DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Tuesday, March 4, 2003

8:36 a.m.

ACS Building
Center for Drug Evaluation and Research
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

Consultants (Voting)

Victor M. Santana, M.D., Chairman
Thomas H. Perez, M.P.H., Executive Secretary
Alice Ettinger, R.N., Association of Pediatric Oncology Nurses
Jerry Finklestein, M.D., University of California, Los Angeles
Patrick C. Reynolds, M.D., Los Angeles Children's Hospital
James Boyett, Ph.D., St. Jude Children's Hospital
Henry Friedman, M.D., Duke University
Susan Cohn, M.D., Northwestern University
Nancy Keene, Independent advocate

Oncologic Drugs Advisory Committee Members

Jody Pelusi, F.N.P., Ph.D., North Arizona Hematology & Oncology Associates
Gregory Reaman, M.D., Children's Hospital National Medical Center, Washington, D.C.

Guest Speakers (Non-Voting)

Malcolm Smith, M.D. Cancer Treatment & Evaluation Program, National Cancer Institute, NIH

International Guests (Non-Voting)

Francesco Pignatti, M.D., European Medicinal Evaluation Agency (EMEA)
Katherine Cheng, M.D., Medicines Control Agency, U.K.
Anne Mathieu-Boue, M.D., Agence Francaise de Securite Sanitaires de Produits de Sante (AFSSAPS)
Gilles Vassal, M.D. AFSSAPS, Institut Gustave Roussy, France
Harald Schweim, M.D. Bundes Institut fur Arzneimittel und Medizinprodukte (Bfarm)
Mark Bernstein, M.D., Health Protection Branch, Canada

Industry Guests (Non-Voting)

Anne Hagey, M.D., Abbott Laboratories Global Oncology Development Group
Alan Melemed, M.D., Eli Lilly

C O N T E N T S

P R O C E E D I N G S

DR. SANTANA: Good morning. We have been convened today by the FDA to give them some specific guidance related to issues of pediatric labeling for oncology products. And as I understand the format today, Dr. Hirschfeld will first give us an overview of the history of labeling as it relates to the FDA and its regulations, and then we will move on to some specific case studies that they want to discuss with us to bring out some issues that hopefully will provide them with further guidance on how to approach this in the pediatric oncology arena. And then we will have later this morning an open public hearing, and I believe so far there is one individual who wishes to address the committee.

With that, I want to welcome everybody this morning. We have robust representation from some international guests, and we want to welcome them, too, and people from across the border, too, Dr. Bernstein.

And with that, I will let then Tom read the conflict of interest, and once we're done with the conflict of interest, I want to go around the table and everybody introduce themselves.

Thank you.

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 today's meeting is an issue of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. 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 pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following special government employees which permits them to participate in today's discussions: Drs. James Boyett, Susan Cohn, Ms. Alice Ettinger, Drs. Jerry Finklestein, Henry Friedman, Jody Pelusi, Gregory Reaman, Charles Reynolds, Victor Santana, and Susan Weiner.

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.

In addition, Ms. Nancy Keene and Dr. Malcolm Smith do not have any current financial interests in pharmaceutical companies; therefore, they do not require a waiver to participate in today's discussion. 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 before the subcommittee, these potential conflicts are mitigated.

In addition, we would like to disclose that Dr. Anne Hagey owns Abbott stock and other pharmaceutical company stock as part of her mutual funds and 401(k) retirement fund. She also has company-granted stock options. Additionally, she is a full-time employee of Abbott Labs and a relative is employed by the pharmaceutical company.

Dr. Alan Melemed is a full-time employee of Eli Lilly and Company and has part-time employment with Indiana University School of Medicine.

In the event that the discussions involve

any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

Thank you.

DR. SANTANA: Anybody else who wants to make any disclosure?

[No response.]

DR. SANTANA: Thank you, Tom.

Could we start our introductions beginning with the left side of the panel, please?

DR. HAGEY: Good morning. Anne Hagey, pediatric oncologist, Abbott Laboratories.

DR. CHENG: Good morning. I'm Katherine Cheng. I'm from the Medicines Control Agency, which is the U.K. regulatory authority. I'm also a pediatrician by training but not in oncology.

DR. SCHWEIM: Good morning, everybody. I'm Harald Schweim from the Bfarm in Germany. I'm heading this institute. I'm educated as medicinal

chemist and as medicinal informatics.

DR. VASSAL: Good morning. I am Gilles Vassal, pediatric oncologist and pharmacologist, working in France in a cancer center called Institut Gustave Roussy in Villejuif. I'm in charge of new drug development in pediatric oncology and chairman of the European program called Innovative Therapies for Children with Cancer.

DR. BERNSTEIN: Mark Bernstein. I'm a pediatric oncologist at the University of Montreal and a Children's Oncology Group member.

DR. MATHIEU-BOUE: Good morning. I'm Anne Mathieu-Boue from the French agency for evaluation of medicinal products called AFSSAPS. And my background is oncology/internal medicine.

DR. PIGNATTI: Francesco Pignatti from the European Medicines Evaluation Agency in London. I'm a medical doctor and biostatistician.

DR. MELEMED: Alan Melemed, pediatric oncologist, Eli Lilly and Company, as well as Indiana University School of Medicine.

MS. ETTINGER: I'm Alice Ettinger, and I'm a certified pediatric nurse practitioner, New Brunswick, New Jersey.

DR. BOYETT: James Boyett, biostatistician from St. Jude Children's Research Hospital.

MR. PEREZ: Tom Perez, executive secretary to this meeting.

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

DR. REAMAN: Gregory Reaman, pediatric oncologist, Children's National Medical Center, George Washington University, chairman of the Children's Oncology Group.

DR. PELUSI: Jody Pelusi. I'm an oncology nurse practitioner at Northern Arizona Hematology & Oncology Associates.

DR. REYNOLDS: Pat Reynolds. I'm in pediatric oncology at Children's Hospital, Los Angeles.

DR. FINKLESTEIN: Jerry Finklestein, pediatric oncologist, representing the American Academy of Pediatrics.

DR. FRIEDMAN: Henry Friedman, pediatric and adult neuro-oncology, Duke.

DR. COHN: Susan Cohn, pediatric oncology, Children's Memorial Hospital in Chicago.

DR. SMITH: Malcolm Smith, pediatric

oncology at Cancer Therapy Evaluation Program. I'm the program director for the Children's Oncology Group.

DR. HIRSCHFELD: Steven Hirschfeld. I'm a pediatric oncologist at the Food and Drug Administration in the Center for Drug Evaluation and Research in the Division of Oncology Drug Products and the Division of Pediatric Drug Development.

DR. GOOTENBERG: Joe Gootenberg. I'm a pediatric oncologist in the Center for Biologics in the Division of Clinical Trials Design and Analysis.

DR. PAZDUR: Richard Pazdur, FDA, Division Director of Oncology Drug Products.

DR. SANTANA: Thank you. Richard, I want to go ahead and give the microphone to you so you could address the committee, or Steve, either one of you.

Okay. Let's go ahead and get started, and I think Steve Hirschfeld will give us an overview of the history of pediatric labeling.

x DR. HIRSCHFELD: Since Dr. Pazdur gave me the honor to welcome and greet everyone, on behalf of Dr. Pazdur and the members of the Division of

Oncology Drug Products, I welcome all of you and especially appreciate the participation of some of our colleagues who have traveled enormous distances to be here for a short but we hope very productive and important discussion.

In order to frame the questions and the discussion, it's important to know the origin and sources and rationale between what is called labeling and pediatric labeling and how we got to where we are today and why we're asking the questions we're asking.

Labeling, as such, was the first of the major principles that guided the establishment of food and drug law in the United States. That was in 1906, and it was in response, as all of the major principles were in response, to public health crises involving children. And while there were many public health crises that led to a call for labeling, one of the key events was the sale of a preparation that was to treat colic in infants. And the sale of this preparation was investigated because it was considered an effective product--the infants would go to sleep--but they wouldn't wake up. And there was a magazine time published in Philadelphia called Collier's Weekly, and it had an

issue that featured on the cover a skull and crossbones that implied that there was something wrong with what was being sold to children. And the particular product that was used as the case was something called Mrs. Winslow's Colic Syrup. And when the ingredients were examined, it turned out to be largely morphine.

So this led to a response by the Congress of the United States where people who were interested in in some way regulating the sale of medicinals combined their efforts with women who were interested in getting the right to vote, and there was then through this coalition a number of laws that were passed. And the critical one was that products had to be labeled according to their contents.

This was challenged in court, but the Supreme Court of the United States upheld the authority of the United States Government to declare that products that are sold for interstate commerce must have their contents properly labeled. And as a quick review, the other principles that evolved were, in 1938, in response to many children that died, as well as adults, because of a preparation of sulfanilamide that was put into a

solvent that turned out to be toxic led to the establishment of the Food, Drug, and Cosmetic Act in 1938. And that was further amended in 1962, again, because of a health crisis involving children, and this time on a global basis. And that is a principle which we have tried to encompass in this committee, to have a global reach and global basis, because not only are children everywhere and products are everywhere, but with the mobility of society and the interactions that we all have here in the 21st century, it is critical that we not act in isolation.

So the principle that was established in 1962 was efficacy, and that led to what has been the longest-running experience in evidence-based medicine, because the law reads that investigations must support the claims that would be approved by the Federal Government. And the regulations, which are derived from the law, state that adequate and well-controlled trials must be used to support the claims that would be approved for interstate commerce by the United States Government.

So pediatric information began to occupy the discussions and the procedures in food and drug law beginning in the 1970s. So recall 1962 was the

amendment which established efficacy, and in 1974, Congress passed the National Research Act and established the National Commission for the Protection of Human Subjects of Medical and Behavioral Research. And this was--at the same time, concurrently, a report was commissioned by the Food and Drug Administration from the American Academy of Pediatrics which has played an essential and critical role in the evolution of drug law and medicinal product development for children in this country and, by extension, in the rest of the world. And this report was entitled "General Guidelines for the Evaluation of Drugs to be Approved for Use during Pregnancy and for Treatment of Infants and Children."

The commission that was established in 1974 began to focus rather early in its deliberations on pediatric research because there were scientific and ethical concerns. One of the concerns that came at the time was not for the evaluation of medicinal products, but actually for the administration of educational testing. And in the 1970s, the department that we now know as Health and Human Services was then Health, Education, and Welfare. Subsequently, the

education functions were separated into a new department, but the charge to the commission involved that educational role.

So they issued a report in 1977 as a result of a series of public hearings and consultation with expert advisers entitled "Research Involving Children." Almost concurrently, the Food and Drug Administration issued a guidance which was based on that American Academy of Pediatrics report called "General Considerations for the Clinical Evaluation of Drugs in Infants and Children." And we will touch on the content of that in a moment.

Again, 1977 being a productive year for trying to frame pediatric research, the American Academy issued the first statement on ethical conduct in pediatric studies.

So the report that the American Academy produced and that the FDA then transformed into a guidance document had an emphasis on unexpected toxicities. It also had an emphasis on adequate and well-controlled trials, and it said reasonable evidence for efficacy should exist prior to study in infants and children, and active or historical controls were preferred over placebo, questioning

the ethics of placebo. Placebo studies were addressed in a mt of the Pediatric Subcommittee of the Anti-Infectives Advisory Committee with a special ethical session a few years ago. And those parameters that could apply to pediatric studies have been published and posted on the Internet.

There was also a suggestion that studies should occur in decreasing age order, so first adults, then adolescents, and then younger children, and then, if studies were warranted, infants and neonates.

In 1979, the Food and Drug Administration issues its first regulation on pediatric use, and that was in a subsection of the product label that's called precautions. Precautions are considerations and limitations on the use of a drug for whatever the claim may be. So, to clarify, the Food and Drug Administration does not approve products. It approves the use of products, claims about the use of the product. And the product label is intended to describe the method on the use of that product so that if one follows that method, the use would be considered safe and effective.

In 1983, there was the issuance of the recommendations of the national commission in

federal regulation on the protection of all experimental subjects, but there was special attention paid to subcategories, and the subcategories were prisoners, pregnant women, and, last, yes, children. And the regulations encompassed some of the limitations and some of the categorization of how one should view children who enrolled in clinical studies. And the critical aspect to this was that there was, for the first time, the delineation of risk categories and the anticipation of risk and contemplation, at least, of benefit versus risk in designing a study and even in allowing it to proceed.

A little more than a decade later, in 1994, there was a revision of the regulation on the product package insert in the pediatric use, and there was a new section added which allowed the use of extrapolation as a basis for establishing pediatric use. And the FDA issued a guidance on this in 1996, and, concurrently, the American Academy of Pediatrics issued an update on its ethical statement.

So the 1996 guidance considers extrapolation of the disease course in adult and pediatric patients should be similar; and if the

effects of the drugs, both beneficial and adverse, in adult and pediatric patients could and should be described. And critical references should be included.

Now, guidance documents are not binding. They just reflect agency thinking but, in general should be considered the default position. And variations from what the guidance recommends generally should be justified or have some other extenuating circumstances.

And this committee has examined in great detail the issue of extrapolation in pediatric oncology, holding meetings on hematological malignancies, on solid tumors and CNS malignancies, and then examining in detail the types of studies that should follow from using extrapolation and thinking of children with cancer as both the participants in the experiment and the beneficiaries indirectly and ultimately from the studies.

In 1997, just to continue the evolution, the Food and Drug Administration Modernization Act, which didn't modernize very much in terms of our facilities--I still had the same computer--did allow some updates in terms of process, took a

principle which was evolved from the orphan drug program, which was to provide a financial incentive in the form of prolonging of the period of marketing exclusivity, and applied that to pediatrics as a remedy for the exclusion of children in the studies that led to the claims for approved products. And in 1998, a pediatric rule was issued which mandated pediatric studies under particular circumstances, which this committee has discussed in great detail.

And in 2001 was the issuance of interim text for an adaptation of the Health and Human Services Subpart D regulations extended to FDA-regulated research because the previous discussions on protection of human participants in clinical studies was limited by design to studies that were funded by the Federal Government. But with the evolution of pediatric investigations and with the relative explosion in the number of pediatric studies and the varied sources of funding, there was a need, which was supported by many parties, to have regulations which could also cover children in those studies.

And then in 2002 came the Best Pharmaceuticals for Children Act--and I always have

to think of our European colleagues who have developed the Better Pharmaceuticals Act for Children or some paraphrase to that, but they're similar in scope and in intent--which renewed the pediatric incentive program and asked for the study of off-patent drugs, which is a very active program, and then specifically mandated the public dissemination of pediatric information. And one of the vehicles for that is the product label.

The product label is also known as the product package insert, and the regulations on product package inserts have several sections. They are a description of the product, the clinical pharmacology, the approved indications and usage--and, again, I will point out these represent claims based on data that the FDA has reviewed and found to be safe and effective, and is not a commentary on all potential uses of the drug or even on what might be considered common uses. This is restricted to claims that the FDA has reviewed and found to be safe and effective.

Then come a series of graded limitations on these claims. The first are contraindications, which means conditions or a population where the product should never be used. Then are warnings,

which are one grade below, which require careful monitoring and careful evaluation and consideration of whether the product is appropriate for a population identified in a warning section. And in oncology, most of the products carry warnings which state the degree of toxicity and state the need for having specialized physicians prescribe and administer the product and, although it's not stated explicitly--it's implied--specialized nursing staff, too.

And then come the precautions which are then a series of limitations which comment on typically different subpopulations--patients with renal impairment, patients with hepatic impairment, geriatric patients--and here is where the pediatric use section is located typically.

Then there are the adverse reactions, which all patients in one form or another could anticipate, and then there's a section called drug abuse and dependence, which is often left out, certainly not included in oncology drugs; an overdosage section; and, finally, we get to the dosage and administration section. And this is the dosage and administration which relates back to the approved indications and usage and not any other

dosage or administration regimens. And then lastly comes the how supplied.

There are additional label sections which are considered optional in the regulations, and these are animal pharmacology or animal use sections; toxicology; clinical studies, which have been routinely included in oncology approvals; and references, which, again, in the realm of oncology, have tended to refer to the safe handing and usage of the drug product.

The principles of the product label, as stated in the regulations, are that the labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug, and in parentheses, for the approved claim.

Secondly, the labeling shall be informative and accurate and neither promotional in tone nor false or misleading in any particular, and the FDA has an entire division which oversees the language in the product labels, and product labeling language can be used in promotion and advertising, and there is a direct linkage, therefore, to the words that are used to describe the safe and effective use and the words which

might be used for promotion.

And, thirdly, the labeling shall be based, whenever possible, on data derived from human experience. Conclusions based on animal data but necessary for safe and effective use of the drug in humans shall be identified as such and included with human data in the appropriate section of the labeling. And this provision has become particularly timely when a number of products which are intended to treat catastrophic events and illnesses, such as poisons from organophosphates or other types of untimely events, are now being approved on the basis of animal data.

There's a section in the product labeling--in the Code of Federal Regulations, Part 201, Subpart B, paragraph (c), section (iv) reads: "If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use of condition." And I'd like the committee to bear

this clause in mind in reviewing the case scenarios and in considering the subsequent discussions.

The pediatric use section under precautions has eight subsections to it, and not all are necessary to be used, but they're all available to address if the circumstances warrant it. The first is the definition of who is a child, and as defined in this case as birth to 16 years of age. But we should note that in other settings for clinical studies, for instance, in the consenting or participation of a child in a study, a child is defined as of minority age in the jurisdiction where the study is occurring, which in most places is 18 years.

Secondly, if there is a pediatric indication different from adult indication, it should be listed under indications and usage and dosage and administration. So to comment on this, if we are considering the same indication in adults and children and we are considering using extrapolation particularly, then the indication that is stated in indications and usage need only be stated in that section, with perhaps some qualifications of ages, and does not need to be repeated separately for children. However, if the

pediatric indication is different, then it needs to be stated so.

The pediatric use section should cite any limitations as well as appropriate information in contraindications, warnings, and elsewhere in precautions. For example, what I didn't mention earlier, there's a section under precautions for pregnancy, and there are categories of pregnancy warnings and pregnancy precautions that the agency has evolved and is continuing to revise which address potential risks to an unborn child.

Thirdly, for pediatric use based on adequate and well-controlled studies, which is always desirable but not always feasible, for an approved adult indication, they should be summarized in pediatric use with additional information in dosage and administration, clinical pharmacology, and clinical studies. Pediatric use will also cite limitations as well as appropriate information in contraindications, warnings, and elsewhere in precautions.

Adequate and well-controlled studies in pediatric oncology have not been submitted to the agency over the last quarter century or so, and there's a recent publication which comments on

this, although we now see that there is greater interest and we anticipate that we will be seeing adequate and well-controlled studies for pediatric oncology submitted.

However, again, if adequate and well-controlled studies, which means studies that independently, by themselves, would support safety and efficacy without additional information, if those are not feasible or possible or reasonable, then pediatric use may also be approved on the basis of adequate and well-controlled adult studies with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. And this, while it sounds like it gives you information, in fact, to interpret is rather difficult. So Dr. Bill Rodriguez, I, and some other colleagues have been working for the last year and a half on attempting to put a framework and a process and an analysis which we hope could be broadly applicable to how one can use data and what kinds of data to support

extrapolation.

The next section, additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric people for determination of appropriate dosage, and in this case, we have specialists in the FDA that we are dependent and reliant on to help us interpret the pharmacokinetic data. But they can only do it if they get the appropriate data to do their analyses. And other information (that may be used)--and the parentheses is mine; otherwise, the rest of the text here is verbatim from the regulations--such as data from pharmacodynamic studies of the drug in the pediatric population; studies supporting the safety or effectiveness of the drug in pediatric patients--that is, one age group to another--or pertinent premarketing or postmarketing studies or experience may be necessary to show that the drug can be used safely and effectively in pediatric patients.

This section states that if the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met, the pediatric use

section shall state "Safety and effectiveness in pediatric patients below the age of"--and then whatever the youngest patients that have been studied is entered--"have not been established."

Now, convention says 18, but often studies don't have patients that young, and so the statement is often rewritten to state, "Safety and effectiveness in pediatric patients have not been established," and not set an age frontier in that case.

Pediatric use will also cite limitations as well as appropriate information in contraindications, warnings, and elsewhere in precautions. So bear this statement in mind in the subsequent discussion.

The sixth of the eight sections states that the absence of substantial evidence for any pediatric population, the label shall state, "Safety and effectiveness in pediatric patients have not been established." And this is the general case for the specific case that was in the previous section.

If the use of the drug in premature or neonatal infants, or as we like to say in the Division of Pediatric Drug Development, the orphans

of the orphans, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, shall be stated in contraindications or warnings, depending on the severity and the impact. And there are International Conference on Harmonization guidelines on what constitute serious adverse events, and these are the general principles which would be adhered to.

And now, lastly, if the sponsor believes none of the above apply, then alternate wording may be proposed. So this gives not only the sponsor but it gives the Food and Drug Administration the option to propose alternate wording.

And if the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made generally in the appropriate section.

So we have had labeling changes, and I bring these up just to demonstrate that the initiatives that the FDA has been working with the community at large on getting pediatric studies done and getting the information in and reviewed

has led to labeling changes. And based on our most recent public statistics, there are at least 12 that could be ascribed to the pediatric rule along, and 48 or maybe 50, depending on how one counts these things, because sometimes two products which are the same will have label changes, from the exclusivity or incentive programs.

