DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Thursday, October 9, 2003

8:00 a.m.

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Victor M. Santana, M.D., Chair
Thomas H. Perez, M.P.H., Executive Secretary

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS (VOTING)

Peter Adamson, M.D.
Jeffrey Blumer, M.D.
James Boyett, Ph.D.
Alice Ettinger, R.N.
Jerry Finklestein, M.D.
Ruth Hoffman, Patient Representative
Patrick C. Reynolds, M.D.
Clinton Stewart, M.D.

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (VOTING)

Steven L. George, M.D. (by telephone)
Donna Przepiorka, M.D., Ph.D.

FEDERAL EMPLOYEES (VOTING)

Don Mattison, M.D. (a.m.)
Malcolm Smith, M.D.
Anne Zajicek

GUEST SPEAKERS (NON-VOTING)

Louis Cooper, M.D.
Douglas Flanagan, Ph.D.
Walter Shaw, Ph.D.

FDA

Richard Pazdur, M.D.
Patricia Dinndorf, M.D.
Steven Hirschfeld, M.D., Ph.D.
Rik Lostrito, Ph.D. (p.m.)
Rosemary Roberts, M.D., (a.m.)

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

MORNING SESSION

Call to Order and Introduction

DR. SANTANA: I apologize to the committee and to the audience that I have a bad cold so I have my radio voice on for today. I know that I have another career. Maybe that will be it.

Welcome everybody and good morning. This is a meeting of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee of the FDA. We have convened today to advise the agency on two matters pertinent to pediatric oncology. One is a discussion this morning of off-patent oncology drugs and then, this afternoon, a discussion on age-appropriate formulations that would impact oncology pediatric patients.

So, with that brief introduction, I will ask the committee to introduce itself. Please state your name and your affiliation for the record and make sure you turn on the mike when you speak so it will be recorded appropriately.

Can we start with the gentleman on the left.

DR. SHAW: I am Walt Shaw with Avanti Polar Lipids.

DR. FLANAGAN: I am Douglas Flanagan with the University of Iowa.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, National Cancer Institute.

DR. ZAJICEK: Anne Zajicek, NICHD, NIH.

MS. HOFFMAN: Ruth Hoffman, Patient Advocate.

DR. STEWART: Clinton Stewart, St. Jude Children's Research Hospital.

DR. BLUMER: Jeff Blumer, Case Western Reserve University.

DR. ADAMSON: Peter Adamson, Children's Hospital of Philadelphia.

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

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

DR. SANTANA: Victor Santana, Pediatric Oncologist at St. Jude Children's Research Hospital.

DR. PRZEPIORKA: Donna Przepiorka, University of Tennessee Cancer Institute.

DR. FINKLESTEIN: Jerry Finklestein, UCLA and the American Academy of Pediatrics.

MS. ETTINGER: Alice Ettinger, Nurse

Practitioner, St. Peter's University Hospital.

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

DR. DINNDORF: Patricia Dinndorf, FDA, Division of Therapeutic Biologic Oncologic Products.

DR. HIRSCHFELD: Steven Hirschfeld, FDA, Division of Oncology Drug Products, Division of Pediatric Drug Development.

DR. PAZDUR: Richard Pazdur, FDA.

DR. SANTANA: Thanks to everybody for being here this morning. Then I will ask Richard if he wants to address the to address the committee.

Welcome

DR. PAZDUR: Just a few words. This, I believe, is our eighth meeting of the Pediatric Oncology Subcommittee of the ODAC or the Oncology Drug Advisory Committee. On behalf of the entire FDA, I would like to thank all of the participants of this panel as well as the public representation here.

Today, we have two important topics that we are going to talk about, the first one stemming from the Best Pharmaceuticals or Children's Act,

and that is examining off-patent drugs for which pediatric drugs are needed. And we really look forward to a diverse input from the entire oncology community on this topic.

