumulation of RBC thioguanine and its nucleotides that result in toxicity.

There are available as well TPMT phenotype tests to measure enzyme activity either directly in the red blood cells or by looking at thioguanine nucleotides in the red blood cells.

In several academic centers, both genotype and phenotype are used together, along with clinical outcome monitoring, in terms of total blood counts. And these are

not to suggest that these tests are going to replace those clinical observations, but rather the tests play a role as an adjunct to help identify and, in particular circumstances where multiple drugs may be on board, the drugs that are causing toxicity.

Now, we had prior discussions of TPMT polymorphism in advisory committees. These were general discussions. We did not ask the committee to vote or we did not ask for a specific recommendation. The first of these was in front of this committee, the Pediatric Subcommittee, back in November of 2001. At that time, you heard from Dr. Mary Relling, one of the experts on thiopurine pharmacology and TPMT testing. And then more recently, we discussed this issue in front of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Sciences, and that meeting was reported in the Pink Sheet November 2002. By and large, the comments from the participants in those meetings were supportive and the discussion was very valuable.

This is the current package insert, a copy of which you have in your background package. It shows the warning section. I might point out that there is another covariate in the warning section, namely allopurinol, and allopurinol is, again, a covariate which I think of as another intrinsic or extrinsic factor that can raise

exposure to thioguanines, and there is some mention in the label about the effect and also the recommendation to reduce the dose.

This is the dosage section, just to remind what's in that section, which brings us around to the questions that we have for you today.

The first question is beyond what you've seen in the package insert, what additional information should be added to the product label for 6-MP regarding what we know about pharmacogenetics of the polymorphism.

Some additional information which the current label now lacks is an idea for the prescribing physician and the patients about the prevalence of those patients with little or no TPMT activity. These prevalences are well established in the literature. One might consider additional statements in the warnings or dosage sections that patients with this deficiency may be unusually sensitive to toxicity and at greater risk.

Additional information might include a statement that laboratory tests, phenotype and/or genotype, are now available to determine the TPMT status of patients if the physician so chooses and some information regarding the use of these tests.

And finally, perhaps some recommendations for adjustment of doses in patients identified as having little

or no or reduced TPMT activity.

The second goal for today is to get your advice on this question. If pharmacogenetic information is added to the label, what other testing information might be added about genotyping or phenotyping for this activity that might be necessary and appropriate for the product label?

Some additional testing information might include a recommendation for testing for the status of TPMT activity before initiating therapy. The recommendation might be for testing for activity within the first week of initiating therapy before overt signs of toxicity became apparent. Third might be a recommendation for testing of activity in those patients that develop severe myelosuppression as a way of better understanding the cause of that, or perhaps some description of information testing for the status of activity that this information could provide. So there's a hierarchy of information and different ways of expressing the information that we know about the pharmacogenetics, and we'd like your advice on that.

I'm going to turn this over to three other presenters this morning. I want to thank them all for joining us. Dr. Weinshilboum, who has been an expert in this field for over 20 years, having first identified many of the polymorphisms in TPMT, will begin. I believe Howard

McLeod will speak next. Howard has hands-on experience with the test in therapeutics, and finally Dr. Winick from the COG group will give a perspective on the topic.

So with that, I'll turn it back to the chair. Thank you.

DR. SANTANA: Thank you.

Any brief questions?

(No response.)

DR. SANTANA: If not, we'll move on to the next speaker.

DR. WEINSHILBOUM: First of all, let me thank Dr. Hirschfeld and Larry Lesko for inviting me to come here. My daughter is a pediatrician in North Carolina and the fact that I, as a poor, benighted internist, would appear before a group of pediatricians is about the only thing I've ever done that's impressed her.

(Laughter.)

DR. WEINSHILBOUM: Larry was quite clear with regard to what my assignment was. My assignment is to provide the scientific background for the discussion. Howard will expand on that, as will Naomi, into the clinical realm, and I've made my credentials fairly clear. I'm an internist, not a pediatric hematologist/oncologist. He also said I should stay on time, and I'll do my best to do that too.

This slide takes us back to the beginning. It was mentioned that it is now 50 years ago since the thiopurine drugs developed by George Hitchings and Gertrude Elion of what was then Burroughs-Wellcome Company were developed as cytotoxic agents. Knowing Gertrude Elion, as I did before she passed away, she said that what they did was rational drug design of that era. They looked at the endogenous purines and said if God had wanted us to have a sulfur there, she would have given it to us.

(Laughter.)

DR. WEINSHILBOUM: And that is exactly what she said. Those of you who knew her, know that's what she said. So this was rational drug design to develop cytotoxic agents which were, in the context of that time, amazingly successful.

Here is 6-mercaptopurine, 6-thioguanine, and as you know, azathioprine, or Imuran, is a prodrug that's converted to 6-mercaptopurine in vivo.

You've already seen this definition of pharmacogenetics. Larry provided this. That is the study of the role of inheritance in individual variation in response to xenobiotics, including the drugs which those of us who care for patients, write prescriptions for and they take, thinking we know what we're doing. Most of the pharmacogenetic knowledge that we have today has evolved

out of studies of drug metabolism. However, as Larry just mentioned a few moments ago, all of these processes of drug absorption, distribution, interaction with the target, and excretion we now know are subject to the same degree of common genetic variation frequently of functional significance. But today our focus is clearly on, as Larry so elegantly put it, a mature field that is an example from drug metabolism.

Here is a schematic representation of the biotransformation of thiopurine drugs. Even the Mayo medical students, who I have to teach on a regular basis, know that xanthine oxidase, a phase I reaction is involved in the metabolism of these drugs. George Hitchings and Gertrude Elion knew that an S-methyl metabolite, undoubtedly the product of a phase II conjugating reaction, was involved because they measured these metabolites in the urine.

The enzyme, when we began our work now nearly a quarter of a century ago, which when I say that, causes me some pause -- when we began our work, it had only been studied in rodents, in rats and mice, by a man named Remy who's now retired from the Department of Biochemistry at what is today Wake Forest University Medical School. My daughter did her pediatric residency there, so I sat in his living room and said, Dr. Remy, why did you study this

enzyme in rats and mice in 1963, and he said because George Hitchings told me it might be interesting. Is it? And I told him, yes, there was some interest in it.

This enzyme, when we began our work 25 years ago, had never been examined in humans, and we asked a series of very simple questions. Is it conceivable that this phase II pathway might show variation among individuals? If so, is it possible that those variations might be genetically mediated? And if so, might that play a role in individual variations in either therapeutic efficacy or toxicity of the drugs? And the reason that we're all here today is that the answers to those questions appear to be yes.

So here's the reaction which basically is a standard S-adenosylmethionine-dependent methyltransferase cytosolic, monomeric enzyme. And I was asked to provide the scientific basis for what we're doing. And being a poor, benighted internist, I actually wanted a clinical test when we started doing this. So we measured the enzyme in the red blood cell.

Now, I was at the NIH last week talking about some of this and the study sections at the NIH said this idiot in Minnesota thinks that red blood cells are the liver. No, no. We were hoping that what we saw in the red blood cell might reflect the level of enzyme activity in

other tissues, and I will tell you, in case I forget to, that the answer is, of course, it does for reasons that will become clear when I come to the molecular basis for this polymorphism.

Now, here is the first paper that we published on the genetics in 1980, and I'll provide the time line because when Larry shook hands with me this morning, he said, I'm glad you're hear. I said, after 20 years I'm pretty glad I'm here too, because this paper was published in 1980. This is a frequency distribution of red blood cell TPMT activity in 298 randomly selected adult blood donors at the Mayo Clinic in Rochester, Minnesota. That has implications of a practical nature that I'll come to in a minute because that means every one that we looked at is named Anderson or Yansen. They're all northern European Scandinavians. That's important because I will show you in just a few moments that there are striking ethnic differences in allele types and frequencies.

So 90 percent of this population has high enzyme activity. 10 percent has intermediate activity. And this one lady down here had 0 enzyme activity. Rochester is a weird town in that 30,000 people out of 90,000 work for the Mayo Clinic, so when I go walking at Apache Mall, her daughter, who is now in her 20s, stops me and says, how's my mom's enzyme doing.

But this is exactly what the Hardy-Weinberg theorem would predict for a genetic single locus with alleles for high and low enzyme activity with allele frequencies of 94 in 6 percent using sophisticated molecular techniques developed by a monk at a monastery in what is today Brno, that is segregation analysis. So you didn't need to clone anything back then to know that this was genetic.

Now, this a more accurate representation, and still not totally accurate, schematically of thiopurine metabolism. Azathioprine is a prodrug. It's converted to 6-mercaptopurine and 6-mercaptopurine is itself a prodrug which undergoes metabolic activation to form 6-thioguanine nucleotides. You can either methylate or oxidize the drug.

And I'm really glad our colleagues from the UK are here because actually just by happenstance we have an excellent example of the importance of international cooperation because I met a woman named Lynne Lennard from Sheffield who has done a tremendous amount of work with acute lymphoblastic leukemia in the United Kingdom. And she said, Dick, I can't understand why we treat these kids with exactly the same dose of these drugs and get such variable 6-thioguanine nucleotide levels. I said, Lynne, is it conceivable that those kids who have this pathway pump more of the drug down here and they're the ones at

increased risk for myelosuppression? So a lot of the data that I'll show you grew directly out of a Minnesota-Sheffield connection, and I think makes the point that you'll be discussing this afternoon actually.

And here are some of those data. These are data which we published in Lancet in 1990. Dr. Lennard sent us samples from 95 consecutive children in the UKALL, United Kingdom Acute Lymphatic Leukemia, UKALL VIII trials. And we measured the enzyme activity blind to the 6-thioguanine nucleotide levels. When you got to the 600 to 800 picomoles per 10 to the 8th red cells -- and don't ask me why she used that number of red cells -- these were the kids who began to have myelosuppression, and the expected inverse relationship between the enzyme activity in the 6-thioguanine nucleotide levels, which has generally been confirmed in subsequent reports, was observed.

That raises immediate questions. What about that lady whose daughter stops me when I'm walking at Apache Mall who had 0 enzyme activity?

Well, Dr. Lennard had samples from individuals treated with "standard" doses of azathioprine for skin disease, for dermatologic disease. I want to be quite clear which drug I'm talking about with this group. And you can see here she sent us those with a group of controls. Now we're up in the thousands of picomoles. All

of these patients developed life-threatening myelosuppression that required prolonged hospitalization. Notice this patient is 26 days after the drug is stopped, and he's still, in terms of the active metabolite, above any of the controls.

I used to present these data and say if they're confirmed, we can now predict and potentially prevent the life-threatening myelosuppression. I don't say that anymore because a great deal of work, which I know Howard will be talking about in more detail and Naomi in a few moments, has clearly demonstrated that this group down here is at greatly increased risk. All of these individuals, by the way, had 0 enzyme activity.

This is not a childhood leukemia example, but it's an example that was published in the Lancet.

These things don't get published anymore. They don't get published anymore for two reasons. Let's be quite clear. Because the journal editors say we already know this and because of litigation issues.

So here this is a heart transplant patient in Germany. Here's the white count. Here's the azathioprine dose. The white count drops. The drug is stopped. The white count goes up. The drug is started again. The white count goes to 0. The drug is started here. The patient expires with massive sepsis. The blood sample was

determined to have 0 TPMT enzyme activity.

So the bottom line -- and you'll hear a great deal more evidence from Howard -- is that genetically low TPMT results in an increased risk for thiopurine toxicity. That seems quite clear, and I think we've already heard that from Larry. We'll hear more from Howard in a moment.

I should point out that Mary Relling and the group at St. Jude -- and we have a lot of representatives around the table -- have also demonstrated that this appears to be a risk factor for the occurrence of secondary neoplasia, and that's been confirmed at least once in one of the Nordic leukemia trials that has been published.

There is less compelling evidence that high TPMT results in decreased therapeutic effect. And that's an interesting concept that hasn't come up in the course of these discussions that I look forward to hearing more about from some of the subsequent presentations.

Let me just say that the phenotypic test measuring the red cell enzyme activity has been a standard test at the Mayo Clinic since 1991. We now do approximately 5,000 of those tests a year in our clinical laboratories, about half for our own patients. The vast majority, obviously, are not ALL patients. They're patients with inflammatory bowel disease, dermatologic disease, organ transplant recipients, et cetera, and about

half that are referred in from outside, supplemented by genotyping also. Clearly the genotyping is available, as is phenotyping, through commercial organizations, and Howard may want to talk about that in just a moment.

There are a couple of important issues here that may relate to future discussions of pharmacogenetics; that is, the ability to work with Dr. Lennard. So if any of you do see Lynne and work with her, please tell her that I gave her credit. She's been a true pleasure and a great scientist to work with -- is the availability of what I've called an intermediate phenotype. These children are treated with a variety of drugs that might cause myelosuppression. Having an intermediate phenotype like the 6-thioguanine nucleotides as an ability to sort out which might be at risk because of the TPMT deficiency was very helpful. Of course, the association with clinical trials on a national and international basis was a tremendous advantage in terms of developing evidence-based data with regard to this genetic variance.

What I had there was what is pharmacogenetics because I pointed out that we began with the phenotype. My definition is the convergence of this kind of genetic information which Mendel would have recognized with the explosive development of new information with regard to genomics. And I'll just point out that Ron Honchel in our

lab in the early 1990s -- Ron is now at the FDA -- cloned the cDNA for TPMT, and then Diane Otterness and Carolyn Szumlanski cloned the gene.

The TPMT gene has 10 exons, 8 of which encode protein. It's on the short arm of chromosome 6. It doesn't have a TATA box. It has a variable number tandem repeat which is GC-rich in the area of the promoter. That's going to be potentially an issue in just a moment, and I'll come back to that.

And the most common variant, which was described virtually simultaneously at Mayo and at St. Jude in Bill Evans' lab, has two nonsynonymous cSNPs, two changes in encoded amino acid. There's a polymorphism in exon 7 and 1 and exon 10. I point that out because that allele to my knowledge has never been found in anyone from China, Japan, or Korea. It is the most common variant allele with an allele frequency of about 4 to 5 percent in caucasians. In East Asians in people like my wife, who is Chinese American, only this variant in exon 10 has been observed. And this is going to be an issue that as you begin to think about how you're going to go forward -- how we, our discipline is going to move forward -- I think it's going to be an interesting challenge because I was visiting professor at the National University of Singapore, and their comment was that to their knowledge -- remember,

Singapore is 80 percent Chinese -- is mainly a problem of the caucasian kids who are referred in. So these are going to be interesting and difficult issues to deal with. You can very rarely get the so-called *3B which is the exon 7 variant alone.

The reason that changing 2 amino acids results in virtually no enzyme activity and virtually no enzyme protein, as we reported back in the early 1980s -- and this is just work from our lab recently that a graduate student, L. Wang put together. It confirms work from Bill Evans' laboratory -- is that those two changes in amino acid result in the protein being very rapidly degraded. This is a reticulocyte lysate system where you can make radioactive protein. The wild type, more common allele, is quite stable, but the variant is very, very rapidly degraded. This is a common phenomenon. Actually it's the most common way in which so-called nonsynonymous cSNPs -- the cell has ways of surveillance. It doesn't like the idea, if you'll allow me to be anthropomorphic for a minute, that that single amino acid has changed. And that's going to be an interesting area that we're going to have to understand better as we move into the future in this field. So that nonsynonymous cSNPs are common, often functionally significant. Most often they result in reduced quantity of protein, not changes in the enzymatic activity. And the

mechanism, where it has been examined, is most often accelerated protein degradation.

This is a frequency distribution. These are data from Dr. Park Ha, a hematologist/oncologist in Korea. And notice these are 300. So the n is about the same as those blood donors in Minnesota. Here we get the sort of anticipated gaussian distribution. We don't have the hump here that we find in most caucasian populations, and nobody down here. Being a dedicated scientist, Dr. Park Ha brought DNA from these samples to Minnesota in the month of February and had us genotype these samples, and none of these individuals with lower activity had the common double variant in exon 7 and 10. They only had the *3C, which is the exon 10 variant.

Here are studies done in Chinese from the two places that you would expect you would study a Chinese population, Aberdeen, Scotland, Howard McLeod's data, and Rochester, Minnesota where, when we moved there, my wife was one of the few Chinese Americans in town.

(Laughter.)

DR. WEINSHILBOUM: Our samples came from Shanghai. Howard, where did yours come from?

DR. McLEOD: Guangdu.

DR. WEINSHILBOUM: All right. So we have two different Han Chinese populations.

And you can see that in the caucasian population in Rochester, it was about 4 percent of the *3A and 0 in the Chinese. This is 250 Shanghai Chinese. But they had a much higher frequency, about 2 percent, for the exon 10 variant. Howard had almost identical data. So it's fascinating. About 4.5 percent among the caucasians and 0 in the Chinese and about 2 percent for the exon 10 variant.

So this brings me back to sort of where we began. We should also point out, though, that from 0 up here to where this break is is about 10 units of activity, but even within those samples that have come from individuals with the same open reading frame, there's also about a 10-unit range of activity. And using population genetic techniques, that variance is due virtually entirely or predominantly to inheritance, which says what other genetic factors are there that swing you once you're set by your open reading frame at high, low, or intermediate.

And I forgot to point out that there are a large number of rare variants. We've talked about *2, *3. There are a large number of rare variants. So if we're talking about genotyping tests, that's an issue. They're very unusual, but they certainly exist. We had one kindred in Rochester where they were compound heterozygous with the *3A and a splice junction variant that ran right down

through the family at the intron 9/exon 10 splice junction of the canonical GTAGs.

So there's going to be allelic heterogeneity, one or two that are common, ethnic variation in allele frequencies as you begin to think about how you want to approach these issues. And the variable number 10 and repeat has been shown by studies, both done in France and studies that we've confirmed in Rochester, to help to modulate level of enzyme activity.

These are reporter gene constructs that have just been recently -- this is unpublished data from our laboratory showing that the most common variable number 10 and repeat -- these are 17 to 18 base pair GC-rich repeats. And you can have from 3 to 9 of them. The French and our group have shown that both in vivo and in vitro, the higher the repeat number, the lower the enzyme activity. This is not anything unanticipated. Jeff Drazen reported similar data with regard to ALOX-5 H gene which also has clinical implications. And this just shows you that the higher the repeat number -- 4 and 5 are the more common. This was from a sample of 2,609 samples from our clinical lab that we drew these -- the lower the enzyme activity.

So I'll just end -- and I think I'm reasonably on time -- with a slide that comes from the New England Journal article that was right in front of a nice article

that Howard wrote showing in caucasians the frequency distribution. The most common reason for high, low, or intermediate relates to the frequency of the double variant exon 7-10, the so-called *3A variant.

Having provided the scientific background now, I'm looking forward to the presentations that will come next from Howard and from Naomi. Thank you very much.

DR. SANTANA: Thank you. That was very thorough.

Any brief questions?

(No response.)

DR. SANTANA: If not, Howard, you're next.

DR. McLEOD: I want to thank you very much for the opportunity to present this data and talk a little bit about the last 5 to 10 years' worth of information regarding the clinical implications of thiopurine methyltransferase deficiency and try to pull together the literature in a way that we can think about how this information should be put into the package insert.

I think it's important to realize that the question that we were asked to address was not should TPMT testing be mandated in every person who can spell 6-MP, but rather should we be informing patients through the insert about the information that's there and should we be providing information on how this could be used in a little

bit more useful manner.

Now, there's a quote that I'd like to start us off with that for me puts the issue into perspective, and that is as shown here. "A surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs, they would have been investigated very carefully a long time ago." Now, this is supposedly from 1849. I don't read this journal.

(Laughter.)

DR. McLEOD: Joachim, you probably do if it's still around.

This quote is very relevant today. Of the anticancer drugs we have available to us, there are virtually none of them that we truly know the mechanism of action and therefore have the precise handle on how to use these medications.

Also, this really turns things around to putting it into the patient's perspective. We are used to talking about the extremes and worrying about the extremes when patients worry about the mundane. If I had grade 1 diarrhea from a therapy I was taking, I would not be presenting to you at this particular moment. Yet, grade 1 diarrhea wouldn't even hit our radar screen. It would be grade 3 or 4 or worse that would make us worry. The same with neutropenia. We don't worry about patients that don't

have to be hospitalized for that fall in white count, but they do. So putting it in that context, in the context of risk prevention, we can start thinking about this test and how it might be useful and ways that it might not be useful.

Now, Dick showed this data from 1980 that reminds us that there is variability in TPMT activity. Now, he focused on the three groups that were present which indeed is a very important issue. There's also quite a lot of variation in enzyme activity across populations, and understanding this variation, at least in part, is what we're discussing this morning.

There are a number of ways of trying to evaluate that variability. The enzyme activity was shown in the previous slide and certainly red blood cells are a good surrogate of TPMT activity measured elsewhere in the body, for example, the liver, the lung, the platelets, the kidneys, and also leukemia blast cells in the two studies that have been performed to date. So red cells do offer an easily assessable surrogate and there are tests commercially available for measuring enzyme activity.

The benefit of a TPMT test in the red cells is that you're measuring functional catalytic activity. You're measuring variability in activity from any source, genetic or otherwise, and therefore you can take into

account the dynamics of this particular measure.

The down side is that the red cells do have to be handled carefully. They do have to be shipped to a reference laboratory, as do most of these tests, and there are nonclinical or nonphysiologic reasons why enzyme activity could be varied, for example, freeze-thaw, some of the influences of shipping, things that have nothing to do with the patient's activity.

Measuring the active metabolites, the thioguanine nucleotides that Dick has shown you, is another way of trying to evaluate this situation, and that has the benefit of not just taking into account thiopurine methyltransferase, but also looking at the variation introduced by xanthine oxidase and any other source of pharmacokinetic variation that is found in that particular patient and therefore is more of a downstream measure of this particular class of agents and can be quite useful. There are very few laboratories offering this test, although it is commercially available, and also has some of the handling issues that I mentioned with the red blood enzyme activity assays.

The last one I'm going to mention is the genotyping for thiopurine methyltransferase. It has the benefit of there being a few defined genetic variants that are responsible for the majority of low activity in the

world's populations, and I'll show you some of that information, and therefore a small number of tests will give you information on the majority of patients. DNA is very stable. We can get DNA from King Tut. Therefore, we can get it from the patients. And this testing is quite robust.

What DNA does not offer is a dynamic measure of what is happening with individual patients, and I'll demonstrate that. You still have variability in enzyme activity in patients with a so-called wild type or normal genotype.

Now, there were several questions that were given to me to be addressed. Therefore, I'll try to make some points regarding those issues.

The first one is really what is the relationship between the TPMT genotype and the clinical phenotype. Dick has demonstrated to you already that there is variability in the enzyme and that high levels of enzyme cause less drug to be shunted down the activation pathway. Indeed, I'll show you that data as well.

When we take the information of genotype that is available to date, there are three alleles that have been commonly found to be associated with low enzyme activity. The wild type normal allele is shown at the top. There's a single nucleotide polymorphism at exon 5 and exon

10 and then the exon 7/exon 10 polymorphisms that have been demonstrated to occur in the general population. As Dick mentioned, the most common variant in the caucasian population or the European extraction population is this so-called *3A mutation, whereas *3C is the most common in continental Africa and Asian populations, both in those continents and here in the United States. *2 allele has primarily been found in the caucasian population at a low rate. And when you take these three variants in compilation, you're able to predict approximately 95 percent of the patients with low enzyme activity.

Now, that number is not a hard number. There are studies that range from about 85 percent up to 100 percent prediction, and looking at them in compilation, it's around 95 percent. But there has not been a prospective study in tens of thousands of patients to determine the genotype/phenotype relationship in toto.

So these three polymorphisms are responsible for low enzyme activity in all continents of the earth and are the primary basis for low enzyme activity in all patients throughout the world.

Now, this is data from the late '90s. It was the first demonstration, in respect to patients that I came across anyway, looking at the genotype/phenotype relationship and it makes a couple of interesting points.

This is data from blood donors from the Memphis area. If you have two variant alleles either as a homozygous state or as a compound heterozygous state, you will have low or undetectable enzyme activity as demonstrated here. If you have one defective copy and one normal copy, you will have intermediate enzyme activity, as demonstrated in this middle portion. And then those folks that have two normal alleles have higher enzyme activity.

Now, a couple of points I want to make from this slide. First of all, what is this individual doing here? This particular individual did not have one of those three variants that I showed you. It turned out that they did have, on repeated testing, intermediate enzyme activity and on further genomic analysis, they had a unique polymorphism that has only been found in that individual and their family. So there are going to be patients out there that do not have the three main polymorphisms but yet do have low or, in this case, intermediate enzyme activity. So the current testing approach with the three primary variant alleles will capture most patients but not all patients with low enzyme activity.

Secondly, there's a lot of variability in enzyme activity in these patients that are genetically normal. They have the reference or wild type sequence. It's just a reminder that there's a lot that goes on in

humans that is post-genomic. We start with DNA, but there's a lot that happens post-DNA. So a lot of this variability may have dietary influences, drug influences, influences that we don't have any understanding about whatsoever. Therefore, we should not assume that understanding the genomics of this enzyme will allow us to predict all variation in enzyme activity but rather some variation and, as I'll show you, some of the key sources of severe toxicities.

Now, this is some data from a prospective study that was conducted at St. Jude. I was a fellow there at the time this was started, so I have painful memories of the Total XII protocol. Many hours of lost sleep went into the collection of this type of data demonstrating that high enzyme activity resulted in low active metabolite levels and vice versa. So it seems to be simple biochemistry. If you don't have enough substrate to active metabolite, you get low levels. If you don't have the enzyme to inactivate the drug, you have more drug shunting down the activation pathway.

Now, as has been demonstrated previously, the complete deficiencies are a very rare instance, about 1 in 300 individuals in the caucasian American population. Therefore, this is only two individuals. So you have a large error bar there demonstrating a couple of things.

First of all, this is a rare event, and secondly, we don't know a lot about rare events. So fairly consistently these patients do get into trouble, but we don't know the precise amount of trouble they get into, at least in terms of active metabolite levels.

This relationship is interesting but it has nothing to do with the question of whether the TPMT genotype is associated with the clinical phenotype. We're all aware of pharmacogenetic influences on pharmacokinetics that have no pharmacodynamic endpoint. So I want to emphasize a little bit more some of the data that's out there for that. Of course, Dr. Winick, will bring that home more completely in her presentation.

This is data that was my first experience that got me interested in the field of pharmacogenetics. This is a 5-year-old little girl with acute lymphoblastic leukemia who was started on the Total XII protocol. After induction therapy, that protocol every 6 weeks gave some consolidation chemotherapy, as I'll show you in a few slides. What is shown up here is her hemoglobin levels, and what's indicated with the asterisks are the points where she required red blood cell transfusions and in many of those instances, she also required platelet transfusions because of anemia and thrombocytopenia. She had to omit some of her high-dose chemotherapy during that period

because of toxicities. The absolute neutrophil count is shown here. She had multiple episodes of neutropenia with hospitalization during that point in time. And more importantly, at the bottom slide here, there should be a red bar all the way across indicating the number of weeks of therapy she was able to tolerate. Every time you see blue here, it reflects that she had to skip her chemotherapy that week or have reduced doses of her 6-MP.

And it has been demonstrated by Don Finkel many years ago that half-dose therapy is not just half as good as full-dose therapy for childhood ALL, but if you have to give half-dose therapy, the outcome is rather dismal. So there's a lot of worry because she was not only having to miss a lot of mercaptopurine, but was missing a lot of her other chemotherapy during this first year of her post-induction therapy.

What is demonstrated in this middle bar here is the active metabolite levels. The range from the other 200-plus kids on the trial is shown in red. Her levels are shown up here. She had active metabolite levels approximately 10 times the average of the rest of the children on this protocol. TPMT activity was measured and she was found to be completely deficient of enzyme activity.

She was reduced to one-fifteenth of the

standard dose. She licked a tablet every once in a while. What was found is that she still had high active metabolite levels but in the tolerable range for this protocol.

More importantly, what's demonstrated here is her red cell profile and similar with her platelet profile after the diagnosis and dose reduction of mercaptopurine. Most importantly, out of the six chemotherapy drugs she received during this first year of chemotherapy, only the mercaptopurine dosage was changed. All the other drugs were given at full doses because the culprit was identified for her extreme toxicity. She still had episodes of neutropenia from the high-dose chemotherapy but was able to avoid some of the red cell and platelet toxicities that she was experiencing.

Now, these sorts of anecdote are not useful at all for deciding our task today, but are a reflection of why we're even having this meeting. There are these patients out there that are the extremes that have driven us to worry about this issue and try to predict this phenomenon.

Also, the resource issues for these few kids are exceedingly high and you may argue that 1 in 300 is not very much, but these kids take up more than their share, more than 300 times their share, of supportive care in many of the instances that are published in the literature,

including the child that I described to you.

What is shown in this slide on the y axis, on the left axis anyway, is the percentage of therapy missed by the child I just mentioned to you and another child we came across while I was a fellow at St. Jude. What's shown in blue is that these two children missed somewhere between 35 and 60 percent of the weeks of therapy prior to the diagnosis of TPMT deficiency, but missed less than 10 percent of the weeks of therapy after that diagnosis and dose reduction to extremely low doses, between 6 and 17 percent of the standard doses that we normally would administer.