So to review the label options for pediatric data, there's precautions, which has a specific pediatric use section; then there are dosing information and indication, if warranted; clinical pharmacology, clinical studies, contraindications, and warnings all as options.

The way pediatric data can be submitted to the FDA--and this is submitted voluntarily, it can be submitted voluntarily in response to a written request or by whatever mechanism it comes in--generally would come through two procedural pathways: as a new indication either for a new product, or as a supplement, or as is known in some of the other regions of the world as a variant for pediatric patients: or, alternatively as a label change with clinical data. That is, the sponsor's proposing to change the label and submitting clinical data that would support that label change.

So the rationale for the questions to the committee this morning are that Federal Government initiatives are aimed at developing therapeutics for pediatric patients and including product information in the approved package insert or product label. One of the criticisms of the earlier incentive program was that studies were being done and data were being submitted to the FDA, but no one outside the sponsor or the FDA would know what those data were. And Congress was aware of that and specifically addressed that in the Best Pharmaceuticals for Children Act. So that if resources are committed to generating pediatric data, those data should benefit children.

Although the majority of children with cancer in the United States are treated on protocols from the National Cancer Institute supported study groups, the majority of products used in children was cancer are used without dosing and safety information in the package insert. The package insert and product label are synonymous.

And the U.S. Congress has indicated that pediatric use information should be included in product labels as one of the mechanisms to public disseminate information about pediatric use.

Now, the questions have various types of scenarios. One is if there is the same adult and pediatric indication, and previously this committee, specifically in November 2001, recommended that to extend efficacy from an adult indication to a pediatric population, pediatric dosing studies and a demonstration of clinical proof of concept should be performed.

If a product is approved for an adult disease or condition that also exists in children, therefore, consider what information from pediatric studies you would consider necessary and appropriate to be in the product label.

If the adult and pediatric conditions are different, and if pediatric dosing information and proof of concept data exist for a pediatric disease or condition that does not exist in adults, consider what information, if any, should be included in the product label. So proof of concept means a study or studies that by themselves independently could not establish safety and efficacy. They're informative, they're ethical, they're scientifically valid, but they cannot independently support safety and efficacy. That would be the framework that we're using proof of

concept in, and we will give the specific examples in the case discussions.

An example might be that a product is approved for second line colorectal cancer in adults and pediatric data are available for dosing and pharmacokinetics in a single arm Phase II study showing a modest response rate in 20 pediatric patients with refractory neuroblastoma. Now, there is no product that fits this profile, so you shouldn't be trying to deduce what it might be. But with such renowned authorities as Dr. Reynolds and Dr. Cohn on the panel, I thought it was appropriate to bring up a neuroblastoma case.

A third scenario would be lack of activity. If dosing, safety, and lack of activity information are available from studies that enrolled children with cancer, consider what information, if any, be included in the product label. An absence of activity in diseases other than the approved indications have not been included, certainly not routinely--and, in fact, I couldn't find a single example--in the label for oncology products for adults. So to be specific, if a product is approved for, say, colorectal cancer and there are studies that were done in

brain tumors that showed that the product was not active in brain tumors--and I have to address Drs. Boyett and Friedman because they, too, represent the cutting edge of CNS malignancy treatments--then it has not been the practice of the agency to include those negative data in the product label.

If there are no pediatric data, that is, we know nothing about the product, when no efficacy or safety data are available in pediatric patients, we would like you to consider if a statement that safety and efficacy have not been tested in children be included in the product label.

And we are now going to review for you some case studies which have come before the agency, and after the presentation of the case studies, you're welcome to ask me or my colleagues any questions that you may have before we begin the session addressing the questions.

So these case studies--

DR. SANTANA: Steve, before you start, I am going to take a point here--

DR. HIRSCHFELD: Sure, take your prerogative.

DR. SANTANA: Yes, to ask just a point of clarification. The pharmaceutical act for children

mandates that we provide information. It doesn't tell us how that information is to be provided. We're making an assumption here that most of the information for practitioners and consumers, in the medical field or for patients, is through the label. But are there not other mechanisms in which information can be made available to those populations, particularly when there is negative data that's important that necessarily does not relate to the indication in the label? And if so, what are those additional mechanisms?

DR. HIRSCHFELD: The Best Pharmaceuticals for Children Act does address some specifics, and it contemplates having information in the label, as you pointed out. It also states that when pediatric supplements are submitted to the Food and Drug Administration, a summary of the clinical review and the biopharmaceutical review be posted on the Internet.

There are other provisions for including pediatric data, which are referenced in Best Pharmaceutical Act, which include under some circumstances data being entered in the Federal Register. But as you point out, there is a fair amount of interpretation, and we apply the

interpretation to convey the intent. But they specifically state that the publication of FDA reviews are to be posted on the Internet and, thus, made publicly available.

I could take any other questions after the case studies, if that can proceed, and the case studies represent real examples which have come to the Oncology Drug Division, and these have all been in response to FDA-initiated written requests. And my colleagues and I will share with you the pertinent aspects of the case, but we will not identify the drug products. I know that there are people in this room who may have participated in or initiated or read or are in some way familiar with the studies, but we ask you not to reveal, even if you think you know what the product being referred to is.

So the first case study will be presented by Dr. Anne Zajicek, who is a board-certified pediatrician and also has a Pharm.D., which is a very potent combination, and we've appreciated her efforts. And I will note for Dr. Santana and Dr. Boyett that part of Dr. Zajicek's training was at St. Jude.

DR. ZAJICEK: A while ago. Thank you.

Good morning. I'm presenting Case No. 1, and this is a case illustrating issues of dosing and proof of concept that were submitted by the applicant. This is the case where pediatric and adult diseases are the same.

Two Phase I dose-finding studies in children with hematologic malignancies were submitted by the applicant. Part of the data came from the original NDA, and part of it came from the supplemental NDA.

The size of the data set consisted of 39 patients that could be evaluated for safety and efficacy: 31 came from the supplemental NDA and 8 from the original NDA. And for the pharmacokinetic studies, there was a data set of 33 patients: 27 from the supplemental NDA and 6 from the original NDA. And I must compliment the applicant on this data set. It was gorgeous. I was very well done, well planned, very nice data set.

The type of information submitted included safety data, pharmacokinetic data, correlations between pharmacokinetic and pharmacodynamic parameters, and proof of concept.

For the results, the safety was similar to adults. The maximum tolerated dose was not reached

during the dose escalation phase of the study. Pharmacokinetic parameters were similar to adult values in the pediatric data set. There was no PK-PD relationship found, as it had been with the adult section, although it must be stated that because of the size of the data set, it's hard to make--you know, it would have been surprising, actually, probably to get a PD-PK relationship for the size of the data set. And proof of concept was submitted by applicant. Remissions were induced in the same malignancy in pediatric as in the adult patients, although, again, in a more limited number of patients. And remissions occurred in approximately the same proportion as adults as well.

For comparison between adults and children, there were the same side effects in pediatrics as in adults, but typically at a lower grade than in the adults.

In the adult population, there was a nice PK-PD relationship between exposure and the Day 28 white blood cell count. Now, you can talk about exposure in different ways. In this case, they used area under the concentration-time curve to make the correlation. And there was as well a lack

of clear dose proportionality. In the adult data set, when the dose was increased by a certain percentage, the AUC was also increased by about the same percentage. This was not the case in this population. But, again, we're talking small numbers here.

The starting dose in the pediatric population was chosen to provide similar exposure to adult doses. So they took the adult dose, divided by typical adult body surface area, which is around 1.73 meters squared, and that was the starting dose. And then there was a 30-percent escalation for the different doses. And there was a lack of relationship between dose and exposure in this population. There was an overlap between the AUCs for the different doses.

This figure illustrates this point. This is, on the far side, the adult area under the curve with the standard deviation bars. So here, again, these aren't real numbers, but the AUC for the adult dose was about 1, and the standard deviation you can see with the pink bars. The Pediatric Dose 1 was designed to provide the same exposure as the adult dose. Pediatric Dose 2 was a 30-percent dose escalation from Dose 1, and what's apparent

statistically and also just by looking at it is that these are all the same AUCs. So it makes it a little bit difficult to judge which is the correct dose, for that matter also for trying to give a pediatric dose that provides the same exposure as the adult dose. You would be hard-pressed to pick one dose versus the other one.

For issues and conclusions, this is the first time extrapolation has been used for approval. But, again, the challenge is in finding the right pediatric dose, again, because of the sort of overlap in the areas under the curve for the different doses.

Thank you.

DR. HIRSCHFELD: The next case will be presented by Dr. Ramzi Dagher.

DR. DAGHER: Good morning. In this case, dosing and limited clinical safety information was provided in a situation where the disease exists both in adults and children.

The study that was provided was a Phase II PK study in malignant and non-malignant life-threatening conditions, which included hematologic and non-hematologic malignancies as well as immune deficiencies. The data set included

24 patients ranging in age from 5 months to 16 years.

For safety information, clinical adverse events and laboratory abnormalities were reported; the hard data were submitted and reviewed. Multiple sampling was conducted in each patient with initial dosing based on body weight and subsequent adjustment based on the pharmacokinetic and pharmacodynamic information.

Generally, the safety profile that we observed in the pediatric data set was similar to that known and described for adults. The pharmacokinetic and pharmacodynamic information suggested a dosing model based on population PK analysis in which one dose would be used for children less than or equal to 12 kilograms and a different dose for children greater than 12 kilograms body weight.

Comparing the pediatric and adult situations, the pediatric data indicated the need for higher dosage in smaller children in order to achieve the same exposure as that in older children or adults.

The outcome in this situation and issues to keep in mind: In this situation, limited safety

information and dosing guidelines were added to the special populations, pediatric section of the label.

I think Steve is presenting Case No. 3.

DR. HIRSCHFELD: I'd like to acknowledge in Case No. 2 the very thorough and innovative PK analysis that Dr. Brian Booth performed, and Dr. Booth has been a strong supporter of our pediatric initiatives, as well as his colleagues. And in this case, I'll acknowledge in advance the PK analysis that Dr. Anne Zajicek performed.

So Case 3 is based on dosing and proof of concept data submitted for pediatrics, with preliminary activity in a disease found only in pediatric patients with the approved indications for diseases found only in adults. So a mismatch between the approved adult indications and where activity was seen in pediatrics. The types of studies were a Phase 1 dose-finding study in children with solid tumors and hematological malignancies and a Phase II open label, single-arm study for response rate in children with refractory or relapsed solid tumors.

The size of the data set: for Phase I, there were 48 patients--30 solid tumor and 18

leukemia--ranging in age from 1 to 15 years. And for the Phase II, there were 108 patients ranging in age from less than 1 year to 15 years.

The type of information submitted were safety, PK, PK-PD, and proof of concept.

The results were that the safety profile was similar for adults; however, an MTD was not reached for leukemia, and an MTD for solid tumors was higher than the approved adult dose.

The PK parameters were similar to adult values; however, there was no relationship between exposure and nadir white blood count which we considered to be a pharmacodynamic indicator of dosing due to maximum suppression at the lowest dose administered. And proof of concept showed consistent tumor responses seen in one class of solid tumors.

Comparing then between children and adults, there were higher doses that were tolerated in children, and responses seen in some pediatric malignancies that are not found in adults. So the conclusions are that the disease where activity was demonstrated in children is a pediatric disease that is rarely found in adults, and the approved indications are diseases found almost exclusively

in adults. Therefore, little overlap. Just what we like to have on a two-armed study, if you want to show a difference between the arms.

The extrapolation of efficacy, however, cannot be used. Product labeling did not include the submitted pediatric data, and the product is currently not approved for use in children.

And to present the fourth case, it's my pleasure to call on my colleague, Dr. Susan Honig.

DR. HONIG: Thank you. Case 4 is a situation where we had dosing information and response data, but the studies were negative and there was no evidence of activity.

We received two general types of studies. We got a Phase I dose-finding trial that was conducted in pediatric patients with both solid tumors and hematologic malignancies. As you can see here from the size of the data set, most of the patients entered had solid tumors. There were 25 evaluable children with solid tumors, 4 evaluable children with hematologic malignancies, and it is just worth noting in the conduct of the study that there were an additional 17 patients that were treated that, for various reasons were inevaluable. They ranged in age from 2 to 17.

We also received a Phase II open-label study that was performed in solid tumors, and as you can see here, this was a stratified Phase II study with three different tumor subtypes deliberately planned into this trial. The primary endpoint was response rate, and the three general tumor types that were looked at were CNS tumors, soft tissue sarcoma, and neuroblastoma. The study, as I mentioned, was designed to enroll at least 14 patients in each of the three subsets, and I've listed here the actual accrual per strata. The CNS and sarcoma arms, each enrolled 21 patients; neuroblastoma, only 4, and I'll show that a little bit more in a minute. And in this study, patients up to age 21 were eligible because of the types of patients that developed these tumors, particularly the sarcomas.

The information that we received included safety data. In this trial, as is typical in many trials of this sort, only adverse events that were attributed to the drug by the principal investigator were collected and submitted. We also, though, received from the applicant all of their available postmarketing pediatric safety reports to round out the safety profile.

For PK-PD, there were PK-PD studies done, but we received an abbreviated study report. We did not actually receive the primary data for this portion. And, similarly, for efficacy, we received abbreviated clinical trial study reports as opposed to every piece of primary data.

What were the results? The safety profile was generally similar in children as in adults. The Phase I trial did identify an MTD for children. There was a recommended Phase II dose that was identified and then used in the Phase II study. PK-PD results, as I said, were presented in summary.

One point worth making about all of this is that even though there was an MTD and a recommended Phase II dose, when the Phase II study was actually conducted, it was found that the Phase II recommended dose was too toxic and the dose was lowered during the course of the trial.

The efficacy results are listed here for you. In two of the three strata the response rate was zero, and in the third strata, the sarcoma, there was one complete response, one partial response seen. And as I mentioned, there were only four neuroblastoma patients enrolled. That was

because, on the whole, the study was deemed to show lack of efficacy, and it was not considered appropriate to continue to enroll to full accrual in the neuroblastoma arm.

The comparison between children and adults: Once the recommended Phase II dose was adjusted for the initial toxicity seen, the toxicity profile was generally similar in adults and children. And as I said, the dose, once adjusted, ended up being the same in both groups as well.

In terms of issues and conclusions, how were these results handled in labeling, a very brief description of the study was placed in the label, and negative efficacy data were included, but we did not include specific PK or dosing data.

So, with that, I'd like to introduce Dr. Alla Shapiro who will present the last case.

DR. SHAPIRO: Thank you. The last case is an illustration of the drug that was approved for adults, but failed to demonstrate efficacy in similar disease in children. This drug, however, showed efficacy in another disease in children.

Two Phase I studies were presented to the FDA for review, and both studies intended to

evaluate pharmacokinetics and dose determination data in patients with non-CNS and CNS refractory or relapsed solid tumors. One single-arm Phase II study was submitted to evaluate efficacy in advanced CNS cancers. Size of data set: Phase I studies included 82 patients, ranging from 3 to 17 years old, but pharmacokinetic data were available only for 19 patients. Phase II study included 122 patients, ages from 3 to 17. For Phase I and for Phase II trials, patients were stratified based on previously received treatment.

Type of information submitted included safety results, pharmacokinetic and pharmacodynamic data. Multiple sampling in each patient were obtained based on body surface areas. Efficacy data also was submitted.

Results showed that toxicity profile was similar in adults and children. Pharmacokinetics data showed that these parameters were independent of previously received treatment. And no relationship between age and clearance was established. Efficacy, 122 patients were assessed for efficacy. A total of six--overall response was six: one complete response and five partial responses were observed.

Comparison between children and adults revealed similar clearance and volume of distribution values. Response to therapy appears to be different, worse in children. And the unique aspect of this situation that--of this scenario that responses occurred in a different histological subtype from an adult disease.

Issues and conclusions: The drug was approved for an adult disease that also exists in children, but did not show efficacy in this disease. Responses wee seen in a disease that occurs primarily in children, and for this disease there is effective therapy. Saying that, our question is: What information, if any, should be included in the labeling?

Thank you.

DR. HIRSCHFELD: The last slide is quite difficult to read, but you have it as the very last page of your handout, and it is a summary of these five cases in a chart form, comparing the various parameters that were presented.

There is, I think, an unstated message from these five case histories, and that is, until this year, 2003, we could not have presented five cases to you. And the fact that we have five cases

to present to you is, I think, testimony to the effectiveness, and maybe the safety, of having the pediatric initiatives in place, and that we can say that there are drugs which are being used in clinical studies in children with cancer, which was not the situation when this committee was meeting to the same degree that it is now, that there was a time lag which had been discussed before, and our perception is that that time lag has been decreasing. But I'll ask Dr. Malcolm Smith if he has that same impression.

DR. SMITH: I think you're clearly seeing an increase in submissions to the label, and in certain instances we're certainly seeing agents moving more quickly into the pediatric population. We appreciate the support of pharmaceutical sponsors when that does occur.

But there is a history of studying agents in children in a systematic manner that goes back three or four decades. And so, you know, we've developed these data for decades in the pediatric oncology research community, my predecessors and everyone around the table and their predecessors. It simply hasn't been included in the label.

It brings a question that I had, Steve,

and perhaps you or others could address this. We're talking about the product label, but more generally, what are the sources of data that a diligent treating physician can use or should use to make decisions about how to use drugs, either alone or in combination, to treat his or her pediatric cancer patients?

DR. HIRSCHFELD: I'll take that as a rhetorical question to the group at large, but we're all aware there are multiple sources of data, but we also know that there are varying qualities to the data. And I think that there are some in this room that may address that, and that the Congress of the United States has put the responsibility and authority in the Food and Drug Administration for quality review of the data, and there is an implicit understanding that if data have been reviewed with the technical expertise and the disinterest that--our part of the review process, that there's a credibility factor to those data.

DR. SMITH: But are there other data that the diligent treating physician could use to make justifiable decisions about how to use a drug other than the data that you've described that you've

reviewed?

DR. HIRSCHFELD: Rick might want to address that.

DR. PAZDUR: The answer to that question is obviously yes. I think, you know, we as the FDA have put a lot of time and energy into the product label, and I've discussed this before with this group. The product label means many things to many people, and that's one of the problems that we may have with the product label. It represents a licensing agreement, as Steve says, between the Federal Government and the sponsor. Hence, every word that goes into that label is carefully scrutinized. Every p value has to have consistency with other labels. So there's a high level of review that has gone into this.

The review that we do of the material obviously is to a level that is not done in just a peer-reviewed journal because no peer-reviewed journal--I should say very few would actually take the raw data and reconstruct survival curves, send out investigators to the sites to document that the information was correct and accurate.

So I think there's other ways that people could get that information, and I think we would be

foolish to think that all pediatricians are just looking at this label and deriving all their information. Likewise, in adult oncology, the product label has a use, but many other information--other routes of professional education are available, and I think we have to keep that in mind, obviously, when we're making these decisions. What is the practicality of including certain amounts of information in the label?

DR. SANTANA: Dr. Boyett?

DR. BOYETT: You bring up the peer-reviewed literature, which is a good source, but there's a publication bias there. And you do a Phase II-type trials, 0 and 14 rule or some other study like that, it turns out to be negative. And I have been frustrated by the fact that some investigators are reluctant to even write up and try to publish their results. And I think it should be published, and I think that one of the things that we could do is to stimulate investigators, that if they're funded to do a particular trial and it turns out to be negative, they at least ought to submit it to the peer-reviewed literature.

DR. PAZDUR: I couldn't agree with you

more. In fact, it's not only negative Phase II trials, but negative Phase III trials that are very important. One finds either an omission of them or such a lag time between the submission that the information almost becomes irrelevant, even though most of the in-the-know oncologists know the data that is in there. So I couldn't agree with you more on that.

DR. SANTANA: Dr. Bernstein?

DR. BERNSTEIN: I'd like to raise another point. Malcolm was talking about the information available to the assiduous treating physician, but there's another use for the label as well, and certainly north of the border, the other use for the labeling information is for submission of protocols to other health authorities. And in those situations, Health Canada, for instance, is very interested in what's available on the product label and is very happy when there's pediatric information available on the product label, and it makes certainly the life of the treating oncologist north of the border much more simple if there is such information on the product label. And that may or may not be true in other jurisdictions as well.

DR. SANTANA: Dr. Cheng?

DR. CHENG: I'd agree that it's very encouraging that these data have been submitted, and I'd just ask you to clarify. Were these data requested by the FDA, these studies? Or did these come in voluntarily? And if there was any discussion with the FDA, did you discuss the design and the types of studies, how much input was put in at the FDA level?

And then the other question is more just because coming from the U.K. I'm not familiar with the U.S. system. When you were talking about public dissemination of information, does the product label get to the patients as well, or is primarily aimed at the physician?

DR. HIRSCHFELD: Excellent questions. I might just try to address those before we continue with the discussion.

These were responses to FDA-initiated written requests, and the process of a written request is that we outline the types of studies and the type of information we would like to see because there's a perception that there's a public health need and that this fulfills an information gap.

The product label, as we will probably--as the discussion evolves this morning, you'll see, as Dr. Pazdur pointed out, can mean many things to many people. But, above all, it's a statement of the agreement between the sponsor and the FDA on what the product is claimed to do and the data that support that claim. And it is used potentially as a primary source of patient information, but there are other routes. The FDA has been encouraging the development of what are called patient package inserts, which are modifications of the formal legalistic product label, in order to impart important information. And then for particular products, there are white papers and other documents that the FDA will produce, and then there are many other sources of information to patients.