The second, afternoon, topic deals with, I think, a topic that is of interest to pediatric oncologists and also an important issue in oncology in general and that is age-appropriate formulation changes to facilitate dosing of products used in the pediatric-oncology setting.

So, although we have two groups of people here, we would like a really robust discussion of both of these and really look forward to this. Again, on behalf of the division as well as the FDA in general, we appreciate the participation of all of the ODAC members as well as the special committee members here today.

Thank you.

DR. SANTANA: Thank you, Richard.

Steven, do you want to say any words?

DR. HIRSCHFELD: I believe I am scheduled for some prepared remarks.

DR. SANTANA: We have to read the conflict of interest first, though. Could you give us a minute to do that?

DR. HIRSCHFELD: Yes.

Conflict of Interest

MR. PEREZ: "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 topics to be discussed at today's meeting are issues of broad applicability. Unlike issues in which a particular firm's product is discussed, issues of broad applicability may affect many sponsors and their products.

"All participants have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in firms that could be affected by today's discussions, the Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in this meeting; Donna Przepiorka, Steven George, Victor Santana, James Boyett, Alice Ettinger, Jerry Finklestein, C. Patrick Reynolds, Peter Adamson, Jeffrey Blumer.

"A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, 5600

Fishers Lane, HFI 35, Rockville, Maryland, 200857.

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

Thank you.

DR. SANTANA: Thanks, Tom.

One last announcement. Stephen George, who also is part of this committee, will be joining us via telephone later on during the discussions.

So, with that last announcement, Dr. Hirschfeld?

Labeling and Formulation Challenges in Pediatric Therapeutics

DR. HIRSCHFELD: Good morning.

[Slide.]

The topics for today center around the need for pediatric labeling and that is reflected in a program contained in the Best Pharmaceuticals for Children Act which allows for the study of off-patent drugs which will be explained in greater detail by the subsequent speakers also, addressing

the issues of formulations, as noted by Drs. Pazdur and Santana in their preliminary introductions. These, together, form challenges in pediatric therapeutics.

[Slide.]

The Food and Drug Administration was established through three principles which arose during the course of the Twentieth Century as a result of healthcare scandals involving children.

The first was the issue of proper labeling which was established in 1906 in response to the poisoning of infants from an elixir designed to treat colic, which contained morphine and the product was not properly labeled and the children were poisoned. This led to legislation establishing the need for proper product labeling.

In 1938, in response to the poisoning of children through formulation of the antibiotic sulfanilamide, Congress enacted the Food, Drug and Cosmetic Act that products must not only be properly labeled but must be safe and, therefore, must be tested before licensing for interstate commerce would be permitted.

in 1962, in response to another healthcare scandal which was the malformations which occurred

secondary to pregnant women taking thalidomide, Congress enacted an amendment to the Food, Drug and Cosmetic Act requiring demonstration of efficacy before a product would receive marketing authorization for interstate commerce.

Despite the fact that, during the first two-thirds of the Twentieth Century, children were the catalysts for the legislation. They were not the beneficiaries.

[Slide.]

So, in the last quarter of the Twentieth Century, there was an evolution of pediatric information beginning in 1974 with the passage of the National Research Act which established a National Commission for the Protection of Human Subjects for Medical and Behavioral Research. Concurrently, the American Academy of Pediatrics, which was an organization established in the Twentieth Century, published its report that was commissioned by the FDA on General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children.

In 1977, the National Commission issued its first report on research involving children

and, in the same year, the FDA issued a guidance on General Considerations for the Clinical Evaluation of Drugs in Infants and Children and the Academy of Pediatrics issued its first statement on the ethical conduct of research involving children.

[Slide.]

These reports led to the issuance of a regulation, in 1979, which placed in the label of the product package insert a pediatric-use subsection. This was the first time any national authority had indicated both an interest and a requirement to comment on the pediatric use.