What's shown on the right axis is the percentage of weeks requiring a transfusion, and again that same phenomenon of somewhere between 10 and 25 percent of the weeks requiring transfusion down to less than 5 percent of the weeks requiring transfusion after that diagnosis, showing what can happen by finding out what the culprit is with this therapy and acting accordingly.

Now, more importantly is what's happening in the context of cohort studies. These extremes are interesting, but this is data from the Total XII protocol. This cohort of patients were selected only for the presence of ALL with the biology that is indicated in the protocol. They were not selected for TPMT deficiency or any other

phenomenon. What was found is, as would be expected, very rare individuals had complete deficiency. The heterozygotes were about 10 percent of the population.

What was seen is that 100 percent or both of the deficient patients -- that's a more appropriate way to say it rather than 100 percent -- required substantial dosage reductions very early on in their therapy. 35 percent of the heterozygous patients required substantial dosage reductions, and 7 percent of the wild type patients.

So for the deficient patients, there was a 14-fold risk, just doing simple math, of requiring substantial dose reductions. For the heterozygotes, there's about a 5-fold risk, and that's in line with the paper that was provided to you from the St. Jude experience looking at referred patients with TPMT deficiency in that there was about a 6-fold excess of variant alleles in the patients with extreme toxicity compared to what you would see in the general population.

So heterozygotes do have a risk. Their risk is lower than the homozygous variant patients, and qualitatively they get their toxicity at a later point in time. But to me it's a simple gene-environment interaction. If you have two variant genes and you have environmental exposure, mercaptopurine administration, you're going to get your risk demonstrated much earlier

than if you have one variant gene, high risk gene, and the same environmental exposure where there will be a later-occurring event.

Now, this phenomenon has not been demonstrated in all cohort studies. This is some data from my time in the UK in collaboration with the MRC, the UKALL group over there, Tim Eden and Brenda Gibson in particular. There's this percentage of weeks with no therapy on the y axis here and genotype on the x axis. What we found is, as with the previous studies, the rare homozygous variant patient misses a lot of therapy, and that's no surprise. Even with dosage reduction, there's a lot of therapy missed. What we did not see is any difference between the heterozygous patients and the homozygous/wild type patients.

And the difference this study and the Total XII study I just mentioned to you was the intensity in consolidation chemotherapy. This therapy was not as intense of a therapy and therefore -- no surprise -- did not demonstrate this phenotype. It's just a reminder that it's gene-environment interactions we're talking about. If there's not a heavy dose of bone marrow toxicity being induced through the therapy, either mercaptopurine or otherwise, we're not going to see dramatic phenotypes with the heterozygotes. We'll come back to that point in the end in terms of the relevant merit of genotyping to find

the heterozygous population, but not all studies find heterozygotes who are at the same risk as other studies found.

So one approach is the approach that's commonly used now, and that is just to use the degree of myelosuppression as a way of trying to accommodate and avoid extreme toxicity. Really the question of genotyping up front versus genotyping when there's a toxicity is one that we may not resolve today, but I'll come back to it at the very end. But the disadvantage of adjusting for mercaptopurine doses based only on toxicity are really twofold.

First of all, early on in modern therapy for childhood ALL, we have a very high incidence of toxicity from a number of different drugs. Therefore, trying to figure out which of those drugs is the culprit and adjust accordingly is difficult to do without specific tests. So the context of 6-mercaptopurine dose adjustments based on neutropenia during the first year of therapy is a very challenging thing to do with most of the protocols that are currently utilized.

Secondly, there are some long-term events that have been associated with low TPMT activity. I'll mention that in the next slide. Therefore, acute myelosuppression is not the only endpoint that we're worried about in this

context.

Now, there's certainly a lot of success with using this approach. This is what many people are doing now and reactive medicine is how most medicine is practiced in all areas, not just in childhood leukemia. The question that comes to mind, going back to that initial quote, is that the way we want to go forward. Our goal is usually to try to make ourselves better, try to do better than we're currently doing. So trying to think about it in that context, reacting to toxicity is okay if we have no alternative. Preventing toxicity is really what our patients expect us to do.

Now, low TPMT has been associated with secondary malignancies, and I want to put a couple of caveats into this data because I think this can be oversold. There is a higher risk, at least in the Total XI protocol, of irradiation-induced brain tumors. Now, this phenomenon has been observed. I do believe the data. But because of this data, there has been a reaction to the data that now in my mind really avoids this issue. The issue was concurrent administration of radiation and mercaptopurine. Most if not all protocols now avoid that particular interaction. Therefore, I personally don't think that the risk of irradiation-induced brain tumors by TPMT genotype is a big issue anymore. I think that has

been accounted for now or should be, if it's not, and therefore is an avoidable event independent of genotyping or phenotype analysis.

Several studies, both in the U.S. and in Scandinavia have found this higher frequency of t-AML in patients with low TPMT activity. Dr. Winick is going to talk about this particular topic, as I peaked ahead in her slides, and therefore I'm not going to talk about it further. But she will be able to talk about whether this is a major issue or not. It probably is not a major issue.

Then there have been the small studies suggesting a higher frequency of skin cancer in patients receiving thiopurine therapy. There have been single studies. There have not been widespread reports on this issue.

Therefore, I think this issue of secondary malignancies has to be in our minds and we have to be thinking about that, but it cannot be the main driver for the decisions that we make today for the use of this particular testing entity.

I think one important question is, is there a loss of efficacy after 6-mercaptopurine dose reduction in the context of the TPMT genotype? And the answer is no. Next topic. No. We'll talk about that data in more detail.

The Total XII protocol is shown here. The backbone of all 2-and-a-half years of therapy was daily 6-mercaptopurine 75 milligrams per meter squared per day both during the consolidation phase where patients received either a milligram per meter squared or blood level-determined dosing of the high-dose methotrexate or teniposide/Ara-C or during the subsequent maintenance phase. Mercaptopurine was a daily event in these kids' lives.

When you look at the outcome data from the Total XII protocol, separating the patients on whether they had a defective allele -- 17 of the 19 are heterozygotes; 2 are homozygous variants -- the complete remission experienced was equal to statistically, superior to graphically the patients with the wild type genotype. So decreasing the dose of mercaptopurine based on genotype, based on thioguanine nucleotide levels, both of which were performed in this study, did not have a detrimental effect in terms of remission rate in these children. If anything, there was some hint of benefit.

The Total XIIIB protocol has not been published yet. A similar backbone of therapy with methotrexate/6-MP, and that data provided by Dr. Mary Relling at St. Jude demonstrated that the confidence intervals for relapse -- I'm sorry. The cumulative incidence of relapse is shown on

the y axis and years on the x axis, and the heterozygous patients are shown in the red dashed line. Their relapse rate was equal to statistically slightly less, in actual visual terms, than that found with the wild type patients.

So this data from two sequential studies from a single center, St. Jude, have demonstrated that certainly the patients that get dose reduction based on genotyping and thioguanine nucleotide levels are not at a higher risk of relapse. If anything, they have a better outcome than their colleagues with the wild type genotype.

Now, the last part is how we should use TPMT genotyping. I think the most important part of the discussion we're having today is not what are the hard guidelines for using the genotyping or phenotyping analyses. I think those are going to come out over the next few years as the Children's Oncology Group does prospective studies to really hammer down the utility of these tests.

To me the most important point is getting information, clearer information into the package insert so we can inform patients in a better fashion. There are some patients that are already finding this information via the internet and acting accordingly. It would be much more appropriate for them to get reasoned information through a package insert than just to go out there and hunt it from

web sites of variable quality.

The second is that I mentioned that more intensive protocols with more taxation on bone marrow reserve -- the genotype has a more dramatic influence in that context. So pretreatment assessment of TPMT genotype in my mind is something that we should be striving for in more intensive protocols. Certainly there are some hints of how to dose on this.

This is data from Mary Relling that was published in the Journal of the National Cancer Institute in 1999, data from the Total XII protocol. What was demonstrated from that protocol is that the wild type patients on average tolerated the full dose, the 75 milligrams per meter squared of mercaptopurine. The heterozygotes tolerated right about 50 milligrams per meter squared of mercaptopurine, and the homozygous variant patients tolerated right about 10 percent, a little bit less than 10 percent of the normal dose for their mercaptopurine therapy. So based on that single prospective cohort study we have some hint on where to start with these doses.

Now, a single prospective cohort study is better than nothing, but it's certainly not ideal and it is not sufficient for our colleagues in the evidence-based medicine arena, but at least gives some data on where this

could be started. I'm not advocating that we put doses based on this into the package insert, but certainly this has provided the basis for many people's decision making off protocol and, of course, is a subject of many protocols throughout the world.

This means that with prospective TPMT genotyping, patients with a homozygous deficiency could have dramatic dosage reductions a priori, cut down to 10 percent or so of the regular dose. The heterozygous patients could be cut down to 50 to 60 percent of the normal dose, and the wild type patients would keep on normal doses and be adjusted based on white cell count. This is not an all-or-none phenomenon. Even those patients that have dosage adjustments for complete deficiency still will have variability that has nothing to do with thiopurine methyltransferase. Therefore, this subject of evaluating levels of myelosuppression will not go away. It is a pharmacodynamic endpoint and a valuable tool. So having initial testing, dosage adjustments before they ever start therapy, so initial therapy being guided, and then reacting to myelosuppression is one paradigm that's put forward.

Another approach is evaluating patients only after they have toxicity, and that is what is really currently being done at most centers. A few are doing the

prospective approaches, often not in the childhood ALL context, more often in the adult setting for off-label usage, and that is driven both by the demands of the patients. They're much more demanding in terms of toxicity. They don't want it. They're not going to let you give it to them. And also because of the litigation issue that has been brought up by Dick previously, that there is a much more litigious situation when you're talking about pemphigus or rheumatoid arthritis than when you're talking about childhood ALL.

But in the context of many centers, when they have a patient with toxicity, they do need to know which drug is the culprit and TPMT testing is being used in that context. In that context, patients with severe toxicity can have dosages being adjusted based on TPMT results. So the homozygous deficient patients have the extreme dosage reduction, less significant reduction but still adjusting the dosage for the heterozygous patients. The complete deficient patients have the dosage reductions. The patients with no TPMT defect have all of their myelosuppressive doses adjusted, and the patients with no toxicity keep being monitored the same way you're doing now with white cell count.

So just to reiterate, if you have TPMT deficiency, either homozygous or heterozygous, you can

react with dosage reductions according to what I've previously shown you. Those without a TPMT deficiency, we do not know the culprit. It's probably not mercaptopurine, but all of the myelosuppressive drugs will need to be adjusted in that context.

So what we have is a situation where there is a phenotype with a molecular mechanism, a molecular diagnostic, and some hints on how to adjust the dose. So at the minimum, the information on frequency, the presence of a diagnostic should be available to patients in a uniform fashion. I would argue that we're not quite ready to put dosage adjustments into the package insert, but it certainly needs to be a focus of the cooperative group studies that are going forward to define who is the at-risk population and what doses do they need to be on.

The platforms for doing this analysis will change over time. Right now you may say, well, it is expensive to do that testing for a 1 in 300 yield, and you can make that argument. But we're going to be adding more and more genotypes in other contexts, and so it will be a case where genotype analysis is being performed for a number of variants, including TPMT. And therefore there will be information on a number of different areas of your patient's management, infection risk, pain control, antinausea and vomiting, cytotoxic therapy, that will make

the cost of an individual test much less and provide that with a much higher utility.

So I think I'll close off with another quote that's a little bit more recent than my last one. Gerhard Levy in 1998 mentioned that the emphasis should not be on the population averages but rather on providing tools for making drugs effective and safe for individual patients. I think the context in which we're operating now is that we know that there is an event, in this case a genetic variant, that predisposes patients to risk of toxicity. Not acting on it at all or at least not informing patients of its presence is really not adequate and not optimal medical care. We may not have the ultimate data set to go in and start changing everyone's dose, but we at least need to take this into account and to start using it accordingly in a prospective fashion.

And I'll stop there.

DR. SANTANA: Howard, thank you so much for a very thorough and informative presentation.

Does anybody have any acute questions? Sue.

DR. COHN: I just have one question, and that is, my understanding is that the hepatotoxicity that's associated with 6-MP does not appear to be related to TPMT deficiency. Is that correct?

DR. McLEOD: It appears that that is the case.

We have had mixed results in that context which makes me think that it's something else. We have people with severe hepatotoxicity that are heterozygous or even homozygous variant, but there are plenty of patients with hepatotoxicity that are wild type, at least as far as we can tell, with this genotype. So I think something else is going on.

DR. COHN: That was going to be follow-up question, whether there was any clue as to what else might be alluding to that particular toxicity with this drug.

DR. McLEOD: There are candidate genes. We showed the pathways of the proteins that are involved in this. Certainly we're taking a pathway approach to try to look at all of those genes. What it really comes down to is we do not have a clue what the other genes are that are modifying other toxicities like you described there. That would be a very important issue for both childhood ALL and all the other uses of thiopurines because that's a common event, relatively speaking, and it's also a common source of extra invasive tests in some contexts. But I do not know. I should say for myself I do not know what the genes are responsible for that.

DR. SANTANA: Howard, I want to make one point of clarification in your presentation. I think you made a reference to the association of brain tumors --

DR. McLEOD: I said the wrong protocol.

DR. SANTANA: Yes. You mentioned Total XI and for the record I do want to correct that it's Total XII. Would you agree with that statement?

DR. McLEOD: Yes. Thank you very much. On the fly in mid-slide, I couldn't remember which one it was. So thank you for correcting that.

DR. SANTANA: We will correct it in the record.

The second issue is at the end you presented some provocative algorithms of potentially what could be done to manage patients. I want to make clear when you were talking about TPMT, were you talking about measuring of activity through enzymatic red cells or were you advocating genotypic analysis in those algorithms? Can you clarify that for me?

DR. McLEOD: Yes. Unfortunately, I was letting my bias show through. While I was at St. Jude, we were using TPMT testing in the activity level, thioguanine nucleotide measurements, and genotype analysis. In my personal experience, the presentation of anemia as one of the initial -- well, anemia, as an initial presentation of ALL, meant that many of the children were coming in transfused. Measuring TPMT activity in the transfused children meant measuring someone else's red blood cell TPMT activity. Therefore, there were several of the cases,

including the two I described to you, that initially looked like they had normal activity, or at least funny-looking activity, that over time, as their own red cells came into prominence, were clearly deficient.

So I was really referring more to the genotype-based testing that can be done a priori. It can be done in the context of even red cell transfusions. It can be done very rapidly, and it can be done at a lot more centers. So that's my personal bias, but it is nothing more than that.

There are many centers that use red cell TPMT activity assays with high success. I mentioned some of the reasons why activity assays are better than genotyping in terms of capturing more of the variability that is out there. So that's my particular bias, but it also has merit.

Thioguanine nucleotides could also be used in that context, but you have to administer the drug and then measure the metabolites. So, obviously, you can't do that without exposure to the drug.

DR. SANTANA: Thanks for clarifying that.

Any other comments or questions? We're going to have plenty of time also during the discussion period.

(No response.)

DR. SANTANA: Thank you, Howard.

Naomi?

DR. WINICK: Good morning. I would like to begin by thanking Steve and Dr. Lesko for inviting me. I'm honored to be a clinician in this audience.

Secondly, I'm afraid that my presentation will include many slides that have already been presented, and I will ask your forgiveness for the duplication. I will try to be relatively quick, but I will be presenting this, I think, from a different viewpoint and you may walk away from this believing that I am, to borrow some of Dr. McLeod's words, the mundane reactionary component of this meeting.

(Laughter.)

DR. WINICK: Just an overview. I come to this presentation with a deep and abiding respect for how horrible cancer is in children, and leukemia is one of the horrors. It's the most common horror, but there has been dramatic improvement over the last 30 years. The lowest event-free survival curve on this slide represents treatment between 1968 and 1970, certainly within the life span of everyone in this room, and then this curve represents therapy between 1996 and 2000. So there's been improvement but we still have a long way to go.

These slides I'm actually going to skip. You all know the history of 6-MP. I'm going to go back one, though, to emphasize something that has been said, which is

that the dose intensity of 6-MP does correlate with event-free survival. And this is something that Mary published several years ago.

This has also been presented. Dr. Weinshilboum gave an elegant presentation of the gene and its variability. I want to point out a case presentation that was actually the first in the pediatric leukemia literature, one published again by Bill Evans and Mary describing a child with severe myelosuppression who had exorbitant TGN concentrations and was found to be homozygous deficient. That case presentation was published in the Journal of Pediatrics in 1991, so actually not that long ago.

So the questions that I was asked to address are going to be illustrated on this slide. We know that TPMT variation has an impact on clinical response to the delivery of 6-MP. We know that this variation is assessable both by phenotype and genotype. One question that's been posed is whether one can knowledgeably titrate therapy for children with ALL without a knowledge of the pharmacogenetics. And then lastly, should TPMT activity -- and I beg your forgiveness. This should also say "and/or genotype" -- be determined prospectively in all children with ALL?

The arguments suggesting that TPMT activity or

genotype should be determined prospectively include the following.

First, this is not a difficult test. 3 to 5 cc's of blood in a green top tube is hardly horrific compared to other things that we put these children through.

Second, the cost is nothing compared to the cost of cytogenic studies, immunophenotyping, et cetera.

Potentially by doing this prospectively, we would avoid severe myelosuppression. However, you've heard from all speakers that severe myelosuppression is not going to be eliminated by a knowledge of TPMT genotype and appropriate dose adjustment. We may or may not prevent second malignancies, and I will have slides later in the presentation that address this.

And something important that I perhaps have not phrased scientifically is another reason to do this prospectively is opposed to genotyping for neurodegenerative diseases, Li-Fraumeni syndrome, et cetera, the results of this genotype are not likely to cause undue emotional stress.

This is a slide from Mary Relling. Mary was kind enough to send me these slides. I don't think she knew the context in which I was going to present them. But this is a slide that Howard just showed, showing that if

you know the child's genotype, you can prospectively, or at least you could prospectively, adjust doses.

The arguments that TPMT genotype should not be mandated prospectively are actually what I will spend the rest of my presentation reviewing.

First, you've all seen the numbers. Too many times you're looking at a very small population that has a homozygous deficiency, and dosing for the heterozygous population is actually quite similar to that for the wild type population. I used as an example the coming Children's Oncology Group standard in low-risk trial.

The Children's Oncology Group, parenthetically, is an international cooperative group that will enroll more than 80 percent of all children in the United States, the majority of children in Australia, children in parts of Switzerland and other places on single, randomized, phase III clinical trials for acute lymphoblastic leukemia.

The estimated projected enrollment for this one trial will be approximately 2,000 children over a 4-year period. If you use the population calculations that have already been presented, this means that 7 children among these roughly 2,000 will be homozygous deficient, and this covers all of the U.S., as I said, most of Australia, and other places over a 4-year period.

So in the United States, even relatively large

institutions -- and Dr. Santana, I apologize. St. Jude is not included here, but most large institutions in the U.S. don't see more than 20 to 30 new patients per year with ALL, and there are some exceptions. There are also obviously exceptions in the other direction where an institution may see 5 new patients with ALL per year. So these institutions may not see a TPMT deficient child ever, and if they do, it may only be once in every decade.

This is, again, Mary's slide. It's already been shown, showing that if you did have the information and did adjust doses appropriately, whether it was prospectively or following toxicity, that child's event-free survival won't be undermined by the dose adjustment.

Now I'm going to just briefly review the therapy that the Children's Oncology Group has put forth and will put forth for the treatment of children with leukemia as a means of defending perhaps my statement that I don't know that the testing should be mandated prospectively.

Induction therapy is fairly straightforward. A glucocorticoid is used and there's enormous debate as to whether or not this should be dexamethasone or prednisone that I won't go into. Vincristine is a standard part of all induction therapies. Asparaginase is almost standard. Intrathecal therapy is the initiation of treatment that

will prevent the occurrence of CNS leukemia, and for many higher-risk patients, an anthracycline is included in the induction.

There is then a period of consolidation wherein CNS prophylaxis is delivered. For standard-risk patients, this is often a relatively simple period where the dominant therapy is the intrathecal therapy, again designed to prevent CNS disease. For higher-risk patients, the Children's Oncology Group will incorporate both cyclophosphamide, cytarabine, intermittent pulses of vincristine and asparaginase, and there will be randomized questions asked in this section. So I've put up a backbone. I have not put up a slide with all of the details.

There is then a period of delayed intensification. The UKALL studies, as well as Children's Cancer Group studies, as well as German trials have all demonstrated that this is a very important part of the treatment of children with acute lymphoblastic leukemia. And there is an anti-purine here, but it is almost universally thioguanine, not 6-MP. And thioguanine does not seem to be as influenced by TPMT as 6-MP.

Maintenance therapy is the area where 6-MP really becomes prominent. This extends for 2 to 3 years. Most children worldwide receive nightly oral doses of 6-MP,

weekly oral doses of methotrexate. Intrathecal therapy is delivered on a variety of schedules, but a common one is every 12 weeks. Many children receive vincristine/dexamethasone pulses. This obviously can also be prednisone. This is the first introduction of 6-MP in any sustained or prolonged sense.

Contrary to what may have been suggested earlier, this therapy is not particularly myelosuppressive in the vast majority of children who receive it. Accordingly, it is often not difficult to believe or to think that it might be the 6-MP in a TPMT deficient or heterozygous child that is responsible for myelosuppression if it is severe.

The other thing that's very important to note is that all protocols adjust to a defined absolute neutrophil count. So some of the modification is instituted regardless as to whether or not genotype or phenotype is known.

I'm now changing subjects. Again, this is a slide that Mary Relling sent me, and this is looking at the incidence of brain tumors in one particular St. Jude protocol which was unique in that 6-MP was delivered concomitantly with cranial radiation. As Dr. McLeod already pointed out, 19 children developed high-grade CNS malignancies. This is essentially unheard of in other

pediatric protocols both at St. Jude and elsewhere.

This is, again, Mary's slide demonstrating that those who had TPMT deficiency were at significantly greater risk than those who had wild type TPMT of developing these brain tumors.

So the St. Jude's group concluded for obvious reasons that there was a higher risk of radiation-induced brain tumors among children who either had high thioguanine nucleotide concentrations or TPMT deficiency. This is an important point in that among the children studied, there were children with wild type enzyme who simply had very high TGN levels and also developed the brain tumors. As I said before, there was a unique combination in that they delivered 6-MP during radiotherapy and that will not likely be repeated in the future. As I said, only 3 of the 6 children initially described actually were TPMT deficient.

The more difficult issue is that relating low TPMT activity and the risk of either secondary myelodysplastic syndromes or treatment-related AML following thiopurine therapy. Again, Mary's data documenting a trend that was actually not statistically significant towards a higher incidence of etoposide-induced secondary AML with lower TPMT activity, all cases described had the 11q23 abnormality which is a hallmark of etoposide-related AML.

My greater concern, though, is the Nordic trial, and Dr. Weinshilboum should comment. I believe he was involved in measuring enzyme activity and looking at the genotype for these patients. This group never gave etoposide, not a single milligram. And the dose of alkylating agent, even in the higher-risk patients, didn't exceed 3 grams per meter squared, which by oncologic standards is low. They documented a higher incidence of treatment-related myelodysplasia and/or AML in patients who had less enzyme activity. This was defined as less than 14 international units per ml of red cells. And it was statistically significant. I can't explain this data away.

But I can present it in the context of other studies that have looked at secondary AML. Again, remember that all of these trials included 6-MP because it is truly ubiquitous among therapies for ALL.

Anna Meadows published a review of CCG data. She looked at an unquestionably impressive number of children, 9,720 who had been treated with ALL without etoposide, and there was one documented case of treatment-related AML among these almost 10,000 patients, all of whom received 6-MP.

And then a smaller study, but nevertheless impressive, from Dana Farber was published in 1990 where they found two cases of treatment-related secondary AML

among 752 children who had been treated at their institutions for ALL. And this is important because even though Dana Farber's protocols never included etoposide, they are very anthracycline intensive, and as this room knows, anthracyclines may also have an effect on topo II and may also predispose to secondary AML. It is also important to note that Boston perhaps to a greater extent than any other group uses cranial radiation. So another secondary malignancy-inducing therapy. Nevertheless, they didn't see them.

So what I actually am comfortable with -- and this is Mary's slide and, Dr. Santana, I promise I will call and beg Mary's forgiveness. I actually like Mary's slide recommending dosing based on toxicity and the results of testing. Patients with serious toxicity or suspected noncompliance, something we haven't discussed here, should have doses adjusted based on the results of testing genotype activity, thioguanine nucleotide concentrations. I think there are reasonable reasons to do all of the above. Those with a TPMT deficiency obviously have to have their doses of 6-MP decreased dramatically and preferentially over the doses of other drugs. Those without a defect would not have the doses of 6-MP preferentially adjusted, and those who don't have 6-TGN concentrations should be evaluated for noncompliance, which

is an issue in and of itself. Those patients without toxicity who achieve ANCs in the target range as dictated by the protocol would not necessarily have the testing done and would not necessarily have changes made in their therapy.

So the availability of testing for TPMT and thioguanine nucleotides clearly improves the care of children with ALL. I am not here to be anti-science. However, prospective testing of all children may not be warranted. It would clearly limit, though it would not eliminate, the incidence of severe myelosuppression and perhaps the risk of second malignancy. However, my greater fear is that it will also actually lead to a decrease in dosing for children with ALL. My reasons for this are as follows.

Number one, as you've seen, the numbers are small so there will be many treating physicians who have never seen a heterozygous phenotype before, who have never seen a homozygous patient or genotype before, and won't necessarily know how to respond and arguably might overreact and cut doses fairly dramatically.

Second, in the real world, I'm afraid that prospective testing isn't always done at exactly the time point that the protocol recommends it, and I have significant fears that a child will arrive at the moment

that they're supposed to begin their 6-MP therapy, that the blood will not have been sent, and that therapy will be delayed, in my opinion, somewhat unnecessarily. There has only been one report of a fatality related to TPMT deficiency. That slide was actually presented earlier. It was an adult patient who had undergone cardiac transplantation who was treated with azathioprine.

So, again, in my role as the mundane reactionary pediatric oncologist, I'm not arguing that myelosuppression is not a serious toxicity. I am certainly not arguing that second malignancies are not one of the worst toxicities that we face. However, in the context of most protocols to treat children with cancer, 6-MP is actually the least toxic drug that we deliver, and the toxicity is far and away some of the more manageable.

Thanks.

DR. SANTANA: Thanks, Naomi.

I'm going to ask you the same question I asked Howard, which is in your presentation of the algorithm that you proposed that should be used, can you clarify for me if your intent is to use phenotypic activity -- and obviously, you're adding toxicity -- in contrast to genotypic typing of all patients? Am I understanding you correctly?

DR. WINICK: I would not choose one or the other. I think that one of the great problems that Howard

pointed out is -- with my recommendation that this be done not mandated prospectively, but perhaps be done in the context of toxicity -- what you don't want to have is a physician with a child with severe myelosuppression who then continuously puts off sending blood for TPMT activity because of the transfusions. So I think you have to be flexible, and in that circumstance, genotyping would clearly be the way to go. But it would also be phenomenally useful I think to the clinician to get TGN nucleotide concentrations because then you have a functional result to match your genotype result.

DR. SMITH: Naomi, I had two questions. One was would it matter or make a difference to you if the first exposure to 6-MP was in a maintenance like course of therapy versus being part of a more toxic part of therapy? And I ask that in the standard risk, I think the first exposure would likely be in some kind of maintenance-like whereas in a high-risk setting, it might be during reinduction to 6TG. Would that make a difference to you in terms of how you would approach the testing?

DR. WINICK: The answer to your first question is simple. Again, this was the slide that Dr. McLeod presented. If you are giving multiple severely myelosuppressive agents, then there's no question that it will be much harder to pinpoint the 6-MP. Unquestionably.

For COG, though -- and this was actually one of the slides that I put up -- the delayed intensification and reinduction phases use TG, and again, there is less of an influence of TPMT activity on thio nucleotide concentrations following the administration of oral thioguanine. So even for the high-risk patients, the schema that I supplied is valid.

What I thought you were going to say is what about the kids with T-cell disease because for the T-cell patients, where the protocol is still in construction phase, if we adopt a Dana Farber-like regimen where anthracycline is delivered concomitantly with 6-MP, then it becomes a bigger issue. The number of children is much smaller. So again, the arguments about testing prospectively I think are still somewhat strained.

DR. SANTANA: Dr. Boyett, I think you had a question.

DR. BOYETT: In several of the presentations, yours included, I guess I'm a bit troubled by continued emphasis on secondary tumors because having been involved in a number of these investigations, it's unclear to me that we truly understand the interactions with the drugs or timing or schedules, et cetera that lead to those. In fact, nobody has mentioned the paper that Dr. Relling and I just published in Blood that shows in the Total XIIIA and B

trial that associates the exposure to irradiation and exposure to G-CSF with developing secondary AMLs.