DR. SCHWEIM: I have one question for clarification. In your presentation, you presented Part 201, Subpart B, indications and usages, and in this paragraph, there is used a common belief and a common use. I think it's very complicated to clarify what means this in this sense, what's common in this sense, consensus conferences and so on. Would you please comment on that for me?

Then I have a remark. I'm also not very

familiar with the situation in the U.S., but I wanted to give you some views of the German situation. In Germany, we have three types of information. One is the package leaflet. The second one is the health professional information. And the third one are brochures done by the pharmaceutical companies for advertising and so on.

The first one I mentioned and the second one I mentioned is according to the German drug law. The third one is according to the Advertising Act amendment to the German drug law. And number one and number two always indicate only information which is proved by the German comparison institution to the FDA, and there the pharmaceutical companies are not allowed to add any advertising or not proved information.

I think in Germany we do not have such a type of Freedom of Information Act, especially not for prescribing-only drugs. This information, prescribing-only drugs, information is only in the health professional information. And if any representative from a company is visiting a doctor and tries to inform him about new indications, new products, he is forced to let the information with the health professional information in his office.

He must hand it over. In any case, it's according to the German law.

And by this type of dividing the information, we have an act, it's a European regulation for the Best Understandable Information for Patients Act, I would translate it, and in the health professional information there, such information as, for example, clinical trials with failures, clinical trials which have not the right results, can be mentioned, and they are not mentioned in the public information for the patient.

So I think the principles to have as much information as possible about the drug to be used is obvious. But this type of dividing the information, addressing health professionals in another way and addressing the public, I am very pleased with.

DR. HIRSCHFELD: Can I address the first part?

DR. SANTANA: Yes.

DR. HIRSCHFELD: Thank you for your comments and your informative response, Dr. Schweim. The regulations are written so that they can be flexible, and there are words that are used

which allow case-by-case interpretation. So in this context, the word "common use" or "common belief" is sufficiently vague that presumably whatever determination needs to be made can be made on the case-by-case basis.

DR. SANTANA: Dr. Reynolds? Then Ettinger, then Pelusi, in that order, please.

DR. REYNOLDS: I think that Mark Bernstein made an interesting point, and that is that the label can, in fact, impact outside of this country. And I just wanted to make sure that the committee and the agency recognized that there were some of these impacts. A good example of this is 13-cis-retinoic acid, which is used off-label in this country and basically throughout Europe for treating neuroblastoma, in fact, has a labeled indication for this in Italy, which I found interesting that they chose to do this. But the drug has no use outside of neuroblastoma in Japan because it doesn't have an (?) problem. So the Japanese cannot get this drug, and the Japanese can't bring it in because their government looks to our label for indicated use, and since they don't see it, then that makes the importation of the drug difficult.

So I think that there are some governments that do look at what happens in the labeling, and the actual availability of a drug could be impacted on by not having pediatric labeling indications.

MS. ETTINGER: I think that for the patient, family, and the nurse, I think labeling is most important. I know that as a nurse I always read the package inserts. I find it invaluable to know exactly what's going on or what went on to get that drug to where it is.

From the patient/parent perspective, they're reading labels, too. I always appreciate the patient inserts that are supplied as a separate entity.

On the other hand, I think that everyone should--I think that the patients and their families absolutely look at them as well, and whatever is available on the Internet is always looked at, whether it's from the company that produces it or from any other source that families can get. The more information that's available out there I think is always important, particularly from my perspective as a nurse.

DR. PELUSI: I agree with those comments. To the colleague from Germany, I appreciate the

fact that in the inserts you have the negative trial results as well. And I think that's very valuable because for me, having patients and families come in, again, they're always asking, "But I hear we're using here and here and here," and yet there is no real definitive place where those negative results can be seen. And sometimes they fell like, well, perhaps you just don't know that you can have access to it or it's used in a different setting. So I think that's very important in the labeling as well.

And the package inserts, I think for patients specifically, really would help tremendously.

DR. PAZDUR: The patient package insert I think is really a critical thing. Anybody that takes a look at these product labels realizes they're somewhat--they're getting somewhat unmanageable. You know, it's sometimes hard even for us to find out where the indication is, and there are initiatives in the agency to really kind of modernize the label and make it a little more user-friendly with an abstract, perhaps, and those have been ongoing.

One of the things that I want to

emphasize, remember, we're not talking about pediatrics in isolation here. And I think when we take votes and have this discussion, we have to understand that oncology is a bit different bird than the rest of medicine in the sense that we do have a tremendous amount of off-label use in adult oncology as well, obviously, in pediatric oncology. And, therefore, what we put in the label, we have to have an understanding of how useful it would be. If we start putting every negative Phase II trial in a label, this could become quite unmanageable, and especially when one sees, you know, some of the more common drugs might have maybe up to 15, 16 different types of tumors that are studied or types of indications. So exactly what to put in there, we really need to have a further discussion on and what would be its importance, because it doesn't just affect pediatrics but would have a wider trend.

So in the deliberations that we're going to be discussing, I really would like people to keep that in mind. We're not acting just in isolation here with pediatrics, that if we start putting in information based on two out of eight patients treated with a certain disease in

neuroblastoma, would we put that information in for two out of eight patients treated with metastatic colon carcinoma?

You know, here, again, we want to get information out, but there is some commonality and some precedents that this could set, and we really have to be cognizant of that also.

DR. SANTANA: I want to kind of follow up on that, because I was struck, since you guys presented five very informative cases and each case has its own unique aspect to it, I was struck by Case No. 4 in that the indications were completely different in that the preponderance of evidence in terms of the numbers of patients was not very big, but a decision was made to include negative data in the label, which would go contrary to some of the discussion we've had so far. And obviously it's a case for discussion, but I was curious to know how, based on the current environment, how that decision was made. Maybe one of you could clarify.

DR. HIRSCHFELD: I want to make what I believe is a critical point of information in that while data can exist from many sources--and I appreciate Malcolm's pointing that out to us--in these particular cases, these are data that are

generated because the FDA requested it, and these are data that in most cases are being in some way subsidized by the taxpayers, which is all of us, in the form of the financial incentives the company receives.

So in these cases, I believe the data not only deserve consideration which would be different from other types of data, but because there's been this public trust in the regard, there's an obligation to use these data in the most effective way.

DR. SANTANA: My point, Steve--and that's what I tried to say a little bit earlier this morning--is that we're really talking either taking a very conservative view of what the product label is, and then trying to introduce these issues, for these issues into the label, or a more liberal approach or a rethinking of what the label should be based on these pediatric initiatives. But I also recognize what Richard said, that this goes beyond pediatrics in terms of the label content.

So though I do recognize that we all have an interest in this, both scientifically, ethically, and financially, maybe for some of this data the label is not the correct vehicle to convey

the information to the public. That's the point I am trying to make, that I think we are either very protective of the label in the way we view it as a community, and if that's not the correct mechanism to provide the information that we're being funded to provide, we then need to discuss what are those other mechanisms so that the public and physicians get that information.

So I'm not saying the information should be put away and not listened to. I'm just questioning--and hopefully it will come out in the discussion--whether the label is the right vehicle. That's my point.

DR. HIRSCHFELD: I think you've summarized exactly the crux of the whole discussion.

DR. SANTANA: Hopefully some other people have something to say.

Dr. Finklestein?

DR. FINKLESTEIN: First a comment for Richard and then some questions for Steve. The comment for Richard is the American Academy of Pediatrics feels very strongly that labeling is important for the general child. So I realize we're discussing oncology, but pediatrics needs labeling badly. This is extremely important.

Now, for Steve, a couple of things. One is I wondered if you could--and they're a series of questions. One, I wonder if you can quantitate over the last three years the number of cases that have now come to your attention because of our interest in oncologic drugs for children and the submissions made by the pharmaceutical industry.

Second, do you have any handle on how many oncology drugs have been approved for labeling in pediatrics; namely, what is that total number?

And the third thing is really for the last case. How do you define in the FDA "effective"?

DR. HIRSCHFELD: I'm going to punt on that last question because that's a whole discussion unto itself. But the short answer to the last question is: Live longer, live better. And we have many discussions and publications on that theme.

But to back up, we have issued approximately 30 written requests for pediatric studies in oncology, and as far as we know, they've all been accepted and are being acted on. We have received the five that you've seen in response, and they're continuing to come in. And we have effected labeling changes in a subset of those

five, as you've seen, with a couple still pending.

We have some programs under development which will be coming in with a pediatric indication as the first approval. And overall, depending on how one counts pediatric indications, but Dr. Pazdur, Dr. Smith, Dr. Peter Ho and I have a manuscript which tabulates these in various ways. And if there is a mention of a pediatric disease somewhere in the product label, then it comes out to be about 16 products. But formal indications, it's actually fewer than 10, and the last time prior to this year that we had a submission was in 1990.

DR. PAZDUR: I wanted to follow up on Jerry's comment. By no means am I discouraging--I want to make that real clear--any inclusion in the pediatric label. I think there is a great need for information, but I think we have to as a group tackle with these difficult problems.

One of the concerns, obviously, if you're putting in relatively preliminary data, two out of 14 patients that got a response in a particular tumor, are you giving a de facto indication to the sponsor by including that data? So I think you have to be--and would that potentially actually be

deleterious in precluding further study and real studies to be done if they already have a claim?

One of the things I'd like to bring out is, you know, one of the areas we're very careful about and concerned about the labeling is promotional claims that sponsors make. Because of the nature of pediatrics--and I'd like some discussion on this--I'm really not that concerned because the pediatric patients, especially pediatric oncology patients, basically have a different type of practice--or pediatric oncologists have a different type of practice much more involved in protocol applications than, say, a claim that a sponsor would make in the treatment of breast cancer based on two out of eight patients having a response in breast cancer and then trying to make some claim that this was active in breast cancer. I think the same promotional concerns, although theoretically could be there, perhaps don't apply that well in a realistic arena to pediatric oncology. And I'd just like to get some feeling on that from some of the people.

DR. SANTANA: I can comment from my own perspective, and others that are more senior can comment, too. I think, you know, as you well know,

pediatric oncology is primarily clinical investigating, protocol-based, so that the impact--I can speak for myself, and I think the people at St. Jude, the impact that promotional has on which drugs we choose to study or how we choose to do our studies is, at best, negligible. It really has no major impact.

But we need to be cautious about that because the field could change, you know, 50 years from now. But I think currently it's a very negligible impact.

Greg, do you want to comment on that?

DR. REAMAN: I would certainly agree with that. My only reservation would be in the setting of recurrent disease. Certainly in newly diagnosed patients, in the context of front-line therapy, I think promotion would have a little impact. But in the setting of recurrence, I would anticipate some potential problems.

DR. SANTANA: Dr. Melemed?

DR. MELEMED: I wanted to reiterate the value of pediatric--or the package insert in regard specifically to the pharmacokinetics, the dosing. Somewhat ironically, in all other indications it's a very valuable resource for pediatric oncologists

to look at. Unfortunately, in oncology there's very little guidance and, therefore, we have to go to other sources to get that. So I think in that area, it's very important to get some sort of guidance on how you use these drugs, even though they may be for a potentially different indication than what it's approved for.

DR. SANTANA: Dr. Schweim?

DR. SCHWEIM: I would again tell you something about the German situation, especially on the topic of label use. In Germany, 90 percent of all children are treated on protocols like in the U.S., and they are treated in clinics. But then we have the follow-up with the outpatient problem that I would tell you about. The German situation can be described that 90 percent of the inhabitants are insured for health occurrences via a governmental based insurance system. And, therefore, it's very complicated that our court of social affairs has said that drugs only can be reimbursed if they are used according to the labeling. That's not the problem--that's not the problem for inpatient because there is another system working, but for outpatient, it's a very bad situation because the oncologist for outpatients has the problem that he

cannot be reimbursed for the treatment he has for the children coming from the clinics, and he also is not reinsured if he makes any failure as a clinician because the insurance company only insures them if they're using in the correct way of the approval. And we have tried to figure out how many cases there are, and I think it's only 20 percent where the treatment is occurring to the labeled indication. And I think it's not the severest problem in oncology, pediatric oncology, but it's much more worthwhile to figure it out in other indications that we have lots of problems with that.

And then I have a question. You mentioned the problem with the package leaflet. I think according to the ICH harmonization process and the CTD comments, it's absolutely obvious that all the items to be mentioned are in the correct place. And they follow up something like a queuing in the system, and I think to follow up very precisely these CTD comments, not having (?) with advertising situation and so on from the company is very useful for patients, for parents of patients, for nurses to read the package leaflet as information.

So in Germany, we have decided that all other information must be in a black box--not a black box as a warning box, but a black box as an advertising box. There they can state some further information which must have to do with the usage of the drug and, two, must be approved by the agency. They're not allowed to use any wording on their own.

DR. HIRSCHFELD: Just as a point of information, CTD that Dr. Schweim referred to is Common Technical Document from the International Conference on Harmonization.

DR. CHENG: Thank you. Getting back to Dr. Pazdur's comments about off-label use and inclusion of negative data, I would encourage the--obviously I think we have to be pragmatic about the size of the studies and what goes in. But, on the other hand, we also have to take into account that often certainly in the U.K., U.K. press, and concerns that health professionals, pediatricians, and parents have is that drugs haven't been tested at all in children. So at least if there was some data, I think that would at least allay some of their anxieties, albeit negative, but obviously I think to put in two out

of eight, I think we would have to have a case-by-case discussion for each one. I think it has to be interpreted carefully. But, on the other hand, overall I would encourage it because certainly in the U.K. press, we get a lot of children being tested or being used as animals because drugs have never been tested in this population.

As far as the label is concerned, I think in the U.K. and Europe, the equivalent is the SPC, the Summary of Product Characteristics, and I would agree with Dr. Santana that it may not always be the appropriate way of communicating to health professionals because they don't always read it. However, I think it's still an important document from a regulatory point of view, and it has to be--it is the agreement between a regulatory authority and the pharmaceutical company, and it shows that that data has been submitted, the data has been reviewed. It may be that it needs to be supplemented by other communications so that it reaches the health professionals and the nurses and the patients.

Then one final question to you is obviously these data, as I said before, are very

encouraging, but they don't fully answer all the questions. What means do you have in the U.S. to go back to the companies and say what plans do you have for further study to answer the unanswered questions that have been raised by these studies?

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

DR. HIRSCHFELD: Yes. We have hopefully just our interest and our persuasive abilities at hand. We don't have other tools, other regulatory tools, but we hope that, again, because we view the pediatric oncology community as a community, if we have discussions with the Children's Oncology Group, with our colleagues at the NCI, with colleagues at some of the independent research hospitals, further development could occur.

DR. SANTANA: Dr. Hagey?

DR. HAGEY: With regards to these five case studies and dosing in particular, perhaps I could ask for a little clarification as to why the dosing information was really provided, it looks like, only in Case 4. It appears that maybe perhaps 450 children were tested, but yet the end result is maybe only any dosing information only included for one of those studies.

DR. HIRSCHFELD: If I could respond to that, Dr. Santana. Case 4, actually, dosing information was not provided in the label. If we're referring to the same case, that's the one where there was lack of activity. Yes, but you meant--I think your point was how can so many children have been involved in studies and yet it doesn't quite make it to the label. And we actually--and I'll ask Dr. Zajicek or Dr. Booth to amend the comments, but on the whole, the data that we submitted, the raw data, could be analyzed and could be used to determine dosing.

Now, whether we decided to--so, therefore, the studies in our view were informative and, therefore, ethical. Whether those data made it into the product label or not varied according to the circumstances, and I should say that we haven't taken final action on all of these cases. So there may be more. But Case 2 was one where there was information that we were able to include in the product label, and I'll ask now Drs. Zajicek and Booth if they have anything further to say.

DR. ZAJICEK: For Case 1, my understanding is there's some plan, if the drug has an indication, to put in the PK data. So it's likely

that that may go in.

DR. SANTANA: I thought she was talking about Case 2. Were you talking about Case 2, just for clarification? There's some confusion about which case you were--

DR. HAGEY: Yes, Case 2 appeared to be the only one where dosing information was included. I incorrectly spoke as Case 4.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: Richard, when you were talking about two out of eight, et cetera, numbers of response and trying to determine efficacy, if these data were generated by a well-designed, planned clinical trial, then the investigators prospectively wrote down how certain observations should be interpreted. And so we shouldn't be talking about them out of the context of the clinical trial in which they were generated. If, in fact, the study said that two out of eight would result in concluding that the drug had no activity, then certainly I think that was an indication that should go into the label, and perhaps that's what happened with Case No. 4, where what was written in the label actually interpreted what was prospectively decided before the clinical trial was

run.

I have a question about Case No. 1. You write down that really the concern is trying to choose the proper pediatric dose, and I'm not sure I know what the definition of "proper" is.

DR. ZAJICEK: The applicant--the doses for the pediatric--the initial dose, the starting dose, was designed to have the same exposure as the adult dose. So the thought was that if the adult exposure, you know, was X for that, the adult dose, then if the pediatric dose had the same exposure and it was effective, then that would be the correct dose. The problem has been the overlap.

DR. BOYETT: Well, actually, is that a well-formulated question to address, anyway? Because there's variability in exposure amongst the adults--

DR. ZAJICEK: Absolutely.

DR. BOYETT: --who got the same dose. So you could say that we want a pediatric dose that achieves the same exposure as in 50 percent of the adults or 75 percent or something like that. But to say the same exposure seems to me like that's not well formulated either.

DR. ZAJICEK: I don't argue. It's a

complicated question about what the right dose was, and, again, we're talking about a small population, you know, a small number of pediatric patients, a small number of everything. And we're still discussing this. So you're right, and we're not sure what the right answer is.

DR. SANTANA: Dr. Smith?

DR. SMITH: We've heard how much both patients and nurses and physicians desire information in the label or in other places that they can get access to. When we're talking about the label, though, the implications of not updating the label in a timely manner, I wonder if you've considered those, particularly as we think of the patient, the family that reads the label, the dose that their child is receiving is different, is being used--rather than single agent, is being used in combination. And because the label hasn't been updated, you know, it's not reflecting what their child is receiving. This creates confusion and sometimes hostility and difficulties, when, in fact, again, as you mentioned before, there may be good reasons that that dose is being chosen, that there are other sources of data that the treating physician has had access to that justify the dose

or the combination that's used.

I wonder if you could comment on the implications for not updating the label in a timely manner and whether it would be possible to include some disclaimer that, you know, there may be additional data that aren't included in the product label that the physician may have access to, to guide the appropriate use of the drug in children.

DR. PAZDUR: This is a very difficult question, you know. We rely basically on companies to submit data to update the product label, and as I said, in oncology there is rampant off-label use. If you take a look at the dose--the label on 5-FU, if somebody was using that as a treatment guide for the treatment of metastatic colon cancer, it would be totally irrelevant. I don't think it's been updated since the mid-1960s.

We started doing this, and really the manpower basically to start updating and reviewing all of these labels to make them as if they were, quote, treatment guides for a disease or the way the drug--every possible indication or how the drug is being used, it is very difficult, it is very time-consuming--would need a huge expenditure of people and time and probably almost a doubling of

the staff, just using a figure out of the air here.

And you then get into a situation where you have varying levels of evidentiary proof in the label. For example, data that we took for the submission, the original NDA, have constructed the survival curves, have audited this data, and then perhaps might include data that we get from a publication where we don't have access to that primary data.

So it becomes a very difficult situation, and labeling has been outdated, and, again, this is a major problem. But it really would require a tremendous amount of resources to address this issue, to make it current, and then how to continue to make it current.

DR. REAMAN: I concur with Malcolm that it is a major problem, and I also understand the magnitude of the problem in trying to continuously update the label.

Alternatively, would there be an option for sort of a general disclaimer to the label or in every label, that there may be clinical trials that are evaluating different doses of this same drug in perhaps a different schedule? That may prevent some of the concerns that Dr. Smith has raised.

DR. HIRSCHFELD: I just would like to amend some of the previous comments and state that the definition and use of the label as a document is perhaps beyond the scope of what we wanted to ask this morning, and what we'd like to get some focus to is, given that we've requested pediatric data, how should those data be mapped onto a product label in different circumstances? And if we have particular cases that fit patterns, then would those patterns help guide us into fulfilling what we've been given as a mandate, which is to dissemination the information that we've asked for?

DR. SANTANA: I agree with that, Steve. I think what I'm hearing Malcolm and Dr. Reaman say is somewhat different. It's saying, yes, you've gone out through whatever mechanisms the FDA has to request sponsors to do these studies in pediatrics. And now you're going to be receiving that data derived from those studies that were part of the request, and now you're trying to decide how that information, if it's valid or not, makes it into the label. I don't think we disagree with that.

I think what I'm hearing is you have to recognize that in pediatric oncology, by the nature of what we do, which is clinical investigation,

there is concurrent therapy that is going on that you are not going to be able to reflect in the label in a timely manner, no matter how much effort you have, but you need to give the oncology community a way and the families a way to recognize that there is a concurrent, ongoing discussion of this product and its indications in pediatric oncology and give us that tool so that parents do become better informed.

I think that's what they're saying. They're not saying, you know, which studies you choose or don't choose that were not part of the written request. I think we all agree that you went out there with a written request, you're going to get that, you're going to evaluate it and make a decision. But you have to recognize that there's another body out here of ongoing research and investigation that's occurring, and you need to give us that tool as part of the label. I think that's what we're saying. I think we're getting a little bit more into the summary issues.

I want to take a couple more questions, and then I want to take a break. I think Drs. Reynolds, Pelusi, Vassal, in that order.