In 1983, Federal Regulations were issued for the protection of federally funded research and included specific provisions for the protection of children and the categorization of research based on the perceived risk to the pediatric population.

In 1994, there was a revision of the Code of Federal Regulations which was encompassed in a Pediatric Rule which added a subsection which allowed extrapolation as a basis for pediatric use. In 1996, the FDA issued a Guidance on the Content and Format of the Pediatric Use Section. Concurrently, the Academy of Pediatrics updated their statement on ethical conduct of clinical

trials.

[Slide.]

All these efforts did not lead to systematic inclusion of pediatric information in the product labels or product package inserts. So two initiatives in the late 1990s attempted to address the problem.

The Food and Drug Administration Modernization Act instituted a pediatric incentive program and, in 1998, a Pediatric Rule was issued--rule and regulation are synonymous--which mandated pediatric studies under particular circumstances.

This was followed, in 2001, by an adaptation of the Health and Human Services Subpart D Regulations to FDA-regulated research and, in 2002, which will be the focus of the discussion this morning, the passage of the Best Pharmaceuticals for Children Act, which had a renewal of the pediatric incentive program from the 1997 Food and Drug Administration Modernization Act and included a provision for the study of off-patent drugs and, as an overriding principle, endorsed the concept of public dissemination of pediatric information.

[Slide.]

By federal regulation, the product package insert, or label, has sections which are listed on this slide. They are: a description of the product; a description of the relevant clinical pharmacology; the indication and usage, which forms the basis for the marketing claims; contradictions; warnings; precautions; adverse reactions; drug abuse and dependence; overdosage, which are all a summary of the safety information; dosage and administration for the indicated use; and how the product is supplied.

[Slide.]

There are additional label sections which are optional, which can be included: animal pharmacology or animal toxicology; clinical studies, which are often included and have been a policy in oncology products; and references.

[Slide.]

The principles of labeling, as stated in the federal regulations, is that the labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug, that the labeling shall informative and accurate and neither promotional in tone nor

false or misleading in any particular. And the labeling shall be based, whenever possible, on data derived from human experiences.

There is a provision that conclusions based on animal data may be necessary for safe and effective use of the drug in humans but it should be identified as such and included with human data in the appropriate section of the labeling.

This provision has been recently applied to products which are designed to treat pathogens for which the study in humans would not be ethical.

[Slide.]

Pediatric information has multiple options for being included in the product label. There is the Pediatric Use Section, as defined in the regulations from 1979, which is in the Precautions Section. There is also an opportunity for pediatric information in the Dosing Section. Pediatric indications would be specifically listed in the Indications Section and then clinical pharmacology study results, contraindications and warnings are all other opportunities for including pediatric information.

[Slide.]

The regulatory mechanisms to submit

pediatric data to the FDA are as a new indication which would come as a new drug application or as a supplement to a new drug application or, alternatively, a label change with clinical data which would come as a supplement to a new drug indication.

[Slide.]

Many of the oncology drugs that are used in the pediatric population are off-patent. They were initially approved for marketing during the 1950s, '60s and '70s when there was a flurry of activity, particularly in the arena of pediatric leukemia. The drugs that are now in use have been refined over the years in their application to the particular diseases and extended to looking at other diseases.

At the time the product labels were prepared, the regulatory standards and scientific methods were different than contemporary approaches so one may ask the question legitimately, if the goal is to put pediatric information in the label and if pediatric information is already in the label, what would be the purpose of undertaking pediatric studies.

The answer to that, simply stated, is that

the information in the product label that exists, if it is considered to be outdated or represents a safety issue, would then be appropriate to update and study that information.

[Slide.]

The reasons for examining pediatric dosing information and safety information is because, as many of the speakers will elaborate in more detail later this afternoon and during the course of the morning, growth and development affect drug disposition and action. There are developmental changes in metabolism. There are changes in body composition, particularly in the ratio of the water and lipid partitions.