DR. WINICK: I actually agree with what you said. I tried to make that point, that the study that stands out as most disturbing to me is the Nordic trial because in the two papers from St. Jude describing second malignancies, in one there was clearly an interaction between thioguanine nucleotide concentrations, TPMT activity, and radiation. And in the other paper from St. Jude, there was a trend that was not statistically significant describing an AML in patients who also received etoposide. Second malignancies are clearly multifactorial.

The Nordic trial stands out in not containing obvious, known -- and there's a great deal that's not known -- agents that lead to secondary AML. I wish that paper included the cytogenetics of those cases or a more detailed description of those cases. I'm afraid it didn't, so it's impossible to tell.

DR. BOYETT: Did it include irradiation?

DR. WINICK: No. I take it back. There were a trivial number of patients who had CNS disease at presentation, but that doesn't count.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: Naomi, just a couple of points. One, you made the statement that the first time children

with ALL are really exposed to 6-MP is in maintenance, but in fact there are two periods prior, or at least one period, of interim maintenance before standard maintenance for all risk groups of patients.

DR. WINICK: You are correct, but as in maintenance therapy, interim maintenance does not include anthracycline, does not include cyclophosphamide, does not include other agents that are significantly myelosuppressive. So I still believe that a clinician is likely to be able to identify the cause.

DR. REAMAN: Right. That's the point I'm trying to make. You could actually look in interim maintenance.

The other is that I'm questioning the statement about the unique association of 6-MP administration during cranial radiation in the St. Jude experience because that was clearly the regimen that has been utilized in multiple series of CCG trials years ago when cranial radiation was administered during consolidation. There was daily oral 6-MP in large numbers of patients.

DR. WINICK: Then I owe you an apology. When I went back, it looked like dominantly the drugs delivered during radiation were vincristine and prednisone.

DR. REAMAN: It was 6-MP daily and then vincristine once a week.

DR. WINICK: Okay.

DR. SANTANA: I think we're going to take a break and we'll come back because I think we have plenty of time for discussion. So with everybody's agreement, can we reconvene in 10 minutes so we don't fall too far behind? Thank you.

(Recess.)

DR. SANTANA: Let's go ahead and get started.

We now have an opportunity for an open public hearing session, if there is anybody in the audience who wishes to address the committee. In the interest of being fair, please state your name and your affiliation. If anybody in the audience wants to address the committee, this is the time to do so.

If there is nobody, we did receive a written comment that I am going to read into the record. We're going to have a period of discussion after the open public hearing session. We're going to have a general discussion.

Yes? Do you want to go to a microphone and state your name and affiliation?

DR. RUSSO: My name is Dr. Mark Russo. I am with GlaxoSmithKline. I would appreciate it if the committee could comment on some of the other agents that are also metabolized by TPMT and give us guidance on suggestions for label adjustments there as well.

DR. SANTANA: Mark, just for the sake of fairness, can you state any potential financial involvement or conflicts that you may have in relation to your question and comments?

DR. RUSSO: I am employed by GlaxoSmithKline. GlaxoSmithKline has in the past manufactured and distributed 6-MP, as well as 6-thioguanine and azathioprine.

DR. SANTANA: Thank you, Mark.

So the question that Mark wants us to address -- if you allow me, Mark, we'll try to put that on the docket for the general discussion that will follow in terms of if any of the participants want to comment on other specific guidelines of target drugs that may be involved in this pathway too.

I'm going to go ahead and then read the comments that we received in writing, and I'm going to read these for the issue of the public record. This is a memo sent to the committee by Dr. Peter Adamson who is the chair of the Developmental Therapeutics Committee of the Children's Oncology Group. It's dated Tuesday, July 15, 2003.

"Comments to the FDA Regarding Pharmacogenetic Testing for Thiopurines.

"It has been 50 years since Dr. Burchenal

published the initial experience with 6-MP in patients with leukemia in the journal Blood, subscript referenced, and thus perhaps it is fitting that a discussion on whether pharmacogenetic testing should now be incorporated into the Purinethol label is taking place. Many experts have presented this morning, so I will only briefly share my view of the potential risk and benefits of requiring pharmacogenetic testing when utilizing 6-MP in children with ALL.

"There is likely uniform agreement that the one subpopulation that will benefit from required pharmacogenetic testing are the 1 in 300 children who are homozygous for TPMT alleles that code for low TPMT enzymatic activity. Knowledge of their TPMT status would greatly diminish their risk of profound myelosuppression when treated with standard doses of 6-MP. However, for patients who are heterozygotes for TPMT alleles that code for low enzymatic activity, a priori knowledge of their genotype has not yet been demonstrated to either diminish the frequency of 6-MP induced myelosuppression or improve outcome. For children with wild-type TPMT alleles, knowledge of their genotype presents minimal to no potential for benefit, as within this largest subpopulation there is a high degree of intra- and inter-patient variability in 6-MP drug disposition and tolerance that

results from factors distinct from the phenotype.

"There are potential risks associated with a product label requiring TPMT genotype testing. The first risk may arise when there is a delay in administering maintenance chemotherapy while awaiting the results of genetic testing. In an ideal world such delays would not exist, yet there will undoubtedly be situations in which the realization that a patient's TPMT status is unknown arises only at the time 6-MP is to be prescribed. Delays in the administration of 6-MP and initiation of maintenance chemotherapy presents a risk to the entire population of children with leukemia.

"The second type of risk centers on the potential for misinterpretation of patients' genotypes. For example, patients who are heterozygotes could inappropriately receive inadequate doses of 6-MP, i.e., doses similar to those recommended for patients who are homozygous.

"6-MP has been routinely administered to children with ALL as the cornerstone of maintenance chemotherapy for more than 40 years, and despite our increase in knowledge, adjusting its dose based upon the WBC, white blood cell count, remains the standard of care. Encouraging determination of TPMT genotype may clearly benefit 1 in 300 children, and potentially augment the

management of patients who are heterozygous for these alleles. For the latter group, however, given the large overlap between the wild type and heterozygote populations in drug disposition and tolerance, the utility of a priori dose adjustment based on genotype remains an important research question, and should not yet be adopted as a standard of care."

I don't think we have any other public comments. So with that, we'll start our discussion of the presentations. Before we took our break, I think Nancy had a question she wanted to ask some of the presenters. Nancy?

MS. KEENE: I just had a couple of questions for Dr. Winick. One is could you tell me -- I don't know -- if there's any standard mechanism now within COG for children enrolled on protocols for ALL, a mechanism that's in place to manage risk for children who have just begun treatment with mercaptopurine? Is there any standardized way to respond to rapid onset of neutropenia? What's done in the group right now?

DR. WINICK: We have recently included I think a fairly detailed paragraph within the protocol -- within the open protocols and obviously, they'll be included in the protocols that have yet to open -- providing the information that's been presented here. So it states very

clearly that TPMT deficiency occurs in 1 in 300 children and it goes on and explains the fact that testing is available and that depending on the results of this testing and the child's degree of myelosuppression, that significant dose adjustments may be required.

The other thing to note is that all ALL protocols, without exception, have hopefully very clear instructions as to what to do in the face of myelosuppression. So step one is always if the absolute neutrophil count falls below whatever level is dictated by the protocol, all chemotherapy or all myelosuppressive chemotherapy is withheld immediately. And then there is an algorithm then. If the level falls to this point, then you may reinstitute therapy at full dose. If the level falls to this point but recovers within 7 days, reinstitute therapy at another level. So they're fairly detailed instructions because myelosuppression is the single biggest problem in association with ALL therapy, 6-MP being one of the players.

Did I answer your question?

MS. KEENE: Yes. So it's based on the absolute numbers and not the rapidity of the decline in the numbers.

DR. WINICK: It's based on the absolute number and not necessarily how quickly it falls because remember that, at least with respect to 6-MP, the vast majority is

delivered in the out-patient setting. So I wouldn't know if a child's neutrophil count fell 2 days after I gave him the drug or 7 days unless that child happened to get sick. So we don't have anything based on rapidity, but we have a great deal that describes how long it takes to recover because, again, several of the slides presented today demonstrated that in a child with TPMT deficiency, it's not only that their neutrophil count falls, but it stays down forever. So duration is addressed.

MS. KEENE: The paragraph that you first described, is that an addendum to the open protocols right now? Because I skimmed through this morning 1991 and didn't see anything on the topic.

DR. WINICK: I can't speak to 1991. Malcolm, do you want to?

MS. KEENE: I just skimmed.

DR. SMITH: Yes. I did a word search on TPMT, and the 1991 protocol does describe for ANC less than 500 -- so this would be during maintenance -- discontinue dose until ANC is greater than 1,000. Restart mercaptopurine at 50 percent of the original dose on the same day that counts recover, and then increase to 75 percent and 100 percent as tolerated. And then the instructions are for patients who cannot tolerate greater than or equal to 50 percent of mercaptopurine dose in maintenance, call Dr. Karen Lewing

in clinical pharmacology at Kansas City for determination of TPMT enzyme activity. That's in the 1991 study. 99-04.

DR. WINICK: 99-04 and 99-05 included a paragraph that's somewhat different in that investigators are not instructed to call a give person but since the testing is commercial available, they're instructed to do it.

DR. SANTANA: I'm going to take this opportunity to ask our European colleagues how do they address this issue in Europe in the ALL trials. So please feel free to comment.

DR. MORLAND: I think the approach is very similar to the current practice in the United States in terms of the guidelines and recommendations for dose alteration of 6-mercaptopurine. They're almost, if not word for word, probably very similar to those that Dr. Smith just expressed.

Within the UK, we're currently undertaking a prospective analysis of both phenotype and genotype in the current trial, which is actually due to close later this year, and to link that information with doses received and morbidity. So I think that over the course of the next year, once that data is analyzed, we'll have a lot more information on the true impact of this screening.

The one question I was going to ask is

throughout all of the presentations, the one piece of data that does seem to be lacking is the real morbidity associated with patients who have homozygous deficiency. There are clearly a number of ad hoc case reports in the literature, but I don't think I've yet got a feel for the true morbidity that these patients are experiencing. Clearly mortality doesn't seem to be an issue. We're very used to running patients on very low neutrophil counts in many solid tumor protocols without too much concern. I'm yet to be persuaded that the morbidity being experienced by these patients is any more significant than some of the more intensive solid tumor protocols that we currently expose patients to.

DR. SANTANA: Do any of the ALL doctors want to comment on that?

DR. WINICK: I think you're right. I think one of the comments that I made is that 6-MP is actually one of the more benign drugs that we use. Sue should comment on this, but when I think of what children with ALL go through compared to children with osteogenic sarcoma or neuroblastoma, there's no comparison. Most of these children have ANCs above 500 for the overwhelming majority of their therapy.

Sue?

DR. COHN: The only thing I was going to say is

that if you want to take a look at it the other way, you also have a very excellent prognosis for this group of patients. So the last thing you want to do is take somebody who's got this very excellent prognosis and potentially subject them to a toxicity that could, in fact, be life-threatening. But I agree. Certainly in my experience in most of these kids, the 6-MP is well tolerated.

DR. MORLAND: You could argue the same for patients with B-cell non-Hodgkin's lymphoma who have an excellent outcome who are exposed to extremely intensive, heavily myelosuppressive chemotherapy with huge morbidity. I just haven't got a feel for whether this is any worse than that.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: With regard to dose recommendation, I was wondering whether Naomi would comment on the recent research of the Scandinavian NOPHO ALL '92 study by Karl Schmiegelow. This study randomized classical controlled prospective adjustment of maintenance therapy versus pharmacokinetically guided adjustment on the basis of 6-thioguanine and methotrexate on erythrocytes, and they showed in this population that there was no difference in boys. However, in girls there was a higher risk in the groups of patients whose maintenance therapy was adjusted

on the basis of a pharmacologic setting. So would you comment on these because it seems it is important to consider it with regard to the recommendation that should be done for these patients and their maintenance therapy?

DR. WINICK: I'm happy to. Dr. Weinshilboum, do you want to comment first?

DR. WEINSHILBOUM: Go ahead.

DR. WINICK: I think it's one of the saddest papers that I've read because one would hope that when you make the effort to use pharmacologic dose adjustment, the outcome would be better. It's just tragically sad.

However, given that reality, I think that in their discussion they really do a very nice job of explaining what all of us have made reference to, that this is a multifactorial process. One of the comments they make that I thought was interesting was they talk about perhaps the higher TGN levels in the girls led to more immunosuppression and that then the host versus leukemia was less effect than in the patients with lower TGN levels. I don't know if there's any data to support that, but I thought it was an interesting comment. I think that it just proves that there's a great deal that we don't know about what it means.

The other thing that Mary and Bill published that I thought was a gorgeous paper is that 6-MP unlike 6-

TG is methylated to a significant extent, and many people, I think, assume that the methylated product is trash, but in actuality there's nothing to say -- in fact, there's a great deal to say -- that if the methylated product decreases de novo purine synthesis by means of feedback inhibition, it is entirely possible that the methylated product, which would have gone down in those girls because they increased the TGN concentration, is more important than we realize.

DR. WEINSHILBOUM: I think that that's an important issue. In the original NOPHO trial that you referred to, the methylated mercaptopurines were also followed, and clearly there was some indication in some patients that they contributed to the therapeutic effect so that the situation is clearly going to be a bit more complicated than just 6-thioguanine nucleotides. Please don't tell Lynne Lennard I said that, but it will go beyond that.

With regard to your question about the morbidity, obviously my experience as an internist who is called in from a biochemical/molecular perspective, but as a physician, it's going to be anecdotal. The morbidity can be quite striking in that without divulging any patient information in this HIPAA age, I will tell you that some of these children are hospitalized for months in referral

centers. These are the homozygous low individuals. So the degree of toxicity which these children can have -- and once again, I'm only called in when there is a train wreck -- can be quite striking.

My initial comments during my presentation were not entirely facetious when I said that as a non-pediatric hematologist/oncologist, but an internist, this is an interesting cross-cultural experience because I heard Naomi say, well, for the homozygous low individuals, this doesn't explain everything. I've been in medicine for 30 years and nothing explains everything in medicine. So, with all due respect, Naomi, that's hardly an argument for not taking advantage of new information as it comes along.

DR. WINICK: And I wasn't --

DR. WEINSHILBOUM: No, no, no. I know, but I heard what you said too.

Having said that, also as someone who works in a cardiovascular arena, I guess I would generally before I prescribed digitalis, measure the serum potassium rather than administering the digitalis and letting the patient develop PAT with 2 to 1 block. That seems a rather arcane way to diagnose hypokalemia.

I understand that culturally in oncology -- and my daughter has explained this to me in words of one syllable that even an internist can understand -- that you

manage toxicity and that this is a part of what goes on. I guess I would say that in some arenas, whatever limited knowledge we have to avoid toxicity might also come into play.

I want to thank all of you. This has been a fascinating experience for me.

DR. SANTANA: Dr. Boos, you had a comment.

DR. BOOS: Yes, a comment on the morbidity question because I think this may be a little bit misleading. It's a significant difference if we have to take morbidity into account because we have to apply a clinical protocol with some expectation of survival or if we can avoid this toxicity. And the question is can we really avoid it.

My feeling is that for the homozygous, the positive predictive value seems to be roughly 100 percent, and this in a 1 to 200 relationship is for preventive medicine aspects extremely good. But the negative predictive value has never been addressed yet today, and I have several patients in my memory where we had extreme toxicity and investigated, all the genomic people of us, and nothing was positive. And we had this toxicity and I think those were the 5-10 last patients. Nobody had TPMT.

In Germany we have, as in England, prospective evaluation of genome and phenotyping for TPMT, and the

results compare I think. In roughly 1,000 patients now, there have been 4 identified.

We had patients where the white blood cell counts didn't drop anyway. They stayed with 6,000, 7,000, 8,000 neutrophils during maintenance therapy, and we sent in these TPMTs and everything was normal. The highest thiopurine level is intracellular. So I think we should have a little bit of focus on the other side. What do we oversee? What about the sensitivity of these assays and on the negative predictive value because the danger to feel safe and not to be safe may be relevant.

DR. SANTANA: Dr. Riccardi.

DR. RICCARDI: First, a general comment. It seems strange that we start with a discussion on the label because we never read the label.

(Laughter.)

DR. RICCARDI: We know what we are doing. At least we should.

The second point. I use 6-MP as an example teaching to the students in pediatric oncology, as an example of variability, other factors like food or what type of food or when you are taking the drug. So it's really an example in which we are used to looking at white cells as a very useful test.

The last point I want to make is I understand

all these aspects are very important, but in Italy we have probably two cases a year of such a situation. Also in view of international cooperation, I think we should avoid going toward tests that are so specific and that are so expensive and also could cause, as was said before, some delay and also some fear from the parents in the situation in which you have a heterozygote situation.

DR. SANTANA: Dr. McLeod, you had a comment.

DR. McLEOD: Well, that was a long time ago.

(Laughter.)

DR. McLEOD: I think the fears that you identified are not real. Patients fear neutropenia more than they fear pharmacogenetic testing. I think one of the things that we -- and I do mean "we" not just everyone but me -- are having a hard time getting our head around is a new way of looking at practicing medicine. I agree with the comment that was made at this end of the table that in the context of diseases where there is not a good outcome, it really doesn't matter in some ways because we just try to do the best we can. In the context of patients where we can do well, we need to try to optimize things. I think this acceptance of we can manage toxicity has to be removed out of our thinking. It has served us very well to this day and will continue to serve us well until we can do better. But when we have an example of where we can avoid

a problem, then I think we need to think about using it.

Now, I agree with the numbers problem. If it's only 1 in 200 to 1 in 300, then we have to see whether that's cost effective, and no one has addressed the cost issue today.

But there's a fundamental issue because really what we're talking about here is not is TPMT testing good for childhood ALL, but is TPMT testing good for thiopurines. Where people get in trouble is not just in the context of childhood ALL therapy where all of you are very good at managing therapy. It's the -- I forget the term you used, Dick, but the poor internist, or whatever the term you used, who is not used to managing, and when a patient gets a white count of 3,000, they start panicking and want to admit them. You would love a white count of 3,000 in most of your patients. You would be treating them right away, probably high dose. So that's kind of the secret behind the door that we haven't really talked about yet that's on the agenda, the implication that it's not just for childhood ALL, but beyond.

But I wanted to make the point that for the next few years people are going to be treating childhood ALL the way they've been treating it for quite a while. Look at those curves Naomi showed. It's wonderful progress.

DR. SANTANA: Steve, I think you have a point you want to raise.

DR. HIRSCHFELD: I want to clarify, with all due respect. The issue is what the product label says, which is acute lymphocytic leukemia, and it's come before the Pediatric Subcommittee because the focus is on children with ALL, and we cannot be addressing the off-label uses or can we address other drugs of a similar molecular structure or similar metabolic pathways.

Which leads me to one question, and I will direct this to Drs. McLeod or Weinshilboum. Has the natural substrate ever been identified for this enzyme, or as far as we know, it exists only to torture people who are getting drugs?

DR. McLEOD: Dick, shall we say no in tandem? As far as I know, there is a natural substrate for TPMT. It's clear from the uremic patients and from other similar situations that there is something that interacts with the enzyme, but I am not aware of anyone having identified what it is yet.

DR. WEINSHILBOUM: That was the study we published years ago where in the plasma of patients with renal failure, a methyl acceptor substrate or substrates accumulate. This enzyme is very widely expressed in a variety of tissues, but if God gave it to us, as Gertrude

Elion would say, to deal with some known substrate, she is the only one who knows the secret because we don't know.

DR. SANTANA: Nancy, I think you had a comment.

MS. KEENE: I have several. I'm here to speak for the children and their families, and I want to bring up a couple of points.

First of all, the economics has been alluded to a couple of times, but not explored. One of the speakers talked about the large amounts of resources that are absorbed by the homozygous kids, and one thing we haven't addressed is the relative amount of resources that are absorbed by the heterozygous kids who have multiple episodes of neutropenia.

I'm probably the only person sitting at the table whose child was a survivor of ALL and was treated with this drug. After reading the literature, I think she was heterozygous. It was a horrific experience to live through and one I hope none of you ever have to experience. When you go in weekly for blood tests and the medications are being adjusted on a weekly basis, when you have a child who has got an absolute neutrophil count of 0 multiple times throughout treatment, and the child was hospitalized many times for treatment, we're going back to economics now and not the psychological impact, but that's absorbing a huge amount of resources. If these children can be tested

for $100 each, and we're talking about 2,500 kids, if someone worked out the economics of it, it probably would be a lot cheaper to test them. That's one issue.

The other is I always am uncomfortable when people compare morbidity and say one thing is not quite as bad as something else. I mean, to compare the leukemia kids to the sarcoma kids and say, well, it's not quite as bad is doing a disservice to what we really should be doing in medicine. In medicine we should be treating that disease the best way that we can, and if we have something that can be prevented rather than managed, I think we have a moral responsibility to do that.

Also, I find it a peculiar argument to say that the two reasons that were put forth by the written comments and also by one of the presenters for not knowing this information is because inexperienced doctors will overreact and under-treat the child and also that delays in treatment because someone didn't do what they were supposed to do at the time, which is send the blood ahead of the time when maintenance would begin to start so you would have the information you need in order to begin treatment for that child at the appropriate time, that is not a very good argument. Do people make mistakes? Yes. We're human beings. We make mistakes. But what we should do is institutionalize methods so that these mistakes will be

minimized rather than using them as an excuse for not knowing the information. I think those are two pretty bad arguments that don't sway me.

I'm going to wrap up. I'll probably say something else later because this is pretty close to my heart, but I would argue for putting on the label -- we'll get back to this, Steven, after listening to all the arguments. I think that frequency should be on the label. I think physicians should know what percentage of children diagnosed with ALL are homozygous and which ones are heterozygous, and I think that diagnostics are available in order to evaluate this. It should be on the label so people know and it won't be just people in this room or a small other cadre of people in the community who know that. Whether or not appropriate doses should be included, it doesn't sound like we have enough information at this time.

But I'm also interested to know if COG has planned any prospective studies like our colleagues in the United Kingdom have so we'll really have more information to go on from a larger data set sometime soon.

DR. SANTANA: I think Dr. Reaman had his hand up, but before I give him the microphone, I do want to make one clarification in terms of the issue of timing of testing. We're really talking about two different sets of testing. The genotypic testing can be done at any time

point in the therapy of the patient. The phenotypic testing has to be contingent upon the patient getting the drug and then measuring the effect in terms of the phenotype, if you're measuring 6-TG levels, thiopurine levels. So the issue of the a priori testing is going to be a little bit different for both of those scenarios. I just want to clarify that for the record.

Greg?

DR. REAMAN: Well, I was just going to address the fact that we have come to the point where we are in pediatric oncology because of evidence-based medicine. I'm not sure that making decisions based on testing for thiopurine methyltransferase ahead of time, that we're at that point right now. I would agree with you that doing a prospective evaluation is something that should be considered within the context of COG ALL trials, however.

MS. KEENE: Is that in process now at all?

DR. REAMAN: It's not in process now. It's not in process now because of limited resources. There are only so many questions that we can afford to ask, and there aren't laboratories that are chomping at the bit to get 1,200 samples a year for some of the testing. But in reality, I think it's something that we should explore.

DR. SANTANA: Jody?

DR. PELUSI: When I was thinking about this

topic, I was trying to think of any other deficiencies that we see and how we label that. The only one that came to mind to me, again being from the adult population, is DPD deficiency in 5-FU, and although there's not a commercial test out there, although you can get it done, it's not easy to do. The question becomes looking and trying to balance looking at clinically how we manage patients as well as if we had that, would it be good. So, again, when we look at this and I think about that other population, I go back and I say, well, what's really in the label. And the label does say that it exists and what to look for.

When you begin to look at this particular topic as well and saying that maintenance and looking at how the counts should be monitored and stuff, I think again people need to know that they do have choices. I think that that's where it comes into play, this whole issue of informed providers, informed consumers, and letting everybody know that there is an option out there if, indeed, it needs to be done.

I have to say that I really like this algorithm that Naomi presented in terms of you can have a choice in the very beginning if you want the testing done or not, but at the same time, because of the numbers being so small, the question is, is the first sign of the myelosuppression in an abnormal kind of situation -- is it then perhaps a

way to go and it's a known way that that is the next step in looking at it. So that's kind of what I'm leaning towards at the time. I realize, being someone who cares for the symptoms and being the one called in for all the symptoms, they are not benign by any means. But again, the numbers -- it's hard to balance.

So I think we're looking at how we do it with DPD deficiency and monitoring as well gives us that option. At least you have a test that is available for us.

DR. SANTANA: Dr. Weiner?

DR. WEINER: I have a technical question actually. Sort of two.

One is, how standard is the test itself, and how does that get evaluated independently of its application?

And second of all, it seems to me that regardless of the status of the test, if something is warranted in the label that has to do with the population that should be treated, the label doesn't necessarily need to refer to the specific test. Those are just sort of technicalities to clarify a little bit more of what we're talking about.

DR. SANTANA: I want to invite Howard or others to comment on this issue of the standardization of testing and how far we are in that that we feel comfortable with

it.

DR. McLEOD: There are three different types of tests that are out there, as I mentioned and others mentioned as well, measuring TPMT activity in red cells, measuring the active metabolites, the thioguanine nucleotides in red cells, and then measuring the polymorphisms that have been shown to be responsible for low enzyme activity using a DNA-based test, a polymerase chain reaction followed by various detection methods.

The assays that are out there that are available for clinical use have had to be certified in two different contexts. One is they have to be approved under CLIA guidelines which define a level of robustness in terms of reproducibility and accuracy of the test itself, not the relationship between the result and a phenotype, but actually the test itself.

I think all of these tests are also performed in facilities that are monitored by CAP. What is it? The College of American Pathologists? The American pathology society, CAP, which evaluates them in terms of their documentation, in terms of the controls that they use for the assay, and looks at basic levels of quality assurance and quality control for the tests. So the commercially available tests have that level of rigor.

The DNA-based tests that are out there have a

very low error rate, and the tests that have been performed to date in that context are virtually 100 percent predictive, as close as you can be to 100 percent, for saying if there is a mutation, they find it and vice versa, for the particular polymorphisms they're looking for.

Now, I mentioned the caveat that there are polymorphisms that are unique to different families that will be missed, but in terms of the accuracy of the test, it's between 99.9 and 100 percent and the results have been published to date.

DR. WEINER: So what is the FDA's role in those tests? You made reference to the literature.

DR. HIRSCHFELD: I was just going to ask for a point of clarification. We don't address in this committee economics. So whether the test costs 75 cents or $1 million, that's not an issue. We deal on whatever the evidence is for any issue.

But could you just clarify for us which of these tests are commercially available, which are research tests? There are some tests which pass through the FDA through the Center for Devices and the data are reviewed and they become what's called an FDA-approved test. Could you tell us how many of these tests are FDA-approved?

DR. McLEOD: It's my understanding that none of the tests that we're talking about have passed through the

FDA's devices committees and are FDA-approved. Now, someone may be able to comment further on that, but that is my understanding currently. The tests that are out there -- what was the other part, the first part of your question?

DR. HIRSCHFELD: You mentioned that some of the tests were commercially available. Could you mention which of the tests, in particular if any of the genotype tests are commercially available?

DR. McLEOD: Yes. All three of those areas have commercially available tests. The genotype assays are available through at least two national organizations, one that is based on the west coast, and I believe Mayo Central Labs, which is an affiliate of the Mayo Clinic, also offers that testing. Then there are other laboratories that offer it as an in-house, so-called "home brew" test within their institution, but not available more widespread. But as far as I know, there are only two companies that are offering TPMT genotype analysis nationally.

DR. HIRSCHFELD: Just one final point. Have there been comparisons where the same samples have been sent to different commercial labs to see if the same results come out from these different commercial labs?

DR. McLEOD: I am not aware if that has been performed. It certainly has been performed between

academic labs, but in the context of clinical testing, I do not know the answer to that.

DR. SANTANA: I'm not an expert in clinical labs, but its my understanding that part of the quality control of clinical labs is that periodically there are samples shared unknowingly between different labs and then that becomes part of your quality institution performance. I don't know if it's specifically done for this test, but if they are commercially available, if I understand you correctly, that must be a part of that process.

DR. HIRSCHFELD: I just didn't want us to assume, and I wanted to know if there were data that told us that one way or another.

DR. SANTANA: If the tests are approved by CLIA, that is a process that approves automatically periodically. But Dr. Lesko and others may want to comment.

DR. LESKO: I'll just comment on what I know about one of the commercial laboratories which is on the west coast. They have transferred their technology to the east coast and have done comparative laboratory assessments of samples to confirm that the same results were coming out of each site.

DR. SANTANA: Is it a commercial test?

DR. LESKO: It's a commercial test. It's

commercially available.

Also, just to go beyond that -- and I'm not sure how this works exactly, but there are two well-known commercial laboratories that offer this test, but if you look on the internet for testing, there are other laboratories that advertise it, the major clinical laboratories, and whether they do it in house, for example, a Quest Lab or something like that, or they send it to these two major labs I'm not sure. But there are many other commercial places you can go to get this sample done with a tube of blood.

DR. SANTANA: For the purpose of clarification, what tests are you referring to that are commercially available?