DR. REYNOLDS: I just wanted to mention

something we haven't discussed, and that is that there are a number of drugs that are used in adult indications that are then taken to the pediatric setting in myeloablative therapy, and that would totally change the pharmacology and the use of them and the safety and a variety of issues. So I think that's a separate category and something that we need to think about as to whether or not labeling indications for use in that context would be appropriate.

DR. SANTANA: Dr. Pelusi?

DR. PELUSI: My comment just got back to, again, the issue that Malcolm brought up in terms of the labeling because, again, patients and families really do look at that. And so if there was a disclaimer--but also there may be another mechanism, whether it's the PDQ or whatever, in terms of what are the current things going on that may be a nice bridge for patient education and consumer--because, again, it's the whole issue of safety and expectations for consumers.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: Yes, I agree with Dr. Santana about his comment, but I would like to highlight the fact that there is a lifestyle--a life after

the labeling for the drug, and it's important that the labeling data encouraging the use, the wide use of the drug in pediatric oncology should be evaluated in protocol, prospectively evaluated in protocol. And the key issue is how these negative results are available in order to avoid duplication of studies, providing that these studies with negative results have been conducted with appropriate and adequate methodology. And my concern about most of the cases here is for the negative data, there are enough data to say with this dose, this schedule, this drug is not active in this disease.

The proof of concept is important when the disease is the same in adults and children. However, when we are considering pediatric tumors, we do need strong data to say it is not active or it is active. And I would say that it is important to make possible a larger number of patients in such studies to really provide the important data, because, otherwise, we will give some information, it's positive, it's not positive, it's active, not active, and it will not be strong data for the patients. So the negative results are important, need to be provided, but they need to be

statistically available and strong.

DR. SANTANA: Dr. Mathieu?

DR. MATHIEU-BOUE: Thank you. First of all, thank you for the clarification for Case 4, because I had the same concerns previously mentioned. And I would like to make a general comment. I fully support my colleagues from U.K. And, of course, we need to have in the product label any kind of relevant information for clinical use and for the nurse or for the family, for the patient, as a kind of guidance for use as you mentioned. But I have some concerns about the implementation in the product label of very limited data because sometimes, and especially maybe it's a European concern only, but some limited data mentioned the SPC or product label would in some cases limit or decrease the accrual of ongoing trials. And I think we have to keep that in mind.

I have also some other comments with regards to the negative study, negative results study. I think that, of course, the whole community needs to have them published, but there's a comment we can have between agency, regulatory agency. Maybe we could encourage, officially encourage the publication of negative results

either through classical publications with strong recommendations, official recommendations--this is a point for discussion, of course--but also as you mentioned, it's very important to have for the public the data when they have been reviewed. When negative have been reviewed, I think this is very important to let them know. But I think we could encourage to help them either through public reports through European system, for example, on the Net or somewhere else. So it's two types, two means, two tools, I would say, to publish the negative results.

And my last comment is about the combination trial, and I'd like to have the--trial, I mean use of chemotherapy and so on, and I'd like to have the discussion today about what do we need in the product label about the combination use.

DR. SANTANA: Dr. Ettinger?

MS. ETTINGER: I just wanted to comment as well about the disclaimer idea and suggestion, something about discussion of ongoing research. I think that's very important, and I don't think we should discount the importance to insurance companies, as you have mentioned. And we constantly are being asked--I am in that position

in what I do--from insurance companies. And I do believe that they do read that, not so much just for billing purposes, as they suggest when we speak with them, but also to see that 5-FU or whatever, I'm using that as an example, hasn't been updated for how many years. And I think that a disclaimer might help in there as well with some form of reference material to say there is ongoing research to indicate the use.

DR. SANTANA: Dr. Schweim?

DR. SCHWEIM: I would like add three comments, the first one on the disclaimer discussion. In Germany, we would reject such a disclaimer. While it is indicated there are ongoing trials of it, there is other information available which the doctor might have used, because to our point of view it's too paternalistic an approach of medicine. The goal is the informed and decidable patient and, therefore, he must have access to full information depending on the age of the child or the decision of the parents.

The second comment I would like to make is about update of the package leaflets and the informational data. In the German drug law, the pharmaceutical company has an obligation for

paramount observation of the market and the use of the drug in the health professional society. And if there is any change, they must be forced to do--to make a variation procedure and to include this new information in their package leaflet voluntarily--voluntarily in brackets; and if they don't do so, then we have a renewal procedure of five years where the agency themselves can change the package leaflets so that we try--we do not always succeed, but we try to update the package leaflets as often as possible so that it's always on the active basis. And any changes have been indicated by printing down the date of the change on the package leaflet as information for the patient.

The last item, the publication of negative data. I totally agree with my colleagues. It's a very, very need to have publication of this. In Germany, we have the problem that all ongoing clinical trials and their results must be sent to my agency, and then they are stored in a database, and that's it. We are not allowed to publish this data. We are not allowed to give scientists access to these databases on behalf of the Intellectual Property Rights Act because in very seldom cases

negative data results to further indications and so on, and so the companies have succeeded that these databases are absolutely confidential.

So I appreciate very much the Freedom of Information Act of the U.S. because we collect our information for the patient via the USA.

DR. SANTANA: A point of clarification for me just so I understand. But if the German study groups participate in multi-international studies, then you are obliged to provide that information, right? Is it only just for studies sponsored--

DR. SCHWEIM: It's only for--the situation for the sponsor. The agency is filing the data and is only obliged to use it in pharmacovigilance cases. This is the only exception we have. All other informations are not allowed to be published via the agency, but they are waived from other sources, for example, in a multi-country clinical trial from the U.S. or from other countries who have similar Freedom of Information Acts.

DR. SANTANA: Dr. Melemed, you have a point?

DR. MELEMED: It's a comment in regard to Malcolm's statement. I think the question is: Is it better to have something in the label regarding

dosing and pharmacokinetics that may be outdated or to have the opposite that is there, that pediatric safety and efficacy cannot be established?

DR. SANTANA: Ms. Keene?

MS. KEENE: I just have a couple of general comments on the conversation that's occurred to this point. I am in favor of full disclosure and as comprehensive information as possible on the label, on pediatric labels. I understand we're not operating in isolation. I understand that adult labels could become, you know, as long as a football field, but that's not the case in pediatrics. So let's put the information that we have on the label so that parents can make informed decisions.

I'm going to think more about the disclaimer concept, although my first response is I wouldn't be in favor of it, namely because most drugs that are currently used in pediatric oncology are not on the labels. They're off-label use. It's a matter for communication between physician and family and explaining to them what's on the label, why it's on the label, what is the evolution of the trial that has been proposed for the child. And often, as you all know because you do this

every day, you explain to families who want this level of detail--some do and some don't, but the ones that do, you explain to them what the evolution of the trial is, the reason this trial is being proposed for their child, and what the information, we hope, will be learned from that trial. And then give them all the information that's available and let them make an informed consent.

I also am not in favor of a few of the discussions that have come up about alternate forms of providing information, especially about negative results. It is very hard to find things in the Federal Register. It's very hard in some cases to find things on the FDA website. I think that if we're going to put information, we should put all the information on the label and let people find it in one place and then go to their physician, have a discussion about the proposed treatment, and make a decision.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: I have a suggestion to help quantitate--and I have to give credit to Pat Reynolds because he gets stuff before they're published, and the article that Steve referred to

that you and Malcolm and Rich published actually quantitates these drugs, lists what's labeled, what isn't labeled, and maybe after the break, Mr. Chairman, if Steve would perhaps--undoubtedly you have it on slides because you always have everything on slides--could show this. I mean, we'll find out what's really in the labeling situation?

DR. SANTANA: Do you have that information?

DR. HIRSCHFELD: I could share it orally. I didn't bring slides on that with me. But I do want to address some of the points--

DR. FINKLESTEIN: After lunch.

DR. HIRSCHFELD: Yes. I want to state--what I'm going to say is my personal opinion and shouldn't be interpreted as the voice of the U.S. Government in this regard. But I think that to consider the product label as the all-purpose, up-to-date, thorough monograph is not desirable in terms of the actual intent of the product label, which is a licensing statement on the use of those data that have been reviewed by the Food and Drug Administration. I think to include a blanket disclaimer that there are other uses and other

doses available and please find them out is an open invitation for all types of promotion, and I'd like Mr. Allera, when he gives his comments, if he might respond or comment on that particular point.

I would request that although we hear loud and clear the need for up-to-date, accurate patient information available, for our purposes what we're trying to seek advice on is we have a body of data and we would like to get the advice on how we should best handle those data that we do have. And the other data, which are in other settings and in the parallel universe, might be a very interesting subsequent discussion.

DR. SANTANA: I think we're going to go ahead and take a break. Make sure you get back on time. We'll take a 15-minute break, reconvene 5 minutes to 11:00. Thank you.

[Recess.]

DR. SANTANA: Let's go ahead and reconvene. We now have an opportunity for our open public hearing session. Only one individual has requested to address the committee, and that is Dr. Allera. So, Dr. Allera, if you could please come to the podium.

I lost him. He was just here a few

minutes ago. We'll give him a couple more minutes.

Then after Dr. Allera, there was a consensus from the committee that Dr. Hirschfeld present some additional information from a recent publication, so we will give Dr. Hirschfeld the opportunity to address the committee again.

So, Dr. Allera, please, could you identify yourself?

MR. ALLERA: My name is Edward Allera. I'm counsel to the National Cooperative Oncology Groups of NCI, also an attorney that represents a variety of clients before FDA. And I'm appearing today pro bono to discuss these issues of dealing with oncology and oncology data based on these. Dr. Hirschfeld and I spoke over the last several weeks, and perhaps trying to look at perhaps the larger picture that you as a practical matter raise today. So he asked me for my thoughts.

I'm an ultimate pragmatist, and I believe we need to develop a system that makes available all information about oncology drugs either in the labeling of the drug products or some publicly accessible documents that provide a rating system for the drug products, such as FDA's Orange Book. Clinicians, patients, and their families and

friends, insurance companies, and others are being exposed to a cacophony of information about oncology drug products. The noise comes from variable sources, is of disparate quality, and is often unfettered. We need to consider a rating system, I think, that would clarify the quality and quantity of the data. Such an approach could be communicated perhaps clearly and concisely to interested parties, and it hopefully would create an incentive for additional research that could be used to support reimbursement. Such an approach is consistent with the historic approaches of FDA's regulation of information, especially as that authority has been refined by the courts.

Now, Dr. Hirschfeld, as always, gave a very thoughtful presentation and went through the history of FDA regulation and the statutes. I think it's interesting that most recently--and he mentioned the '62 act, which added adequate and well-controlled investigations to the statutory definition and gave FDA the authority over drug advertising.

That was an interesting era where you had basic media, radio and television networks, newspapers, and national magazines, and it was

expensive to provide that information. Regulation was straightforward. We were also pre-Medicare, pre-Medicaid, pre-cable television, pre-computer, let along pre-Internet. Health care information of any kind was generated in limited amounts, was accessible through limited means. Health care professionals and government were accorded a deference that's almost unfathomable today.

In the early 1970s, FDA through rulemaking established the format for the package insert and drug labeling. And one goal of that revision was to provide health care professionals and others with a standardized format for comparing the data that FDA had analyzed and reached a conclusion about. Data from clinical and other trials as well as relevant studies of new drugs were submitted to FDA, and only that data deemed appropriate were included in labeling and characterized by the agency. Also, you had a very nice, controlled clinical system.

That simple system began to crack in the 1970s and 1980s with the so-called patient package insert. After that came direct-to-consumer advertising. Then the courts began to limit FDA's ability to regulate truthful information about

drugs, holding that the agency's constrained by the rules that apply to the regulation of commercial speech.

For almost 30 years, information about drugs was limited, and that information was available only through the FDA filter. For the past decade, however, that model has not been true. Formularies, both public and private, are the norm. Therapeutic decisions are made routinely on the basis of economics. Economic decisions are made on the basis of data comparisons that FDA would never permit pharmaceutical companies to make.

So today we face a new paradigm. Through technical advances, information of all quality and quantity and veracity are available. Data are available from chat rooms and unregulated sources, from true believers and charlatans. Patients and their families have, we have found, an insatiable appetite for information about their diseases, particularly as they become more life-threatening.

Negative data are often not published or released. The courts have recognized the rights and the needs of the public to receive information.

We also have a coalescence of technologies and products that are subject to potentially

differing legal standards. We have drugs, devices, biologics, all coalescing in therapy and all being used. Practitioners are pressed for time to evaluate these data, and payment for these treatments is critical to the patients. The information must be available, therefore, in a manner that's useful to payers.

Most importantly, I think, patients, although they must be informed, they must be alerted to worthless and misleading, or worse, data. I think perhaps the most important thing we can think about is preventing people--having people have a clear view as to the quality and quantity of data.

In the U.S., we've created a fabulous oncology research machine that has both public and private arms. The cooperative groups of NCI enroll about 35,000 patients in clinical trials. The number is about half of the total oncology patients, so we have a nice private sector arm. For children, it's estimated, as we've discussed, about 90 percent are on clinical trials, and these trials are designed to provide improvements of the existing standard of care.

But for adults, it's estimated only 3 to 5

percent of oncology patients are enrolled in such trials. A congressional report of several years ago indicated that about 70 percent of oncology drug use is off-label, but much of this usage, of course, is accepted standard of care among oncologists. So we need to develop a system, an information system that addresses the needs of the patients and practitioners within the real world of research guidelines and the need to encourage enrollment in controlled clinical trials and push the standards of care and cure rates even higher.

Congress attempted to restrict the dissemination of information about off-label uses by FDA in the Food and Drug Modernization Act of 1997, and the court rejected those restrictions. But that's only one movement in this symphony of information that's available. The courts have held and believe that the world can no longer be seen only through the prism of FDA. Decisions, critical decisions about life and death and payment are made on the basis of information or data that may have never been fully analyzed or critiqued by the agency. I'm a big believer in the old Buckminster Fuller adage that there's no such thing as negative information, so we need to think about a procedure

that provides everyone with the information available in a useful form so that it can be used in thoughtful decisionmaking processes.

Procedures are also necessary that encourage the submission of information to FDA and others for review, and such a system should provide an incentive toward enrollment in clinical trials, in my view. For oncology drugs, affirmative reimbursement decisions are already made on the basis of data that may not meet FDA's statutory standards. Nevertheless, Congress and others have concluded that such decisions are appropriate.

With the appropriate process, the failure to participate could be reviewed in the decision, and people can then weigh the decision of failing to submit the information for FDA review or inclusion in the information system. And objective response rates, as you've discussed, need to be clearly identified, perhaps, and assessed so people can recognize what a real effective rate is.

A negative result in a small study may reflect an absence of power, and a clinical trial where anecdotal claims of great effectiveness may have zero merit. Data are generated from a spectrum of studies, from adequate, well-controlled

clinical trials through the range that we've seen discussed here.

So we need some mechanism. FDA's regulation established a content and format for the labeling of prescription drugs, as Dr. Hirschfeld mentioned. Contained within that format, I think, is the germ of a model for this area. There would be a rating system based on data. If one looks at the discussion of pregnancy effects and teratogenicity in the regulations, perhaps we can--it has an alpha system for rating the quality and quantity of data. That system rates drugs in various numeric or alpha categories: A, if adequate and well-controlled studies have failed to demonstrate a risk of pregnancy; B, if reproductive studies have failed to demonstrate a risk and there are no adequate and well-controlled studies in pregnant women; C, if animal studies have presented a risk, and it goes on through D and X.

So for patients and the needs of insurers, a system is used that--perhaps that system is too primitive, but ASCO has a system, the National High Blood Pressure and Education System have a program. So in these discussions, I think perhaps an alpha-numeric system where one rated the necessary

data that gave it an alpha and a numeric as to the veracity of it might be useful.

I think that information need not be restricted to the labeling. FDA, for example, posts on a monthly basis the therapeutic equivalence ratings of generic drugs in the Orange Book on their website which gives people an idea as to which drugs are therapeutically equivalent. So it is not a system that is completely out of the blue, and as you've discussed today, there's so much information out there from a variety of sources that perhaps, in my view, a rating system that's alpha-numeric is useful and will provide a mechanism for dealing with the difficulties you face, particularly from pediatric oncology, which could be used perhaps as a primer system for this.

By the way, I wanted to introduce Ajoy Matthew, who's Director of Regulatory Affairs now for the Children's Oncology Group and who will be very active in this area.

Thank you very much.

DR. SANTANA: Thank you, Dr. Allera.

[Applause.]

DR. SANTANA: Anybody else in the audience who wishes to address the committee, this is the

opportunity to do so.

[No response.]

DR. SANTANA: If there are no additional public comments, then I'll invite Dr. Hirschfeld to give us this long-awaited summary that we keep talking about. Steve?

DR. HIRSCHFELD: Thank you. This is a pre-print of a paper that will be appearing in the Journal of Clinical Oncology in the March 15th issue, and the Journal of Clinical Oncology is the clinical journal from the American Association of Clinical Oncology.

The purpose of this study was to examine regulatory experience in the approval of pediatric oncology drugs, and I'll just summarize the abstract and show you two tables, and I think that will convey the information that the committee was interested in.

The method was a retrospective review of FDA archival documents, published literature, and in some cases some interviews with the people who were involved in the studies. And the summary is that over 100 drugs have been approved, plus another 15 to 20 biologicals, but in this case, we restricted our universe to the applications that

have gone through the Division of Oncology Drug Products.

Of the over 100 drugs, only 15 have pediatric use information in their labeling, and according to a summary that Archie Bleyer of MD Anderson, University of Texas, published several years ago, there are 30 to 40 drugs which are commonly used in pediatric oncology of this universe of 100 approved drugs. And, therefore, these 15 represent less than 50 percent of the drugs commonly used.

In the past 20 years, there have been six submissions to the FDA for pediatric oncology indications, and the rest of the paper is a discussion of these submissions. So I'll show you the key data tables.

This table is a listing of the 15 drugs that have pediatric use and pediatric dosing information in the label, and anyone familiar with the field will notice that these 15 drugs more or less recapitulate the history of pediatric and oncology drug development from approximately 1952 to 1970.

Since then, the following submissions have occurred between 1980 and 2001, which was our

cutoff date for the analysis here. And of those submissions, you can see that there was one new molecular entity that was approved in 1990 as salvage therapy for acute lymphocytic leukemia, and there were two submissions, one for daunorubicin and one for methotrexate, that were approved as supplements. And these are old drugs.

What we were looking for and hoping to stimulate by this study, by our initiatives, and by dissemination of the information through publications such as this and through other fora is to be able to write in, we hope, the very near future another paper which would say recent submissions to the FDA on pediatric oncology drug approvals.

I'll take any questions on the data or the study.

DR. FINKLESTEIN: Steve, there's another table, which I know is long and may be hard to show, which is Table 2. For example, when you have a column in there that says approved indication, does that mean within that indication--I mean, it's more than the 15 drugs. Am I correct?

DR. HIRSCHFELD: The criteria for including the 15 drugs was when there was both an

approved indication and approved dosing. So in the 1950s through the 1980s, as the evolution of how to apply the concept of adequate and well-controlled studies evolved, it was possible to submit pooled data on a variety of patients with malignancies and describe response rates. And we included these historic data because the product label mentions the pediatric disease, even if the data by contemporary standards would not be considered persuasive.

In the 1980s, the Oncologic Drug Advisory Committee began to hold its discussions, and there's a series of discussions which support the notion that efficacy in oncology should translate into patient benefit, and the approval standards from the mid-1980s forward have been in continuing evolution of that concept of patient benefit.

The approved indications in these instances refer to the historic standards and shouldn't be misinterpreted as the contemporary standards applying.

DR. FINKLESTEIN: So, for example, the germ cell tumors do not list either carboplatin or cisplatin as approved; prednisone has no rating for leukemia--just to let everyone know where we sort

of stand. There's a whole emptiness put there, and some of Henry's brain tumor drugs aren't listed either.

DR. HIRSCHFELD: Right, and this is precisely the point, and all that white space between those yeses represent the gaps in information and the absence of submissions for review.

DR. SANTANA: Any further comments or questions to Dr. Hirschfeld? Dr. Smith?

DR. SMITH: I would just amend Steve's comment slightly. In some cases, they may represent gaps in information, but in some cases, they simply represent gaps in submission. There's plenty of information in the published literature or, you know, from cooperative group clinical trials. And so it's again the issue of the importance of recognizing that, at least in the imperfect world we live in, you know, there are multiple sources of information that are used to make decisions about appropriate treatment.

DR. SANTANA: Any further comments? Dr. Vassal?

DR. VASSAL: Yes, just a short comment to highlight the fact that the situation is clearly

the same in Europe. I did a survey in October 2002 to look at the approvals in terms of marketing authorization at the EMEA, and out of 280 medicinal products that were granted on October 8, 2002, 26 were related to cancer or related malignancy conditions. And only two out of these 26 had appropriate labeling in terms of pediatric use.

This is not all the anti-cancer compounds registered in Europe, but those centrally registered clearly are in the same situation, poor and no information about pediatric use. And the sentence, "Safety and effectiveness have not been established in the pediatric population," is clearly something we don't want to see anymore.

DR. SANTANA: I want a point of clarification from the agency that may shed some light when we get into the questions. When written requests and exclusivity guidelines are applied to a product, that is, the agency goes out and says do these studies in these pediatric patients under these conditions, and the sponsors do that, when the information comes in, is that interpreted as a mechanism for a supplemental NDA? Is there a link between those two processes? Answer that first, and then I'll lead to the next one. How is that

information interpreted from the regulatory perspective?