There are developmental changes in receptor expression and function. The growth rate alters and there are some analyses which now subdivide the growth phases of children into multiple periods, each with its own characteristics. Organ functional capacity will change and service-to-volume and distribution change, which are fundamental characteristics for predicting and understanding drug metabolism.

[Slide.]

In order to administer medications

properly to children, one must have a formulation which can provide a predicable exposure of the active agent to that patient. Pediatric formulations have always been a challenge. There are considered by most people in the field various categories of formulations. These include bona fide pediatric formulations such as drops, suspensions, chewable tablets or syrups. That is a formulation that is prepared and manufactured specifically for the intended use.

Then there are extemporaneous pediatric formulations which are made with standardized extemporaneous vehicles which are non-formulary or could be from the U.S. Pharmacopoeia or other marketed vehicles. Then there are extemporaneous pediatric formulations which are made with food or other carrier substances such as sprinkles on applesauce or yogurt.

Again, these will be addressed in a little more detail this afternoon.

[Slide.]

There are some very practical issues which must be considered, and that is the ability to swallow capsules or tablets--the correct dose or concentration may not be available in a solid oral

dosage form--the appropriate dosing parameters, whether to use weight or body-surface area, and the need to change dose as a child grows, which is of particular importance for medications given over a long period of time, chronic medications such as antihypertensives, anticonvulsants or some of the maintenance therapies which are used in oncology.

[Slide.]

One may ask what is appropriate. These questions are raised as questions with the expectation that some of them will be addressed in the discussions later today. Is an oral liquid solution the preferred delivery system for a less-than-two-year old, for the middle child? Are solutions, suspensions or chewable tablets preferred? Are children greater than ten years able to take solid oral dosage forms or should alternatives be considered? And what about children with difficulty swallowing or who require nasogastric tubes or who have other chronic illnesses.

[Slide.]

The general purpose of bioavailability studies is to assess absolute or relative bioavailability of a dosage form or new formulation

and to characterize the pharmacokinetics of the active drug ingredient or therapeutic moiety. For example, the rate and extent of absorption, half-life and metabolism further allow dose determination adjustment and to assess the safety for locally acting drug products such as cremes or patches.

[Slide.]

But there are a number of physiologic variables that affect bioavailability which include age, weight, surface-to-volume ratio, protein binding, carrier proteins, gastric emptying, gastric function, intestinal-residence time, hepatic and renal function and even the intestinal flora which can change with age.

[Slide.]

The bona fide formulation approaches that have been used in approved products include solution, suspensions, chewable tablets and elixirs. But there is some controversy as to the acceptable amounts of alcohol and other carriers.

[Slide.]

Some of the issues which need to be addressed in terms of extemporaneous formulations are stability, bioavailability, concentration

variability and an increased risk for medication errors. This is particularly critical in products with a narrow therapeutic index.

[Slide.]

So, in conclusion, for pediatric formulations, there are many approaches and many challenges including the minimization of excipients, a need to determine safety and dosing accuracy, the recognition and management of unpredictability and, as always, we hope that development could proceed in partnership with the Food and Drug Administration.

So, I will now turn the podium over to my colleague, Dr. Louis Cooper, from the Division of Pediatric Drug Development, who will go into some detail followed by Dr. Anne Zajicek from the National Institute of Child Health and Human Development who will go into further detail on the process involved in the study of medications, both on-patent and off-patent, in the Best Pharmaceuticals for Children Act.

When we have finished our discussions, when Dr. Malcolm Smith from the National Cancer Institute has presented an analysis and some proposals, and Dr. Adamson from the Children's

Hospital of Philadelphia has presented some methodologic approaches which may be useful for the types of studies that we would like to discuss, then all of us will be available for questions.

Dr. Cooper?

BPCA: for Oncology Drugs

DR. COOPER: Thank you, Dr. Hirschfeld, and good morning.

[Slide.]