DR. LESKO: I'm referring to the genotype as well as the phenotype test that we've been talking about. I think both of the labs that offer this test do both on the same sample either routinely or if requested.

DR. McLEOD: I made the discernment between home brews and the national labs because there are a limited number of labs that actually are licensed to do the testing and a lot of others that supply it by other means. That's why I mentioned there are just a couple that are available. Many institutions do the testing internally but are not licensed to offer it outside their institution.

DR. SANTANA: Dr. Shurin, you had a comment?

DR. SHURIN: I think this is probably the first of what's going to be a series of discussions about how we're going to incorporate pharmacogenomics, and I think it's important that we address this in a reasonably systematic and appropriate fashion. I lived through two instances in recent years in which we've introduced tests without knowing what to do with the answers, and I have to say that I didn't find that to be a pleasant experience with either the HIV testing or more recently with the PSA testing. It creates considerable amount of anxiety.

In reading over the background material here, it wasn't at all clear to me that we know how to dose people who are deficient in this enzyme. So what we're looking at is mandating a test with which we don't what to do with the result, and that's concerning to me.

I'm delighted at the group that's been brought together because I think both the involvement of our European colleagues and the fact that Greg Reaman is head of COG and Malcolm Smith and Barry Anderson is important. We certainly have several ways we can go about this. What we've clearly identified is that this an important problem and we need to do something. Then I guess the question is what do we do. We can impose some guidelines. We can impose regulations or we can really mandate and make a

legal requirement.

I would wonder if in this specific indication, which is lymphocytic leukemia, for which the overwhelming majority of the children not only in this country but worldwide are treated on protocols, if the more appropriate way to respond to this isn't to try to move the priorities up so that we actually answer the question in a scientific way and have some idea of what to do with the answer, that that might not be a much better approach both for the children who have these deficiencies and for the children who don't whose care won't be compromised by sort of, gee, I can't give 6-MP because I don't know the result of this test that I've treated hundreds of other children without knowing the result of the test. That might be a much more reasonable approach. It might result in having a much clearer answer much more quickly and actually protect the patients better.

DR. SANTANA: Dr. Morland?

DR. MORLAND: Just to reinforce that really in the spirit of international collaboration that we've all been talking about. I think it's vital that any scientific approaches that are made with regard to future research is done on a truly internationally collaborative basis. Sure, COG may want to develop a prospective study, but actually just duplicating studies which have been performed

elsewhere is not going to help anyone. So I think there is a real enthusiasm for doing international research and clearly there is already a field of expertise, both here in the States and in Europe, that should be tapped into to design some more prospective data capture to start addressing some of these key issues. So I think just a plea that we all work together rather than doing our own individual things.

DR. WINICK: Can I make a comment, Victor?

DR. SANTANA: Yes, Naomi.

DR. WINICK: Just to address Nancy's concerns. I don't think that anyone in this room is against testing. This has nothing to do with that. It's just a question of whether or not you mandate it prospectively or not. I think that Susan's statements and Dr. Morland's were extremely well made. We don't want to mandate a test for which we don't know what to do with the results, and what we don't want to do, especially for children who are heterozygous who are going to be obviously larger in number than homozygotes, we don't want to have investigators lowering the dose and potentially increasing the likelihood that that child's leukemia will recur in the absence of solid data defending that practice. So no one is against the test. No one wants to have children suffering needlessly. The question is just when do you do the test.

DR. SANTANA: Dr. Smith?

DR. SMITH: There are two points of information that I think are critical for the committee and for FDA to consider. One is the point that was raised earlier about what is the morbidity. The algorithm that Naomi described that came from Mary Relling -- if you followed that algorithm and what's the morbidity, if it's 4 months in the hospital and it's a substantial proportion of kids with terrible toxicity, then that changes the equation. If it's neutropenia that resolves when you stop the drug and you do the test and you appropriately dose thereafter, then it's a different situation. So it would be very helpful, if those data exist, to try to get a better handle on what the morbidity is when the homozygotes are treated in a manner similar to the algorithm that's been described.

The other question relates to what Susan was saying. Do we have any information about benefit to heterozygotes from doing the testing? If there is no benefit that we can define for testing heterozygotes, then whatever testing or labeling that's done we'd have to be very clear about. These results just don't apply to heterozygotes, so don't even think about using these data to base your dosing for heterozygous individuals. So that's additional information that's needed. How would we use that information? What are the data that we could

build upon to use information about how to dose heterozygotes?

DR. SANTANA: Yes, David.

DR. POPLACK: I'd just like to follow up in support of Malcolm's comments and Susan's. I think clearly we have new information and all the information you suggest about the phenotype and the genotype and percentages of population who may be at risk. All of the relevant information needs to be included in the label.

But I have significant concerns about the heterozygotes as well, and I think that the likelihood is that given our lack of evidence-based information about this population, that there's more potential for a risk to this group of under-treatment by having a result that indicates that someone is a heterozygote. I think before we go down that slippery slope, we need to have more data and more information and studies of that population.

The other point I'd like to make just generically about this drug is that if you had to identify a drug in usage in oncology that is least appropriate for therapeutic drug monitoring, it's probably 6-mercaptopurine because of the tremendous variability between patients and within patients, et cetera. So it is an illusion, to some extent, that we have the type of control of a dosing and what our dosing modifications do in individual patients. I

think we need to keep that in mind.

Finally, however, I also believe we need to further study this in other populations. I don't know. I was asking Howard about what do we know about this, for example, within the Hispanic population. How prevalent are the various permutations and combinations? I think we treat all kinds of people with these agents and we have a responsibility to everyone in this country. I think prospectively we need to do those types of studies as well.

DR. SANTANA: Dr. Reynolds and then Dr. Reaman.

DR. REYNOLDS: We've heard a recurring theme here and that's the concern that if we mandate some testing, that it's going to impact on the heterozygotes, which I think we don't see a lot of clear-cut data as to what one can do with those. That's the reason why I raised earlier on the question about 13-cis retinoic acid and mandated tests. I think we need to recognize that if a test is mandated on a label, it's going to get broadly applied, and once you do that, going backwards is very difficult. It's much easier to go forward incrementally than it is to go forward in a big step and then try and take two steps backwards. So I just want us to think about the implications of that if we consider mandating anything.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: I'm struck by the concern about

the heterozygotes. Even though the homozygotes may be a population for whom there is a definite benefit by testing, I'm not aware that there are specific instructions in the label for how the dose should be modified. So we've heard some criticism about how as pediatric oncologists, we have modified dose based on toxicity. For the two homozygote patients that I've managed, basically we came upon a dose by trial and error, eventually maintaining their absolute neutrophil count somewhere between 1,000 and 1,500. So we're never really going to get beyond what might be considered the realm of the mundane practitioner.

And I would certainly agree that we should take every opportunity to investigate this and to investigate this at an international level and address differences in populations.

DR. WINICK: Dr. Morland, could you review once more for us the studies that you referred to that are ongoing in the UK?

DR. MORLAND: I can't give you any data, but the studies that have been undertaken were at the launch of the most recent MRC sponsored leukemia trial, which is 97. An attempt has been made to obtain samples from all patients entered into that study both for genotyping and phenotyping, analyzed centrally at the reference laboratory in Sheffield. So linked with those studies is obviously

the ability to then look at what dose manipulation has been done for patients with 6-mercaptopurine.

DR. WINICK: I just asked if they were recommending a specific --

DR. MORLAND: No. There are no recommendations being made on the analysis. In fact, I think the analysis is still blinded to the physicians who have been treating patients.

DR. SANTANA: Dr. Boos?

DR. BOOS: This is a bit different in Germany where the homozygous results will be told to the departments and the dose will then start with roughly 10 percent.

DR. SANTANA: But that's arbitrarily decided, or is that protocol-mandated?

DR. BOOS: No. It's not protocol-mandated.

DR. SANTANA: Dr. Williams.

DR. WILLIAMS: Several of you have mentioned opposition to mandating something in the labeling, and it wasn't really clear to me exactly what you were talking about. You could be saying don't put it in the labeling because people may consider you have to do it, or you could be saying that it's mandated as part of the dosage and administration, or it could be one of these programs where you can't get the drug unless you do it. You are opposed

to mandating, but it wasn't clear to me what that meant.

DR. SANTANA: My interpretation of that -- and I certainly didn't make those statements -- is that the label specifically says if you use this drug, you should do this test. That was my interpretation of the concept of mandating.

DR. LESKO: Just to go a step further, that wasn't taking into account putting information in the label that would be more informative. That's different than what you're talking about.

DR. SANTANA: That's different.

DR. REYNOLDS: Just to address that, what I was thinking about was the "no blood, no drug" concept. Providing information is a whole different kettle of fish.

DR. SANTANA: I think with that I do want to go ahead and start addressing the questions. There's a long introductory, very well detailed page to the questions to the committee. I'm not going to read that. If Dr. Hirschfeld and Dr. Williams allow me, I'm going to start with page 2 in which there are specifically some comments that we want to address. So I'll start with page 2.

It says, what additional information should be included in the product label with regard to TPMT metabolic activity and the potential for exposure to excessive bone marrow toxicity in pediatric patients with acute

lymphoblastic leukemia? And they're proposing four potential pieces of information. Am I correct, Steve?

DR. HIRSCHFELD: I don't want to say that we are proposing. We just put as suggestions as to the kind of information that you might want to include, and those statements aren't necessarily mutually exclusive, nor do any of them have to be included. It was just to give you a framework to try to answer the question. There are really only two questions, the one you just articulated and the next one. Your recommendations do not have to necessarily include any of the language that's proposed.

DR. SANTANA: So, thanks for clarifying that. So in regards to additional information, one of the points that may be considered is adding information on the prevalence of pediatric patients in the general population that have little or no activity or reduced activity. So that information, it's my understanding from the presentations and from what I know in the literature, is fairly well established, that we do have some prevalence rates, obviously not studied in 10,000 patients, but some indication of what this number potentially could be.

Malcolm?

DR. SMITH: Is the data about ethnic variation enough that you would want to say that persons of Chinese descent have a lower rate of this abnormality?

DR. SANTANA: Howard, do you want to try to address that?

DR. McLEOD: There is clear data that the frequency of the three mutations is different between different ethnic groups when studied in situ, as in in their continent of origin. When we get to the United States, none of us are homogeneous. I have a Scottish surname but I'm equally Irish, German, and mutt. So it starts getting more confusing when you actually get into the American population where someone may identify themselves as being Indian but have equal amounts of various others. It's especially important in the African American population where they certainly have a predominance of the allele that's more common in continental Africa but also have alleles that are seen in other geographic populations. So indicating that there are ethnic differences may be appropriate but defining them explicitly would be, I think, a hard thing to do currently.

DR. SANTANA: Any other comments?

(No response.)

DR. SANTANA: So I sense that the committee has some agreement that there should be some information about prevalence with the caveat that that is obviously linked to ethnic subgroups for which we currently don't have a body of information. Does everybody agree with that summary?

Okay.

Let's try to tackle number 2. An additional statement in the warning section that children with hereditary deficiency may be unusually sensitive to the myelosuppressive effects of 6-MP and at greater risk of toxicity.

DR. HIRSCHFELD: Just to clarify, the current statement says there are individuals. It doesn't say children. It says there are individuals with inherent deficiency of the enzyme thiopurine methyltransferase who may be unusually sensitive to the myelosuppressive effect of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment.

DR. SANTANA: So really, the difference between the two statements is one of the population. In the current warning label, it's a general statement on patients. Here it refers specifically to children. Did I pick that up correctly?

DR. HIRSCHFELD: Right.

DR. SANTANA: And hereditary. The label already says hereditary? So the distinction here is children versus what is currently in the label?

DR. HIRSCHFELD: I'll ask Dr. Lesko to comment here.

DR. LESKO: It seems a bit redundant from

what's currently in the label to what's put here, and I wonder in retrospect if the committee might consider that statement in the dosage section. In other words, labels can have redundant information if it's deemed pertinent to the safe and effective use of the drug, and would something like this statement be reiterated in the dosage section just as a reminder to the prescriber that this information is important to be aware of.

DR. SANTANA: So not to supersede the current statement that's in the warning section.

DR. LESKO: Right. I don't see it as a superseding thing because it's not that different. But we do have labels where information is placed in several sections of the label if it's considered important enough to the reader of the label.

DR. SANTANA: Can the FDA give us any advice on this issue of where statements go in the label?

DR. WILLIAMS: I would think the closer you put it to the dosage section, the closer you are to making an inference that they should adjust the dose based on that. I think we'd have to think closely about that. Certainly if everybody felt strongly that we could adjust dosing, then it would go right in there as a part of how to dose. Certainly we could edit the other statement where it is.

DR. SANTANA: The recommendations of dose

adjustment are under number 4. We'll get to that in a minute.

Any other comments on this statement? Malcolm?

DR. SMITH: Is the intent here to describe the unusual severe sensitivity in the homozygous group or to include the moderately sensitive heterozygous group?

DR. SANTANA: It's a good point because this could be interpreted both for the homozygous and the heterozygous, and we could spend a few minutes discussing how there's lack of data in that subgroup to make any type of definitive statement. So I think we better be careful with that word "hereditary" to what we're specifically referring to, if we're encompassing both or selecting one versus the other.

DR. SMITH: That could be addressed by hereditary complete or near complete deficiency.

DR. WILLIAMS: And it could be fleshed out a bit to give a little more of the quantitation associated with the homozygote versus the heterozygote so that people didn't take an inappropriate action.

DR. SANTANA: Greg, you had a comment.

DR. REAMAN: I just have a question about the word "hereditary" which implies direct inheritance, but do we have family studies on all of these?

DR. WEINSHILBOUM: Yes. The answer is yes.

DR. SANTANA: So it's truly hereditary.

DR. WEINSHILBOUM: That's what I meant when I referred to Mendel.

DR. HIRSCHFELD: Maybe if we substitute the word "homozygous" for "hereditary" in that sentence, it would be more descriptive of the situation.

DR. SANTANA: That was going to be my comment. I think we do have enough evidence that it's a strong statement that those patients are truly very sensitive to the myelosuppressive effects. I think practicing physicians do know what a homozygote is.

DR. WILLIAMS: I would think we would need to think carefully about the wording because clearly it's true for the heterozygotes too. What I can tell you want to make certain is that people don't walk away with a heterozygous and take an action. So maybe we can come up with some wording.

DR. SANTANA: Yes. That's the point of distinction I think we want to advise you on that you need to be careful with.

Any other comments? Howard.

DR. McLEOD: I kind of go back and forth on this but I think there is data saying that the heterozygotes do worse than the wild type patients. It's just that we don't believe it to the point where we want to

urge people to act on it. The worry is that we water it down to the point where people are no longer even informed, and our assumption is that the package insert will be sort of a role of informing the people that read it, agreeing with Professor Riccardi's comments, that at least it's there and if they didn't read it, that was their own fault. Professor Poplack is making the same comment that we need to inform. So by removing the heterozygous data altogether, it assumes that there's no literature suggesting that the heterozygotes are at risk, whereas there is literature. It's just that we don't believe it enough.

I think we can indicate that heterozygotes may be at risk. There is litigation going forward in that context. Whether they win or not is a different story. So we can't ignore it. We may not believe it, but we can't ignore it. I guess the point I want to make is that we need to make sure there's enough information in there so that people know that heterozygotes exist and they can choose to believe what they want as far as whether anything needs to be done about it.

DR. HIRSCHFELD: I just would want to clarify. The way the phrasing is now, it says "unusually sensitive." But what we're seeking is recommendations, and we'll do the wordsmithing. But we would just want to get a sense of

the overall thinking of the community here so that we can have some basis on which to proceed.

DR. WILLIAMS: Let me make a suggestion. In the first one, it's not necessarily a warning. If there is more information about some of the quantitation of the degree of myelosuppression but the lack of evidence that we know what to do with the heterozygotes and then the more severe and the homozygote. The warning could clearly relate to the homozygote perhaps. But providing more information and yet not leading one to the conclusion that you need to treat heterozygotes, do you think that would be a reasonable thing?

DR. SANTANA: Yes. I don't think we're here to write the label. That's not the exercise we're having, but I think the sense the committee is presenting to you is that somehow the public and the practicing physicians have to be conveyed the message that there is a body of evidence that is much stronger in one group than there is in the other. That message has to be transmitted in the statement. I can't write the statement for you, but hopefully you'll take that into account.

Dr. Boos and then Dr. Smith.

DR. BOOS: I wonder if it would be helpful in this section to point it out a little bit the other way around, to say even if the result is wild type, this does

not reduce the risk of toxicity for the patient because this is in the end the truth. And if there is anybody who thinks, okay, there is no pediatric formulation at all, therefore I don't want to break the tablets, and my patient is not at risk, or if there's one to say, okay, you are too far away from the hospital, I think it's enough to come in 3 weeks again because you are wild type, this is a risk we have to address.

DR. SANTANA: Oh, no. I interpreted this as a conditional statement, that if you have this deficiency, then you are likely to have these effects. It doesn't exclude that other people who don't have the deficiency may also have the toxic effects.

DR. BOOS: Yes, but this is one of the significant misunderstandings of statistics sometimes. If you say everybody can run into toxicity depending on the dose, and even the dose calculation, the bioavailability, the not-available pediatric formulation, all of these things make the dosage extremely variable. If up to 100 percent may have toxicity and only 3 percent are homozygotes, then you reduce the risk to run into toxicity roughly by 6 percent or 3 percent, and this should be noted here.

DR. SANTANA: If you turn to the first page of this document, do you think that message is covered under

the first point under the dosage section where it clearly tells you that you do have issues of toxicity and that you have to then dose based on that variable?

DR. BOOS: For me, all these phrases point out there is a specific risk and this can be identified. But the other way to see it is to think I'm not at risk, therefore I have no risk, and this is wrong and it's not pointed out here anywhere.

DR. SANTANA: Malcolm, did you have a comment?

DR. SMITH: It's not that we don't believe that there is an association between heterozygotes and increased myelosuppression. It's just that in terms of how you take that information and translate it into a starting dose, that's the association that we don't have. Whereas, for the homozygotes, I think everyone would agree there's a need for dose modification there.

DR. SANTANA: Yes, Howard.

DR. McLEOD: The same source for the heterozygous dosing recommendations is where we get our homozygous dosing recommendations except the number is even smaller. So there's the same problem. It's just that 100 percent so far of the homozygous deficient patients get into trouble, where it's only about 35 percent or so of the heterozygotes.

DR. SMITH: So over half tolerate the standard

dose no differently from the wild type population.

DR. McLEOD: Exactly.

Dr. Boos' point is illustrated in the paper that was included in tab 5 of our document. About 35 percent of the patients referred for TPMT testing with the TPMT-like scenario were wild type, backing up his point that there's a lot of the patients out there that have the extreme toxicity and don't have TPMT for the explanation. So the point you're making, that myelosuppression is not only caused by TPMT in the context of these kids.

DR. SANTANA: Hopefully the FDA can address that somewhere in the label in terms of the general statements.

Yes, Nancy.

MS. KEENE: One way to address that issue that you brought up is to say that there's significant variability across all three groups. Identify the groups, let people know they exist, and then say there's significant variability across all three.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: The existing label seems to address that under dosing. If you look at those two bullets, it says that it varies from patient to patient. As long as you don't qualify that by saying you've got to be homozygote or heterozygote, it says from patient to

patient.

DR. SANTANA: Let's move on to the third point, a statement that laboratory tests are available to determine TPMT status of pediatric patients, genotyping or phenotyping, and some information regarding the use of these tests.

I think the problem I have with this statement is, what is the "some information"? Obviously, it's a very open-ended statement. So maybe the committee can offer you some advice on that.

So I think the point is should there be a statement that there are laboratory tests available that could help you determine whether your patient is deficient or not, and then the second point is how that information can be used. Comments?

DR. POPLACK: I think the first point is fine. The second is --

DR. SANTANA: That's why I separated it.

(Laughter.)

DR. SANTANA: In my own mind, that's why I separated it.

Yes?

DR. LESKO: Just as a point of reference, the laboratories that offer this test do report out the specific alleles and what the alleles mean in terms of

enzyme activity. They don't report out what the physician ought to do with that result. One idea for the label might be to include what are we talking about in terms of a *3A or a *3B. That's what we actually measure in the laboratory, and then relate that to the phenotype in terms of TPMT activity. That's one example of what could be done here.

DR. SANTANA: I agree with David. In my own mind when I read this, I separated it into two parts, and personally I have no issue with the first statement. I think in the spirit of providing information, you should inform people that there are laboratory tests that can specifically measure this either phenotypically or genotypically.

I have a little bit more problem with how to use the information because I'm not sure that information is totally validated at present from what I heard in the earlier discussion.

Susan.

DR. SHURIN: One of the other things in the label, not in the paragraph that's given here, is that this should be used only by people who are experienced in treating leukemia, and if people who are treating leukemia don't know about this, I think it's a much bigger problem.

(Laughter.)

DR. SANTANA: Yes, but the problem the FDA has is that once a drug is out there with the label, it's up to the practicing physician to use that information so we can't tell them only practicing oncologists can do it. So although I share your concern and I agree with it --

DR. SHURIN: But it sort of says that already. It doesn't say practicing oncologists, but it says persons experienced in the use. I don't have it in front of me exactly what it is, but I remember noticing that was in the label and it seems to me that that's subsumed under that wording.

DR. SANTANA: Dr. Boos, you had a comment?

DR. BOOS: I'm not sure if it really helps, but I still have the comment because if we talk about heterozygotes and homozygotes, we talk about genotyping and not phenotyping. The problem with the phenotyping is that there is a continuous scale of results and then you need normal values for this, and the lab depends on the pre-analytical problems and things like this. It's my feeling this all should, with the current state of knowledge, be reduced to genotyping because then you have a clear-cut decision, is it homo or heterozygous.

DR. SANTANA: Is a way to address the issue from the FDA perspective that you make statements that laboratory tests are available but there's no contingency

in the label on how to interpret those tests? You leave that up to the reference labs and to the information that's available. Because that potentially could be a way of getting out of the latter part of the statement, that the label does say these tests are available, you can use them, but the label itself is not going to tell you how to interpret them. You have to do the cross-referencing to the current test that you're using. We're not recommending one test. There may be a number of tests, but those get cross-referenced to the specifics of that test in terms of how to interpret and use them.

DR. HIRSCHFELD: The short answer is that's a clear possibility.

DR. SANTANA: Because that would be what I would certainly encourage because I think Dr. Boos' comment is very real. Based on the different populations and the tests that are used, it may be difficult to interpret in subpopulations how to use that information.

DR. WILLIAMS: Perhaps Dr. Lesko can help us look into that, whether or not there's a way you can talk generally about genotypes and generally about phenotypes and come up with a concise, yet meaningful label.

DR. LESKO: Yes. I was just going through my mind of other labels that include genetic information and how we worded that. I think we need to go back and look at

that, whether we characterize a genotype by a well-known phenotype or specifically express the genotype information. So I think we need to look at some precedent for that on how to express that.

DR. HIRSCHFELD: I would just ask a clarification, Dr. Santana, and that is, if you could ask the committee to clarify whether the statement "genotyping or phenotyping tests are available," or whether there's a recommendation that the statement should only address the genotype testing.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: I vote for genotype testing.

DR. SANTANA: And why is that, Jim? Why do you specifically restrict it to that?

DR. BOYETT: Because I think, as Dr. Boos pointed out, it's more interpretable. You're not worried about variability. You know exactly what you've got when you've done it.

DR. SANTANA: Dr. Boos?

DR. BOOS: We didn't address two questions today with phenotyping. One is I remember data from Lynne Lennard in Sheffield where she showed that phenotypic activity depends on age of erythrocytes, for example. We did not see any data about inter-patient variability or reproducibility up to now, and it's a gene where we do not

really know the physiological role of this protein and therefore do not know enough about theoretical aspects of regulation, for example, up and down regulation. I think with the current knowledge we should just restrict to genotyping.

DR. SANTANA: So your comments are in favor of Dr. Boyett's statement, that it should be restricted to genotyping.

DR. McLEOD: While there is data to address some of the points that Joachim made, they all point towards genotyping being a more dependable, reproducible type of assay. With all the caveats that I and others mentioned as far as the benefits of phenotyping tests in terms of the stability of the assays across places, genotyping wins today in that context.

DR. SANTANA: Mr. Ohye?

DR. WINICK: I have two comments. First, in favor -- oh, I'm sorry.

DR. SANTANA: That's all right. Go ahead, Dr. Ohye.

MR. OHYE: Please. No. I'm the lay person here. I defer to the scientists.

DR. SANTANA: Naomi, go ahead.

DR. WINICK: First, the other thing that's been mentioned by several people is that the advantage to

genotyping is that the physician can send that regardless as to transfusion status, and I think that that's an important note to put in the explanatory material.

But I would love to see the phenotyping provided as information, especially with all this debate about what you do with the patient who is heterozygous because certainly in that patient, even though there is phenomenal variability in TGN levels, if that patient, as the first child that Bill and Mary reported, had a TGN concentration in the many thousands, it would certainly tend to support the notion in the treating physician's mind -- I'm not saying the label should say this -- that that patient with heterozygous activity may need a greater dose reduction than a child with heterozygous activity who has a relatively low concentration of TGN.

DR. SANTANA: But what I heard earlier, Naomi, in response to your comment, is that how to manage the toxicity, in terms of dose modifications for the patients that are heterozygous, is still an area that we have no clear, uniform guideline. It's a protocol mandate or protocol-driven, and until we get to that --

DR. WINICK: Right. And I'm not saying that the label should do that, but I think that the label should make people aware of the fact that phenotype data may be useful.

DR. SANTANA: Yes.

DR. LESKO: I'm somewhat in favor of that because we talked a little bit about the variability within the wild type group, and some of the data that shows greater or lesser efficacy in heterozygotes versus the wild type may somehow be related to the thioguanine nucleotide concentrations, so that phenotyping would actually give some insight into why some of the wild types are toxic, that is to say, if they had high levels related to their metabolic status, or why they were perhaps not therapeutic. It would also give some insight into compliance if somebody wanted to use it that way. So there are benefits to having phenotyping information, at least to say that such information is available in the label without specific recommendations. I think people could view that easily as a therapeutic drug monitoring tool that they can use to address certain clinical questions.

DR. SANTANA: So let me see if I understand both of your comments. A statement in the label in this section also that says phenotypic testing or 6-TG levels, thiopurine levels may also provide additional information in terms of -- is that what you guys are kind of heading towards?

DR. WINICK: Absolutely.

DR. SANTANA: But if we leave it very vague,

how do we help the practicing physician? That's the problem I have. I know how to do it because I have a protocol and I can open it up, but remember, there's a whole population of people out there who read this and that's what we have to be sensitive to. We can't leave it very vague.

DR. LESKO: I think the advice not to leave it vague is good. I think we just need to think about the right words to say that. I don't know if we can do that right here on the spot, but that's sort of the concept that I think would be beneficial to include in the label.

DR. WILLIAMS: You might be able to give the benefits of the assays, to describe the strengths and benefits.

DR. SANTANA: Wow.

DR. WILLIAMS: Certainly as you were talking about, if you're contaminated with red cells, then the DNA assay is the only one you can use.

DR. HIRSCHFELD: Yes. I'll raise a voice of caution. I'm not sure our drug labels should go into commentaries on the strengths and weaknesses of commercially available assays which can be used for the drug under question or a variety of other assays. I'll just raise a caution.

But, Dr. Boyett, I think you were going to make

a statement.

DR. BOYETT: My comment is I think we saw some data today that suggested the variability in activity in the heterozygotes depends upon the treatments that you're getting. Different protocols result in different types of -- and so I don't know how you could be that in there and suggest any way people can interpret it because you're not going to know how they're being treated.

DR. SANTANA: Dr. Ohye, I don't want to ignore you.

MR. OHYE: First of all, it's "Mr."

These discussions are almost identical to the labeling discussions that go on in a corporation when we develop labeling. It's not unusual for us to sometimes consider statements such as "data suggest, although more definitive studies are underway or must be done" when you discuss issues of labeling of dosing, for example. I'm getting to the next question obviously.

I also wanted to mention that this particular package insert has a number of references. I think the most recent data is 1996, I think if there's a section that cries out to have a reference, it's the section under discussion now. So if there are papers that are on point that would be instructive to people that will actually seriously research what goes behind these labeling

statements, there should be a bibliographic reference attached to this section.

DR. HIRSCHFELD: I'll just, as a point of information, state it's been certainly the policy in the Oncology Division, which reflects our office director's concept of labeling, that the references should be minimized and that this label has references because it's essentially a legacy label. But the strategy of trying to clarify or address public health issues by augmenting the bibliography of the label is not one that's considered a pertinent option.

DR. SANTANA: But I think the comment is pertinent, that if we're going to go down the route of a statement regarding genotyping, that there be a reference to that which is not currently in the label.

DR. HIRSCHFELD: That's well taken.

DR. SANTANA: That was my interpretation of that.

Dr. Vassal.

DR. VASSAL: Should the label mention that current available tests will identify most of the mutations but not all the mutations since it's what? 85 percent? So the limits of genotyping.