DR. HIRSCHFELD: There are two mechanisms to submit the information to the agency in response to a written request. The first mechanism is as an NDA supplement, and that would imply that the data that are contained in those study reports would be sufficient to support a new indication. The second mechanism is as a labeling supplement with clinical data. And there the implication is that the questions have been answered, and what we have to then contemplate and wrestle with is of those data, how much of it should actually go into the label, and that's the focus of what we're asking you this morning.

DR. SANTANA: Okay, good. So it leads me to my second question, which is: If it's viewed as information for a supplemental NDA, and the agency finds that the information is just not there and, therefore, the sNDA can't be approved, that information never makes it to the label, because technically the sNDA was not approved?

DR. HIRSCHFELD: No, it still could make it in the label, depending, again, on--we could--if, let us say, the data don't support

approval for that indication, but the data still tell us something about safety or tell us--because it's a negative study, or in some other way informative, it's quite possible, even reasonable, to consider putting it in the label in appropriate sections. And I will go back to say that the pediatric use section of the label is not the comprehensive summary of the use of the drug in children. It's a subsection under the precautions, and it's intended to state any limitations or other considerations in using the drug in the pediatric population.

DR. SANTANA: Then, given that position, why when a sponsor comes to the agency with the required studies for the exclusivity, why does the agency struggle with what information goes into changes in label or not? Why not adopt the principle that these were studies that were requested by the agency, they were obviously reviewed ahead of time, whether they're positive or negative, provide complete or incomplete information, why is that information--why are we struggling with the discussion of trying or not trying to put that information in the label?

Do you see what I'm getting at? If there

was a process where we requested the information independent of the end result, what we're saying is we're committed to that information. And within the review process, if that information is valid, why is that information not put in the label?

DR. HIRSCHFELD: Well, Dr. Santana, I think that's a very beautiful introduction to asking the questions, because perhaps by the end of an hour or two, we could have a consensus on that point.

DR. SANTANA: Okay, good. So for the purpose of the record, I have to read the questions to the committee, and what I'd like to do is hopefully before lunch--we'll take a break at 12 o'clock--at least try to discuss Questions 1 and 2, and then we'll take a brief lunch break at 12:00. The original schedule said lunch from 12:00 to 1:00. I think we could do 12:00 to 12:30 if the committee agrees, and then reconvene at 12:30 to see if we could complete this in a more timely manner for the afternoon.

So everybody has a copy of the questions, and for the record, I will read the introduction, and then pose the questions for further discussion.

The Federal Government initiatives are

aimed at developing therapeutics for pediatric patients and including product information in the approved package insert or product label. Although the majority of children with cancer in the United States are treated on protocols from the National Cancer Institute-supported study groups, the majority of products used in children with cancer are used without dosing and safety information in the package insert. Given that the United States Congress has indicated in the Best Pharmaceuticals for Children Act of 2002 that pediatric use information should be included in product labels as one of the mechanisms to publicly disseminate that information, please consider each of the following situations:

If adequate and well-controlled trials in children that independently establish safety and efficacy are submitted to the FDA as a New Drug Application (NDA) or as a Biological Licensing Application (BLA) or as a supplement to an NDA or BLA, then product labeling would follow standard procedures. The situations that follow describe circumstances when information other than adequate and adequate and well-controlled trials sufficient to independently establish safety and efficacy are

submitted.

The first questions pertain to the situation where a product is approved (safety and efficacy established) for an adult indication and the same disease or condition exists in a pediatric population.

Previously this committee, the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, at a meeting held in November 2001, recommended that to extend efficacy from an adult indication to a pediatric population--that is, using extrapolation--pediatric dosing studies and a demonstration of clinical proof of concept should be performed.

So Question No. 1: If a product is approved for an adult disease or condition that also exists in children and extrapolation is used, consider what information you would consider necessary and appropriate to be in the product label. Factors to consider may include dosing, safety information, proof of concept data regarding clinical effect in children, separation of pediatric and adult safety data if differences exist.

I'll start with a comment on that. I

think--I don't want to assume anything, but I think the intention of dosing is that there would be pediatric data on schedules and pharmacokinetics, that that encompasses that broad category?

DR. HIRSCHFELD: We would not issue a request, and, in fact, prior to the incentive program, it was still in the regulations that pediatric data must include pharmacokinetic and safety information.

DR. SANTANA: And schedules.

DR. HIRSCHFELD: Correct.

DR. SANTANA: Of how the product was used in that population.

DR. HIRSCHFELD: Correct.

DR. SANTANA: Comments? Does everybody agree that that's sufficient additional information that should be put into the label? Yes?

DR. HAGEY: For dosing, just to clarify, is this to be an MTD or should this be, quote, a sanctioned efficacious dose? Because there are distinctions between the two.

DR. HIRSCHFELD: I think whichever--we were asking for advice, so if you feel it would be appropriate and useful to have both an MTD and the dose which was able to demonstrate pharmacodynamic

properties in the proof of concept data that we could extrapolate or use extrapolation, then that would be a consideration. So I would ask for some discussion on that.

DR. SANTANA: Dr. Bernstein?

DR. BERNSTEIN: I think that MTD information and the toxicity is seen--that dose-limiting toxicities would be useful information to include in a product label, although Dr. Reynolds' comments need to be taken into consideration, that is, those considerations are different if it's used in a standard dose in a more standard kind of single-agent or multi-agent regimen, or if it's used in the myeloablative context. So they're different. But I think that that information is useful.

I also think it would be useful, if it exists, to have a dose that dose provide a pharmacodynamic endpoint so that you can show some--or if efficacy has been shown.

T3A DR. SANTANA: Dr. Ettinger?

MS. ETTINGER: I was going to say the same thing, that I think it's very important to know the context in which it was used. And so I'd say both need to be addressed.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: In the Pediatric Brain Tumor Consortium, we actually have a trial now looking at a dose escalation scheme where the endpoint is not the maximum tolerated dose, but the dose that achieves a biological--measurable biological endpoint. And so, you know, if that was the endpoint of the study, that dosing information should be provided.

DR. SANTANA: Ms. Keene?

MS. KEENE: Does safety information include adverse effects? It does. Okay.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Does safety information in this context include late effects and things like secondary malignancies that might be associated with the use of--

DR. HIRSCHFELD: If those data were available, yes. The anticipation would be that at the time of early submission, those data would not be known, but yes.

DR. PAZDUR: The point that I just wanted to bring out, I think the answer whether one studies an MTD and includes that information or a more pharmacodynamically directed dose really

depends on the development picture of the drug, obviously. If one is taking a look in the whole development plan of the drug in adults and the whole emphasis is on an estimation of a targeted dose, a plasma dose, et cetera, that would interact with a target, then one might not want to take that to the MTD. So I think that this has a tremendous contextual or having to be in the context of how the drug is being developed, and that's kind of the most important thing, I think, because we're seeing many agents that are not going to an MTD. And to say, well, we need an MTD in children would not be an appropriate situation, obviously.

DR. SANTANA: Yes, I think that that's why somebody on this side of the room made the comment that it should also extend to the proof of concept principle, the pharmacodynamics relate to some other endpoint.

DR. PAZDUR: When we were asking the proof of concept data regarding clinical effect in children, you were after actually some clinical data in children, and we'd like to ask people what their thoughts about that would be and what would constitute a proof of concept.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: Yes. Regarding dosing in this situation, I think the information should be very precise, especially in the case where the dose in children is higher than the dose recommended in adults. And this is illustrated by Case No. 2 you showed previously. And I think there should be enough data to really give the information about higher doses used in children, especially in young population.

DR. SANTANA: Dr. Schweim?

DR. SCHWEIM: If the dosing is found by calculation, in Germany in the health professional information the method how this has been calculated would be added, by weight or by skin square meters and so on. In the official package leaflet, it would not be included. But I would recommend to have some information for the doctor about the method of calculation.

DR. HIRSCHFELD: I'll just add that that was used in Case No. 2, and that is, I think, a good paradigm to follow. And I would also point out that in the 100-plus drugs that have been approved for adults, many of them are approved in combinations and not approved as single agents. And the combinations are noted in the label, and

specifically the doses. So the components of the combinations are noted in the product label. So if there's pediatric circumstance, I just would raise the question: If, let us say, Phase I data exists as a single agent but the use is in a combination, how would the committee feel about including which components of the information?

DR. SANTANA: I would argue that you include both and you distinctly identify them as separate so that people don't confuse them. But you should include both.

DR. PAZDUR: If the dose is determined by calculation, what do people think about actual clinical experience looking at that dose? Don't forget, this will be going out and being announced as the dose to be used in children. Do people feel that there should be some clinical experience? And that's getting down to this proof of concept that not only deals with the clinical effect, the response rate in children, but the safety of the dose. Because, heaven forbid, you know, that our calculations for all we know about a drug may not be 100 percent, yet here, again, it's in the label. People can have widespread use. It could have international repercussions. Obviously people take

a look at our label. And no child would have ever received that dose.

What is the feeling on this? I sometimes am uncomfortable about that.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: I'd like to take a step back because I think we have to have a little overview here. If we labeled methotrexate when I started oncology, the way we're using it today is completely different. So I'm very concerned about also the fact that labels can't change very rapidly. I am very concerned about what dose will be placed in the labeling because, as you point out, it may change and this will be disseminated throughout the world and whatever--for some reason--for some of you--none of you, probably--maybe Greg, maybe not--we used methotrexate 6-MP, vamp, and bryche (ph) and all kinds of heavy doses that people don't even know what these acronyms stand for anymore, but had it entered the labeling in those days, it would be completely different.

Therefore, I'd like to get back to a phrase which will help me in my discussions for the rest of the day that actually our Chair suggested

and was pointed out both from across the continent and we know here in the United States: 90 percent-plus of young people under the age of 14 are on protocol. Our discipline is a protocol division discipline. I'd feel comfortable--and I don't know whether the FDA could do this. I'd feel comfortable knowing that in our discussions there's also an agreement that somewhere in the label it will indicate that children with cancer are treated on approved research protocols. If we had that kind of information to let us know that the information is going to change and it's ongoing, that would make me feel a little better with the disclaimers, and it would be certainly informing the public that whatever they read, they should also discuss it with their clinical research oncologist, because that's what we are.

I need something in there to make me feel comfortable when we enter into the discussion of labeling.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I agree, Jerry, in concept, but just a correction. I don't think that 90 percent of children in this country are on protocols. Ninety percent of eligible patients

under the age of 15 are probably on clinical trials, but there are a number of patients with cancer for whom we don't have clinical trials and who are treated off-label with some of the drugs that we're talking about.

When I made the comment earlier about a disclaimer, I wasn't suggesting that we make a wild disclaimer invalidating any of the dosage information that might be provided in the label. But I would certainly agree that if there is difficulty in updating the information in the label, then there has to be a comment that the dose is indication-specific and schedule-specific and that there may be other doses that are being evaluated within the context of clinical trials.

DR. SANTANA: Dr. Friedman?

DR. FRIEDMAN: Just to answer Richard's question, extrapolation analysis, prediction, correlation is wonderful. You need three patients. You need the hard data to have any kind of confidence. You're not going to disseminate a disaster.

DR. SANTANA: Dr. Smith?

DR. SMITH: The question of proof of concept, you know, presumably the agents that we're

seeing are primarily going to be the single agents that have shown activity and gotten approval or some interesting combination. And to show in a general way that the same type level of activity that was observed in the adult cancer with that diagnosis is also observed in children, i.e., something like a Phase II trial that has 20 or 30 or 40 patients and the toxicity feasibility data, you know, allows you to demonstrate some comparability between children and adults, or at least to see what the toxicity profile is. So in my mind that would be a kind of proof of concept for most of the drugs that we'll be seeing.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: I'm sitting here having some trouble now with the MTD going on to the label because the truth of the matter is the classical definition of MTD is a function of the dose levels that you set out to study. And what might be more informative is the dose level that's unacceptably toxic because the definition of the MTD traditionally is the previous lower dose level that had acceptable toxicity when the higher one had unacceptable toxicity. We're running some trials where the distance between, if you will, the

unacceptable toxic dose and the one that perhaps empirically we would call the MTD, it's a broad range. And so, you know, I don't think the MTD classically is well defined. Maybe the dose that's unacceptably toxic is well defined.

DR. SANTANA: Dr. Smith, do you want to address that?

DR. SMITH: In what we were just saying, there would be a proof of concept, a Phase II study, and you're going to take some dose for it. And so to describe that dose, that schedule, I think is what, you know, would be most useful to have in the label.

DR. BOYETT: If you're using the label for that purpose. But if you're using the label for safety, maybe by telling people the dose that's unacceptably toxic, it gives them an upper bound to stop when you get there.

DR. SMITH: Certainly that could be included as additional information, but the dose that you're using and that you have the most experience with I think would provide the most useful information.

DR. SANTANA: Dr. Melemed?

DR. MELEMED: I'm somewhat uncomfortable

separating the pediatric safety doses, and one of the questions I have is if you're then having significant differences from a Phase II compared to a large Phase II data that you have with adults, how do you compare that? I mean, are you seeing differences? Is this to give an idea where the differences are?

I understand safety has to be in there, but you don't want to make comparisons in a small Phase II of proof of concept compared to a larger Phase III.

DR. SANTANA: I mean, I think that's a valid point. Actually, I was in a different discussion yesterday where we were talking about adverse event reporting and mechanisms of that, and one of the points I made in that discussion was that when I look at adverse event data, I'm looking for two things. I'm looking for the unique adverse events, the unique things that may be particular to that population, and you have to have a way of identifying those. And then the other information that I look at, because that's the reality, that there's going to be a lot more data in adults than there ever will be in children, so I want some comparative mechanism where I could say this

toxicity is more frequent in this population, in the adults versus kids, or vice versa, recognizing that the database for the pediatric population is going to be very limited and it's going to be historically different in different types of patients.

But what I want from the safety perspective is to be able to make that comparison. So I agree with you that I think, you know, you have to be careful what data is and how you interpret it. But I think it's useful as a practicing physician to look at the separation of adults and pediatrics when it comes to safety data, recognizing the limitations of that, because that's what would be useful for me as a practicing physician to note the differences, recognizing that the differences may be somewhat invalid based on the data set that you have.

DR. PAZDUR: One of the aspects I just wanted to bring us is perhaps this would be a case where pharmacodynamic relations and some PK information could help us feel comfortable about a discrepancy in the dose. But one of the things that kind of rings in my mind as we discuss dose is what Steve mentioned in some of his introductory

remarks. Remember, the dosing that we generally put in for an adult indication--for the adult dose reflects the indication that is being studied here. And this puts us kind of in a Catch-22 situation because we don't have sometimes a pediatric indication as such.

So it's kind of a gray area that we're dealing with because the dose may vary for the indication that one is using, potentially the degree of toxicity; the risk/benefit relationship may vary. And I think it's important for people to understand that the dose that we're giving in that dosage administration reflects clinical trials for a specific indication. And this is relatively unchartered territory that we're just giving a pediatric dose for general use without an indication.

DR. HIRSCHFELD: But in this case, this first question is focusing on where you would be contemplating giving the same pediatric indication as the adult indication. And when we get to the other questions, other situations will come up.

DR. SANTANA: Any further comments?

MS. KEENE: Has there been any thought to considering putting a last updated function on

labels like you have on the PDQ? So when people read the label they know when it was last updated, if that label has been updated within the last six months or the last six years

DR. HIRSCHFELD: That's always on the label, just as it is in Germany.

MS. KEENE: It is?

DR. HIRSCHFELD: Yes. Micro-print.

[Inaudible comments off microphone.]

DR. SANTANA: The comment was--and I think it's a very good comment--that the label should reflect the timeliness of the data, and I think the remark that you hear around the table was that a lot of us find it difficult where it currently is located and how it's presented. So that's something else to consider, but separate from this discussion.

Dr. Smith, you had another comment?

DR. SMITH: Just related to that, even if there were a date, you wouldn't know that the pediatric section had been updated, and so, you know, if this were possible, you know, to know what sections were updated, maybe there's--

DR. HIRSCHFELD: I'd like to address that. Our friends and colleagues in the Pediatric Drug

Development Division are posting all the time the pediatric updates. And we not only post them to make them available, we have to report them. So for pediatric data, separate from all other label changes, there are several mechanisms that are, I think, relatively easy found to indicate that pediatric information has been updated.

DR. SANTANA: Dr. Gootenberg?

DR. GOOTENBERG: I just wanted to maybe expand and clarify something that Nancy mentioned that probably everybody here is well aware of, and that is that there is another government entity whose mission is to disseminate comprehensive and up-to-date information regarding oncology drug use and clinical trials, and it has a very specific pediatric oncology subgroup, and that's the National Cancer Institute's PDQ, which has a pediatric editorial board, a separate pediatric editorial board, and meets monthly to go over and review literature data and clinical trials that are ongoing. It's organized more by disease than by drug, but it has the mission to have an updated compendium, and it's online.

DR. SANTANA: Before we leave this question, though, I want to get back to a comment

that Dr. Pazdur made regarding this issue of population PK and deriving suggested doses without hard, fixed doses. I want to have a little bit more discussion about that because, as I read Case No. 2, Case No. 2 was an example of precisely where population PK was used to decide between this weight and that weight, these are the doses that are to be used. But after hearing your comment, I've become very sensitive of the pitfalls of that without truly demonstrating that the actual doses patients are receiving are safe.

Does anybody else feel that way? Can we have a little bit more discussion on that point? There's something there that you said that bothered me, and I want to reflect it. And I don't know how to fix it except to be honest and say this dose was a derivative dose based on this information rather than a dose that was obtained from a Phase II single study or Phase III study. Maybe that's the way around it, but I think the clarity of that message should be made.

DR. PAZDUR: I guess the thing that really makes me uncomfortable about this, we go through a tremendous amount of work to review these applications, to verify the dose, to verify

accuracy of information, and then we have a dose for pediatrics that nobody ever used, that we think, from the best of our science and calculations, et cetera, and extrapolation, is a safe dose but nobody has ever used that dose. And this is not unique to pediatrics. In other subpopulations, for example, we've debated this, for example, in calculating doses in renal failure patients, what to put in the label, or hepatically compromised patients. And it always has been a degree of angst for me to include that information if nobody's gotten a dose. It perhaps reflects a healthy skepticism about the accuracy of some of these calculations and assumptions.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: I would just say that I think that if you're going to put on a label a calculated dose with no pediatric data, I would agree with Henry, I mean, you've got to have pediatric data. So if you feel compelled to put such a dose, it should be correctly identified as a derivative dose in which there is no pediatric data to support it. And then you could have in addition an addendum to the label, once pediatric data was available, that would allow you to then label an

actual pediatric dose.

DR. PAZDUR: Should it even be put in? That's the question, because it encourages people to use it. That's the issue here. Yes, you could make all of these disclaimers.

DR. REYNOLDS: I would agree with Henry. No.

DR. BERNSTEIN: Maybe I read Case No. 2 incorrectly, but it said that there were--what's described is that there were 24 patients treated between the ages of 5 months and 16 years. And so I absolutely grant that this is a limited data set, but the way I read it, anyway, it's more than simply a derived calculated dose. In other words, some child actually got that dose and it was safe for that child. Not a lot of children got that dose, but there were some children who got that dose.

DR. HIRSCHFELD: If Dr. Booth or Dr. Dagher are here, I think--is Dr. Booth here? No. Dr. Dagher can address that explicitly, but in essence, there are children who got the dose.

DR. DAGHER: Yes, there were children who received either dose. The issue was that you had a starting dose that, a priori, was decided on based

on the age and size. And then, subsequent, there were dose modifications based on the exposure, which, without going into the detail of this particular product, is not unusual in this regimen that is used in certain settings that I outlined, the hematologic malignancies, immune deficiencies, et cetera. And there were then dose modifications made subsequently.

So what we actually inserted in the label is not just those two cutoffs that I showed for the two different recommended starting doses that are clearly labeled as recommended starting doses. We actually then had guidelines for dose modifications, which included also the formula that is suggested, et cetera, et cetera, all the issues that you've--or many of the issues that you've raised. So that wasn't part of the presentation, but all those issues were taken into account.

Now, one point I want to address that was brought up before, Malcolm brought up the issue of a disclaimer. In this particular case, we clearly recognized that there's an issue where you have dosing information provided in a situation where we clearly felt that, you know, there's not enough data to support a new efficacy supplement or a new

indication. So the way we dealt with that is--we did, you know, several things. One, we made sure that that information was provided in the pediatric subsection, nothing in the indication. The second thing is that in that subsection, in the beginning part of that subsection, the first statement is that the efficacy of the drug in the pediatric setting has not been established.

Another element that somebody brought up earlier was, you know, if there's a concern about combination use, concern about maybe misinterpreting the context in terms of we're providing a dose, but how does that fit in with the clinical context where there are many different uses?

In this case, as in Case No. 4, where Susan mentioned that they provided a very brief description of the trial, we did that in this case, too. In that pediatric subsection, the special populations section, we did provide a brief description of the clinical study which provided starting doses used, planned and used. This was a combination setting, so there was information about the combination context, and a very brief description of the patient population, including the age range, et cetera. So that's one way in

which we tried to address the issue that this information has to be taken into context given the limitations of the data that are provided.