I am Louis Cooper. I am a pediatric hematologist in the Division of Pediatric Drug Development in the Office of Counterterrorism and Pediatrics. I will present, in the next several minutes, a brief overview of the Best Pharmaceuticals for Children Act as it relates to oncology drug development.

[Slide.]

The goal, which will include the on-patent exclusivity process and the off-patent process is to introduce new pediatric information into the drug label. These mechanisms utilizing the on-patent and off-patent processes will be discussed in greater detail.

[Slide.]

The Best Pharmaceuticals for Children Act

provisions include the on-patent process wherein the FDA will issue a written request to holders of an approved application which is protected either by a patent or by marketing exclusivity. The second category are the off-patent older drugs wherein the FDA will issue a written request to holders of approved application for these drugs that have no patent or market exclusivity protection.

These are the drugs which this forum will be concentrating on today.

[Slide.]

Pediatric exclusivity and what does this really represent. It is called the carrot. Basically, it allows a drug which is on patent an economic stimulus or incentive to conduct pediatric studies by the originator of the drug. The incentive represents six additional months of marketing exclusivity which can attach to existing patents and/or existing exclusivity.

For the off-patent drugs, there is no financial incentive to the holders of these drugs as there is no longer any patent protection and, therefore, there is no financial incentive to the sponsors or originators of the drug to perform

pediatric studies.

An example of this might be if a drug brought a revenue to a company of, say, $2 billion a year, if that marketing exclusivity were granted to them for an additional six months, this would bring revenue to that company of an additional $1 billion considering $2 billion as their revenue for the year.

So, therefore, it provides significant financial incentive to the drug companies to consider doing these pediatric studies.

[Slide.]

Written request; the written request is a legal document that requests pediatric studies. This document is written and sent by the FDA to the sponsors requesting studies in the pediatric population. The components of a written request typically include the intended pediatric indication, meaning the disease or condition to be studied, the population, the types and numbers of studies, any general safety parameter and any drug-specific safety parameter that should be monitored.

Plans for long-term follow up in a time frame within which the studies should be completed

and the results sent to the FDA, the specific results sent to the FDA. The specific components of a written request may vary according to the indication, population and product.

[Slide.]

Who is involved? The written request process involves several steps and entities. The sponsor is generally the developer of the drug. The Center for Drug Evaluation and Research, CDER, at the FDA, is organized into offices and, within each office, are divisions. The review divisions are organized on the basis of the disease or condition that a product is intended to treat.

The Division of Pediatric Drug Development within the FDA functions as a resource for the pediatric activities of the review divisions. The Pediatric Implementation Team, or PdIT, is a multidisciplinary team with representatives throughout CDER. The purpose of the PdIT is to ensure consistency and quality.

The Pediatric Exclusivity Board is a different multidisciplinary panel from the PdIT that makes the determination of whether a sponsor fairly has met the terms of a pediatric written request and, therefore, granting of exclusivity.

[Slide.]

I will now walk you through the steps for the study of on-patent drugs under the BPCA. Industry, up in the upper left-hand corner, if you will, please, submits a proposed pediatric study request or the FDA, by its own initiative, may determine a public-health benefit to support a specific pediatric study.

The FDA subsequently issues a written request. Industry has 180 days to respond as to whether or not they will perform the studies. If the sponsor agrees, they inform the FDA and can qualify for exclusivity. If the sponsor declines, the written request can be forwarded to the Foundation for the National Institutes of Health, a non-profit foundation associated with the NIH for funding of the studies.

In that case, the original sponsor would not be eligible for exclusivity.

[Slide.]

What does all this mean? Since the 1997 creating of FDAMA, there have been 334 proposals from industry of which the FDA has issued 284 written requests. 91 exclusivity determinations were made. 82 exclusivity grants were offered

resulting, at this time, in 61 labeling changes including pediatric information into the drug label.