DR. SANTANA: That will be in the reference.

(Laughter.)

DR. SANTANA: Because I think it gets into a lot of detail then and then the label becomes nonfunctional for the reader.

Let me see if I can recap the summary of this. I think there's a consensus that at least as regards genotyping that there should be a statement there.

With regards to phenotyping, I'm not quite sure how I read the committee on that one yet. I heard comments that some people felt that there was some information about phenotyping, particularly in heterozygotes, that would be clinically useful and that information is available although it hasn't been completely validated. I heard comments that we should restrict ourselves to the genotyping because that's more solid information. So I'm not sure -- the committee needs to help me sort that one out because I'm not sure I had a clear read on that latter one.

DR. HIRSCHFELD: I'll just ask. We'll discount those of us in this corner who are of the FDA in terms of the advice. Other than Dr. Winick, Dr. Santana, could you see if there are other individuals who felt there should be a phenotyping statement?

DR. SANTANA: And if so, I want to hear why you're recommending that. Dr. Reaman?

DR. REAMAN: I think there should be mention of

the phenotypic assays as well. As Mr. Ohye said, the data suggest that this information may be useful and is currently under investigation. So I think that should be included.

DR. SANTANA: Does everybody agree with that statement? Okay. That's the recommendation.

And then lastly for that question, should there be recommendations for adjustment of doses in children identified as having little or no or reduced TPMT activity? Dr. Reaman, Dr. Shurin?

DR. SHURIN: It wasn't clear to me that we knew what to do. So I don't know how you can make recommendations if we don't know what to do.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: Other than to exercise extreme caution. But I would be hard put to say you should begin with a dose of 10 percent. That may be correct, but I think that warrants further prospective investigation as well.

DR. SANTANA: Dr. Cohn?

DR. COHN: I was just going to say it could be nebulous and kind of say it may be necessary to reduce the dose in patients who have this genotype, but without being specific about what the actual recommendation is.

DR. REAMAN: And monitor closely, as well.

DR. SANTANA: Howard?

DR. McLEOD: Significant doses have been required is a true statement of the literature to date, and something like that may make it clear that something big has to be done. I agree that there is no data saying that one-tenth is the dose that has worked.

DR. REAMAN: Less than that has worked as well.

DR. McLEOD: Yes, exactly.

DR. SANTANA: So the consensus is there should be a statement not with specific recommendations but that these patients do require serious consideration of dose adjustments and ongoing monitoring.

Malcolm.

DR. SMITH: That also has reduced TPMT activity. So is the discussion of the heterozygotes off the table or is that --

DR. SANTANA: Good point.

DR. SMITH: And if it is going to include reduced activity, then to comment that while these patients may eventually require dose reduction, over half of them are able to tolerate standard doses of 6-MP.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I thought we were confining the recommendations to genotypically demonstrated patients with the absence of TPMT activity.

DR. SANTANA: That was my interpretation too.

DR. REAMAN: So by definition it would exclude, but maybe a statement needs to be made that there are no specific dose modifications for heterozygous individuals who may have reduced activity and that that's under investigation.

DR. SMITH: Yes. I think to state that over half of the children will tolerate standard doses may help to address some of the concerns about the data being misused for the heterozygous population. There may be a way to use that type of information.

DR. SANTANA: I think that's important information that needs to be conveyed too, that at least half of them tolerate it well.

Dr. Shurin.

DR. SHURIN: I'm a little concerned about anything that looks at anything statistical because it doesn't seem to me that we have remotely enough numbers, including the incidence of any of these things. So it seems to me it's perfectly appropriate for it to stay vague and not that over half the patients may tolerate it. We don't know that. That's been the experience. That's what's published in the literature, but it's not a population study.

DR. HIRSCHFELD: So just to clarify, the

committee would be recommending a statement for the homozygous condition --

DR. SANTANA: Right.

DR. HIRSCHFELD: -- and remain vague or silent with regard to the heterozygous.

DR. SANTANA: Except there is some dissent on that latter point. There are some that feel that there is some information that should be conveyed regarding that. A good proportion of patients who are heterozygous also tolerate the full dose. I heard that comment at least being made by one or two individuals.

DR. REAMAN: Instead of remaining silent, maybe there could be a statement that the recommendation shouldn't necessarily be extrapolated to the heterozygous population. The specific recommendation is made for homozygotes.

DR. HIRSCHFELD: So a statement that would say no specific dosing recommendations for heterozygous patients are made, or something to that --

DR. SMITH: Again, the concern about that is, well, maybe I need to be safe. I agree, we don't know if it's 50 percent or 70 percent or 80 percent or 40 percent, but many children who are heterozygous will tolerate standard doses.

DR. SHURIN: I'll endorse "many."

DR. WILLIAMS: Can we say that it hasn't been prospectively studied?

DR. BOYETT: You could wait till the English study is --

(Laughter.)

DR. SANTANA: Dave, do you have a comment?

DR. POPLACK: Well, my assumption is that dose reduction in the face of toxicity is a standard and is inherent in the label, and that would occur under any circumstance, including the heterozygous. So by not having a statement in, we don't necessarily remove the fact that they are going to have dose modification.

DR. HIRSCHFELD: In light of Dr. Poplack's statement, is the committee recommending a specific comment on the heterozygotes or remain silent?

DR. COHN: I would agree with Malcolm's statement. I think to remain silent is potentially a problem because the children may be under-dosed, and that I think is the concern. If you say many children can tolerate it and then, as David said, if they get the drug and they become neutropenic, obviously they'll have their dose modified. But I think what we don't want is to have a heterozygote necessarily be started out at 50 percent of a dose when that may or may not be appropriate for that particular individual.

DR. HIRSCHFELD: Thank you for that clarification, Dr. Cohn.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I would agree because I think even though these are recommendations being made under dose modifications, they may well be utilized preemptively, and that's the situation that we're trying to avoid with the heterozygote patients.

DR. SANTANA: So I think the consensus is there should be some comment regarding heterozygotes.

Dr. Morland.

DR. MORLAND: I just wondered. One of my anxieties is that an individual experience of this is going to be very limited. We've already heard that the average physician may see this once or probably never. It may be slightly different for the heterozygotes. Is there a possibility of including in the label specific recommendations that these cases are discussed with, say, the chairman of the current, ongoing leukemia protocols?

DR. SANTANA: I don't know of any such prior experience, but certainly we'll look to the FDA for guidance. I don't think there's ever been a label that specifically says do that. So I think we want to stay away from that.

Question number 2. If pharmacogenetic

information is added to the label, what other testing information, if any, about genotyping or phenotyping for TPMT activity in pediatric patients would be considered necessary or appropriate to include in the product label? Once again, they're giving us a series of comments, not necessarily that we have to agree or disagree or take them, or potentially we could add others.

So the first one is, a recommendation for testing for the status of TPMT activity in children before initiating treatment with 6-MP. If you read those subsequent ones, they're all kind of tied in chronology. You either do it first before you initiate therapy or the second point is, within the first week of initiating therapy, and then the third point is, once they've gotten the drug, if they get severe neutropenia.

Dr. Boyett.

DR. BOYETT: We're going to go together.

DR. SANTANA: No. You can only speak once for the record. So one of you decide. Dr. Boyett.

DR. BOYETT: We vote no for number 1.

DR. SANTANA: Any other comments?

(No response.)

DR. SANTANA: So a consensus that we would not endorse testing before initiation of therapy.

How about the second point, within the first

week of initiating therapy? Malcolm?

DR. SMITH: Is there a possibility for having a venue of options in the label? You could argue that there are several defensible ways that this test could be used for children with ALL. One of the ways is before treatment. One of the ways is at the first signs of toxicity during the first time they see 6-MP and that both of these strategies could be described and people can have the information and use it as they see fit or use it as well defined in the label.

DR. SANTANA: I actually kind of like that strategy because it leaves it up to the practicing physician to decide when he decides to test.

DR. WILLIAMS: The other option, of course, is you don't make any specifications about when you should test, just like we don't tell people how often to check their blood counts, et cetera. That's another possibility.

DR. SANTANA: We don't tell them in the product labels people should have their blood counts checked once a month if they're getting X drug?

DR. WILLIAMS: Variably, but we don't tell people every test they need to take to give a drug. We might need to say you need to have your blood counts checked if that is a particular safety issue, but if this is a test that will be used variably, one option is not to

describe the issues but just to describe the results as you have in number 4. But certainly that's what we're here to ask.

DR. HIRSCHFELD: To clarify, the goal of the label is to provide some sense of risk management. So the question is, what's the risk? And if you have some mechanism of assessing that risk, what do you do with that information? So that's another way of thinking about what this is asking. If the sense is that there's already sufficient information to assess the risk, then it becomes moot. If the issue is that there ought to be more information in the product label about assessing the risk, then the statement would be if you feel you want to assess the risk, when should you assess the risk and then what do you do about it.

DR. LESKO: I was just going to bring to the attention of the committee other laboratory tests in the current label where they talk about hemoglobin, blood cell count, et cetera. They recommend weekly and then they go into more detail about strategies to monitor blood count. So getting back to the first suggestion, there could conceivably be ways to word using the test in a way analogous to how the current label reads with regard to the blood counts.

DR. SANTANA: But my interpretation of that

would be that you use them together or you use them separately. So let me give you a couple of scenarios the way that I would interpret that.

One is you would only order the test if a patient has already received the drug and has trouble, and in addition to getting additional blood counts and things like that to monitor the patient, when that scenario occurs, if the patient becomes neutropenic or severely neutropenic, you would order the test to either confirm or not confirm your suspicion that it's related. That's one possible scenario. Right?

The other scenario is you order on everybody if you're too concerned because, remember, the issue is in the absence of testing the drug on the patient, how do you know which is the patient that truly is going to be affected. So that's the other scenario. I order it on everybody and if it comes back negative, it's okay. If it comes back positive, then I have to figure out how I'm going to dose the patient. But it's up to me to decide in my practice whether I order it on everybody or whether I order it when the patient has an event that triggers me ordering the test. To me as a practicing physician, those are the two scenarios.

DR. HIRSCHFELD: I would just comment again philosophically the intent of the label is to be

informative. So if a menu of options are outlined which represent the full array of logical possibilities, we might pose the question how informative is that. We already state tests are available. I think the question being asked here is we've stated that tests are available. Are we going to make any statements about to use the test?

DR. WILLIAMS: To follow up on that, I think that there probably could be two "should" statements. I think most appropriate for testing, how to do it, would be if we could say you should do that. One would be you should do this in everybody so that you detect the heterozygotes. The other would be if you have toxicity, you should do this -- or maybe you could do this in order to help you weed out what it's from. There is a whole array of different ways you could use the test. That probably, as Steve was saying, is outside the scope of a drug label.

But I wonder if the committee feels that in either of those cases it really should be done; that is, you have toxicity, should you do it? Or should it be done at the first to identify the homozygotes?

DR. HIRSCHFELD: Well, let me try to rephrase and try to parse this out a little bit. Is there a sense from the committee that the product label should say all patients should be tested? Parse out that one aspect.

DR. SANTANA: My sense from the discussion this morning is that the answer is no. There is no strong recommendation that everybody needs to be tested up front. Does everybody agree with my comment on it?

DR. PELUSI: Victor?

DR. SANTANA: Yes.

DR. PELUSI: If I could. I think somehow we need to make sure, though, that patients and families know that the test is available, and I don't know in the product labeling if there is a way to ensure that parents know that that is a test that is available. It's the discussion between the provider and the parents on do they think it's appropriate and at what time and how and why, but I think this is a time when I think parents really want to know that there is an option there because it's not being done in everyone.

DR. HIRSCHFELD: Right. I think we've agreed that there will be a statement in the product label to the effect that testing is available.

DR. PELUSI: I just want to make sure that, again, family members know because many times they don't know. They can read the whole thing and it doesn't make a lot of sense. But that's just my comment.

DR. SANTANA: Yes. So getting back to the issue, though, if the committee has a consensus

recommendation that we're not recommending testing on everybody -- I think we've made that very clear -- then to me the scenario where we do have to be more explicit is once a patient develops X event, this is when you should be doing testing and this is how you would use the information. Obviously the event would be myelosuppression. And it's up to the practicing physician to incorporate the tests or not do the tests. So the first scenario is out because we're not making a statement that everybody should be tested, but it should be as an adjunct test in the management of the patient once this particular side effect occurs.

Susan?

DR. SHURIN: Doing that is defining that this is a test which is indicated when you have unusual toxicity. So that's a clinical indication. That seems fairly straightforward. So basically some variant of number 3 would probably be appropriate.

I'm not sure there is a screening test. The genomic test is awfully specific. That's number 4.

DR. WILLIAMS: Do you feel like the statement should be more of a "may" statement or a "should" statement?

DR. SANTANA: Help me with the differences between those.

DR. WILLIAMS: Well, you may do this test if the patient has toxicity. You may do this test to help weed things out. Or versus you should do the test.

DR. SHURIN: I would argue that it should be a "may" test because you're dealing with patients who are all getting polypharmacy. They're getting multiple myelosuppressive drugs. This is not the only thing that they're getting. The doctor has to look at it as what's clinically indicated.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: I would agree and then maybe just mention that it should be considered as a potential cause of protracted or prolonged recovery in myelosuppression.

DR. SANTANA: It should be part of your evaluation in a patient who is getting this drug and is developing this problem.

DR. McLEOD: I think the critical point is not to box someone in because there are other drugs that can cause the same thing. The "should" versus "may" or "might" or whatever it was also has other connotations in terms of the "butt in a sling" test in terms of if you don't do it, you're in trouble or not, even if there were clinical reasons not to.

DR. SANTANA: So I think what we're saying, what I gather from the committee, is that there should be a

statement that this should be a test you should consider in the context of the patient having a toxicity, particularly myelosuppression, and you decide how to use it.

DR. HIRSCHFELD: Just to get to the fine points, phenotype, genotype, or it doesn't matter?

DR. REAMAN: Let them make the choice.

DR. HIRSCHFELD: Okay. So a statement which says testing for thiopurine methyltransferase deficiency should be considered for severe toxicity or something to that effect.

DR. SANTANA: Right.

Dr. Poplack.

DR. POPLACK: I think the terminology "may be advisable" might be more appropriate, and it's also used in the existing label.

DR. SANTANA: Right.

I think there was a hand up. Dr. Boos?

DR. BOOS: Yes. I'm a little bit confused, but we felt that it is not mandatory to run the test, and we had two suggestions. One is to explain toxicity and the other was to avoid toxicity. And now we discuss about explanation of toxicity. My feeling is all these four recommendations are not necessary because everything has been written down prior and it depends on the decision of the physician, his relation to the kid, the prior tolerance

of chemotherapy, the combination therapy, the distance from home to the practice, and things like this, if and when he decides to run the test. He can do it front line if he feels I cannot allow toxicity now because it's induction therapy including mercaptopurine and methotrexate and Ara-C, NBB 16 and Total XII and Total XIII or whatever, and he can do it as the maintenance therapy just if he has toxicity. I think these four recommendations from my point of view are not necessary.

DR. HIRSCHFELD: I'll just state, as we've often stated before, the FDA does not regulate the practice of medicine. Our goal is to provide information for the safe and effective use of drugs which includes some level of risk management. And given that the top of the label says "physicians experienced in the treatment of acute lymphatic leukemia," to quote the nomenclature there, should be the ones giving it, they would be aware that testing exists and could use it in any way they wished, just as this drug and many others are used off label. So we shouldn't look at it as practice guidelines, but rather as information about the drug.

DR. SANTANA: Yes. I would agree with that caveat, that as you well know, sometimes that does occur. But having said that, we will not continue the discussion.

Does anybody else have any other comments or

advice to the FDA? Dr. Poplack?

DR. POPLACK: Victor, I'll just make one point. If one looks at the existing label, there's very much practice guidelines in there in terms of when to get certain blood tests. So there's a dichotomy which may reflect historical evolution of writing these documents.

DR. SANTANA: Absolutely.

I don't think we have any other advice to give you this morning. So we will consider this session of the morning concluded.

I think if the FDA agrees, we'll get started at 1:15, give people 45 minutes for lunch. We'll try to reconvene on time so we can finish on time this afternoon. Thank you so much.

(Whereupon, at 12:36 p.m., the subcommittee was recessed, to reconvene at 1:15 p.m., this same day.)

AFTERNOON SESSION

(1:18 p.m.)

DR. SANTANA: So the topic that we will try to address this afternoon is identifying barriers and overcoming challenges in pediatric oncology product development, in particular, regulatory oversight over multinational international studies. We have a series of speakers, and then we'll have an open session for discussion.

There are a couple of formalities that we have to undertake, and so Mr. Perez will get started.

MR. PEREZ: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topic of this afternoon's session is an issue of broad applicability. Unlike issues in which a particular firm's product is discussed, issues of broad applicability may affect many sponsors and their products.

All participants have been screened for their financial interests as they may apply to the general topic at hand. Because they have reported interests in firms that could be affected by today's discussions, the Food and Drug Administration has granted waivers to the following

special government employees which permits them to participate in this afternoon's discussions: Drs. Jody Pelusi, Gregory Reaman, Victor Santana, James Boyett, C. Patrick Reynolds, Howard McLeod, Susan Cohn, Susan Weiner.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion, these conflicts are mitigated.

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

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow participants to objectively evaluate their comments.

Dr. Richard Weinshilboum previously served as a consultant to Abbott Labs, Eli Lilly, Johnson & Johnson and he is currently consulting with Merck. All consulting fees go back to the Mayo Foundation to support research and education missions.

We would like to note that Mr. George Ohye is participating in the meeting as an acting industry representative, acting on behalf of regulated industry. Mr. Ohye owns stock in Abbott, Amgen, Ergo, Gilead, Johnson

& Johnson, Ligand, Lilly, MedImmune, Merck, Omnicare, Pfizer, Schering-Plough, and various mutual funds that may have drug company holdings. He also has stock options in NeoRx. Mr. Ohye receives consulting fees from Johnson & Johnson, NeoRx, Abbott, and Cephalon. Mr. Ohye's wife works for Johnson & Johnson and he receives retirement pay from Novartis and Johnson & Johnson.

We would like to remind the special government employees of the need to exclude themselves from discussions involving specific products or firms for which they have not been screened for conflicts of interest. 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 product they may wish to comment upon.

Thank you.

DR. SANTANA: Does any member of the committee have anything else they wish to disclose publicly? Yes, go ahead.

MR. OHYE: To complete the record, I also have a beneficial interest in GlaxoSmithKline because my wife owns some stock in that company.

DR. SANTANA: Thank you for the update.

Dr. Lumpkin, Williams, or Hirschfeld, do you

want to make any introductory comments or do you want to just go ahead and get started with the introductions of the members of the committee?

DR. HIRSCHFELD: Well, I just think for the record that Dr. Lumpkin's presence should be acknowledged for the afternoon.

DR. SANTANA: We also have Dr. Mark Bernstein on the phone. Are you with us mark?

DR. BERNSTEIN: Yes.

DR. SANTANA: So we're going to start with you. Can you introduce yourself by name and affiliation?

DR. BERNSTEIN: Sure. I'm Mark Bernstein at the University of Montreal and a Children's Oncology Group member, and I have been involved with some of the regulatory issues for Canadian Children's Oncology Group institutions.

DR. SANTANA: Thank you, Mark.

Dr. Ball, do you want to get started from your side?

DR. BALL: Dr. Leslie Ball. I'm with the Office for Human Research Protection, Department of Health and Human Services.

DR. KERN: I'm Ursula Kern from the Federal Institute for Drugs and Medical Devices in Germany. I'm responsible for managing our national advisory committees.

DR. DAVIES: Hugh Davies from the Central Office of Research Ethics Committee in the United Kingdom.

DR. MORLAND: Bruce Morland representing the United Kingdom Children's Cancer Study Group.

DR. BOOS: Joachim Boos, Department of Pediatric Hematology and Oncology at the University of Muenster in Germany and the German Pediatric Oncologist Society.

DR. VASSAL: Gilles Vassal from the Institute Gustave Roussy in France, Chairman of the European Consortium for Innovative Therapies for Children with Cancer.

DR. RICCARDI: Riccardo Riccardi from the Catholic University of Rome, Department of Pediatric Oncology and Hematology, and I also represent the Italian Association for Cancer in Children.

MR. OHYE: George Ohye, acting industry rep, Naples, Florida.

DR. SHURIN: Susan Shurin, Case Western Reserve University and Children's Oncology Group.

DR. WINICK: Naomi Winick, University of Texas, Southwestern Medical Center, and the Children's Oncology Group.

DR. POPLACK: David Poplack, Texas Children's Cancer Center, Baylor College of Medicine.

DR. WEINER: I'm Susan Weiner from the Children's Cause. I'm the patient/family representative. I'm a member of the Secretary's Advisory Committee on Human Research Protections and also a liaison from the National Cancer Policy Board to the Institute of Medicine Committee on Research Involving Children.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. SANTANA: Victor Santana from St. Jude Children's Research Hospital.

DR. COHN: Susan Cohn from Children's Memorial Hospital in Chicago.

DR. REYNOLDS: Pat Reynolds from Children's Hospital, Los Angeles.

DR. BOYETT: James Boyett from St. Jude Children's Research Hospital, chairman of biostatistics.

DR. REAMAN: Greg Reaman, Chairman of the Children's Oncology Group, George Washington University and the Children's Hospital, D.C.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, and I sit as the consumer rep.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, NCI.

DR. ANDERSON: Barry Anderson, NCI, CTEP as well.

DR. MAYBEE: Dave Maybee, Center for Biologics, Office of Cell and Gene Therapy.

DR. HIRSCHFELD: Steven Hirschfeld, FDA, Department of Oncology Drug Products and Department of Pediatric Drug Development in CDER.

DR. WILLIAMS: Grant Williams, Deputy Director, Division of Oncology Drug Products.

DR. LUMPKIN: Murray Lumpkin, Principal Associate Commissioner, FDA.

DR. SANTANA: Well, thanks to everyone.

We're going to go ahead and get started with the afternoon session. We have three presentations to cover overview of research oversight, and I'll ask Dr. Ball to get started. Thank you.

DR. BALL: Good afternoon. Dr. Hirschfeld has asked me to speak about the topic of overcoming some of the challenges in pediatric oncology development, specifically with regard to international research, and I'm going to provide an overview of research oversight, the U.S. perspective.

First, I wanted to provide you with an overview of what I'll be talking about. First, we all know that there's an increased pace and scope of international research particularly with regard to biomedical research and also involving children.

I'm going to provide a framework of U.S. regulatory oversight and specifically provide you an explanation of the role of OHRP in relationship to the FDA.

I'm also going to be discussing some of the regulations that involve research involving children, as well as international research, and finally present briefly some of the issues and obstacles.

We're here today in part because of the increase in international clinical trials for new drugs, and this slide depicts the increase. The y axis is the actual numbers of trials. In yellow are those conducted in developed countries and in blue are less developed countries, and we see an increase particularly in the last couple of years in both developed and less developed countries.

In addition, funding of international research by the U.S. Department of Health and Human Services has increased. The red line here depicts the increase in the funding of foreign components of domestic research.

Part of what I think we're here to discuss today is the clinical research balance that everyone struggles with, which is providing a balance between regulatory oversight and human subject protections on one hand and scientific advancement and product development on the other hand.

Now I'm going to provide a brief overview of the framework of U.S. regulatory oversight. I think no discussion of regulations is complete without an obtuse slide and here I present my obtuse slide. This particular slide presents the framework of human subject protections. In the center is the common rule, which I'll discuss a little bit more in a moment. Around the spokes of the wheel are the various federal agencies. Not all of them are Department of Health and Human Services. There are various other federal agencies that also ascribe to the common rule. You can see on the far right side is the FDA. FDA is part of HHS, but they have their own set of regulations that are parallel to the HHS regulations.

This slide tries to depict where the responsibilities are with regard to the oversight of human research protections. The first column is OHRP. OHRP regulations apply to research that is HHS-conducted or supported, both domestic and international. The regulations that provide these protections are codified in 45 C.F.R. 46 and there are four subparts, subpart A which is known as the common rule, and there are also subparts B, C, and D, subpart D involving children.

With regard to FDA, we all know that FDA regulations apply to research that involve products regulated by the FDA. Classically there are certain

regulations that are actually called the protection of human subjects, and that's part 50. In addition, 21 C.F.R. 56 involves regulations that oversee IRB functioning. In addition, there are additional regulations that the FDA has that provide some protections for human subjects such as the IND regs at 312. One example might be the mechanism by which FDA can put certain clinical trials on clinical hold.

This slide is a reminder, because I think sometimes it's forgotten because there are two sets of regs, that FDA is actually part of HHS. The Secretary is at the top of the pyramid and the FDA is one component, as well as the other public health service agencies. Where OHRP fits in is under the Assistant Secretary of Health in the Office of Public Health and Science.

This slide depicts regulatory oversight as it pertains HHS regulations and FDA regulations. On the one hand, there are certain trials that are HHS-funded or supported, and those fall under OHRP's purview. FDA-regulated products fall under FDA purview, but there is an intersection and overlap between the two, as depicted by the center of the diagram there. It's also important to remember that there are some studies that are neither HHS-conducted nor funded by the FDA and therefore not regulated by either agency.

So now I was going to move on to the Office for

Human Research Protection. Its mission is to develop and implement regulations, policies, and programs for protecting the rights and welfare of human subjects participating in research that is conducted or supported by the U.S. Department of Health and Human Services.

Now I'm specifically going to be talking about some of the regulations involving children.

First, I wanted to provide you with some historical context and the evolution of the regulations protecting children. In the '60s and early '70s, there was an increased focus and attention on the part of both the scientific literature as well as the media with regard to ethical lapses in the conduct of research. There was a very important article by Henry Beecher in 1996 in the New England Journal of Medicine that documented 22 instances of perceived research abuses, some of which involved children.

As a result of a lot of this attention, in 1974 Congress passed the National Research Act that created the National Commission. Its charge included recommendations on research involving children, as well as research more broadly.

In 1979, the National Commission published the Belmont Report, and I'll talk about that a little bit later.

In 1981, there was a publication of the final

rule for 45 C.F.R. 46. It came upon the foundation provided by the Belmont Report.

In 1983, there was a publication of the final rule for subpart D which provided additional protections for children involved as research subjects.

Also in the mix, we add different laws that affected the FDA. In 1997, the FDA Modernization Act was passed and this provided economic incentives to conduct pediatric drug studies, specifically market exclusivity.

In 1998, FDA's Pediatric Rule was enacted that provided for the requirement of assessing the safety and effectiveness of certain drugs in pediatric subjects. It's important to note that last year there was a court ruling that FDA did not have the authority to issue the Pediatric Rule and barred the FDA from enforcing this.

In the year 2000, the Children's Health Act was passed. This directed the Secretary of HHS to require that all research involving children that is conducted, supported, or regulated by HHS, including that regulated by the FDA, to be in compliance with subpart D. So as a result of that, to that point FDA did not have separate subpart D regulations, and in April 2001, they enacted their own interim final rule for subpart D.

In 2002, the Best Pharmaceuticals for Children Act was passed, and among other things, it reauthorized

pediatric exclusivity incentives for drug products, and it also provided for the IOM review of research involving children.

I wanted to touch briefly on the Belmont Report which provides the foundation for the current HHS regs, as well as the FDA human subject protection regs. The ethical principles outlined by the Belmont Report include respect for persons. Specifically, individuals should be treated as autonomous agents and persons with diminished autonomy are entitled to special protection.

The second principle was the principal of beneficence, namely the maximization of benefits and the minimization of possible harms that might occur as a result of the research.

And justice. It's important to remember that justice operates on both an individual and a societal level. In particular, the National Commission noted that the selection of subjects deserves scrutiny to determine whether some classes of subjects are unduly targeted for research.

So the Belmont Report proceeded to provide an application of those ethical principles in the form, first, of informed consent. With regard to children, it's important to realize that there are special provisions that should be made when comprehension is limited.

Secondly, it provided for a full assessment of the risks and benefits. Specifically when vulnerable populations are involved in research, the appropriateness of involving them should be demonstrated.

Also, finally, there was discussion of the equitable selection of subjects. The National Commission addressed this by discussing that there may be an order of preference in selection of classes of subjects, for example, using adults in trials before children, and that some classes of potential subjects may be involved as research subjects, if at all, only under certain restricted conditions.

So using the Belmont Report as the foundation, 45 C.F.R. 46 codified this by providing for the informed consent of research subjects, the independent review of research, and institutional assurances of compliance.

I wanted to touch a little bit about what an assurance is. Under the regs, each institution engaged in research, which is covered by this policy, and which is supported by a federal department or agency shall provide written assurance that it will comply with requirements set forth in this policy. So essentially it's an agreement between an institution and OHRP that they will abide by 45 C.F.R. 46. These assurances are negotiated with and approved by OHRP.

Basically what they do is formalize the institution's commitment to the protection of human subjects, and it's important to remember that filing of an assurance is required by both an awardee, an institution receiving the money, as well as the collaborating institutions that might be overseas.

In addition, it also requires the designation of an IRB or independent ethics committee to review the research.