DR. PAZDUR: I guess, you know, that focuses nicely on this whole area and why we're asking these questions. You know, everyone is for more information about pediatrics to be included in the label. That was the whole part of, you know, since we started meeting two years ago to encourage that. So nobody is against that. But we have to put it in the issue of what information is clinically useful to somebody, and if it isn't clinically useful, could it actually be abused in the sense of making erroneous decisions, treating children in an inappropriate fashion, interfering with further clinical development of the drug? We want to include information, but I think in the context of--in the discussions we have to say what is the usefulness. Will somebody understand how to use this drug and be better off for it rather than, okay, let's just put everything in the product label here. And the use of disclaimers, I don't know, to be honest with you. It may be great for cigarette packages, but I don't know how useful they are, because when you see it in the product

label, there's an implicitness about perhaps it should be used or could be used. I'm not against putting in disclaimers, by any means, but I think that we just can't say, well, if we don't know anything, let's just put a disclaimer on it.

How useful is the information going to be that we put in the label to making a clinical decision? And that is really the whole context of all of these questions.

DR. SANTANA: Richard, I interpreted the disclaimer issue maybe a little bit different from you. I interpreted the discussion that there is data; it's limited data. You provide the information that's more relevant to that indication based on the data that you have. You can't deny that data. And the disclaimer just indicates that because the field is a clinical investigative field, it's an evolving target, if you want to use that phrase. It's an evolving issue, and people should note that this dose that's recommended or this safety profile based on this study is an evolution. And you could use it in this context, but you have to understand that there's a parallel universe. That's what we're saying. We're not saying disclaiming the first.

DR. PAZDUR: I guess, you know, one of the questions that I have, information is always in an evolutionary process. Where do we make that cutoff before--yes, this is good enough to go into the label or should there be further studies that are done that really would give people more information on how actually to use this. And this is a very gray area of judgment, and that's why we're bringing this up. And I think you could all see the sense of uncomfortableness here. You could have--you know, do you--after one Phase II study, do you put that information in? Should you wait for further information or duplication of it? People are going to be making decisions based on--not an inadequate database, but a database that is in evolution. And that's true for all of medicine as it goes on. Even when we approve the drug, that drug is going to have a life and further studies to be done.

But I guess this is the important aspect that I want to frame all of these questions on, is the clinical utility of the information that we're putting in here and the safety aspects of putting in information.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I have no concerns about the safety aspects of the information. I do have some concerns about the appropriateness or the completeness of the clinical utility information. And I would certainly agree that in medicine in general, these databases are evolving. But I think it's a little bit more dynamic in pediatric cancer. So that if you were to include a dose from a Phase II study, recognizing that we generally don't treat childhood cancer with single agents, there may be a different dose in a combination regime which may also be different depending on the schedule in which the agent is used.

So my only reason for mentioning the disclaimer was to make it clear that the dose that was in the label was the dose that resulted from this Phase II trial of 22 patients with these diseases and these were the toxicities, and shouldn't be viewed as the recommended dose for every patient with every possible malignancy, or even the one for which there is the indication, because there may be other contexts in which the drug is used.

DR. SANTANA: Dr. Bernstein?

DR. BERNSTEIN: I'd like to support what

Greg said and also say that the label to me is also part of the process, and the process is that the Food and Drug Administration asks for a study to be done for a pediatric indication, and that study is done with a certain dose and schedule for a particular indication. And so I think what we're suggesting is that then that information be incorporated in the label as the end of that process, and that it's certainly far from all of the information that's available, and the information will be further developed, but it is, nonetheless, the end of that process of initial drug development.

DR. SANTANA: I want to move on to Question 2, but before I leave this question, because I think it frames the whole discussion, maybe part of the struggle we're having is that the label is a box, and now we have this additional mechanism that we've gone out to request pediatric studies, and now we're trying to fit that into this box where that box was created for a very different purpose. It was created for here's your drug, go sell it, and make sure that people use it in the right way and that we know when things are going wrong. And maybe that's the struggle, that we're

trying to put this information into a box, and maybe if we can't modify the box--and maybe this is more of a philosophical discussion rather than a practical discussion today. But maybe we should revisit issues within the box that would allow these pediatric studies that have limited data to be reflected in that box carrying that unique message, because I think that's the struggle. And I agree with the agency. You guys approve something for an indication, and you have to live within that indication. And now we're having these pediatric studies that we want to get done that we have pediatric data. They don't quite fit that mold, but, on the other hand, we have that information that we can deny. But maybe that's a separate discussion.

DR. HIRSCHFELD: I'd like to respond to that. I think that the label is not necessarily a box. It's just a template. It's just headings. And you can put in whatever you believe is appropriate for it. So I wouldn't want the discussion to try to think of how we can revise the content and format of labels because there are mechanisms that have been tested that outside the realm of oncology have been successful in conveying

pediatric information.

I think what we'd want to focus on is, given that data has been submitted to us, how should we map those data into the label? And in that framework, then, if you wanted to move on to the next question.

DR. SANTANA: I can give you--the quick answer to that one is then if you went and asked for the studies, the box should reflect all the studies. Anyway, we'll move on to the second question.

DR. PAZDUR: Let me address that. Remember the pediatric plan which we devised, do the Phase I studies and you could even get an approval--I mean, exclusivity, rather, I should say exclusivity if the results show that you cannot continue. A lot of that was done to encourage pediatric drug development and is somewhat different from other areas in that we're really kind of exploring areas here because we realize when we constructed this whole pediatric plan that the risk of pediatric oncology drug development is probably much different than developing an anti-hypertensive in kids, or something like that.

The problem here is, as in adult oncology,

you don't know in what indication this drug is going to work, so you're kind of like let's do it in neuroblastoma, let's do it in leukemia, let's do it in brain tumors. If you've got an anti-hypertensive, it's pretty clear how you're going to develop that drug in a kid with hypertension.

So the game plan was to be a little more exploratory, and, granted, it was to increase information and product labeling. But do we want that level of exploration necessary reflected in the product label? It is a little different. I'm just asking the question.

DR. SANTANA: I agree with you, but we need to find a way--I think that's what we're saying here. We need to find a way--I mean, if you go out there and request these studies, and I agree they're not studies being requested for indication. In some cases they are, but in general, they're being requested to provide an additional mechanism for pediatric data, for pediatric research, and so on and so forth. If you have that data, you have to somehow find a way to reflect it in the information. That's what we're saying. And if the label doesn't allow us--or maybe it does allow us,

like Steve says. If the label doesn't allow us, then we should find other ways to have that. We just can't say because it's just one Phase I study or two Phase II studies that we're just not going to reflect it anywhere. I think that's what we're saying.

DR. SMITH: The question, though--you know, the FDA has asked for Phase II studies. Are we going to list every Phase II study and the results from that in the label? And what does two of 20 neuroblastoma and two of 12 med-(?) blastoma mean? And does that provide useful information? I'm not sure it does. I think that information needs to be publicly available, and I think, you know, the FDA--the challenge to me to the FDA would be to find ways to make that information publicly available, and the details that you really need to be able to interpret, you know, what that Phase II result means. But does it have to go into the label?

I think safety and PK and things like that may be different, but I'm not sure what benefit you get from the label--to the label by including lots of Phase II data. And there may be other ways to provide much greater detail, and the FDA can make

that data that they've requested available to the public.

DR. HIRSCHFELD: Well, I think you've anticipated Question 3, so let's see if we can get to Question 2 before we get to Question 3.

DR. SANTANA: So Question 2 is--let's go ahead and deal with Question 2 before the lunch break. If pediatric dosing and safety information are available but the clinical proof of concept has not been established, consider whether dosing and safety information be included in the product label. This circumstance could arise if studies were done in children with diseases other than the one that is being considered for an indication yet extrapolation is being considered on the basis of other evidence.

So the scenario is there is safety and dosing information, but clinical data in support of the indication or different indication is not yet available, as I understand it.

DR. HIRSCHFELD: Well, this is an extension of the same--of 1. The disease in adults is the same as the disease in children. And let us say the disease in adults is relatively rare and the disease in children is vanishingly rare. You

could expect to get only a few patients.

DR. SANTANA: Rarer.

DR. HIRSCHFELD: Rarer. Okay. But it's ethically and scientifically valid to test the drug in other contexts, so you now do a study and you have 25 patients, but only two or three have the disease that you're trying to relate to the adults.

Now, you believe from other evidence that the disease in children is the same in adults. That's an assumption in this question. But you don't have a robust data set to say, well, we've proved it, we've taken 20 patients of this rare disease and now we have a response rate of whatever or a remission rate of whatever. You only have a very few patients, but you have much broader data that gives you dosing and safety. That would be the situation that is being asked.

DR. SANTANA: I think I don't have any issue with the safety data. I do have a little bit of issue with the dosing data because of the limitation of age groups and so on and so forth. You see what I'm getting at? So I think the safety data is extrapolatable, you know, if that's a correct English word. But the dosing information, how can you reach a conclusion of a dosing

information with two or three patients?

DR. HIRSCHFELD: Well, you wouldn't have two or three patients. You'd have, we'll say, 25 patients that you have dosing information on, but only two or three have the particular diagnosis that you're trying to borrow from adults. And this--I'll rephrase it. This is a question where you have a very rare disease, and it's unlikely that you could put together 25 patients with that specific indication. But you can put together pediatric data which would include some of those patients.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: So is the intent here to provide a dose for this very rare disease in the pediatric population? And what safeguard would there be that this agent, which might be effective in a different dose or schedule in other diseases, might not be able to be tested?

T3B DR. HIRSCHFELD: That's exactly the question. What we're asking for is some input into that.

DR. SANTANA: Dr. Friedman?

DR. FRIEDMAN: Obviously you've got a little puzzle, but I'm not sure why you'd ever want

to put any information in the label in the absence of providing a pediatric situation, the absence of pediatric clinical data. I guess that's where I'm stumbling now.

DR. HIRSCHFELD: Yes, there's no absence of pediatric clinical data. I'll try to be as concrete as I can. Let us say we have a drug that's approved for an adult brain tumor, and we know the dose for that, and we know that there's efficacy established. This tumor is very rare in children. But you have done at your institute a study of this drug in children that include many kinds of CNS malignancies, and among that population, you've established, you think with reasonable confidence intervals, a pediatric dose. You have some pediatric safety information. And you have two or three of this very rare tumor type. That would be the circumstance.

Should any of that information go into the product label?

DR. FRIEDMAN: I think it should go into JCO and not the product label.

DR. SANTANA: Dr. Hagey? Dr. Cheng?

DR. CHENG: I think that potentially that information could go into the product label if it

was very clear on--if the statements were extremely clear on exactly what the indication was and what the indication for the very rare in the indication for which children has been--where the assumptions have been made needs to be very clear in the product label if that were to go in the product label.

I think we also need to take a step back and try and look at what these pediatric initiatives were aimed at. They were aimed to try and increase the number of drugs that are labeled for children, both within the U.S. and hopefully internationally as well, because that is what the crux of the problem is, that there are a very large number of drugs that are used off-label or even unlicensed. And the gold standard for the product label is that there should be clinical studies, a full-scale clinical trial program, and that would be the gold standard in children as well. And what we're thinking about here is where we don't achieve that gold standard, how should that information go into the product label? And although I sense and I understand the clinician's anxieties about what's going into the label, how that might be confusing to prescribers, on the other hand, if we have got

sub-gold standard data, we should still aim to use at least some of that in a way that is clinically useful. And I think there's danger of trying to--of, I suppose, getting away from what the initial aim of the--or what I understand the initial aim of these pediatric initiatives are.

DR. PAZDUR: Because we're really not talking about giving an indication here as such.

DR. SANTANA: Dr. Melemed I think was first, and then I'll go back--

DR. MELEMED: I have a question for Steve, because this goes back to the label by extrapolation. In that scenario, say have a disease that's very rare, but you then have PK and dosing label that you could potentially approve that drug if there's a disease in pediatrics that is similar or identical to that. So how does that differ just because you don't have a burden of proof, what you're saying. I don't think on the extrapolation you require burden of proof in that specific situation.

DR. HIRSCHFELD: I think you've framed circumstance, so the difference between Question 1 and Question 2 is that in Question 1 you have an unequivocal proof of concept study. In Question 2,

you have the lack of that proof of concept study. And what we're asking is: Should you be silent and, in essence, act as if those data don't exist? Or should you--if you're comfortable with your extrapolation criteria--which is another issue altogether. But let's say we are comfortable with the extrapolation criteria. What should you include in the label?

DR. SANTANA: But there's a difference. There's two scenarios. One is that you don't have the population that you are ever going to be able to establish the proof of principle, which is the scenario you're presenting. And is that an exception? Or the other scenario is just the studies haven't been done, and do you have to wait until those studies get done, you eventually do have the population? I'm presenting it to you in terms of graded scenarios because what applies to one may apply to the next one, is what I'm trying to get at. So the second scenario is that the studies just haven't been done yet, but the population exists, but somebody already has some preliminary--you know, some dosing and safety information, and why would you deny those not putting it in the label, whereas the other ones you

would not deny them putting it in the label?

So I think the issue is: Does this present such a unique population that you're never going to get the proof of principle answer? That is to me the question. And if the question is that the population is so unique that you're never going to get the proof of principle, no matter what you do, then I think whatever data you have is important, and you should put it in. If the information is different, it's just that the studies haven't been done or nobody wants to do them, then I wouldn't do it. That's my vote on that.

Dr. Finklestein?

DR. FINKLESTEIN: I agree with Victor, and I'd like to give you more concrete examples: malignant melanoma. You could have a drug that's very active in malignant melanoma, a very rare tumor in children, we'll probably never be able to do a study. But we certainly would like to know there's active drugs in malignant melanoma. Carcinoma of the colon would probably be another one, or GI carcinoma.

Then my question is: Is that the kind of data you then go to an advisory board to get some

help for?

DR. HIRSCHFELD: I think we're here right now.

DR. FINKLESTEIN: But in terms of specifics. In other words, what I'm saying is I agree with Victor. I'd like to know there's data on malignant melanoma in the label, or GI carcinoma.

DR. HIRSCHFELD: I think those are excellent examples, Jerry, and would be the paradigm that's being asked.

DR. SANTANA: Dr. Hagey?

DR. HAGEY: In terms of safety information, since presumably most of these drugs are already marketed in adult drugs, I think it would be useful to request that the sponsor interrogate their postmarketing safety database and provide sort of an analysis of the safety data available to date in the pediatric population, and see if they can tease out whether any differences do exist between the adult and pediatric patients that have received the drug.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I guess I would just question Richard's statement that this isn't for an

indication, but it really is an implied indication. So would it not be interpreted as such by the public? And I have difficulties with that, quite honestly.

DR. PAZDUR: That is a dilemma, and that is part of the internal discussions at the FDA that we're having on an ongoing basis. Is this basically an indication that you're giving somebody without--with a very minimal database that somebody could not say that these are adequate and well-controlled trials? I don't think we would put it in in the indications section. That's what I was getting at. But here, again, as Jerry had mentioned, you do want more information in the package insert. So this would be a consideration, and there is some tension here, obviously.

DR. REAMAN: And the information would just be limited to safety and dose and no statement about efficacy if it's in two of 20 patients that happen to have this particular diagnosis.

DR. HIRSCHFELD: That's what we're asking for some input on.

DR. REAMAN: I think it would be terribly misleading to put in detailed information that would only confuse the public to some extent when

the proof of principle information doesn't meet the criteria that we would generally use for proof of principle. Including safety and dose information I don't think would be a problem if that data is actually sufficient quantity and quality.

DR. PAZDUR: But aren't you then kind of just not addressing the issue here? Because why are you putting dose and safety information if there's no reason to use the drug?

DR. REAMAN: Because you've requested a study and there's dosage and safety information.

DR. PAZDUR: Okay.

DR. REAMAN: But there also isn't information on its efficacy.

DR. HIRSCHFELD: Except by extrapolation.

DR. REAMAN: Maybe.

DR. HIRSCHFELD: Well, if you believe the extrapolation and you have already demonstrated it in adults, then--that's the assumption.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: If I take the previous example about melanoma, on the patient and physician point of view what is important is to have the information that this drug is active in adults, there are some data about safety and

dosing, and when the patient arrives in my consultation, I know this drug has been studied, even though there is no data of efficacy in this patient. And the major point is when such a patient is seen by a physician, the drug can be proposed to the patient in such a way that the information from this patient can be benefit for all the patients. And I think this is the way maybe we should look at the labeling, about the use of the label of the drug by the physicians and the parents.

DR. SANTANA: One last question and then we'll break for lunch. Dr. Boyett?

DR. BOYETT: Steve, I think you should let the reader do the extrapolation, and the label should not go beyond what you have defensible data for. And if you've got safety and dosing information, let it be that. I mean, they already use it off-label anyway. At least you're giving them some more information that's based on fact. And you talked about early on that everyone in the label you have to check all the data, information, so why would the agency want to go beyond what they have information to support? Let the reader do the extrapolation. They'll do it.

DR. HIRSCHFELD: May I respond?

DR. SANTANA: Yes.

DR. HIRSCHFELD: Okay. I think the issue is not whether we would automatically give an indication because we believe in the biological basis of the extrapolation. What we're asking is: In this unusual circumstance, what information should go in? And I think what I'm hearing is dosing and safety should go in. And it's going to already have the adult efficacy data in there. And then if we were to describe and say of the 30 patients that were studied, there were two that had melanoma, and just leave it at that, that might be something to--or maybe we shouldn't say that at all.

[Inaudible comments off microphone.]

DR. HIRSCHFELD: Okay. But that would be the kind of information that we were asking advice on. So I provoked that intentionally to clarify that point.

DR. BOYETT: Your study doesn't sound like a Phase II trial, incidentally. It's got too many patients--too many different diagnoses with too few patients.

[Inaudible comments off microphone.]

DR. PAZDUR: So not include any preliminary Phase II trials, three out of 14, one out of 14.

DR. SANTANA: Exactly. There you go.

DR. PAZDUR: Okay.

DR. SANTANA: It's the same statement. There's no definitive activity established in pediatrics. All we have is this Phase I safety data derived from these studies. You're passing no judgment.

Okay. So, with that, we will conclude. And can we reconvene at quarter to 1:00? Is that reasonable for most people?

[Whereupon, at 12:20 p.m., the subcommittee recessed, to reconvene at 12:45 p.m.]

AFTERNOON SESSION

[12:50 p.m.]

DR. SANTANA: So to continue our discussion, we'll reconvene with Question No. 3, and this question pertains to the situation where there is not a linkage between an adult indication and data from pediatric studies. And the question is: If pediatric dosing information and proof of concept data exist for a pediatric disease or condition that does not exist in adults, what information, if any, should be included in the product label?

An example is provided, and the example is a product is approved for second-line colorectal cancer in adults and pediatric data are available for dosing and pharmacokinetics, plus a single arm Phase II study showing a modest response rate in 20 pediatric patients with refractory or relapsed neuroblastoma. And an editorial note is that there is no existing product with this profile.

And the factors that are suggested that may be included include dosing, safety information, and clinical response data.

So here is a situation where there is pediatric Phase I data, safety data, and a limited

Phase II study with some activity in a completely different disease than the adult indication.

Comments? Questions? Yes?

DR. HAGEY: I think that within the reality of the world we live, most of the drugs developed are in adult indications for which there isn't a pediatric counterpart, for example, breast, lung, colon, ovarian, prostate cancers. And due to the fact that pediatric drug development is typically going to lag eight to ten years behind the adult data, I think during that ten-year period it would be useful to have some information, just the basic information in terms of safety information and whatever dosing has been done available.

DR. SANTANA: So your comment is that the minimum data, if any, is to be included in this scenario would be the safety information of the pediatric studies and relating that safety information to the doses that were used, not doses in terms of efficacy but doses in terms of the safety profile.

DR. HAGEY: And, in addition, the safety profile should include an interrogation of the postmarketing safety database.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: I am comfortable with the proof of concept when the disease is the same in adults and children. I am not comfortable with proof of concept when the disease is specific to pediatric patients. And this is my concern of having efficacy data which are not enough in terms of numbers, which is the case of some of the cases we were shown before, which may indicate that the drug is active but strong evidence--there is not strong evidence that it is the case. So to me, it would be important on these early Phase II data, large Phase II data, several tumor types within these data--within the study, sorry, to make possible--to increase the number of patients, even by enlargement of the number of participation--center participation to the study to really have the strong evidence that there is X percent response rate in this disease and this can be provided in the label.

So proof of concept in a specific pediatric disease is something I'm not comfortable with.

Maybe I was not clear. Sorry.

DR. SANTANA: Because the issue here is

that they've requested specific trials to be conducted by the sponsor, and that's the data they have.

DR. VASSAL: Yes. So the question is: Is the study adequate to answer the question?

DR. SANTANA: Hopefully it is, that if they're well-designed, you know, studies that have undergone rigorous review.

Dr. Bernstein?

DR. BERNSTEIN: Right, that's pretty much--it's a reflection of what Dr. Boyett said before, that it depends if the study has been previously designed and approved and the study goals have been met, then it would be reasonable to include that data in the label. And certainly--however, what's most important--I would agree with what the two previous speakers said. What's most important would be to include the toxicity and safety information.

DR. SANTANA: How would you then respond to comments made earlier from the FDA that potentially providing clinical response data in a disease for which the drug is not indicated for or commercially labeled for, would that lead to difficulty in terms of people misinterpreting the

indication, et cetera, et cetera? I heard that comment earlier this morning, that the FDA--part of this question is that the FDA is concerned that this is not what this drug was developed for, this is not the indication. Why should the label provide information in a completely different disease? And is that a green light to suggest that this is a new indication? Do you want to respond to that?