This represents a significant benefit to children. Remember, and there is a disparity in the 82 and 61 because the new labeling changes are not able to be including all of the exclusivity studies which have been requested which, at this time, there are still studies pending and, as a result, the variance in the 82 and 61.

The studies take two years or longer, depending on the study. How does all of this affect oncology? We have looked at the broad picture within the FDA of the total exclusivity granted thus far in the past six years. For pediatric oncology exclusivity, there have been 18 proposals for industry. The FDA has issued 28 written requests which implies that the FDA has de novo, on their own initiative, sought some studies.

Exclusivity determinations have been done in five cases. Exclusivity was granted in five, resulting in new labeling in four specific drugs.

[Slide.]

The drugs which thus far have been granted exclusivity include busulfan, vinorelbine,

topotecan, temozolomide and fludarabine.

[Slide.]

Now I will speak about the off-patent process involving the older drugs for which there is no exclusivity and the reason we are here today.

[Slide.]

Legislation created a partnership between the NIH and the FDA. Within the FDA, the same people and committees I mentioned earlier are involved. However, the off-patent also involves the NIH.

[Slide.]

The process for the study of off-patent drugs; the process for off-patent is similar but differs in several aspects from on-patent process. The initial source of drugs is a priority list which will be discussed in significantly more detail by Dr. Anne Zajicek who will be speaking subsequent to myself.

The FDA written request is issued to all manufacturers or distributors of the off-patent product and each one has the opportunity to perform the studies. However, because there is no financial incentive, the companies usually have not elected to perform the studies. The time frame for

the pharmaceutical industry response is 30 days compared to the 180 days for the on-patent process.

If, within the 30 days, companies or sponsors do not agree to the studies, the written request is referred to the NIH which will be considered in the next talk.

[Slide.]

I invite you, at your convenience, to review the FDA web page whose address is www.fda.gov. If you look down toward the bottom section, which I will show you in the next slide--

[Slide.]

You see there is a pediatric section that you can refer to specifically and it will give you significant amounts of new information and highlights on new drug labeling.

[Slide.]

In summary, the goal of the on-patent and off-patent processes is to make efforts for new information in oncology labels. We look forward to the remainder of the conference. If I may, I will turn the podium over to my colleague, Dr. Anne Zajicek, and I thank you for your attention.

DR. SANTANA: Thank you, Dr. Cooper.

BPCA: Role of NIH

DR. ZAJICEK: Good morning.

[Slide.]

I am going to talk about the NIH portion of the Best Pharmaceuticals for Children Act.

[Slide.]

The point of the Best Pharmaceuticals for Children Act, again, for the most part, is to get some pediatric labeling for off-patent drugs. So this process, as Dr. Cooper alluded to, is a nice interaction between the FDA and the NIH. So, to start with, the NIH receives from the FDA a master list of all off-patent drugs which lack adequate pediatric labeling. This year, there were about 169 drugs that fell into this category.

Now, the job is to whittle this list of 169 drugs down into some manageable number of drugs that are prioritized for study for the coming year. So, the goal, again, is to develop, prioritize and publish an annual list of somewhere around 15 to 25 drugs somewhere in there. The Best Pharmaceuticals for Children Act mandates that the NIH do this prioritization in consultation with experts in pediatric practice and research, which is you in the Oncology Section and, in considering the drugs that should be prioritized for study, we are

mandated to take into consideration the availability of safety and efficacy data to determine whether additional data are needed from the literature. If new studies are funded, will they produce health benefits and are there reformulation issues.

So these are some things for you to take into consideration today.

[Slide.]

For consultation for prioritization, we at the NIH have consulted with members of other institutes of the NIH. The list of oncology drugs that are off-patent has been sent to the National Cancer Institute; for example, cardiac drugs have been sent to the National Institute for Heart Lung and Blood and so on.

A multitude of pediatric subspecialty groups have been consulted and the American Academy of Pediatrics Committee on Drugs is also being consulted in this process.