This slide I included to just depict some of the differences between OHRP and FDA. With regard to OHRP, we interact primarily with institutions that oversee research. However, FDA, as you're all aware, interacts primarily with the sponsor of the research.

The common rule, subpart A, provides some additional protections for children, and I wanted to point out some specific provisions that are relevant to research involving children. With regard to IRB membership, if an IRB regularly reviews research that involves children, then the regs provide that there should be individuals on the IRB that are knowledgeable about and experienced in working with children.

In addition, there's a regulation for providing criteria for IRB approval that requires that selection of subjects be equitable and that the IRB should be

particularly cognizant of the special problems of research involving vulnerable subjects, including children.

Subpart D is the part of the regulations that provide specific protections for children. In this part, it requires that the IRB that is reviewing such research make specific findings before approving the research. It must satisfy one of the conditions which are outlined in subpart D regulations. And generally speaking, as the risk increases in relationship to the presence or absence of direct benefit, the criteria for IRB approval under the subpart D category becomes more stringent.

Many people here may be more familiar with these in terms of the numbers of the FDA regs, but I'll be referring to them here for the HHS regs. 45 C.F.R. 46 involves research not involving more than minimal risk.

I think the category that probably most accurately describes most of the research conducted in pediatric oncology trials is probably a category, 45 C.F.R. 46.405 which is research that involves more than minimal risk but provides the prospect of direct benefit to the individual subjects. And if an IRB makes a finding here, they must also make the finding that the risk in studying children is justified by the anticipated benefit in that child, that the relationship of the anticipated benefit is at least as favorable to subjects as that presented by the

available alternative, and finally, that there are adequate provisions made for assent of the child and permission of their parents or guardian.

Finally, I wanted to touch briefly on some international research issues. I wanted to emphasize that with regard to the regulatory requirements for research conducted in international settings that is HHS-funded or supported, the regulatory requirements are identical to those requirements for U.S. trials.

I also wanted to point out one particular provision of the regulations, 45 C.F.R. 46.101(h) which states that procedures normally followed in foreign countries to protect human subjects may differ from those set forth in this policy, namely 45 C.F.R. 46. If the foreign institution's protections are at least equivalent, the U.S. department or agency head may approve the substitution of foreign procedures. It's important to realize that HHS has not implemented this provision, but there is a working group that is involved with advising the Secretary on implementation of this provision.

So with regard specifically to international assurances, if you go to the OHRP web site and click on "assurances" and scroll down to "international assurances," you will see that international assurances, unlike domestic assurances, will require an institution to state that they

will be guided by ethical principles that could include principles other than the Belmont Report. And under "international assurances," you can check off Declaration of Helsinki, Belmont Report, or other appropriate international ethical standards.

In addition, for international assurances, the institution will assure that they will comply with procedural standards and they can check one or more of one of these particular procedural standards that have been developed. It includes ICH-GCP-E-6, as well as the CIOMS ethical guidelines and some others.

But it is important to emphasize that under the terms of assurances for the federal-wide assurances, all U.S. federally supported research much comply with the requirements of any applicable U.S. federal regulatory agency and that may be FDA regs and that may also be the HHS human subject protection regs.

Last, I wanted to just discuss some of the issues and obstacles in regulatory oversight of international research. One of the issues is the desire to harmonize regulatory requirements wherever possible and that different requirements of each regulatory agency perhaps can be minimized to allow for better and easier product development.

In addition, one of the obstacles is the lack

of consistent approaches for study monitoring, reporting of adverse events.

In addition, there is a need to ensure review by IRB/ethics review committees having knowledge of the local research context. For example, if an NIH-sponsored research protocol is occurring overseas, it may be reviewed by the IRB in the U.S. However, they need to provide some evidence that they have knowledge of the local research context and when, if at all possible, it makes sense to consider a local IRB review as well.

For developing countries, it's particularly important to begin to develop host country capacity to conduct and review research. And this effort is ongoing with regard to the development of IRBs in various sites around the world by Dr. Melody Lin who is the Deputy Director of the Office for Human Research Protection and is the head of the Office for Human Research Protection's international activities.

This slide provides some contact information with regard to our OHRP web site and some information on assurances.

I'd be happy to answer any questions if there are any. Thank you for allowing me the opportunity to speak here.

DR. SANTANA: Thank you, Dr. Ball.

Any questions for Dr. Ball? We'll have some time, after all the presentations, to have a general discussion, but any urgent questions? Dr. Smith?

DR. SMITH: Could you say more about the commission that's looking at the procedures, the setting where procedures normally followed in foreign countries differ but are sufficiently congruent to allow the research to continue, what that committee is and what its time line is?

DR. BALL: That particular committee is chaired by Dr. Jim Lavery of the NIH Fogarty Center, and in fact, he is planning on submitting the report of this HHS working group to the Acting Director of OHRP this week. So there will at least be some recommendations by the working group and then deliberations by OHRP in terms of advising the Secretary on implementation.

DR. SMITH: Is that a report that will be publicly available or not?

DR. BALL: I'm not sure at what stage it will be publicly available, but it will be publicly available. In fact, there is a provision to solicit input from interested parties.

DR. POPLACK: Leslie, do you know whether they specifically dealt with the issue of children, research in children?

DR. BALL: I was involved with that activity, and there were discussions more broadly. I think there were some issues that touched on children and research, but I can't think of anything in particular that was specific to children.

DR. SANTANA: Thanks again, Leslie.

The second presentation will be Dr. Hugh Davies from the United Kingdom perspective.

DR. DAVIES: Thank you very much. May I first extend my gratitude to being invited to talk to this group. I've certainly found the morning most interesting and illuminating, and I think it's probably, putting the cart before the horse, an excellent example of international collaboration that I think should be commended and this should be recorded.

DR. HIRSCHFELD: Dr. Davies, it is recorded.

(Laughter.)

DR. DAVIES: Mindful of Oscar Wilde, who stated that we really have everything in common with America, apart, of course, from the language --

(Laughter.)

DR. DAVIES: I'll give you some worse ones if you want. I thought I'd put some abbreviations up so that if I do lapse into the vernacular, as I do tend to on occasion, you'll hopefully know where I am.

Research ethics committees translate to IRBs, but we have two types. We have what might be called the local research ethics committee which is institutionally based -- I'll come on to that -- and the multi-center research ethics committee. I suppose if you wanted it to translate internationally, you might say that these would be state-based, but they would have a federal role.

Central to the MRECs is something called the Central Office for Research Ethics Committee, COREC, which I represent. We are charged by the NHS, Department of Health and NHS, to supervise research ethics committees. Initially we only had charge of multi-center research ethics committees, but we know have responsibility for all of them. As I said last night, if you've ever tried herding cats, you know what our job is like.

The UKCCSG is the United Kingdom Children's Cancer Study Group which I think has particular relevance to this study.

Finally, in terms of vocabulary, GAfREC, the Governance Arrangements for Research Ethics Committees. That's a document that really tries to lay down how ethics committees should behave, at least in terms of process.

The Department of Health requires that all research falling within certain categories is reviewed independently to ensure it meets the required ethical

standards. I think that that's fairly brief and it's a sort of a philosophy. It's not currently really backed up by law, but it's in force in a variety of ways.

The categories of research that require review are patients and users of our National Health Service, relatives or carers of patients, access to data, organs, or other bodily material of past and present NHS patients, and that's particularly relevant due to our recent experience, fetal material and IVF, the recently dead on NHS premises, and the use of NHS resources.

Reviews undertaken by the research ethics committees -- and as I said, these are comparable with the IRBs -- and their support and management is overseen by the Central Office for Research Ethics Committees; i.e., we manage the budget within certain limits. We have some responsibility for defining the procedures, and we have a responsibility to try to define competence and to accredit the ethics committees. That's underway at the moment, the process by which we are doing it. I am specifically charged with trying to design the training program for research ethics committee members. There are other people trying to establish an accreditation process.

I don't think details need to bother us much further because I want to try to move on to more specific issues that might be of relevant interest to this group.

In deference to my boss, Professor Terry Stacey, he always draws three circles whenever he comes along. I don't know if he's been over to America to draw his three circles, but he doesn't use PowerPoint. He just draws it on acetate and then writes in it. I've moved on a little bit and I'm hoping that he'll eventually move on the PowerPoint.

(Laughter.)

DR. DAVIES: But nevertheless, it's extremely useful. It's a clear and succinct demonstration.

There are three circles really. Policy, which is the remit of government. That's the Department of Health. The NHS has input. It's basically our elected representatives. They charge the Central Office of Research Ethics Committees to administer the process, and I think the aim really is to provide a coherent and consistent process. They pass on the ethical review to the research ethics committees, and as far as possible, we try to leave them to make their own decisions.

Now, I have a suspicion that the UK member on my right might say, well, I wish you could actually try to curtail some of the decisions because they're a bit idiosyncratic. Some of them are. What I think we have to do is we have to balance a permissible variation and we have to allow that, but we also have to recognize and try

to rule out impermissible variation when committees may make some rather bizarre decisions.

That is the background, and if we look at pediatric oncology, I want to sort of look at two broad types. The single site studies, which are probably the phase I/phase II studies, although I recognize that some may become multi-center, will be reviewed by a local research ethics committee, or an IRB. The important difference, I suspect, in terms of differences is that the LREC is actually not an institution or body. It's responsible to what we call a local health authority, which is outside the trust institution. Nevertheless, a large amount of its resources, its personnel come through that institution, but it's a means by which we hope that we can try to maintain some independence and some separation between the reviewing body, which I think has a principle of being independent, and the research that they're undertaking.

If we look at multi-center research -- and that's more than four sites. It's going to change in the European Directive. In 1997, multi-center research ethics committees were established. There were 8 when I started and I think there are 11 now. They're based around the country in the health regions. As I said, you can consider that they might be sort of state-based. But their opinion

will cover the whole country, so that if you have a study that's approved by a multi-center research ethics committee, that's the end of the ethical issue theoretically for the rest of the country. That study stands approved. In certain circumstances, that's it and then the research can be conducted, and the local research ethics committees have no further input.

In terms of pediatric oncology, I would argue that there are local issues. There are local resources used, and therefore the study needs to be also submitted to the local research ethics committee but for consideration of local issues only. That's quite important. Unfortunately, some of these ethics committees overstep their boundary and it's a matter of policing it and trying to define and trying to refer them back to the Health Service guidance for what their role exactly is. It works in some places extremely well; in other places it doesn't work so well. Like the curate's egg, it's good in parts; it's bad in other parts.

That's the background in terms of pediatric oncology, and maybe what I want to do is spend some time just describing in more detail the process that has developed in the United Kingdom. This is a geographical accident. It's a geographical plan. It depends on which way you look at it. It may be intentional. It may be this

has happened.

But the UKCCSG, the Children's Cancer Study group is based in Lester, which is in the middle of England. That is covered by the Trent MREC. Trent is an area of England. And the Trent Multi-center Research Ethics Committee over a period of time has built up a relationship with the UKCCSG. I think it has particular advantages. It means that pediatric oncology studies tend to go through one ethics committee, and in this complex and challenging area, I think content expertise is vital. There is a debate about content expertise and ethics, whether it's necessary, whether it's unnecessary, how you achieve it, and where you go for it. But I would argue -- and I would be happy to discuss it afterwards -- that an ethics committee that has content expertise will deliver a more sensible ethical decision.

I think the other advantage is that the committee is up to speed that having received one, two, three, four, five -- I don't know how many it is now -- they understand the ethos of the UKCCSG. They understand how it works and they can, therefore, expedite their methodology. And it simply means that the UKCCSG can say we have this process, we have this data collection, and they can get that approved, and then if they want to separate studies, based on the same material, they don't

have to go back to square one every time and re-explain the studies to a new ethics committee. So I hope that it's efficient and it saves people time.

The relationship does need careful monitoring. This is called Stacey's devil. I thought in view of the fact that my boss is called Stacey, I'd have him on the slide. How close can you sup with the devil?

(Laughter.)

DR. DAVIES: I think that I would argue that it's perfectly feasible to conduct this relationship and maintain high ethical standards. In some sense I argue that collusion is a state of mind and not a state of geography and that if you won't collude with people a long way away, you can avoid collusion with people who are very nearby.

But I think it is a relationship that needs careful nurturing, and it's a relationship that needs guarding because it is open to criticism and if you suddenly find, for example, that members of the committee are offering independent advice to oncologists, you immediately start seeing a conflict of interest and that's got to be quite carefully monitored.

I have met several of the members of the Trent MREC. I've met the chairman. It's with a slight caution that I would sort of suggest how they look at pediatric

protocols, but I would suggest that they probably adopt the utilitarian approach rather than a duty-based approach. I.e., usually they will look at the benefits and they'll look at the risks and they'll see whether the benefits outweigh the risks.

They also follow what I might describe as the various august bodies. And I was interested to hear Leslie talk because I think that we have similar ideas but we're not sort of tied into legislation. I think we have a group of august bodies who write down their opinion. They hold lengthy committee meetings and they deliver it as opinion. That is then taken on by what we might describe as the policeman of the ethics system, the ethics committees. They try to interpret those and then apply them to the applications that they see before them.

They see that some diseases are unique to children and there's no way round that. You can't do the research on adults. Physiologically, pharmacokinetically, behaviorally children are not little adults, and therefore research is needed on children and not adults.

One thing that Bob Bing, the chairman, was quite keen to point out is that pragmatically children do better in trials.

They also refer to the guidance from the Royal College of Pediatrics and Child Health. I'm not going to

go into those, but they essentially say that research should be encouraged and they reiterate some of the points of the Trent MREC have made. They define some guidance as to how studies should be conducted in the pediatric population.

So I think that we've got a model. There are several august bodies, the Medical Research Council, the Department of Health, the Wellcome Foundation, the Royal Colleges which I think is equivalent to your Institute of Medicine -- I'm not sure -- who, through a period of time, have tried to lay down some ideas. These are incorporated into the MREC way of working, and they were then trying to look at them, use them when reviewing a protocol.

When we get on to trial monitoring, I think that we're on less clear ground, and I think that up until recently the trial monitoring of pediatric oncology studies has been relatively limited. The stipulations are really laid down in the Government's Arrangement for Research Ethics Committees, and if I read some of them out, they're fairly vague. The researcher is required to notify the committee of any proposed deviation. No deviation is possible without approval from the REC. The research sponsor is responsible for ensuring the arrangements are in place to review significant developments. And then it concludes: "Other than by means of these required reports,

the REC has no responsibility for pro-active monitoring of research. The accountability lies with the host NHS institution."

That's probably one of the problems or the differences is that the hospitals -- I don't know what the U.S. system is, but the hospitals are independent legal entities and therefore carry their own risk and their indemnity. While they will stipulate you have to get ethics committee approval, they will want to look at the consequences for the institution themselves.

Having said that, I think that the European Clinical Trials Directive, which is due to be subsumed into United Kingdom law in 2004 -- but don't hold your breath -- will get a more uniform approach, and that there will be a more standardized approach across the European Union.

What tends to happen at the moment from my experience is that the pharmaceutical trials are fairly tightly monitored. They are very closely monitored. The trials that come through academia are less closely monitored. Now, very often that's quite reasonable because they carry less risk, and I think the European Clinical Trials Directive carries the important concept that monitoring needs to be commensurate with risk, and I think there needs to be some dialogue and negotiation beforehand to try to define that.

In terms of international collaboration, there are no specific arrangements that I know of through the research ethics committee, at least in terms of ethical review. I think it's important that the research ethics committees, the IRBs for the country, will review these aspects of research projects.

The problems for international studies come down to a slightly provocative title of ethical imperialism. You'll play my way or you won't play with me at all. I think that Europe is likely to be guilty of this as the EMEA builds up its authority and the FDA or America likewise.

I think it's important to also add the caveat that very often there's a game of Chinese whispers going on and that what the FDA or the EMEA insists, or whoever it is, is not actually what they've insisted. What's reported to one person is reported to another person is reported to another person and what comes down -- what started off as send reenforcements, we're going to advance, as in the famous First World War Chinese whispers, came as send three and fourpence, we're going to a dance.

(Laughter.)

DR. DAVIES: So we need to be very clear as to what the stipulations, what the regulations are. From my inspection -- and I've spent some time because I've had

occasional transatlantic phone calls -- actually when you read the regulations or the stipulations from other countries -- and I've had them from Australia. I've had them from the USA -- actually they've been misinterpreted. Usually if I've said the ethics committee is ICH-GCP compliant, the study was conducted according to that, then there's no further issue about it, although they do occasionally send me very large forms I'm supposed to fill in and sign in triplicate. I'll do that.

So what conclusions? Well, we're in a big of a mess. I think that there's one certainty in this business, and that's called change. I've been on ethics committees now for 15 years and it never stands still. The European Union Clinical Trials Directive is certainly further change, and one could think once the European Clinical Trials Directive is in place, we'll all settle down and we'll go and sort of sow carrots or grow broccoli or something. I don't believe that's the case. I'm absolutely certain there will new regulation. There will be new stipulations. Well, that's not difficult for somebody who has worked in the National Health Service because it's always changing.

I think if we look at the differences between the USA and the United Kingdom -- I was interested. Leslie and I had a conversation last night. Many of the

philosophical problems are very similar. Many of the practical problems are very similar. It seems to me that you have a tighter legal framework and it may be that we will move towards that through the European Clinical Trials Directive. I hope that we can balance things out. I think a legal framework will help us enormously and I think it will help the researchers. But I also believe there's no substitute for reasoning and thinking and argument, debate, and discussion. But unfortunately, the legal brethren I talk to don't like that very much and they want everything laid out in sort of words of one syllable. But I hope that we can sort of maintain that balance.

I'll conclude. I've only really talked about approval, ethical approval of research, the research applications. I haven't talked about designing them and I haven't talked about data that subsequently emerges from them. But may I just reiterate that I think a group like this with a true international flavor is really the way forward to exchange ideas about how we're going to move forward, and I don't understand much about enzymology. I'm interested in pharmacogenetics. But it seems to me this is where to thrash out the problems. We have similar problems, and maybe if we have similar problems, we can achieve and reach some mutually acceptable arrangements for initiation, review, and then data analysis of studies.

I'm also grateful I've had an opportunity to look around Washington which I rather admire. Thank you very much.

DR. SANTANA: Thank you, Hugh.

I have maybe two minor comments I'd like you to address. Did I understand you correctly that this current system in the UK has no provisions for international research, so if there are studies that are being conducted between the UK and, let's say, France or Australia, there is no written guidance in that relationship? That's the first comment.

The second comment is, can you expand a little bit on this relationship between the multi-center IRBs and when things have to go to the local IRB and who decides that? Are there spelled-out criteria that dictate when the latter occurs, or is it left to the local IRB to decide that they also want to review it?

DR. DAVIES: In terms of international collaboration, I think COREC sees its role to look after its own patch, and if it's about ethical review, the Multi-center Research Ethics Committee will review the ethics of a study and then locality issues are dealt with by the local research ethics committees. That doesn't mean that the protocol coming from elsewhere needs to be drastically changed. What I suppose we would say is you have to fill

in our form, which actually is not much more than a protocol that has just been amended and adapted a bit, and then we will consider it and we will follow ICH-GCP. We're ICH-GCP compliant. We believe in the Declaration of Helsinki. I don't know if we believe in 2000, but we believe in earlier versions. We have difficulties with that. And the Belmont Report. I think that we have the same views. So I don't see this should be particular problems about that.

What I would like to feel is if a researcher sends a protocol to the USA, he or she can say that it's reviewed there, providing it follows your regulations and we'll accept it, and please send us the data. And I'd like to think that similarly if workers in the United States sent us a protocol, we could review it and then the USA would say, right, well, the London Multi-Center Research Ethics Committee, which I used to chair, is ICH-GCP compliant. It's met all the regulations that we want met, and therefore we don't have to take it any further. If you want the chairman of the ethics committee to fill in a long, complicated form, you'll have to speak nicely to him, but I think that the basic principles should be the same.

In terms of the relationship with the Multi-center Research Ethics Committee and the local research ethics committee, it's been a difficult one. When we first

started -- I'll tell a few anecdotes -- the local research ethics committees felt that their nose was out of joint and that these organizations, these larger, sort of national organizations were sort of usurping their patch, and some were quite difficult about it. Theoretically once the study is approved by this Multi-center Research Ethics Committee, it should only go to the local research ethics committee for locality issues. But if I told you that on one occasion somebody had to apply to 170 LRECs to do a study, somebody else had to go back to their funding body to ask for 2,000 pounds for photocopying money to fill in applications forms, it became unacceptable.

So in November 2000, I chaired a group to look at how to work this out. We basically said if you can say that there are no locality issues, then the MREC makes the decision for the United Kingdom. And no locality issues means that there's no local researcher. The contact with the local individual is limited.

And we also said that if the local researcher is trained centrally -- i.e., he has attended a central training program that is sort of recognized, accredited -- then there should be locality issues there. That should not involve the local research ethics committee.

And we also stipulated that if the individual clinician practicing was undertaking work that could be

expected to be within his remit, his clinical expertise, then there shouldn't be any locality issues in that.

I know that there are difficulties with this, and some ethics committees accept this. Others have difficulty. The policing is quite difficult. I think we're moving towards a process where we are getting one view for country, and locality issues, where they arise, are being dealt with by the local research ethics committees.

DR. SANTANA: Does the legality always become a local issue?

DR. DAVIES: Sorry?

DR. SANTANA: Do the legal aspects of the conduct of the trial, in terms of indemnity or payment, always become a local issue at that level? Do all hospitals say we want to review it locally because of the issue of --

DR. DAVIES: No. The payment of research tends to be a central issue. The indemnity for the trust or for the local hospital -- their research development fund may want to look at it to ensure that it matches their sort of broad strategy. Also, what they're particularly concerned about usually is resources and to ensure the research doesn't absorb resources that should be going elsewhere.

DR. POPLACK: Just one brief question and that

relates to whether there is an ongoing forum for discussion between you and any analog here in the United States or elsewhere in Europe about these issues. Because clearly what you've talked about, the concept of central IRBs, et cetera is very topical in the States. And I wondered, is there a forum where you get together with colleagues here or elsewhere in the U.S. to talk about these issues, the commonality of problems, et cetera, or not?

DR. DAVIES: No, but we would be very keen to, and I think that we would offer a voice and sort of talk about the problem. Certainly Terry Stacey, who is my boss, has been out to Australia where they're trying to set up such a system, and I think that it's quite a good idea to try and learn from people's mistakes. You don't want to reinvent wheels.

In terms of Europe, we've got the European Union, the European Parliament, and there are one or two bodies, European Forum of Good Clinical Practice. But I think it's an area that is begging for international collaboration. Ethics committees established themselves in the UK for some very bizarre reasons and they sort of became individual fiefdoms that have limited accountability. I don't know if that's the same across the world, but it screams out for accountability and some international agreement.

DR. WEINER: Actually this is a follow-up comment to the title of your slide, is the United Kingdom being untidy. The United States is actually quite untidy as well, as we heard this morning with respect to ethnic and racial backgrounds and language backgrounds as well, which I understand is also true of the UK. Do the local review boards -- how does that get handled? Because that's a topic of active discussion and something that the local review boards are sensitive to. In New York, there's a central IRB which translates the consent form into, as you can imagine, over 50 languages.

DR. DAVIES: The language in which the patient information sheet is written is a locality issue, although personally from my experience from the London MREC, I feel that that's not particularly necessary. We have clinicians who know full well what the issues are, and it can be simply a matter of ensuring that the sponsor agrees to translate the patient information sheet into different languages.

If I go back to your first point about what is the relationship, then there are defined locality issues. It's not the definitions. The definitions are there. It's policing and it's the interpretation by the local research ethics committees who sometimes over-interpret their role and thereafter the policing of that system. What's

necessary is for people to say that's not your remit. Leave it alone. That sometimes happens and sometimes doesn't happen.

DR. WEINER: So there's lay representation on the local committees as well as the MREC.

DR. DAVIES: Yes.

DR. ANDERSON: Yes. I've been involved with helping the Children's Oncology Group get involved potentially with a multi-center trial involving institutions in Europe, in England, in the UK. A question that's come up is, so if you do have the trial approved and the trial is being conducted and an institution was to not follow the consent form properly or the procedures as it had been approved, who calls them to task.

DR. DAVIES: I think that you would probably need a sponsor, somebody who sponsors the project in the country and they would be the person who would be carrying the responsibility. That's in the European Clinical Trials Directive. I think they would be the person who would be called to task.

DR. SMITH: Do you see major changes in your system in the UK that you've described with any new EU regulations, and if so, can you give us an idea of what those changes might be?

DR. DAVIES: I think that we have strived very

hard to follow ICH-GCP, and therefore, the European Clinical Trials Directive is not hugely different. That's probably not fair. In broad, ethical terms, it's not different. There are a few details that are different in the sense that multi-center research ethics committees are going to have to review research that's conducted on more than one site, but we've got round that by redefining the word "site," which is a smart move by my boss. There will be a legal framework through the European Clinical Trials Directive, but the legal framework is stipulating really only what's in the ICH-GCP, which we have been following anyway. I'm contradicting myself. I don't see huge changes but there will be changes, but I can't think of them yet.

DR. SANTANA: Thank you again, Hugh.

I'm going to invite Dr. Kern to talk about the German perspective.

DR. KERN: Thank you very much. First of all, I would like to thank you for giving me to opportunity to talk about challenges in pediatric oncology drug development from the regulatory point of view.

Pooling patients in international multi-center studies is highly desirable for a number of reasons, among them in order to speed up the development in pediatric oncology. We're talking about a small population and it

makes sense to cooperate internationally. It's furthermore desirable in order to reduce costs, but we learned this morning that we are not talking about costs here. So let me state another reason. It's about avoiding duplication in clinical studies. This is a highly ethical issue, you know, no unnecessary exposure. That's why it makes sense to cooperate internationally.

International multi-center studies should have a solid basis in our common ICH, International Conference on Harmonization, guidelines. We have been working on this project for years and have a number of guidelines that we all agreed upon together, and we have come to reach unified quality standards. That's ICH-GCP guidelines, and as Dr. Davies says, that's nothing new. That came into force a couple of years ago already.

We furthermore have common harmonized ethical standards on the basis of the Declaration of Helsinki and of the GCP guidelines. We have unified guidelines, very important, for safety data management requirements in international studies, and we have unified scientific standards. Let me just name the statistical guideline and the role of statistical expertise, or let me, for instance, mention the guideline on choice of control groups in clinical trials. This altogether should form a solid basis for our cooperation.

In Europe, national legislation has to be seen in the framework of European legislation, and that means that national legislation has to follow the new and legally binding Clinical Directive and the detailed guidelines of the European Parliament and the Council of the European Union.

Let me give a short comment on this term of "detailed guidelines." As you know, when we talk about guidelines, these are normally recommendations that are not legally binding, but in case you deviate, you should have good reasons to.

These detailed guidelines of the European Parliament are binding as well, and they refer to, for instance, the application for an ethics committee opinion. There are certain rules, which formal requirements to follow and which information to give. The detailed guidelines, furthermore, refer to the request to the competent authorities for authorization of a clinical trial. This also refers to the format of the application and the content. "Content" means what you have to send as pharmaceutical documentation, the preclinical documentation that has to be submitted, and the clinical documentation. Furthermore, there's the study protocol and the investigators' brochure.

This all sounds like a lot of paperwork and it

certainly is. However, when submitting this documentation, this request for authorization, the applicant is required to really find out what do we know up to now, what's the rationale for the new study, where do we want to go, and will the benefits of the trial, the possible benefits, the knowledge derived from the trial outweigh the risks.

Then there are detailed guidelines referring to the adverse reaction reporting obligations within the trial and more guidance about the inspection procedures and the qualification of inspectors.

Our national German drug law is being modified right now in order to comply with the Directive, and I understand that same process is going on in other European countries. There are always common core requirements to put it this way. There is certain room for national particularities and this will have to be regulated as well.

It is the intention of the Directive to prevent repetitive tests, whether within the community or in third countries. Sorry to have to call the USA a third country in this respect.

ICH is explicitly mentioned as an appropriate forum for discussion in order to reach this aim. According to my feeling, these ICH guidelines are a kind of regulatory oversight that is given in advance because what does it mean "regulatory ICH guidelines"? It doesn't mean

that we sit down in an arm chair and fantasize a scenario about how studies might be and should be, but these regulatory guidelines derive from definite experiences with new drug applications, drug approval applications that failed and were turned down and those applications that were approved and new drugs that were licensed. You can do something right and you can make mistakes, and all this regulatory experience is put into guidelines and applicants are well advised to follow these guidelines.

It's a further aim of this Clinical Trial Directive to simplify and harmonize the rules on commencement of trials and to establish transparent procedures and effective communication between the parties involved. The parties involved with that -- that's the sponsor, the monitor, the clinical investigator. That's the regulatory authorities and all this in different countries. You know, we are 15 plus 2 observers right now, and we are going to have 10 more countries within the European member states within the European Union next year. So this is a very complicated harmonization process and communication process, and there will really have to be very transparent rules.

The clinical trials authorization will, as a rule, be implicit on the basis of the vote, often a positive vote, a positive opinion of an ethics committee.