DR. BERNSTEIN: Well, again, the study would have been done in a specific response to a request for a study, and the request for a study would have included the Phase I and then some preliminary Phase II. And so I think including that data is simply including the information that was generated in response to a request letter from the Food and Drug Administration. So, yes, I think it would be reasonable to include that information, assuming that the study had achieved its designated endpoint.

DR. SCHWEIM: I would like to comment on the remarks in the records. In the European Community and in Germany, it would be possible in this case, if you have enough safety data, to have time-limited access, time-limited approval, and the

company has to submit additional data if they want to prolong this period of time. And I think this is the classical case in which we in Europe would give such a time-limited access and would refuse the ongoing approval if there is not any further data submitted.

DR. PAZDUR: I don't think that's what we're talking about. That is our accelerated approval provisions, and I think what we interpreted this is that this falls below that level, your threshold, below the radar here for accelerated approval.

DR. SANTANA: Dr. Smith?

DR. SMITH: The data need to be publicly available. I'm less optimistic than Mark, perhaps, that meaningful data can be explained, you know, in a short paragraph or a few sentences in the label about the activity, and all the information that would really be needed to interpret in the Phase II data. And, you know, this information could be available in other ways and perhaps referenced--referred to in the product label that at the FDA website at a certain URL there are details of the Phase II experience, without actually including it in the product label. This

might also be a way to update that information more quickly so that today you have, you know, 14 patients with neuroblastoma, a year from now you've gotten really excited about it and you've treated 60 patients, and as opposed--there may be greater facility to update the kind of Phase II information that is, as everyone has said, evolving over time.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: At a previous meeting, we decided that we weren't going to lower the bar for approval of agents in pediatrics just because there are smaller numbers of patients. I think that putting information on activity in trials that aren't enough to meet standards in a label is, in effect, lowering that bar in another way. And I would suggest that we not do that.

I agree very much with Dr. Smith's comment, though, that I think data needs to be available, so it would seem to me that we're not going to lower the bar on safety data and dosing data, and that could be put in the label. And if there is not enough of a controlled study to say this can be used in a disease, then we can put a statement that additional data on the use in investigational settings of this agent can be found

at the following website, and the FDA could compile that data. Because the reason I suggested that way is that there's a feeling, at least from a lot of us, that when a product label is a stamp of approval by the agency that says this really is the gold standard, and I think that you could take the information on--you could have information on that stamp of approval that says there's additional information without blessing it with that stamp and provide that via the website.

DR. HIRSCHFELD: I would then ask a further question. If the FDA label is a certain standard of evidence, and if there's dosing information in there--and safety information, but if there's a dose that you open this package insert and it says, "The dose in children is..." but you have no other information, would that be informative, particularly if it's approved for a disease in adults that doesn't exist in children? And would it be safe to include that? I just raise that as a question.

DR. SANTANA: The details are the important thing, and I think it was expressed very well by Dr. Hagey, that I think the intent is that you provide the safety information and that the

safety information is provided in the context of the doses that were used, not that those are the doses that you're recommending for efficacy and for treatment. It's a different twist. It's not a play on words. It's really the reality that you present the safety information based in the context of the doses that were used. There is no judgment that this is the appropriate dose to produce response or lack of activity.

I think if you think about it that way, then I think you could providing dosing information not in the dosing area of the package--of the label, but in a different area, which is all related to safety. And I think you can circumvent that issue that people would misinterpret it.

DR. HIRSCHFELD: Thank you for addressing that.

DR. REYNOLDS: Steve, I would just answer that by saying that if you establish that a dose is safe, you know, in a well-controlled Phase I trial and perhaps with some Phase II as well, then can't you put safely on a label a dosing--that this dose is safely established for pediatrics? What you use that dose for is a different issue, including investigations will be ongoing, but at least people

who are trying to use this off-label and maybe off-investigation would have the established safe dose.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: In recent years, there have been different schedules evaluating children than the one approved in adults. So what would be the type of information available in terms of safety and dosing in this situation?

DR. SANTANA: Dr. Reaman?

DR. REAMAN: I think as Dr. Reynolds mentioned, instead of giving specific information on efficacy, and if you're going to provide safety and dosing, it would have to be a safe dose in the schedule that was used in this limited trial, not precluding that other schedules may also--or other--investigation of other schedules may also give rise to safe doses and more effective doses.

DR. HIRSCHFELD: In my job description as a provocateur, let me then--

DR. REYNOLDS: You excel exceptionally.

DR. HIRSCHFELD: I'll ask you for my next rating. Thank you.

If there's dosing information, the interpretation of safety in oncology is very

different than what safety is in any other context. And safety in oncology could still result in rather marked, in fact, severe adverse events--they might be transient, but certainly there would be Grade 1, Grade 2 adverse events.

So if we put a dose and we put safety information, would that not potentially encourage someone to give a child that dose and that safety information even if there was no efficacy? So it becomes the ethical question. If you're providing an adverse event profile and a dose, but you say nothing else--and I'm asking it as a question. I'm not advocating it. I just want to make sure we've explored this thoroughly. Where would you lean--or where would that lead you ethically?

DR. PAZDUR: Could I add a follow-up question to that to add to the provocation here? One of the problems that we see with even accelerated approval of drugs that in one of our concerns that may have very modest activity is that may prevent further drugs from being developed in that area. Would it have--what would be the downside of putting, let's say, clinical trial information into the label that we've been debating? I don't see the downside being one of

promotional activities to the pediatric oncologist. That simply is not there. But one thing that I could see potentially is off-label use and potentially interfering with ongoing clinical trials and other trials looking at other agents, for example, in this disease. Because, in essence, you've already declared a therapy in that disease. It's in the product label, and people would say, you know, it's here, this drug is going to be given in this dose.

So do you have a problem that this could--providing either dosing information without a diagnosis--without an indication or providing the full clinical information could actually be doing more harm than good for the development of the field?

DR. COHN: I was just going to say that, you know, so many of our drugs are used off-label, anyway, so whether you have an indication or you don't have an indication, it just doesn't seem to matter. So if indeed a physician is going to take a drug off the shelf and use it, I think to provide safety information is a good thing to do.

DR. REAMAN: Especially in the context that the efficacy data is not available, or is

available but is extremely limited.

DR. SANTANA: Dr. Smith?

DR. SMITH: Steve and I think Richard are both saying the efficacy data are not available, but the other proposal was that, in fact, they are available. They're available in substantial detail so that someone can really understand better what the two out of 20 or the three out of 15 means and, you know, what type of patients they were, how long the responses lasted, and so on.

So it's not that you're not providing that information. It's actually that you're providing more of it for people to base their decisions on. And I think there's probably less risk if you separate out a simple three out of 15 on the label and specifically say neuroblastoma, there's probably less risk of the promotional aspects compared to the alternative of just, you know, stating that the response--the Phase II data are available in detail at the following--at a certain place.

DR. SANTANA: You're actually arguing that Phase II data should be included--

DR. SMITH: No, I'm arguing that they should be included, but not in the label. But they

should be available to the public. You know, to physicians, to families, they should be available, but that they shouldn't be summarized in two or three sentences that really oversimplify what, in fact, is a very complex discussion.

DR. SANTANA: Dr. Melemed?

DR. MELEMED: I'd like to address Dr. Hirschfeld's concern that by having a dose would actually encourage usage. I have a hard time imagining oncologists looking for a label to find a usage for the drug. It would be more of I need a patient with this disease, I need to know how to give it, and looking at the label for that information. So I know you put it out as a provocative question, but I have a hard time taking that a step further to see how it would be used that way.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: As I said before, the label is not the end of the life of the product, and clearly we do need additional data afterwards. And the point is: Is the information in the label such that it will encourage the use of this drug outside any protocols by anyone, or will it give information and encourage people to propose to

patients and parents to be registered in such trials? So this is a question of--is it the end, or how can we promote further evaluation of this drug in sufficient numbers in Phase III, including in standards and (?) to stop, we have the drug, that's it, but really to go forward with it.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: I'd feel more comfortable--and I'm coming back to something we discussed this morning, and I don't know if my colleagues here agree, but I think they do. Is the FDA willing to put in the label that pediatric oncology is a protocol-driven discipline, or some word to that effect? Because--or a research-driven discipline? Because if indeed you have something in there regarding the label, then all these other comments become a little moot because safety data would be helpful, and as long as you are putting in the label that we are protocol-driven discipline, or words to that effect, you will be actually putting in the label, which is the policy statement of the academy and in actual fact is the way things are happening on this side of the ocean as well as the other side of the ocean.

DR. SANTANA: Let me address that. Let me

take a minute. For the purpose of discussion, I would argue that that would be coercive to the physician who does not believe in clinical trials. I'm preaching to the wrong crowd. We all around this table believe in clinical trials. But we have to remember that I think the position of the FDA is how the products are used by the community at large, not just this community, pediatric oncology. So somebody could come and say--take your argument and say that putting such a statement in the label would actually be very coercive and unwarranted. It's a comment. I'm not disagreeing with you. I'm just saying--

DR. PAZDUR: We do not regulate the practice of medicine, period.

DR. SANTANA: Exactly.

Dr. Boyett?

DR. BOYETT: I want to echo what Malcolm said. I don't think you can put sufficient information in the label to interpret three out of 20. Three out of 20 may be a negative result, and only until you understand what the design of the clinical trial was that gave rise to those data can you interpret it. So I don't think--I'd disagree with putting three out of 20 in there and calling

that clinical information.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Both Malcolm and I have suggested that maybe a repository of information that is centralized as a supplement to the label could be useful. Is there any plans for doing such a thing, or is any possibility for such plans being developed by the FDA?

DR. HIRSCHFELD: I could address that. That's something that several people have been thinking about for, oh, the last five or six years at a minimum, you know, have a website for every label, have some web address where you'd have www.fda.gov/, the name of the drug, and you'd always get the updated information, having dynamic labels. But there are a lot of practical barriers and resource barriers to doing that.

So the short answer is yes, it's been considered, it's being considered, but the likelihood of something being implemented in a relatively short time frame is not great.

DR. REYNOLDS: Well, if I could just take that one step further, then, and say that I understand why this hasn't been implemented given the scope and the size of that, but it would seem

to me that maybe one way to pilot this would be for the FDA to work with CTAP and the Children's Oncology Group to do this in the setting of pediatric oncology for those drugs that are being used off-label in pediatric oncology, to provide a centralized website where meaningful information is conveyed about the use of those specific agents. This would be a limited approach to this and allow you to see what the impact of doing such a thing would be.

DR. HIRSCHFELD: I'm not sure we would have the authority to publicize the off-label uses.

DR. SANTANA: But you do currently, though, for the drugs that you're reviewing under the written request. You are posting in your website--I can't remember the exact location, but you are posting in your website your determination first and then the data. Are you not?

DR. HIRSCHFELD: Yes, this is correct. Our reviews are posted on the website, and summaries of the pediatric information are posted on the website.

DR. SANTANA: I think the comment is: How do you make that more accessible and available to the public at large?

DR. PAZDUR: In the context of practicing medicine, remember, we're treating a disease here, and the product label is not a treatment guide for a disease. It is basically a marketing agreement. Number one, it provides information about a drug, and I'd hate to get into a situation where we're trying to contrive this product label to be the be-all and end-all of treatment of a disease. If you have a disease, go read about the disease, and there are multiple treatments, and this has to be placed into the context of combination chemotherapy, ongoing protocols, other off-label uses, et cetera, that are out there, different combinations which will never get into the label because they don't isolate drugs effects.

So I think it's important that we, you know, see exactly what we're doing with this product label. It is not a treatise for how to treat osteosarcoma because there is a mention of osteosarcoma in the product label.

T4A DR. SANTANA: Agree, Richard. I was just trying to address the point Malcolm made that once we conclude for this question, the information that we believe would be relevant would be the safety information and the dosing and relevance to that

safety, that all of that other information needs to be made available in some other--

DR. PAZDUR: But I wonder if more appropriate sources for--you know, like the--you know, there are treatment guidelines. The NCCN, or whatever it's called, have, you know, guidelines on how to treat. I don't know if they have them in pediatrics, but adult diseases, for example, first-line treatment for colon cancer, second-line treatment, third-line, if people would not be--if that's what we're really trying to frame here, and that can't be framed with a product label, basically, without having a misconstruing of the label.

DR. SANTANA: Dr. Reaman, then Dr. Pelusi.

DR. REAMAN: I didn't see the request for information really being one of treatment guidelines or how to treat a particular disease, but really one of demonstrating what the current data are as related to ongoing investigations and evaluations. So I think having this information available is good. I would question: Can you make it available? Is this not proprietary information? So can you make it available to the public?

DR. HIRSCHFELD: The short answer is yes,

and it is available certainly and posted on the Internet in our reviews. What we're asking here is--

DR. REAMAN: But that's with the review. I mean--

DR. HIRSCHFELD: Right. Well, that's the context for it, actually. The question that we're asking here is should it go into the label. But making the information available, assuming that that's not an issue.

DR. SANTANA: Dr. Pelusi?

DR. PELUSI: When I look at Question 3, I think I've heard the same thing, is people are comfortable with the dosing and the safety information going in in that context. But the question again comes up in terms of I think the public really looks to you, and that's what we have the FDA for, is for the issue of safety. And so the question is in children who have a reoccurrence or who may be treated not in a clinical trial, and where I come from, in rural settings may not have access by choice because they don't have transportation, that type of stuff, is this whole issue of where do they find the information, whether it's a patient guide that is in addition to

this label or whether it's a website.

But I think that it is important for the public to say we do look to you for safety, so can you be that repository of good information to continue? Because people will look all over the Internet, and, again, that becomes an issue as well.

So I think that there is this question of it doesn't fit in the package insert is a good one because it's just going to come up over and over again.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: I'm sensitive to what you're saying, Dr. Pazdur, and I also was not suggesting in any way that we are trying to ask you to provide treatment guides. But the bottom line is that from the outside community the FDA is really the centralized repository of information about pharmaceutical agents. And I think that whereas there's certainly guides within--the NCI has them and there's books, there's textbooks, and there's review articles for people to look at on diseases. But those are complex issues, and it doesn't break it down by a particular drug. And having it organized in a fashion by drug with

studies that were linked to that drug, if they were focused on that particular drug, I think would be a useful thing to have.

DR. HIRSCHFELD: I'll ask our regulatory colleagues whether the perception of your agency, each of you, is as the repository of safety information and drug information.

DR. SANTANA: We'll start from one end and go up the row. Dr. Pignatti?

DR. PIGNATTI: Thank you for the question, and I've listened to the various arguments. I think, if I have to summarize what my view is on our perception on these issues so far, it's that we have been rather more conservative. The first point is the agency needs to make up their mind whether the drug can be used safely and effectively in a certain population. Once that is established on the basis of the data submitted, then this should be further qualified with appropriate statements on dosing and safety and so on.

As long as the agency has been unable, based on the data submitted, to make up their mind if the drug is truly safe and efficacious, then it has not been perceived as the role of what we would call labeling in Europe, the role to disseminate

this highly valuable scientific information, but which is just maybe a window on a rapidly evolving field, and there are better qualified associations and places where this discussion could take place. And this is the official view that we have consolidated in our guideline. It's true, it keeps coming up every time a product is discussed, but in the end we have not yet found a reasonable justification to deviate strongly from this.

Of course, one wants to be as pragmatic as possible.

DR. SANTANA: Dr. Mathieu?

DR. MATHIEU-BOUE: In addition, I could say that as we are less flexible, for us the discussion is very strange because what we call a product label, which is SPC as defined this morning by our colleague, is linked to an approved drug in an approved indication. So many situations you have discussed are far away from our concerns if we want to be very conservative. But I don't know, I'm not sure I'm very clear, but when we have a summary of the product, a characteristic in one indication, this means the indication is approved. So we need to put the data we have, safety, efficacy, and it could happen that if we have

not--well, if we have only limited data, then we can mention that only limited data in such indication or in the sub-indication are the label or only safety data are the label. But we have appropriate section well defining our guidelines for the SPC, and we don't need to have--we have to follow the rule and the guideline. But most of the situations we have discussed today are outside of the scope of our guidelines.

I am not sure I am very clear.

DR. SANTANA: You were very clear. I understood it.

DR. MATHIEU-BOUE: But I would say from a physician point of view, I could say unfortunately they're out of the scope, because, of course, we would be very interested to add many things, but it's not the scope of the SPC. That's why this morning I made a comment that probably the regulatory agency has a kind of power to make strong recommendations to publish studies or to have a public report on the Net or things like that. But it's not the scope of the SPC.

DR. SANTANA: But trying to address Dr. Hirschfeld's question, does the public, both the physician, medical community, and the patients,

view the agency as a repository of data that they could look into?

DR. MATHIEU-BOUE: Then we need to go in some details about Europe's system. We have the centralized procedure, and then when a drug is approved, we make public a European Public Report, which is called EPR, and which is available on the Net some weeks after the approval. Then we have different rules according to different countries for the other procedures. But when the drug is centrally approved, we have some a central, common SPC, and this is common and the same for all the 15 members of the European Community.

For instance, in France, the SPC is available through the compounded package and in some books restricted to the physician. But if somebody requires the entire text of the SPC to the agency--that's a French example--with a written request we can send the SPC. But it's not a very, I would say, neither transparent nor flexible situation. So we have some differences in culture for that, and we have a very strict guideline for the SPC. We don't have the same transparency that you have. So one can regret, one can say it's better. But for this particular situation, medical

condition, I would say from physician point of view sometimes we would like to get more flexibility.

DR. SANTANA: Dr. Vassal?

DR. VASSAL: One comment, since I'm not part of any agency, so I will let my colleague go.

DR. SCHWEIM: Okay, and then I would add some comments from the German perspective. The situation pointed out by our French colleague for centralized procedures is correct, and for the rest, I must say the answer can't be clear. It depends. It depends because we have a publicly available database with all information about the drugs we have that are not confidential, like composition of the substances and so on. We have also the SPC in the system, and we have also the data from the pharmaceutical manufacturers associations. We have three of them. They're all together combined in the database. But up to now, this is not very often used by the public. It's very often used by the companies themselves and by the health professionals, but not for the public. And I think this is according to the fact that we do not have completely finished the implementation of the User-Friendly Package Leaflet Act, what we have in the regulation in the European Community up

to now.

But I think as a situation for the perspective of the agency to be a trust center, and Germany is increasing, as I pointed out in the early morning, the social court has told the public that only drugs that are approved for the indication will be reimbursed by the insurance companies. And I think if this is widely spread, the public will much more often use our databases to look upon the data.

The last item to mention, the political situation is a little bit different because of budgetary restrictions. We have several additional lists in Germany dealing with the topic of reimbursement, and they are subsidarily used as scientific information. We have a positive list. We have a negative list. They are created by the government for reimbursement purposes, but they're partly used by the clinicians and the physicians as scientific information.

So it's a little bit confusing, the situation, but I think the main answer to your question is, yes, we are on the way to be a trust center for the public.

DR. SANTANA: Dr. Cheng?

DR. CHENG: Thank you. I would think that in the U.K. the SPC, or product label, I'm not sure that it's seen as the repository as such, but it's certainly seen as the document whereby studies have been submitted by companies and have then been reviewed and assessed and then gone into the SPC.

As far as pediatrics is concerned, you in the U.S. are much further ahead than we are in both U.K. and Europe. In Europe, there is the intention that there will be some legislation forthcoming along the lines of the U.S. legislation, but it's going to be a couple of years yet before that comes on board.

However, I think within the current European guidelines and in the SPC, even if a drug isn't indicated in that particular indication section for children, there is allowances for us to put specific pediatric statements in other sections of the SPC if that information has been submitted and has been assessed and deemed to be appropriate to go in. And I know, for example, certainly at the U.K. level, there have been a number of examples where we have looked at the FDA list, exclusivity list, and asked companies to submit data that was submitted to the U.S. and ask them if

they could submit to the U.K. for assessment by the U.K., and then certain statements have gone into the SPC. So maybe a pediatric PK statement will have gone into a certain section, but not as an approved indication as such. But I think it is generally knowledge that the SPC is a document that--how do you explain it? Steven has explained it already, that it's a document between the regulatory--a licensing document between the regulatory authority and the company and isn't seen as the totality of information that's available on that drug. And it's well recognized that there is other information that's available in the peer-reviewed literature.

DR. SANTANA: Thank you, all of you, for your comments and review.

I think we've covered this question rather extensively, so we'll move on to the fourth question. The question pertains to the situation where there is no evidence of clinical benefit in a pediatric oncology population and there are data of a lack of activity. So the question is: If dosing, safety, and lack of activity information are available from studies that enrolled children with cancer, consider what information, if any, be

included in the product label. And the factors may include: number one, a statement restricted to stating that no meaningful clinical activity has been observed; a statement to the effect of the number and the diagnoses of the patients enrolled in these studies; and the third statement potentially could be dosing information.

This reminds me a little bit of Case No. 4.

DR. HIRSCHFELD: I would add that it's implicit that if any information would go in, that safety information would accompany it. So that's implicit and you needn't comment further on that point.

DR. SANTANA: Comments on this question? Mark?

DR. BERNSTEIN: Well, Malcolm has left so I'll speak for Malcolm.

[Laughter.]

DR. BERNSTEIN: It goes back a little bit to what's been previously said, that is, it would be very useful to have dosing and safety information if at some point there is an identified database to which people can have access by clicking on the right site. Then that would be the

simplest answer to the question. Just go to the studies and the studies would then outline what's been shown in terms of efficacy or, in this case, inefficacy.