[Slide.]

As Dr. Cooper mentioned, just as a side mention for on-patent drugs, if the FDA determines that there is a need for pediatric labeling, a written request is issued from the FDA. If the

holder of the NDA declines to perform pediatric studies, the drug is referred to the Foundation for the National Institutes of Health. The rest of the talk will be about off-patent drugs.

[Slide.]

Also, as Dr. Cooper mentioned, from this priority list, again this whittled-down list of 15, 20 drugs, something like that, the FDA issues a written request. So the FDA has given us the list of 169. The NIH parcels it into this priority list of 20 drugs, somewhere in there, and that gets sent back to the FDA. The FDA then issues written requests.

The written request is sent to the holders of either the new drug application or the abbreviated new drug application, in that case, the generic holder, and they are given 30 days to either accept or decline. If there is no answer within 30 days, that assumption is they have declined and, in that case, the written request gets referred to the NIH for contract.

[Slide.]

The process of contracting is a little complicated. The NIH publishes a request for proposals at this website which is Commerce

Business Daily. So there are postings of proposals that the NIH would like to have performed. The proposals are then submitted to the NIH. The proposals are reviewed by a scientific peer-review panel. Contracts are awarded. The studies are performed with the NIH acting as the sponsor, again funding the study and holding the IND. And the results are submitted to the NIH and to the FDA for labeling changes.

[Slide.]

This structure at the NIH is two-fold. The National Institute of Child Health and Human Development oversees the contracting process, writes their request for proposals, again reviews the proposals and funds the proposals. The management of these projects that will go on is managed by a coordinating center which, again, oversees the management, the data collection from the contracting center. So that is how this will physically work.

[Slide.]

The results so far; written requests referred to the NIH from the FDA include lorazepam for two indications, one for sedation and one for treatment of status epilepticus, written requests

for nitroprusside and one for azithromycin. There are others that are within that 30-day waiting period so there will be others to come.

Requests for proposals have been published for lorazepam again for the two indications, for sedation and status epilepticus, and for nitroprusside. The one for azithromycin is in process.

Scientific peer-review panel reviews have convened to evaluate the proposals from coordinating centers and, for the two lorazepam protocols, and a contract has been awarded to the contracting center.

[Slide.]

So, just to summarize what the FDA does as opposed to what the NIH does, the FDA formulates, again, this list of 169 drugs. The NIH is responsible for prioritizing this list. The FDA writes the written request and the NIH is active in providing input with the written request. The FDA refers drugs to the NIH for study if the written requests are declined and the NIH is responsible for writing requests for proposals and sponsoring the clinical trials.

[Slide.]

The role of you today, basically, the role of the Pediatric Subcommittee of ODAC, is to act as consultants to us to prioritize the pediatric oncology, or the oncology, drug list. Just to review, we would be interested in your views of what drugs should have priority, taking into consideration the availability of safety and efficacy data. So, in other words, if there is sufficient data in the literature, it is probably not necessary to go on and sponsor a study.

Is there a need for additional data? Is there data but there is a chunk of it missing in a certain population, certain indication? Would there be health benefits from additional studies? The last issue has to do with reformulation. Are there oncology products that are good products but should be reformulated in a way that would be better for pediatric application?

[Slide.]

So, in summary, the NIH is in a partnership with the FDA. The NIH is responsible for prioritizing the drug list, for commenting on the written request and for sponsoring the clinical studies in children that will produce pediatric labeling changes.

Thank you.

DR. SANTANA: Thank you. Malcolm?

Off-Patent Drugs for Young Children with Cancer

Gaps in Knowledge and Public Health Needs

DR. SMITH: Good morning.

[Slide.]

I thank Dr. Hirschfeld and others at the FDA for this opportunity to speak on this issue of off-patent drugs for young children with cancer and how the Best Pharmaceuticals for Children Act can be used to help us gain additional knowledge to address the needs of particularly young children.