We talked already about this problem of one single opinion per member state. Also, in Germany we are still having a system of local ethics committees and multiple votes, and industry has been complaining a lot about complicated and time-consuming procedures. This has to be regulated in another forum. We currently have a working group of ethics committees and we will see how these things will be regulated in the new drug law.

This delegation of responsibility for the clinical trial authorization to ethics committees and their vote makes sense in a way because all the regulatory authorities are supposed to have the oversight of our clinical trials. We simply can't do everything. It's a question of personnel resources and we have to cooperate with other independent institutions.

The ethics committees have to judge the suitability of the trial protocol, the investigators, the recruitment procedures, and the informed consent. Nevertheless, the competent authority may inform the sponsor of any grounds for nonacceptance, and we have had examples of that.

For instance, we had a positive vote for a clinical trial in the field of neurology, positive opinion by a renowned ethics committee situated at a German university hospital, but as regulators, when we heard about

this clinical trial, we had some doubts concerning the personal integrity of the clinical investigator because he had issued positive opinions about the efficacy of this new drug before any controlled studies had been made.

So we took a closer look at the study protocol and found out that this study protocol was really deficient, was basically deficient, and the clinical trial would never have had a real result, either positive or negative, because the protocol was inconclusive in itself. So we made an inspection. The trial had already started, and then we found out that there were, for instance, no case report forms at all, and finally the clinical trial was stopped.

Protection of trial subjects includes insurance to cover the liability of the sponsor and the investigator. Clinical trials on children, clinical trials in minors are related in this new Directive, and they require at least some direct benefit for the group of patients concerned. The ethics committee has to have pediatric expertise to judge these trials. Exchange of information will include the establishment of a European database for clinical trials and for adverse reactions.

So this implementation of the European Clinical Trial Directive means a supreme effort to promote multinational studies, first of all, within Europe.

However, there is considerable resistance and some clinical investigators feel that this is the death of academic trials.

I'm showing you a slide that was shown at a recent conference in Brussels on clinical drug development in children. The speaker addressed the subject of cooperation and said that there was a joint responsibility shared by two of the main stakeholders in pediatric medicine development: the regulatory authorities and the research-based industry. And the question I'm asking myself of course is, where is the clinical investigator, the clinical investigator with the link to the patient, to the pediatric patient's parents, to their hopes, to their fears, to their expectations? So the problem seems to be that as regulators we have too closely cooperated with the pharmaceutical industry and we have forgotten the dialogue with the clinical investigators.

So what happened on the clinical investigator side, on the other hand, the investigators initiated development of their own. They felt an urgent need to apply new medicine and products in children with cancer and to develop a new treatment regimen. The situation is such that oncology products are widely used off label in children. Nevertheless, there's a widespread lack of interest on the part of the pharmaceutical industry to act

as a sponsor.

In this situation, pediatric oncologists have taken the initiative and have developed a system of cooperative study groups with standard treatment protocols which means, from the regulatory point of view, systematic off-label use. There are, of course, many financial constraints for the clinical investigators and the lack of funding, especially in Germany, lack of public funding, insufficient funding, and so the situation of the clinical investigators was really bad. The progress is undeniable. The cure rates improved dramatically. However, all these research endeavors suffer from the fact that they are not GCP compliant and they deviate from many regulatory requirements.

So pediatric oncology studies. Do they bypass regulatory oversight? As you all know, we have the usual terminology concerning clinical trials. We are used to speaking about clinical trials, phase I, II, III, or IV if it's about an approved drug and within the approved labeling. We are used to differentiating exploratory or hypothesis finding studies from confirmatory ones. The vocabulary, the glossary in the field of pediatric oncology is different. They talk about approval studies as opposed to therapeutic studies or therapy optimization studies, as if approval studies were not therapeutic in intent as well.

I think this is a very dysfunctional situation.

The challenge for the future. Can there be supranational networks of excellence? I called that "networks of excellence" because certainly not every study site will be able to perform GCP-like international studies. My thesis is that there are definitely no two classes of studies for which different criteria apply, such as approval studies versus therapeutic studies. Investigators willing to participate in multinational studies will have to accept this without feeling over-regulated. Regulatory oversight includes oversight of compliance with the EU Clinical Trial Directive.

Conflicts between the clinical investigators' perspective and the regulatory perspective are obvious. We heard this morning that clinicians never read the label.

Practical difficulties can be expected as the implementation means a modification of current practice and legislation. There are certain habits on the part of the clinical investigators, and these are not in line with the new GCP European Directive requirements.

One of the core principles of this challenge that we are supposed to master is adverse reaction reporting. Detailed guidance is available and is essential, especially in multi-center studies. One of the key elements is the institution of an independent data and

safety monitoring committee especially in trials in high mortality disease states, such as in oncology, and the independent data and safety monitoring committee, another independent institution that helps regulators to have oversight, is responsible for continuing review of the risks and expected benefits of the clinical trial. This has to decide whether, for instance, the informed consent has to be revised and has to make decisions about modifications, amendments of the clinical trial, or even premature termination of the trial. There are, furthermore, key elements such as adverse event reporting in general, especially expedited reporting and notification of suspected unexpected serious adverse reactions.

Another key issue is, in my eyes, that the trial protocol should follow the highest methodological standards. Regulatory oversight should start with scientific advice whenever possible just because these nonapprovable decisions often originate from deficiencies of study protocols and might have noticed earlier, right from the beginning. This, of course, doesn't mean that regulatory scientific advice is to replace the expertise of the clinical pediatric oncologist, but it's meant to come in addition to that.

At this point of the discussion, the head of our national pediatric advisory committee, our expert

group, usually says, well, well, well, these are really two different worlds. This is not what I feel. I don't feel that these are two different worlds, but two different ways to look at the same world, to look from different angles. But if it's really two different worlds, my appeal would be to try and combine the best of these two worlds.

Thanks.

DR. SANTANA: Thank you, Dr. Kern.

Any questions for Dr. Kern? Dr. Vassal.

DR. VASSAL: Just a few comments. I do agree with you perfectly on the fact that the approval and therapeutic studies are not the appropriate name for these studies, and phase I, phase II, phase III, phase IV have been used during the last 10-15 years in terms of development of clinical studies in children with cancer. So I do agree very much with your point.

In addition, with regard to pediatric oncologists thinking that they might do their clinical trials outside the regulatory frame, just to mention that in 1988 in France, the first law for GCP was launched, and pediatric oncology said, oh, no, it's not for us. We will not be able to continue to take care of children within clinical protocols if we do follow this rule. And the government said, yes, you will go. And clearly, it did improve the quality of the study. It did improve the

safety of the patients. So clearly, there is no way to me that pediatric oncologists should do the clinical trials outside a regulatory framework.

Just with regard to what's going on in France, in a few words, it's a little bit more simple than what is going on in the UK. Each clinical trial has a sponsor, a sponsor responsible for conducting the study, reporting, monitoring the data, financing the insurance for the patients, and each study should be submitted to one ethics committee which is a little bit like the MREC. There are several ethical committees in France and one is enough to really look at all the items in terms of ethics. And then all the study goes to AFSSAPS, which is the French equivalent of the FDA, and should be approved by the French drug agency before being launched in terms of clinical trials.

Indeed, the main point in terms of clinically driven phase II/phase III studies is the point of improving monitoring and the point made before by you on the fact that monitoring maybe adapted to the risk of the patients in the trial might be a way to really get enough data in terms of safety, but not too many in heavy works in terms of reporting and monitoring of all this.

DR. SANTANA: Malcolm.

DR. SMITH: I would just comment from a U.S.

perspective that in the pediatric trials that we sponsor through the Children's Oncology Group and the Pediatric Brain Tumor Consortium, the various rules that we apply to our adult clinical trials that we sponsor apply equally to the pediatric clinical trials. So the adverse event reporting guidelines and expedited, when they need to be, all apply. The same rules concerning independent data and safety monitoring committees apply. So we try to make sure that our pediatric clinical trials system is compliant with all of the rules and regulations whether they be related to OHRP or FDA or the NIH regulations.

DR. SANTANA: Dr. Reynolds.

DR. REYNOLDS: I just had a question. You said that in Germany in pediatric oncology trials, however, these studies frequently deviate from regulatory requirements. Could you give us some examples and then how do you deal with that? If your deviating from regulatory requirements, are you giving exceptions or are you just looking the other way?

DR. KERN: I mean that these studies that are performed according to common protocols, there's no notification procedure. There is no inspection procedure. There is mostly no study monitoring. All those elements that are contained in GCP guideline are not executed within these trials. For instance, an investigator brochure or

these requirements that are laid down in the ICH Directive are not within the realm of these studies.

DR. HIRSCHFELD: I'd just like a clarification. On your last slide, could you clarify whether the German federal government is reviewing all protocols prior to implementation or whether the review begins and ends at the ethics committee level?

DR. KERN: No. We are definitely not reviewing all protocols. It would be impossible for reasons of personnel resources. We generally rely on the positive opinion unless we have some reason to suspect that something might be wrong. Then we take the study protocol. As a rule I'd say if it is about narcotic drugs and special permission to perform the clinical trial, we usually review the study protocol ourselves as well.

DR. SANTANA: So what criteria are used to have the government review a study? I'm trying to differentiate how that decision is made and what criteria are specifically used to say it has to have a governmental review versus it doesn't have to.

DR. KERN: There are no criteria. That's on a case-by-case basis.

DR. SANTANA: So the investigator voluntarily requests a review or you guys know about a study and request a review?

DR. KERN: No. The investigators have to contact the ethics committee first, get a positive opinion, and together with this positive vote, they notify our regulatory authority.

DR. SANTANA: Okay, and then what triggers the regulatory office to then say they do want to review the study too?

DR. KERN: As in this example I gave to you, we knew that the investigator in this case had already issued a personal opinion about the result of the trial he was just beginning to perform.

DR. HIRSCHFELD: So just to pursue that, the federal government will have then at least a superficial review of all protocols. That is, there will be someone who acknowledges a study is about to occur and someone that will acknowledge that an ethics committee has approved it. And then in that review process, if there's anything else that arouses suspicion or triggers an inquiry, then it would be at that level that the formal review would be initiated?

DR. KERN: I'm sorry. I'm even unable to say that we do a kind of superficial review of the study protocol. In first line, we just check whether there is a positive vote of the ethics committee, and I even doubt whether a superficial review of the protocol would

contribute very much. My personal experience with the review of study protocols is that this is a very challenging task, not easy to do, and it's time-consuming, and a superficial review wouldn't help. Probably I would even, for instance, have to consult a colleague from the statistical department. So it's really a challenging task.

DR. SANTANA: Dr. Poplack.

DR. POPLACK: Ursula, I was quite taken by one of your slides in which it stated that insurance is provided both for the investigator and for the sponsor. Is that truly the case? So that individual investigators are not at risk because their insurance is covered by the government.

DR. KERN: It's not by the government, but the sponsor has to make an insurance for the trial subjects and, by an indirect way, the insurance covers the clinical investigator as well.

DR. SANTANA: Any other comments or questions for Ursula? David.

DR. POPLACK: Just one general comment. I'm always good at stating the obvious. But I want to compliment Steven and you, Victor, for having this be a topic of interest for this committee because it is so important. As you very astutely pointed out, there's a tremendous need for us to do cooperative trials in

pediatric oncology and I would say probably in other pediatric illnesses as well, although pediatric oncology is our focus, because of the fact that, ironically, the more successful we've been, the fewer the numbers of patients that are available for study despite the fact that we have many, many more agents to study of potential interest. So it's in all of our national interests, whether you are German or French or Italian or American, to be able to look now beyond our borders to pursue international studies. I guess the question is how can this be done efficiently with appropriate safeguards. So the discussion session should be very interesting.

DR. SANTANA: Thanks, David.

Any other comments or questions?

(No response.)

DR. SANTANA: We have now an opportunity for an open public hearing. Is there anybody in the audience that wishes to address the committee?

(No response.)

DR. SANTANA: If nobody does, I do want to ask Dr. Ohye to make a brief comment about the industry perspective on this issue because many times sponsors have to go to different countries to conduct research. I wondered if you could give us a brief synopsis of your experience with this issue and what you perceive the

barriers and the problems are from the sponsor perspective.

MR. OHYE: First, I'd like to say I think the barriers are coming down.

With reference to what industry is doing, I think years ago they used to think in terms of having two programs, a program for the United States and a program for Europe, and a smaller program even for Japan where you'd probably have to have some bridging studies using the data generated in the United States and in Europe. But it's driven by economics. It's easier to do one multinational development program than separate programs. So I think that's a given and that's happening.

With reference to how they deal with local standards or cultural standards with reference to ethical compliance, I think the ICH has gone a long way to shrink the world and make everybody think almost in one mind in terms of how to deal with the ethical considerations or, as we sometimes call it, the duty of care when doing studies in children.

DR. SANTANA: Can I expand a little bit on your comment about how sometimes sponsors historically have made a distinction between a development plan in America and a development plan in Europe or another country? What triggers that decision? Or what's behind the separation or that distinction? Is it purely economics?

MR. OHYE: Quite frankly, the standards were sometimes different, and the resources that you would use in Europe, for example, you might use some of the consortiums available in Europe and their protocols might differ from what the FDA might demand or what you might think the FDA might demand in terms of control medications, use of placebo, and things like that. But I think now there is now international thought on what should go into a development program.

For example, it is acceptable today -- and I'll defer to Dr. Williams on this -- to use as a control drug an unapproved drug in the United States that may be approved in Europe because you know that drug is widely used and will, no doubt, be approved in the United States. So you can have a common protocol, and that's a lot easier to do today than it was in years past.

DR. WILLIAMS: There's no special requirement that a drug be approved for a certain -- are you talking about for a drug that's not approved in the U.S. or a drug that would not be approved for a specific indication?

MR. OHYE: A drug that may not be approved for a particular indication in the States be allowed to be used as a control drug in an ongoing trial.

DR. WILLIAMS: I mean, I guess even theoretically you can have a drug that wasn't approved in

the U.S. as long as we knew that it wasn't harmful. That's correct. The main requirement is a demonstration of efficacy. It might be important in certain settings where you have a very good approved drug, but in most settings the main requirement is just to show a benefit.

DR. SANTANA: Dr. Weiner?

DR. WEINER: Actually this question is for Dr. Ball and for Dr. Reaman. The Children's Oncology Group is an international group. It has, as I understand it, sites in Switzerland and Australia and New Zealand. Are there any lessons to be learned from those collaborations that might be useful in this context?

DR. SANTANA: Mark, you too in Canada.

DR. BERNSTEIN: Thanks, Victor.

DR. BALL: I'll defer to Dr. Reaman because I'm not sure what the question is with regard to OHRP. You were asking?

DR. WEINER: Well, you have a working group that is presumably addressing this topic, and I'm just wondering whether or not your deliberations have included any of the lessons that presumably come out of the COG collaboration and how that meshes.

DR. REAMAN: How the Children's Oncology Group operates in foreign sites, because we are supported by the federal government, those foreign sites have to comply with

all U.S. regulations, which includes have a federal-wide assurance number. So simply stated, the reason they are able to participate is because they are willing to follow the regulations which sites in the United States have to follow.

DR. BERNSTEIN: In addition, we have to comply with our national regulations, which can make life difficult on some occasions.

DR. BALL: With regard to the working group, we did consider more broadly the issues that have been brought to OHRP with regard to the difficulties in conducting research and some of the advantages that might follow from having an equivalent protection determination by the Secretary for other standards. So I think broadly. We did not specifically with regard to oncology trials, however.

DR. SANTANA: Mark, I want to follow up on your last comment. You kind of hinted about additional problems or issues with Canadian review. Can you comment specifically on what those barriers are, what the differences are, and what additional hoops you perceive are problematic?

DR. BERNSTEIN: Well, it's clear we have additional hoops, and so all of our trials, in addition, need to be submitted to the health protection branch, Health Canada, and that means that we need to submit a so-

called clinical trials agreement which includes the protocol, the consent document, and what has been difficult to date for investigational drugs, which is either a letter from the pharmaceutical sponsor of cross reference if there's an ongoing study in Canada or chemistry and manufacturing information. So this has represented for us an additional barrier to participation in the Children's Oncology Group studies, although, as Greg says, we do meet all of the U.S. regulatory standards. So this is a subject of ongoing negotiation to try to facilitate our compliance with all Canadian regulations.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: And just to clarify that the hoops through which people jump aren't only in Canada. Because of bilateral agreements between the United States and Canada, we have to be sure the we have mechanisms in place to assure compliance with those Canadian regulations. So as Mark mentioned, drugs that are not approved for use in Canada for which we are doing trials in which there's participation by Canadian sites, we have to file a clinical trials agreement. We have to have a mechanism in place by which we do not enter patients on those trials from Canadian sites until we have evidence of non-objection from Health Canada. So it implies a bit of work on our part as well.

DR. BERNSTEIN: Yes. Which brings me back to a question I had. For the International Committee on Harmonization, is there some sort of target schedule for when there might actually be regulations in place that all European and North American authorities would recognize?

DR. SANTANA: Does somebody from the FDA want to address that?

DR. LUMPKIN: I guess there's the question, when you say about recognize -- the example that people have talked about so far, the ICH documents, indeed are recognized by the Canadian and the U.S. and the European authorities. I think what you're running into is the issue of the implementation of those. I think what you're asking is would there ever be a time that the Canadian authorities would say, oh, well, never mind. The Europeans have looked at this, the Americans have looked at this, we're not going to look at it, or vice versa, anywhere around. I think that's going to be the hard one to get over for two reasons.

Number one, at the end of the day, when someone has to take responsibility for it, there's not an international taking of responsibility. At the end of the day, we here at the FDA are responsible for what happens within the jurisdiction of the United States as is Health Canada in Canada and our European colleagues there.

The other thing I think you have to ask yourself is, remember, if that happens, that means one person gets to say yes or no because if somebody is competent to say yes, they're also competent to say no. And that means if the first authority says no, we are not going to let this happen, it's over. Nobody else can raise their hand and say, well, wait a minute. Let's think this over again. Maybe it is okay here. And I think that's one of the things that when people start talking about are all of the government jurisdictions simply going to allow another government to make the decision for them, you've got to ask your question, are you willing for one jurisdiction to have the competence to say yes and no as opposed to just say yes.

So it's a bit of a long-winded of answering your question. I think there are several very complicated issues of responsibility that come through.

The real thing that we tried in ICH is to say, well, look, we realize each of us is going to always have responsibility for what happens in our jurisdiction, but can't we get agreement on the technical requirements because that's the big issue. And if we can work through the technical requirements, then hopefully it will be a yes, yes, yes kind of thing instead of yes, but or yes, but.

DR. BERNSTEIN: And is there a time frame for that?

DR. LUMPKIN: I think what we're trying to find here is what are the issues that we need to address within some kind of a framework, whether it's ICH or whether it's a bilateral agreement or whatever it is. The ones that have gone through ICH are, indeed, agreed at this point if they've gone through the ICH process. The issue now is -- and what we're interested in hearing from you guys -- the specifics of where are the problems, what are the issues that are standing in the way that we need to find some agreement on.

DR. SANTANA: Since you said that, I'll start. You mentioned some issues of technical requirements, and I won't address those. And you also mentioned the issue of defining responsibility and accountability, and I won't get into those.

But I think there are two things that I think when we look at if international studies are relevant. One is the lack of uniformity in the review process where different countries look at studies somewhat differently. A good example would be should a phase I study be a phase I study in England as it is in Brazil, as it is in America, and would review process look at the same elements to assure that all those are the same as it regards the design

of the study and the conduct of the study.

That gets into this issue then of the elements of the clinical study. Many times when you have studies that are reviewed in South America and the U.S., different review committees ask for different things in the paperwork of the study, and I think that creates a lot of barriers for review committees to have to go back and amend, change studies and you wind up with clearly a different, on paper, clinical study in South America as you do in the U.S. So there needs to be some uniformity of the elements of the clinical study and that everybody is talking the same language when they're talking about elements of the clinical study.

And then not to monopolize the discussion, I think another issue is the monitoring of the study. The monitoring of the study should be uniform across countries. There may be some local context issues that I think we need to talk about subsequently, but the monitoring of the study has to be uniform across all countries and it has to be independent of the country, so as much as possible have monitoring systems that are independent of the actual individuals who are running the study. I think that's more feasible when you have international studies than when you have local studies in which usually it's the people doing the study who are monitoring the study.

And then lastly is the issue of resources. There are always financial impacts. I've been dealing with trying to do a study in another country in South America through St. Jude, and there are financial issues that get tied by the country in the South America telling me I can't do this or I cannot do that and who is going to pay for this. So when we're talking about cooperative group studies, there is some element of financial backing, but the reality is many sponsors and many academic institutions, when they do international studies, have to look at the dollar sign and see how much it's going to cost in one country versus the other. So the financial impact of the study is also, I think, something to me that's a barrier when we start thinking about international studies.

So I just mentioned briefly three or four things that as an investigator I see are potentially problematic when you're trying to do studies across countries.

Yes.

DR. POPLACK: Just to follow up on the economic issue, even though costs shouldn't be one of our foci, it's gratifying, I think, to hear that for pharmaceutical corporations that the supranational view is the view of the day, but they can afford to work with existing circumstances as far as regulations are concerned because

they have the financial resources to deal with these differences. If a trial is initiated by an academic institution in any of these countries that don't have the resources, then we are much more hampered by not having the resources to cut through a lot of the bureaucracy. So I think that to some extent one could argue for the need for change because of the threat that the only trials one will ever see may end up being trials that are done by pharmaceutical corporations.

DR. SANTANA: I have another issue that I think to me is a barrier. I don't want anybody leaving the room today thinking that I'm an expert in this area, but I've read and I've been here many times that I've listened to different aspects of international research. When I listened to our colleagues from Germany and France and England talking -- and I think I'm an educated person -- it's appalling that I'm not aware of everything. So I think there's a lack of education about what the different standards are across different countries. The pharmaceutical industry is very aware of this and they're very keen to it, and that's why I think, in part, they develop different clinical development plans for Europe versus the U.S. because they're very versed in the regulatory aspects and the differences, whereas I think the rest of us in cooperative groups and academia are not as

versed, and I think there's a lack of education of trying to understand the differences, not the commonality, but the differences between regulatory issues across countries that would make our lives easier when we want to propose doing a study. So I think lack of education at the general level of the investigator is very critical in understanding this.

DR. LUMPKIN: Can I ask, just in follow-up for my education, if you were to design a trial that would have U.S. sites -- and say, for example, since we have experts from the United Kingdom, if you wanted sites in the United Kingdom, would you work with the Children's Cancer Group that was mentioned earlier? Would that be the mechanism by which this would occur outside of the pharmaceutical company perspective? It would be the working of the two children's cancer groups together?

DR. SANTANA: I think that's potentially a model. It's not the only model, but I think a potential model is if I wanted to do a study either through COG or as a single institution and I wanted to search other sites, I could go to the COG if I was a single institution and say, can we do this together, or I could go to Europe and the UK and say, can we do this together. That's one potential model, but it's not the only model.

Greg, I think you had your hand up and other people on this side.

DR. REAMAN: (Inaudible.)

DR. SANTANA: Dr. Anderson.

DR. ANDERSON: We've talked about ICH guidelines which we recognize the European countries recognize. So we seem to have a basis there. There are problems that come up when you have multi-center trials, which we have to do basically in pediatrics, in multiple sites in Europe, as well as the U.S., in that when we try to even start to bridge the gap there, the regulatory assumptions that come with who is following ICH guidelines differs from the U.S. side versus from the European side such that the U.S. basically takes the role of saying here are the forms -- I think this was referred to earlier -- that all the institutions within Europe must fill out if any U.S. institution is to participate or interact with the European institutions. That, I think, if you want to talk about a barrier, has caused many studies, I'd say, to become non-starters.

At NCI we're trying to work through that with several different models trying to work with what are sort of the OHRP guidelines that are in place, but it's a long road. It's not a clear road and I can tell you it just takes a long, long time. And I don't know whether from the European side the U.S. will face a similar situation on either the ICH guidelines or on other issues in the near

future as well.

DR. SANTANA: Dr. Morland?

DR. MORLAND: I think Barry has made a very important point. The truth is that we've done this before. We've done a collaborative phase III study with CCSG and with SIOP in France which was a very successful collaboration some five, six, seven years ago I guess. I get the sense that it's now more difficult to do that than it was six or seven years ago. I don't know whether Mark might want to comment on some of the difficulties that have been going on with the discussions around the proposal for a new multinational osteosarcoma study, but my understanding is that the regulatory issues rather than the clinical issues are one of the major barriers to this study being launched.

I think the concern about the perceived bureaucracy that we all have to deal with is one of these big barriers. It's particularly the issue I think about all of the science in Europe getting FDA approval, whatever that means. I think it's seen as quite a challenge.

I'm not sure why we can't just deal with this nationally in that if this is a cooperative study, the responsibility for patients in the UK are the responsibility of the UK; the responsibility for the patients in the U.S. are the responsibility of the U.S.

And why we have to go through the degree of cross-checking and cross-referencing is to me a little mind-boggling.

DR. SANTANA: Mark, do you want to comment on that?

DR. BERNSTEIN: Yes, I'll comment briefly. Then I'm afraid I need to go.

Barry is well aware of these issues and with his help we are -- there were two studies that would be worth mentioning because it turns out the requirements are somewhat different. The Children's Oncology Group bone sarcoma group will be participating in a Euro Ewing's study. That study was already ongoing at the time that we said we would join. So, therefore, it turns out that the regulatory requirements are somewhat simpler than for the osteosarcoma study that Bruce referred to where we have participated in its planning. So again, it turns out that the regulatory requirements are a little bit stickier for that study.

What we have, I think, successfully done is that as you say, Bruce, each national group has acquired a federal-wide assurance number, so an FWA, not an FDA. And each national group will serve as the supervisory body for the institutions within that country that are participating and will serve kind of as their guarantor, and actually the Medical Research Council will serve as the European conduit

for that guarantee. I would say that certainly our colleagues from Germany and COSS have been quite firm in their adherence to the ICH and GCP guidelines as they are written. So it is a complicated process to work through, and certainly a simplification of that process would be very welcome.

DR. HIRSCHFELD: Mark, could you just clarify what you meant by "sticky"? Is it just the volume of having to go through so many different authorities in sequence and so many IRBs or are there actual discrepancies and differing requirements?

DR. BERNSTEIN: There were a bit different requirements. For our participation in Euro Ewing's, Muenster, which is the COSS headquarters, needed to acquire a federal-wide assurance number, but after that, the requirements were relatively simple for us to join an ongoing study. It seemed to be a bit more difficult in terms of guaranteeing that we had a monitoring plan in place for quality assurance and the institutional monitoring and so on for the localized osteosarcoma study.

DR. HIRSCHFELD: Could you just be a little more specific in terms of, again, the differences that you had to overcome getting the de novo study organized?

DR. BERNSTEIN: For the de novo study, we not only needed each national group to have a federal-wide

assurance number for their principal site, but we also need to ensure that there is an independent data safety and monitoring board, which there is in any case for Euro Ewing's, but we needed to guarantee and approve the setup of the data safety and monitoring board for the osteosarcoma study. We're in the process, because the study is still not open, of planning how institutional monitoring will go forward in terms of quality assurance in terms of setting up site audits based in the national groups although, as I said, for Europe with overall oversight from the MRC.

DR. SANTANA: Mark, clarify something for me. This issue of the independent monitoring, if the study were done in the U.S. and it did not include Europe, it still may mandate an independent safety and monitoring board, or are you mentioning the fact of how the data is collected across different sites to allow that group to review the study? Are you addressing both or just one of those?

DR. BERNSTEIN: Well, we're doing both.

DR. SANTANA: Is the barrier in both or in one of those?

DR. BERNSTEIN: Well, the data safety and monitoring board was simpler because all of the European osteosarcoma intergroup and all of the COSS studies and all of the MRC studies already had a mechanism in place to set

up an independent data safety and monitoring board. So that is in addition to the Children's Oncology Group solid tumor data safety and monitoring board. So that mechanism was already in place, and so we simply utilized that mechanism to have such a DSMB setup.

In terms of the monitoring, that was a bit more complicated because as the German speaker mentioned, site audits and so on aren't necessarily currently in place in Germany although they are moving toward that system. So what we needed to ensure for the osteosarcoma study is that such site audits and auditing of data quality would be implemented.

Does that clarify that?

DR. SANTANA: Yes.

Dr. Anderson?

DR. BERNSTEIN: I'm going to need to go. So thank you for inviting me.

DR. SANTANA: Thank you, Mark.

DR. BERNSTEIN: I enjoyed listening.

DR. HIRSCHFELD: Thank you, Mark.

DR. BERNSTEIN: Thanks, Steve.

DR. ANDERSON: Related to what Mark had said, one of the other major hurdles for a while was trying to figure out how to bridge. If you just look at the regulations or guidelines, whether each institution within

each of the countries, such as Germany -- there are perhaps 80 to 100 of the institutions that would participate in the study -- would each have to get their own FWA, meaning the federal-wide assurance, for COG to be able to participate with them. And we have worked it such that the central coordinating center in Muenster has that assurance, as well as the data center there, as well as each of the other groups in Scandinavia and in the UK that will participate. They have their own FWAs in place. A number of individual institutions within each of the countries already had FWAs in place, but the MRC will be the coordinating center and the data center through which everything would come through basically. They will be actually where all the data will go to, as well as from the U.S. It will go to them.