In other words, we would include dosing and safety information or the dose and schedule used in the label, and then refer people to the appropriate site where the information about the activity or inactivity would be available. That would be the simplest solution.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: But I think there should be a statement that there's no demonstrated activity, and not include in the label any of the dosing, which I think would only be of interest to clinical investigators, probably.

DR. SANTANA: So let me understand you. You're saying that only the first statement should be included, statements B and C should not be included? Based on your comment, there should--

DR. REAMAN: Yes.

DR. SANTANA: --just be just one general statement.

DR. REAMAN: Yes, that in the studies performed, no clinical efficacy was established.

DR. SANTANA: But no further information provided.

DR. REAMAN: Correct.

DR. BERNSTEIN: You wouldn't even include dose or schedule and safety?

DR. REAMAN: I guess in describing the study, I would say at the dose and schedule utilized. But I think I would use whatever central repository becomes developed as the source for the dose information.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: I think this is pretty complicated, because meaningful clinical activity is going to vary from disease to disease, and you're covering a lot of territory when you say there's no clinical indication for any oncology cases or any cancers seen in children. That's a pretty broad spectrum. I think you have to be very specific about it. Simply giving the number and the diagnoses of the patients on the study, again, as I said earlier, may not tell the whole story. You've got to know more about what the design of the study was and how you came to this conclusion that there's no clinical activity. If it's totally dead, that's one thing, but that's usually not the

case. So I think this is more complicated than putting together the information, I think.

DR. HIRSCHFELD: What information would you suggest, Dr. Boyett?

DR. BOYETT: I'm not sure I can say at the moment.

DR. SANTANA: I think that speaks, though-- [inaudible - off microphone]--general statement; whereas I think what you're saying is there needs to be a general statement but there has to be some specifics about the patient population so that people have an idea that it was tested in these populations, not taken as a blanket statement. Did I understand you correctly?

DR. BOYETT: This goes back to what was said before. You've got to have the schedule and the doses that were actually studied because, depending on the schedule, you know, and actually how it was given, whether it's an oral drug or IV or how it was given, that makes a difference. You just can't summarily just write it off.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: And just to clarify, I did say that you had to give those specific pieces of information. And I assume that the study that

would be requested by the agency would be a definitive Phase II study in a specific disease, not in pediatric cancer in general.

DR. SANTANA: Well, but yes and no, because my interpretation was on Case 4.

DR. REAMAN: I wasn't just using Case 4.

DR. SANTANA: No, no, but Case 4 was not a specific disease but was a conglomerate of Phase II different strata, and the final conclusion was in all of these strata there was a lack of activity.

DR. BOYETT: Well, one of the strata was inadequately investigated.

DR. SANTANA: That's true. That's correct.

DR. HIRSCHFELD: Right. Just to refresh, Case 4, I believe there were 108 patients? 122? Well, we'll say over 100 patients, and--

DR. REAMAN: 71.

DR. HIRSCHFELD: Yes, okay. Thank you. I just don't have it in front of me. Seventy-one patients with, I believe, one complete response and one partial response. And in the case that the strata was closed prematurely, that was a decision taken by the investigators that it would be not ethical to proceed given the lack of activity in

the other strata.

DR. BOYETT: But actually, I don't even think you can interpret the one response, because you told me that you changed the dose, you lowered the dose. And since these were a two-stage design, in fact, going beyond the first stage, you probably got your responses at the higher dose, which is always unacceptably toxic. So, you know, I don't think there's enough information here to interpret. I wouldn't know what to tell somebody from this.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Steve, I worry about this making statements that no meaningful clinical activity has been observed, you know, in a study of pediatric oncology when I don't think that a drug would be necessarily tested in all potential settings in pediatric oncology. And, therefore you're somehow--you're pre-empting or doing a pre-emptive strike, if you will, against the possibility of finding an indication for it in pediatric oncology. It would seem to me that if you don't--it's like my mother taught me not to say anything--you know, if you can't say something good, don't say anything at all. And it may be that in this setting--it may be in this setting

that that's the way the label should be approached. If you don't have meaningful data, you shouldn't be putting anything on there, and you shouldn't be putting a dose on if there's no possibility of an indication in the label. That doesn't mean that years later that couldn't be established by clinical trials and then incorporated in the label later.

DR. SANTANA: Dr. Bernstein?

DR. BERNSTEIN: It still goes back to the question of whether you would include anything or nothing. I agree with what you say, Pat, that if you can't say anything nice, you shouldn't say anything. But you do have some dosage and--dosing and safety information, which is neutral, in a way. It's neither nice nor not nice, but it's just not clear to me that you shouldn't make it available at all.

DR. REYNOLDS: Well, I agree with you on that standpoint, but there's nothing wrong with making it available. One of the visions I've been having on this is that we'll get all our drugs packaged inside of what looks like a roll of toilet paper, but that's actually the label. You have to actually roll it out to see all the information.

[Laughter.]

DR. REYNOLDS: So that was the only reason I was suggesting a minimalist approach. But I think really, though, the key thing is that I don't think we should be making statements that there's no use for this drug unless we've really proven across the board in pediatrics there's no use for it.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: This question says "in a pediatric oncology population." It doesn't say "in the pediatric oncology population." So I interpreted this to mean in a specific disease setting in an appropriately designed and conducted trial, if there's no activity, why shouldn't the label say there's no activity? You've asked for the study to be done. The study's been done. The data are available at this dose and schedule. The drug has no activity.

DR. SANTANA: Ms. Ettinger?

MS. ETTINGER: And I agree with Greg completely because I think that also gives informed consent. I think it really speaks to what was done. It doesn't preclude other studies or other entities being investigated, but I think it

explains exactly what happened. And I think it should be clearly delineated, with the safety, you know, information available.

DR. SANTANA: Dr. Mathieu?

DR. MATHIEU-BOUE: It's a question. In this particular case, in No. 4, you have requested the data, the study and the data. But what would be your recommendation, I mean all of you, if in such a case you wouldn't have requested the study?

DR. HIRSCHFELD: I think that would be the next subcommittee hearing.

DR. SANTANA: If you haven't requested the studies but somebody brought you the information? Is that what you're saying?

DR. MATHIEU-BOUE: Well, my question is the same information would exist, but the case wouldn't be the FDA has requested such a study. Would you recommend exactly the same or not?

DR. SANTANA: I mean, ethically, if you're aware of information, you should make it public and you should use it. You shouldn't hide it, no matter where it came from, as long as it's valid.

DR. MATHIEU-BOUE: The information, the public information is not obviously in the product label. That's the key point. To me it's not

obvious that it has to be in the product label. I do agree with you.

DR. PAZDUR: But we have many negative studies in adult indications. We don't have a whole listing of the study--unless we are given the information, and even then we don't put it in the label. Why would somebody be coming to us with negative information unless there was a big safety concern? For example, there was the one slide that Steve had. If there was a perception that the drug was active in a disease, and now we have new information that it no--you know, that decision was in error, that would be a particular situation. But, in general, we don't have listings in the label of drug X is inactive in this disease, this disease, this disease, this disease.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: Steve, I think I can answer the question now maybe what I think, and it goes very close to what Greg said. But when you put in there about meaningful clinical activity, you know, statistically you can't rule out any. What you have to put is with what confidence level you are that the level of activity is below some threshold. That's what has to be put in there so you can

interpret that, and maybe you want to supplement that with the number of patients. But, again, interpreting like Greg did is specific to a particular pediatric population, a particular disease, and not just say there's no--that there's a general lack of clinical activity. It's got to be specifically listed for each disease that it was adequately tested in, and what level of activity do you rule out? You never say that it's actually zero.

DR. HIRSCHFELD: Hence, the "meaningful," because we know we couldn't. It's something you only approach asymptotically. I agree with you, Jim. So would you suggest then putting confidence intervals?

DR. BOYETT: I like confidence intervals.

[Laughter.]

DR. SANTANA: That's what he gets paid to do.

Dr. Hagey?

DR. HAGEY: I would agree that I think a statement to this effect should not be in the label. It's not in there for adult indications, and there are too many to list. But with the caveat that if it is being used, for example, a

company reviews their sales data and realizes that 20 percent of sales are going toward an indication where it's clearly not efficacious, then a statement should be issued to that effect in the label. And I think that the website everybody's mentioning can also--if it's going to include the positive data, it might as well also include the negative data, because you have to be balanced in the data that you do present in the label.

DR. SANTANA: Dr. Cheng?

DR. CHENG: I take the opposite view. I take the view of--sorry, I can't see your surname. Can I call you Greg? I would agree with Greg's view, provided that the statement was specific and it was very clear in what patient population and what disease. Perhaps it's the wording that is causing us to struggle. Perhaps the wording could be improved. And I realize that we don't list every negative indication for adults, but in children, it at least gives us the information that the drug has been studied at all, which is certainly an improvement on no study at all.

If we start putting information in other aspects, I would worry that there's too many different places to look for it, and where do

you--how would Dr. X sitting in surgery know whether to look on the FDA website or on the product label or in Medline or wherever? If it was in the product label, at least that would be clear.

DR. HIRSCHFELD: Just before the--these are, again, studies that the FDA has requested as opposed to a summation of all available knowledge.

DR. SANTANA: Dr. Reaman?

DR. REAMAN: And I think this is an opportunity to respond to a particular congressional request to provide information about pediatric studies. And I think it also extends the definition of safety information, because generally these drugs have significant side effects associated with them. And I think it goes to safety to say that a drug that has no activity that's been well studied but does have associated toxicity, I see no problem in putting that in the label and would support it.

DR. SANTANA: I did hear, though, a couple of committee members kind of opposed to that view. Would it be helpful if we took a vote? I've heard a couple committee members feeling that--I think there's some majority that says some information should be in the label, as you've heard the

discussion. But I heard at least two strong statements that say that they would not--no information--

[Inaudible comment off microphone.]

DR. SANTANA: Okay.

DR. HIRSCHFELD: We're soliciting comments, and then we get into the issue of who can vote and who can't vote and whether--

DR. SANTANA: Okay. I just wanted to--

DR. HIRSCHFELD: But I appreciate your--

DR. SANTANA: --thinks that we need to resolve this by a vote, we can do it. If you just want to hear both sides of the story, I think you're getting that.

Dr. Reynolds--

DR. PAZDUR: And I think they were well founded, i.e., we want to define the population, we want to, you know, be specific when we say it has no activity, you know, it's not just a blanket statement. So I think it's helpful to us.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: I just want to ask--you know, I think Greg's comments refining this are very good. I just wanted to clarify if putting that kind of negative data into a label is in any

way perceived as burdensome to the industry. And maybe industry could comment on that. Is that extra work for them, in other words? Is that an issue that--

DR. PAZDUR: Well, we asked--I think the important thing that differs this from my previous statements about many negative adult studies, we asked for this. Okay? And, therefore, they got a report back.

DR. REYNOLDS: So the specific thing that you asked when you specifically put that in. So in essence, then, it is--that's the clarification. It is no real extra work. They have to incorporate that into the label. The work has already been done.

DR. HIRSCHFELD: Yes, and they would get a six-month sales extension on exclusivity, which is not to be trivialized.

DR. REYNOLDS: Right. I just wanted to clarify that point. Thank you.

DR. SANTANA: Dr. Vassal? Since you came from so far away.

DR. VASSAL: Thank you. Just if I come back to Case 4, which illustrates the point, before the request by the FDA, maybe in this label was

written the sentence, "Safety and efficacy was not tested or evaluated in children." Right now it's no longer the case. So clearly for me, the safety data acquired in these Phase II studies should be available in the label.

On the other side, if we consider efficacy, clearly considering the large number of tumor types, especially the case of neuroblastoma, which was earlier stopped because of many, many reasons, I think it's very difficult to say there is no activity because there is maybe not enough data to really demonstrate that there is no activity. So to me, in this situation it would be important to have the safety data clearly available, and the sentence showing that at the moment there is no evidence or not enough evidence of activity, but maybe not detailed on all the different tumor types with not enough data to--

DR. PAZDUR: I think we hear that clearly, that there has to be some scientific precision and not to make a blanket terminology of no clinical activity in pediatric oncology here.

DR. SANTANA: And I think Steve did preface his question--

DR. PAZDUR: And that's really--

DR. SANTANA: --that safety--

DR. PAZDUR: --science. That's not even a regulatory--

DR. SANTANA: And that safety information would be inherent in this information, too. Okay. Let's move on. I think we did reach a consensus on that, or at least some comments.

Let's read the last one, then. The following question pertains to the situation where there is no efficacy or safety data available in pediatric patients. And when no efficacy or safety data are available in pediatric patients, consider if a statement that safety and efficacy have not been tested in children be included in the product label.

My comment to this goes back to a discussion we had earlier this morning, which is the rapidity and timing of the update of the label. I'm concerned that such a blanket statement when there are currently studies that are ongoing that potentially could change the statement once that information becomes available, what is the commitment to turn that around in a reasonable way that the public and the practitioners could be informed that there is now information? So I'm not

so worried about the statement. I'm just worried that once you put that statement here in the discussion this morning, that statement may stay there for eternity, and it may no longer be true six months from now. So what is the mechanism to get that taken care of in a time fashion to change it?

DR. HIRSCHFELD: Well, the context here would be because we're trying to focus this on--we are asking for data and then what to do with it. If we ask for data and don't get any data--

DR. SANTANA: There's no data.

DR. HIRSCHFELD: Yes. What should we do? Should we say there are no data? Or should we say something else? That's the nature of it. It's not to say in the known human experience there are no data. The question is we've made a request for data, there are no data, and we don't foresee data.

DR. SANTANA: Comments? Dr. Schweim?

DR. SCHWEIM: If this situation would occur in Germany, we were forced as an agency to point out this sentence in the package leaflet. We're forced in any cases where there is no data for children available that we do not have any data, there's a special paragraph in the German

drug law only for the purpose for children. It's not necessary for pregnant women or other specialized groups of the population. But for children it's necessary. If there is no data, we have to state it out.

But I would add a further comment. I think the main problem is the update method you have for SPC or package leaflet in the U.S. In our system, we have an automatic update if there is any new data available, and the company is forced to present this data, even if they collect it from the literature--not only if they collect it from their own clinical trials. And I think if you would have established such an update, automatic update period, this would be a less problematic situation.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: It's a two-part question. What do you do now? Say you don't request the information and a drug is submitted and there's no pediatric data, what do you do with the label right now?

DR. HIRSCHFELD: We have the default statement, which is safety and efficacy have not been--or safety and effectiveness have not been established--

DR. FINKLESTEIN: Then why would that default statement not apply to Question 5?

DR. HIRSCHFELD: Well, we're just trying to, in effect, parse it out a little finer. The first case, you could have data that exist but someone chooses not to submit it, and we would say that statement, it hasn't been established. Or you could have negative data, and you could say safety and effectiveness have not been established. Or you could have no data. You don't have the ability to distinguish among those possibilities.

The regulations allow alternate wording, and so we were just requesting some advice from the committee. The default statement we find is perhaps not sufficiently informative, and here's a case where we might be able to adjust that.

DR. FINKLESTEIN: The second part of the question has to do with a comment from our colleague from Germany. This is the era of Internet and electronic transmission, and what are your plans in terms of updating information so that everyone can obtain it in a more--there's a phrase.

DR. SANTANA: Timely manner?

DR. FINKLESTEIN: Well, friendly manner. There's an Internet phrase you use, virtually

effective, concurrently, and all other terminology. In other words, putting it in a--

DR. SANTANA: Realtime.

DR. FINKLESTEIN: Yes, realtime. Thank you. Putting it in a label that then gets killed, that's for 1940s. What are your plans now for the year 2003?

DR. HIRSCHFELD: That's a broader agency policy question, but it's an issue that I know the Commissioner has expressed particular interest in. There are some initiatives underway, and it's going to require cooperation among investigators getting data to the pharmaceutical sponsors and pharmaceutical sponsors getting the data to the FDA. So it's going to be a system solution.

DR. SANTANA: Dr. Cohn? And then Dr. Hagey.

DR. COHN: I was just going to follow up on your point, which was that things change. And so to say that there's no data available at this point in time won't necessarily be correct a couple weeks from now. But since you have dates on your labels, can't you say as of this date no safety and efficacy data are available, and then everybody will know what the last update is, and hopefully

eventually it will become realtime and, you know, you'll have it as of last Monday instead of as of six years ago.

DR. SANTANA: My comment was also related to a comment I heard earlier this morning from Richard about a specific drug that hadn't been updated for 20 years, although there was a lot of information. So I wanted to press the issue that in pediatric oncology, if there are studies that need to be updated that are providing information, that at least in this arena we establish a mechanism where that doesn't take us 20 years to get it back in the label. That was my point. It's just a comment to the agency of the importance, at least in this field, if we're going to make these kind of statements in pediatric oncology where the focus is right now, that we be cognizant of the need to move very quickly so that the label reflects what actually has happened.

DR. PAZDUR: And it can. You know, I didn't mean that it's a static document that never changes. Obviously we get updates on our INDs, which the European system doesn't even have, looking at--right? You guys don't have an IND mechanism?

[Inaudible comment off microphone.]

DR. PAZDUR: Okay. So, you know, we get regular and routine safety updates. We have trials that are coming in, and obviously the product label would be changed with those trials that the sponsor submits. But also we have a vast postmarketing safety system looking at drugs that are marketed, and if we have clues that there are safety issues, then these have to be investigated, and we have conferences with--not only inside the U.S. but internationally and with the sponsors to take a look at this. So I don't want to infer that it is totally a static document here.

DR. HAGEY: Perhaps I could ask what's done now in the case of pregnant women in situations where perhaps safety and efficacy in pregnancy has not been established, then when you do get some information, how timely is that update?

DR. HIRSCHFELD: The short answer is it's variable, but there's a certain urgency that's perceived about it, and, again, I think the operative process is to make it a cooperate process. What was the source of those data? Was it picked up through postmarketing surveillance? Was it picked up through a published study? Was it

picked up through anecdotal information? How reliable is it? Discussions with the sponsor would follow as soon as the signal is detected. And then there have been actually--not only is the label updated, but there are postings on the website and in some cases "Dear Doctor" letters are sent out.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: One minor question. You interpret the words "are available" for point No. 5 as meaning that no efficacy and safety data have been received by the FDA? Is that the way that's to be interpreted?

DR. HIRSCHFELD: For this particular question, correct. And this would be not because there are no data that we're unable to find, but we've requested data. And usually if people have any data, no matter what the source, with the financial incentive waiting for them just to send it in, they usually manage to find whatever is available.

DR. SCHWEIM: As a part of old Europe, I have a question of clarification.

[Laughter.]

DR. SCHWEIM: Steve, if I understand you correct, you said that it could happen that the

company has negative data but is not willing to send it to you so you can publish it. If this is the case, it's totally opposite to the German and the European situation. If a pharmaceutical company has negative data, they must submit it. Otherwise, they will be punished by the law. So if you have indicated on a German or European package leaflet there is no data available, it means there is no data available. It does not mean that a company has negative data and doesn't present it.

DR. HIRSCHFELD: Right. The clarification would be if there's any safety issues, we have the authority to demand the information regarding the safety issue. That would be a public health question.

The concept here would be that there's an incentive for the company to provide data in any fashion, even negative data, because negative data can, nevertheless, be in the economic risk/benefit equation a highly favorable undertaking. So the anticipation would be that it's likely that there are no data.

DR. SANTANA: I'm taking this maybe a little too far, but what would happen in a situation where you grant a waiver because, you

know, you're not going to study the drug? I mean, this statement--

DR. HIRSCHFELD: That would be the pediatric rule, Dr. Santana, and in this case--

DR. SANTANA: I take it back.

DR. HIRSCHFELD: Okay.

DR. SANTANA: Further discussion on that point?

DR. HIRSCHFELD: Thank you.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: I'm just trying to understand this again. This seems like a dialogue between you and a specific company, okay, so that's the only communication. Do you have blinders on? And if there's published data out there in JCO that was done by COG, you know, in some other setting, I mean, wouldn't you take advantage and use that information?

DR. HIRSCHFELD: The short answer is if it's a safety concern, absolutely. If it's for other reasons, then we can ask--we can make a company aware of data. Other people can submit data. And if there are data--we don't have blinders, in effect. What we do, though, is we try to encourage data to be submitted so it can be

verified. And the context for this question is that we and no one else apparently can identify data. There's lots of data that might exist that might be unpublished or unaccessible. But if it's publicly available data, that's certainly something that's accessible to everyone.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Steve, maybe you could clarify for us in the setting you're talking about where someone else can, quote-unquote, submit the data. What about drugs that are now off patent and that may be made by two or three different companies? I must say the Cooperative Group has data on one of those drugs. Can the Cooperative Group then submit the data, and then does the labeling take place for all companies that are making it on a generic basis?

DR. HIRSCHFELD: That's a highly plausible scenario.

DR. SANTANA: Any other comments or points of discussion before I make a comment?

[No response.]

DR. SANTANA: Well, I'm not going to do a summary because we, I think, covered all the cases and the questions rather thoroughly. I just want

to say again from the pediatric oncology community how grateful we always are to the FDA to listen to what we have to say and that we think you are partners with us in this endeavor. I specifically want to thank Steve and Richard for their involvement and allowing us to express our views, as we do so well. Thank you.

DR. HIRSCHFELD: Thank you.

[Whereupon, at 2:01 p.m., the subcommittee was adjourned.]

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