I think when I had asked about who has the oversight role in the UK if someone doesn't follow the ICH guidelines, the MRC is going to play that role because when we were having our discussions with the Europeans, we were trying to figure out who is the OHRP equivalent, who do you go to to say this institution or this investigator really shouldn't be participating and we need to have them taken out of the study or invalidate their results or something like that. So the MRC will play that role.

But it's something we had to figure out over time and it's not something that's easy to do because there

are very few institutions or bodies within Europe that NCI can work with in this way. The EORTC would be one. The MRC would be one. There would be few if any others. The only other route would be that each institution would have to have their own assurance, and while it's only several pages of a form, to get each institution within a country to fill those out, understand what they're doing just takes a lot of time.

DR. SANTANA: But that was an issue of lack of education of understanding that there are different ways of getting to the same point. You either have a center that holds the FWA or you have multiple centers that independently each holds their FWA. Am I correct?

DR. ANDERSON: Yes.

DR. REAMAN: It went way beyond education.

(Laughter.)

DR. REAMAN: Because this evolves and changes on a regular basis, and some of it actually relates to who is the coordinating center or who is actually doing the study. In the case of the Euro Ewing's, COG was joining a study. So the only group that had to have the federal-wide assurance number was, in fact, the coordinating group and the coordinating center, which was in Muenster.

DR. ANDERSON: And the data center as well.

DR. REAMAN: And the data center as well.

For de novo studies being developed, early on it was every institution regardless of where they were had to have a federal-wide assurance number.

So I'm not sure that education is really involved here. There's just a changing thought process and decision making.

DR. HIRSCHFELD: Could you just clarify? Was there a requirement for every country or region to have its own data safety and monitoring board?

DR. REAMAN: Well, that's another issue because there's some discrepancy in what is the role and the responsibility of the data safety and monitoring board. For our studies, the data safety and monitoring board is independent, and the data safety and monitoring board has the responsibility of, for reasons of patient safety, basically halting accrual to a study. In other places, the data safety and monitoring board is advisory to the coordinating center or to the study committee, which I think -- correct me if I'm wrong, Barry -- is still something that is being discussed and negotiated about how the osteosarcoma study is going to be done, if it's going to be done.

DR. HIRSCHFELD: So one data safety and monitoring board could say, stop the study and another one could say, we've examined this and our advice is to

continue.

DR. REAMAN: Well, no. What would happen was that the data safety and monitoring board would say, stop the study, but in one country they would say, well, the data safety and monitoring board only provides advice to us, the organizing committee, and we're not going to heed that advice and we'll keep the study open.

DR. SANTANA: Dr. Lumpkin, did you have a comment?

DR. LUMPKIN: I just want to make sure that I'm understanding this correctly. It sounds like a lot of the issues that you guys are putting on the table are issues that derive from the fact that these studies about which you are talking are federally funded. Correct? Therefore, you're falling under the OHRP regulations that require you to have these federal-wide numbers, et cetera, as opposed to these are FDA requirements that you're falling under.

DR. REAMAN: I think they're all OHRP requirements. They're not FDA requirements.

DR. LUMPKIN: I think so too. And I just wanted to make sure that I was clear on that so that if there were things that we could do or if there were issues we needed to address on the FDA side, that it was clear what the FDA issues were. If there are things that are OHRP issues that need to be addressed, we need to make sure

that we're clear what those are just so we know who needs to take what home to deal with. From what I'm hearing, it sounds like it's primarily this piece of the OHRP regulations that Dr. Ball was talking about that the committee is trying to work on to see if there's a way that you guys can look at some of the foreign sites or foreign ways of doing this as equivalent. But that's the main issue that you're trying to deal with right now. Is that correct?

DR. REAMAN: Correct. The only difference would be with respect to some of the studies that we're doing -- well, all of the studies are being done in Canadian sites, and the assistance that's required sometimes on the part of the FDA in obtaining the clinical trial agreements in Canada, particularly when it comes to providing chemical and manufacturing information. But I think all of the other barriers, obstacles are really more OHRP than FDA related.

DR. HIRSCHFELD: But what we're touching on are studies that are done with already-marketed drugs.

DR. REAMAN: Correct.

DR. HIRSCHFELD: And we haven't even touched on the issue of using investigational agents in this discussion.

DR. REAMAN: And I think the reason for that is

that we're having so much difficulty with already-approved and marketed drugs that no one is even fathoming going to the next level with IND drugs.

DR. SANTANA: Dr. Reynolds.

DR. REYNOLDS: I want to touch on an issue that Greg just mentioned that Mark mentioned earlier that I think is an FDA issue because we've been hammering on OHRP here, and this is an FDA meeting, and that is access to new agents. In addressing that question to you also, I noticed that there's a report due, I believe, from you all on access to new agents to Congress. I wondered if we would be able to have a copy of that to look at. It's just a general question because I think it's a general question on the access to new agents issue.

But specifically with respect to access to new agents for the foreign studies, I know exactly what Mark is talking about. It's a phase II he can't get open in Canada -- he very much wants to -- because the IND has been assumed by the NIH and they can't get the manufacturing data out of the company that dropped the IND because they just don't seem to be able to provide it, which is also holding up a phase I study that we want to do in the U.S.

So the question there is really how can the FDA help that. I think one thing that could help with the foreign sites in general would be that if you guys could

develop an agreement between at least the major countries that we interact with on a pediatric oncology basis to where letters of cross reference or something can go smoothly; in other words, a reciprocal agreement, that if the FDA in the U.S. has said a drug is manufactured according to specs and it's okay to go here, that they would just reciprocally agree to that without having to force the investigators to go out and beat this information out of someone.

DR. HIRSCHFELD: That's a point that I think I can just share that we've seen. We're called, I would say, regularly for assistance because somebody wants to do a study and would like to cross reference an IND and we cannot acknowledge whether the IND exists or does not exist. We cannot direct them toward the appropriate party or share the IND number that they could cross reference, provided that one exists, because of a number of constraints. And then we watch people -- and I would say just speaking personally -- in a helpless way while they're floundering around writing letters and trying to figure out who holds the IND and then trying to get permission to cross reference. Then they may or may not get that permission to cross reference and then come back to us and say, well, can we do the study anyway if we open up our own IND? And we've just watched six months go by.

DR. REYNOLDS: Well, see, these are examples of barriers that the agency could help with. You don't have to go talk to OHRP to help with those problems. You can do it within yourselves.

DR. SANTANA: Dr. Ball?

DR. BALL: Yes. I just wanted to address Dr. Reaman's comments. I think that it is very important to remember that even with any potential implementation of the equivalent protections provision of the regulations, it may still require an assurance. So I think that it's very important for our agency to hear exactly where the barriers are because I'm told by our assurance division that there are over 5,000 FWAs currently. 20 percent are in sites outside the U.S. and that there is now an electronic submission mechanism by which you can have an answer, have an FWA number in as little as five days. I'm sure there are barriers, but if we can help identify those and we can try to fine tune that and work and see if there's a way to get around those.

DR. SANTANA: Barry?

DR. ANDERSON: I've been on the OHRP web site. I've helped people who were trying to put trials together find out does this institution in Brazil have an FWA. But that all I understand.

The issue comes up whenever the European

institution says, why do I need an FWA for us to collaborate, because they are also sponsoring the study. The U.S. is putting in some money to support the COG institutions, but I'm not supporting the UK institution. I'm not supporting the German institution. So what I was saying is that they have, I think, then the right to say to us, here's all the paperwork you have to fill out now for the German government, for the UK government, for this or that, which is going to be retaliatory strike, in a sense, that will stop COG again from being able to collaborate because it's not whether it's easy to fill out. It's why do I have to fill out something that comes from the U.S.

DR. BALL: Are they accepting HHS funds in those circumstances?

DR. ANDERSON: I don't know how you draw the lines. It's a cooperative trial. So we are accepting in a sense UK and German funds as well. In both these cases, they're not run by the U.S. The European data center is going to be the main data center. It's going to be the coordinating center for the trial overall. U.S. funds would go into it because COG is a participant. So essentially COG is the one who is blocked from participating if the European institutions don't obtain an FWA. That's what the reality is.

DR. BALL: I could see that as a difficulty,

and I think that there really does need to be some more dialogue with the OHRP on how that might be addressed because I think it is a complex problem. But I also want to emphasize that if a foreign institution is receiving HHS funds, similar to the FDA regulatory authority regarding FDA-regulated products, OHRP has the responsibility to oversee the use of funds in those sites.

DR. SANTANA: Dr. Boos.

DR. BOOS: This is a bit difficult. I once read a draft guidance of the FDA where it was pointed out that the phase III trial is the standard of care in pediatric oncology, and this is still true. And it makes an important difficulty for us because what we discussed today is how to organize GCP in worldwide trials. At several points we come to difficulties to decide what is now GCP or what is the problem with GCP, and this is significantly different if we have, for example, this French-English group that did several explorative or confirmative phase II trials in 10 centers, which is quite easy compared to an osteosarcoma trial with maybe 100 centers in Germany. There is a broad spectrum of experimentality and organizational problems in the spectrum of clinical trials between phase I and phase III or even standard of care organization, what we try to bring under the phrase "therapeutic optimization trials." Those were

those trials where we even couldn't say which was the drug we address questions to.

And the osteosarcoma trial is in this first part. Just the standardization of what has been done on a routine basis in several countries in the world, now to bring to one protocol and just to make quality control of what happens, and at the end it then is a randomization of an experimental drug in patients in remission with the question, does it prolong remission, does it reduce recurrence rates or relapse rates.

What we need there is a very, very detailed discussion, what of GCP is necessary. GCP is always a frame, but where in this frame do we have to organize the trial? Do we have to take one sponsor or can we take seven sponsors for every country? Do we need one data safety committee or do we need seven data safety committees? How do they have to organize the exchange? How do we have to initiate the trial sites? Do we need CVs of every investigator or every sub-investigator, or do we need signature logs for every involved physician in these hospitals? Or do we need working procedures for the local pathologists in these hospitals? Or what else do we need? Do we need double data entry? Or do we need specifically validated databases? Or how about handling of surgery? Is the source data the first written note in the surgical

protocol, or is it the letter of the surgeon to the physician on the pediatric ward? What is the source data? Do we want to sample them in the centers or not? How do we organize the monitoring? 10 percent of the trial size or 10 percent of the data? And all these things have to be organized.

And this is an enormous amount of work if you compare such a trial with what has been on a standard basis even in companies because I think never any company runs trials where up to 95 percent of the specifically ill patients had been involved. And this is the breaking point because you in your talk told us that the GCP guidelines were where you worked on what developed on criticisms of the regulatory capacities to the pharmaceutical industry and therefore quite a significant different situation.

We all agree that the principal ideas, data safety and more than this, patient safety, there's no doubt. This is the aim of everybody here, but how to translate this, how to define the hundreds of guidelines with respect to these aims is the critical point. From my point of view, we need a guidance which offers us, really actively offers us, the frame in what we can decide, that we do not have to discuss every protocol with every authority and every ethical committee, that we have guidance where we can say, okay, this is within what we are

allowed to decide.

DR. SANTANA: Let me see if I follow you. So your comment is that there already exists a number of documents out there, GCP, international harmonization guidance, et cetera. They kind of provide a template or a framework to kind of generically conduct studies, but what is lacking is a guidance on the organizational structure of how those studies get conducted and how you overcome regulatory hurdles, international legal hurdles.

Let me not put words in your mouth, but that's how I understood it, that we already have a template of how to conduct the study and we have variances among countries, but in general, most people agree that those guidance documents we try to follow to some degree. But what's lacking is the organizational framework in which that can be conducted equally among countries without having to do this discussion every single time we have a study.

DR. BOOS: We have a guidance how to handle pharmacokinetics in children. And this is a bit different than in adults. What I wish to have is a guidance on how to interpret guidelines in the variety of pediatric oncology situations because there is not one situation. There are hundreds of situations.

Even if we take the EU Directive, which has been mentioned several times, it has the phrase "non-

commercial" clinical trial. This has not been translated into the German version, unfortunately. But the only thing which is a compromise there is that the labeling of the investigational drug is not that strong. We have lots of discussions with authorities and our inspectors which drug do we have to label as investigational. This is one of the first things we normally cannot decide because we prove concepts in many of the trials. Therefore, I think the discussion has to discriminate between clear-cut drug-related drug developmental trials, phase I, II, and phase III, and between trials which clearly are drug-related but have more aspects of quality control.

DR. SANTANA: Any other comments? Dr. Poplack.

DR. POPLACK: Just a couple of comments. To follow up on Greg's point, the discussion today has focused to a great degree on phase III studies and the difficulties of carrying out phase III studies, but the need is for international phase I and phase II studies. I think you've heard that people are very skittish about even attempting this at this point. So one has to look at what's going to happen if we're not able to circumvent the barriers that exist.

Well, there are many new agents that are "targeted" towards unique targets which make our small pediatric population even smaller, and it may be that

without having the opportunity to go beyond either the European borders or the U.S. borders, we just won't be able to do those studies.

What will also happen -- because it's happened to date, and I think this is an ethical challenge -- is that you'll see that phase I and phase II studies of the same compound will get done in both spheres. So you take a very precious resource that's crying out for new therapies, and that is kids with cancer, where we end up doing duplication, as Ursula pointed out.

So some way or another, we have to be able to address this issue, and whether it means a commission of European and U.S. regulatory authorities getting together to go through point by point the areas of potential conflict to find commonality, I'm not certain what the right approach is, but the losers in this are going to be the children.

DR. SANTANA: Dr. Shurin.

DR. SHURIN: I think this in many ways sort of an organizational and administrative challenge because we've already got not only the clinical practice, at least some common definition with the ICH-GCP, but the general principles of conduct of research actually we all agree on. It's how to implement it rather than what they are.

It seems to me that the worst thing we could do

would be to create an infrastructure which is very top heavy and very centralized. What you need is something that delegates the trusts people to assume responsibility to be accountable. It's going to require a tremendous amount of education and it absolutely, I think, is going to require, as David mentioned, having some sort of commission to sit down and hammer out how we need to do these. We don't necessarily need to do exactly everything in the same way other than the fact that adverse event reporting and the response to adverse event reporting has got to be the same whether you're in Brazil or in Muenster or in San Francisco.

Beyond that, the biggest issue really is allowing the people at the local area to figure out how they're going to solve their particular problems. I think what Hugh described in terms of the local IRB -- we're not going to sit here -- Greg will tell you as well -- and say that we know how to do this because we already have these problems with the local IRBs. But there are certain things that are properly determined at a local level, and there are other things -- I think we already sort of know what they are. It's really, I think, sort of a matter of sitting down and doing it.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: Just to follow up on Dr. Ball's

question -- and it just sort of clicked -- the issue of federal funds going to institutions outside of the United States and when that happens, the need for compliance with all U.S. federal regulations. I don't know who does the interpreting here, but in the cases that we've been talking about, there are no U.S. funds going to any institutions outside of the United States other than those institutions that are already members of the Children's Oncology Group. But there's no money going to any of the institutions in the UK or to Germany. But the concept is that this is a trial that is sponsored, conducted by a group supported by federal funds, and therefore the conduct of that trial has to be in total compliance with U.S. federal regulations which includes all centers having federal-wide assurance numbers.

DR. SANTANA: Do you want to respond, Dr. Ball?

DR. BALL: Just that I think that with regard to any ruling of equivalent protections, while it may well require an assurance, there may be a set of guidelines from other countries or other bodies that would be deemed to be equivalent. Therefore, there would not be the requirement that all human subject protection regs, 45 C.F.R. 46, were followed, which would allow the countries to use their own standards.

DR. SANTANA: I'm going to look to the FDA for

some guidance here. I think we've covered a lot in the discussion. I'm not sure, as I think through the two questions that you have posed for us, that we need to address them. I think we've covered most of the issues in enough depth, that I think you guys have some sense of what our concerns are. Rather than spending a lot more time rehashing the same subject, I'd rather, if the FDA agrees, unless anybody has any other points to make, to end the discussion at this point.

DR. HIRSCHFELD: I'll defer to Dr. Reaman and then come back.

DR. REAMAN: I would also like to just follow up on the point that David made. I made the comment earlier that we've had so much difficulty trying to do phase III trials internationally that it has really precluded our even fantasizing about doing earlier phase studies. But maybe we should think outside the box and, maybe since the critical issue is really one of early phase studies, maybe really look at creating opportunities for how we can do international phase I and phase II studies and make specific suggestions. Maybe we can do it in such a way that we don't have to be concerned about whether or not a site or a study is being supported by federal funds. Maybe we could look to industry in part to support this effort as well. But I would just like to make that plea,

that we not just throw up our hands and say we can't do anything. Maybe we're really doing it the wrong way, trying to start with phase III studies. Maybe we should really be starting with phase I and phase II studies.

DR. SANTANA: Yes. Maybe a different model is --

DR. REAMAN: And use this as an opportunity to create that model, or at least a group that would help create that model.

DR. HIRSCHFELD: Well, thank you, Dr. Reaman, because that was exactly what I wanted to bring up. We're in the position where we've issued about 30 written requests now in pediatric oncology, and we want to be sure that when we issue a written request -- and more than half of these are for investigational agents -- that there's an opportunity for someone to actually perform those studies and perform them in a timely way. There might be some type of a clue in the fact that if a sponsor to whom the written request is issued does submit a study report, they will get a financial reward for completing that study report. So this might be the arena to think about certain types of partnerships.

In answer to Dr. Santana's question, are there specific suggestions that the committee might have of either areas to pursue or unresolved issues that should be

carried forward before we conclude today?

DR. SANTANA: Does anybody want to volunteer some answers for Dr. Hirschfeld?

DR. HIRSCHFELD: Or recommendations of things that could be done right now.

DR. SANTANA: Dr. Reynolds.

DR. REYNOLDS: I just want to return one more time to what Greg is suggesting. We're doing new agent trials on an international basis, and we've got to have the availability, the access of those agents to the international population. And it's really going to take you guys talking to the FDA equivalents in those other countries to make this happen without us chasing around trying to get this stuff done. We need some help there.

DR. SANTANA: Susan.

DR. WEINER: For some reason at these meetings, it always comes to me to make the moral point, but in this instance it's a follow-up to something that David made. Families want rapid access to new agents, and it really is a moral imperative for those kids with solid tumors and those who have poor outcomes.

And we've also heard at these meetings that it can take as long as 10 years for a drug that can become standard therapy in pediatric oncology, and we also know from the various phase I consortia that it takes about 2

years to complete a phase I trial in pediatrics in the States alone. So to think that that time could be cut in half is an extraordinary notion for a family to consider and families that I deal with to be able to say them.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: Yes, I will fully agree on this proposal by Greg Reaman. I like the point made before, that these studies should be considered at the cooperative level and not at the individual level because the risk is just to pick up in Europe in this way and this place one or two investigational sites, and this should be done through a really well-structured cooperative group working together with the same approach.

DR. SANTANA: But within that model, within the cooperative group, you could have smaller groups that address some specific issue with phase I so that --

DR. VASSAL: Sure. I'm referring to recent experience considering pharmaceutical companies wanting to develop phase I and phase II which we're not considering exactly the same way.

DR. SANTANA: No. I was referring to the model that in order to identify what the hurdles are and to begin to address some of the hurdles, if you wanted to get into the arena of international phase I studies, you probably don't want to do that in 150 institutions, but

within the cooperative group, you identify some institutions you can collaborate with and try to resolve the hurdles first --

DR. VASSAL: Absolutely, but not outside this.

DR. SANTANA: Dr. Morland.

DR. MORLAND: Yes. I couldn't agree more. I think probably Gilles and I have the example of this where eight years ago the UK and French groups came together in order to start undertaking joint collaborative phase I and phase II studies, and we recognized that there were some regulatory differences between the two countries, but broadly speaking the philosophy of managing patients was absolutely identical. And I guess that's the sense I get round this table today. The thing that fueled our collaboration was access to a drug and an ability to do a study. So there's nothing like learning by experience.

I think that Greg's point was well made in that actually to get on and do a study as a proof of principle, if nothing else, and that the groups can collaborate and cut through some of the regulatory issues in the process is probably the way of driving this forward and actually proving to us all that we can do it because I think it's probably easier than we think it is going to be.

DR. SANTANA: Dr. Boos.

DR. BOOS: Yes. I'm sure that today running

early clinical trials as may be mentioned in a written request is multinationally feasible. There's no problem. We did it several times. There are many examples. If there is financial backing and few institutions are involved, I think this is possible.

One of the mistakes which often is done I think is that companies then contact CROs in Europe they are familiar with and not the societies which have access to the sites. This could probably become better.

With non-commercial trials, with investigator-initiated trials, I'm sure that phase II trials would be much easier because then in Germany we have not the idea to bring everybody into this trial and that the scientific advice you mentioned before would be helpful as it is really inflexible response on the needs of GCP which can then be discussed.

And the third thing for phase III, I think Mark Bernstein mentioned the Ewing's sarcoma trial is one where we are involved and is one which has been done in, I think, currently five or six European countries and jumped across the Atlantic now, and I think it is an example for what is possible in these international links. As the experience of the guidelines comes from industry trials and their problems, I would think it's an enormously important thing -- and today is the best step in this direction -- to look

how is the pediatric society organized, what really is running very good and take these good things and push them and stabilize them and not put energy in new guidelines, new problems, strong legal frames which destroy what we still have and does not enable us to become better in other fields.

DR. SANTANA: Dr. Winick.

DR. WINICK: This may be repetitive but I think that in the context of doing phase I and phase II trials, multiple countries and institutions have adverse event report forms that I would guess are relatively similar. Several people here -- I'm sorry Malcolm isn't here -- just went through the exercise in defining common data elements, and I think that some of these things with respect to monitoring and making sure that data exists -- I understand that process has come to something of a roadblock, but I think that there are multiple tools already in place that would truly facilitate international phase I and phase II trials.

DR. SANTANA: Yes, that's a good point. There are already a lot of items that have been defined very well through some of the NCI mechanisms that I think, if we adopt those and agree that everybody will use the same, really will improve this process.

Dr. Shurin.

DR. SHURIN: You're looking at next steps, and it seems to me the next step really ought to be for a small group of people to sit down and enunciate what needs to be in place and then look for what works the best. I don't think that would take long. I think you could probably get a small group of people together for maybe two days and actually make that happen.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: I think the specific next step really ought to be to decide that there should be an international consortium to do pediatric phase I and phase II studies in childhood cancer. So I would propose that as being the next step and then following, as Susan suggested, putting together a small working group to make that happen. Each of us already has a consortium, and I don't think we're talking about doing these studies in 500 institutions. We're talking about maybe 20 or 30 institutions in the U.S., 5 or 10 in the UK and in France and Germany. So I would suggest the next step really is a recommendation maybe from this committee that there should be an international consortium for early phase studies in childhood cancer.

DR. SANTANA: Greg, who do you think will take ownership of that?

DR. REAMAN: The international consortium and I

would hope that the FDA would also take some ownership. I mean, this is our recommendation to them. They invited us to this meeting. And I would hope, as they've invited federal regulatory representatives from abroad, that they would continue to do the same and play a role in mediating the regulatory challenges that we would face.

DR. SANTANA: Dr. Riccardi.

DR. RICCARDI: I think what we are looking for is for uniformity and high quality and to be able to produce a certain number of studies. So, however, I think that in this sense, at least from Europe's side, I think the organization that has been built by the French and the English group, now called ITCC, in which we have a European consortium, probably will be the ideal starting point because one of the problems that we can see with phase III trials, there are too many centers and bigger differences. I think already we are reaching, at least in this consortium, a certain degree of uniformity and capability also to work together with colleagues in the U.S.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: I'm afraid I'm listening to people who tried to do phase III trials and all of a sudden they decided, well, it's very difficult to do, so now maybe it's easier to do phase I trials. Well, I'll tell you, I'm involved with a group who are doing mostly phase I trials

with 10 sites within the United States, and you're not going to avoid the monitoring problem that you talked about in phase III. In fact, the monitoring problem has even increased because the success to doing rapid phase I trials is rapid communication of accurate, timely data regarding toxicities, et cetera during the observational period that you define. You have to have a really slick, good infrastructure for communicating and getting that information and verifying that information in time to dose escalate.

Also, you're not going to avoid the problem of having data safety and monitoring boards because we had to instigate a data safety and monitoring board for our phase I trials. So you have to figure out how to integrate those in there.

So while it's laudable to do it, I think that you need to realize that the monitoring, I think, is going to be more intense than it is in a phase III where you have more time.

DR. SANTANA: Dr. Poplack and then Dr. Reaman.

DR. POPLACK: That may be the case and I don't think anyone was suggesting that we do phase I trials because it involves less monitoring.

(Laughter.)

DR. POPLACK: Not the case at all. We

understand that.

But the virtue of doing phase I's is something alluded to by Riccardo, that they require a smaller number of institutions. You can be much more selective about the institutions. You already have, as was mentioned, existing consortia that have the expertise. So a lot of the concerns about quality control that you might address in larger group studies are sort of off the board and taken care of. So I think that is an advantage in many ways.

In following up on what almost everyone has, I think, suggested, I think it would be wonderful if we could suggest as a committee that the FDA consider bringing together their colleagues, European colleagues, and the appropriate representatives of the different, important constituents in this to sort of begin to pursue this in a really intensive way. Whether it's around a single phase I study as an example or case in point which might, in many ways, flesh out the specific issues or whether it's to take a look at the existing regulations and find commonality, I'm not sure exactly what the appropriate way to do it is. But I think it would be great if we could suggest that to you and if you would take up the challenge.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: I just wanted to respond to Dr. Boyett that he was preaching to the choir.

(Laughter.)

DR. REAMAN: We come from a present and a past of consortia that do phase I studies. So we are very well aware of the need for monitoring. I don't think any of us is the least bit opposed to monitoring. It's overcoming the obstacles and the barriers to that monitoring because of the multiplicity of mechanisms and means of doing it. So I think it's not to say that it's going to be easier. It's really that this is more focused, more efficient. We already have some good models in place. We also have phase I/II data safety and monitoring boards, and I think we can do this and I think we should do this, more importantly.

DR. SANTANA: Dr. Vassal.

DR. VASSAL: Just two comments.

First of all, I think one of the main objectives could be to really address early drug development in terms of phase II because clearly to have in a relatively short time enough patients to really address the activity of the new compounds with a recommended dose in such and such disease and avoid these type of studies we saw on the previous ODAC committee where the drug was given to 80 to 70 patients and we don't have enough patients with a neuroblastoma, brain tumor, and so on to really conclude. So it might be one of the aims of this international consortium to really address in a timely fashion the

activity of this new compound, once it is established in terms of recommended dose, in several diseases.

And the second point is you mentioned the regulatory body in Europe. I just wanted to say for the record, there is no representative of EMEA, but EMEA is clearly dedicated to pediatrics and pediatric oncology, and they have been working on the guidance for registration of compounds in childhood cancer. There is now a pediatric expert group and there is now a therapeutic advisory group in oncology with pediatric oncology experts. So clearly EMEA is wanted to be a real partner of this dynamics in terms of pediatric oncology and improvement of the way to develop drugs.

DR. SANTANA: Dr. Weiner.

DR. WEINER: The Best Pharmaceuticals for Children Act has in it a provision that asks the FDA to describe its approaches to getting access to new oncology drugs for kids. Those of us who worked on that legislation did it for a very specific reason; that is, we were really interested in addressing some of the barriers that have been brought up today. And I would hope that the report, since it hasn't been filed, would take the kind of broad approach that this discussion has taken and would include the recommendation that this committee has made. This committee doesn't review drugs. This committee was really

brought together and codified to be strategic with everybody around the table. It's exactly this sort of conversation today and set of recommendations that support that act.

DR. LUMPKIN: The only thing I would add -- I think you've given us some wonderful ideas and some things for us to begin to work with you on. It's been a very interesting discussion for me as a pediatrician but not from the oncology world, but from other parts of pediatrics. At least my experience has been that international phase I/phase II studies in other areas of drug development are clearly basically the norm and where things exist. It's interesting to hear why, within the world of oncology, that is not where we are at this point in time.

So I think, having been part of the discussion today, has been extremely helpful to me and I think the ideas of getting our colleagues at EMEA, our colleagues at Health Canada, the various consortia within the investigator group together to see if we can come up with dealing with some of these issues on the oncology products is obviously, as Dr. Weiner says, one of the major emphases behind the BPCA. And we thank you very, very much for the input today.

DR. SANTANA: Yes. I also want to thank all of

our international visitors for being here today and certainly expressing your points of view and helping us through this conversation and also all of our American colleagues who stayed until the designated time to have this discussion. I personally want to appreciate Steve for his commitment to pediatric oncology and to helping us resolve these issues. Thank you.

DR. HIRSCHFELD: Thank you, Dr. Santana.

DR. SANTANA: We're adjourned.

(Whereupon, at 4:04 p.m., the subcommittee was adjourned.)