[Slide.]

The issues that I will be focussing on, especially on the younger children, and first on the increased susceptibility of young children to drug-induced toxicities, the reduced outcome that we see for some young children for certain diseases, the variability in prescribed dosing for young children for cancer indications, the potential contribution of additional pharmacologic data, but then potential ways to study off-patent agents within the context of ongoing clinical trials and possible off-patent agents for additional study for you to consider and discuss.

[Slide.]

The comments that I will be making are informed to a large extent by a meeting that CTEP and the Children's Oncology Group sponsored in May of 2003 on Cancer Pharmacology in Infants and Young Children. The organizers of this meeting were my colleague, Dr. Barry Anderson, who was unable to be here today because of a competing meeting, Dr. Peter Adamson from the Children's Oncology Group who is here, and Dr. Clinton Stewart who is here. They can correct me when I misrepresent anything from that meeting.

The meeting addressed gaps in the discussion of cancer-drug pharmacology in infants and young children. It discussed toxic and therapeutic consequences of these informational gaps and discussed methods to incorporate pharmacokinetic research into cancer clinical trials to develop more rationale dosing guidelines.

[Slide.]

A point that I would emphasize to you is that pediatric oncology is different. I think when we look at BPCA and how it applies, the significance of agents, drugs used, off-patent drugs used, can't be measured in how many thousands

or hundreds of thousands of doses are administered.

In pediatric oncology, most tumors are fatal if not adequately treated. So the risks of undertreatment are substantial. Most treatments are toxic and have narrow therapeutic windows and, hence, the risks of overtreatment are substantial. So suboptimal use of off-patent drugs can have very serious consequences; death due to inadequate treatment, life-threatening acute toxicities as well as long-term sequelae that reduce quality of life.

[Slide.]

So, first of all, now, then, to focus on some examples of the increased risk of toxicity for infants and young children. I will give two examples. The first is hepatic toxicity associated with dactinomycin.

[Slide.]

I could go back to the Wilms' tumor literature in a historical context, but I will focus on a more recent example from actually an ongoing clinical trial for rhabdomyosarcoma. The primary purpose of this trial was to evaluate the contribution of topotecan. So the comparison was between the standard three-drug VAC, vincristine,

dactinomycin and cyclophosphamide, plus those same three drugs alternating with the topotecan treatment course.

The doses of the agents are shown here. For the vincristine, dactinomycin and cyclophosphamide, dosing by body-surface area over one year of age. In children less than one year, half dosing of these same agents.

[Slide.]

In this trial for children with rhabdomyosarcoma, serious toxicity, serious liver damage, or hepatopathy, was observed, 16 cases among the 328 children enrolled at the time. And there were four hepatopathy-related deaths. The estimated cumulative incidence of this serious toxicity was 7 percent and there was a segregation by age, younger children at increased risk, zero to 35 months of age, a 15 percent risk, and over three years of age, three years or older, 4 percent risk.

In terms of children of hepatopathy-related deaths, there was a trend towards more deaths in the younger age group, so age being a risk factor for this very serious toxicity.

[Slide.]

Another example goes back into the literature, a report from Bill Woods, Mara Leary and Mark Nesbitt in 1981 looking at the incidence of neurotoxicity for vincristine by patient size. The smallest group of patients, those less than 0.5 meters squared, had a much higher incidence of severe neurotoxicity. This led to the recommendation that children less than 1 meter squared should be given doses calculated by body weight rather than by body-surface area. That has the de facto result of being a reduction in dose.

[Slide.]

There are other examples that I won't go into of possibly increased toxicity for infants and young children. When you look at infants with ALL, there is certainly a higher rate of treatment-related mortality for these and particularly the very youngest infants than for older children. Ototoxicity among young children treated with cisplatin, there were reports that the risk of ototoxicity is increased and also, for cardiac toxicity, reports that young children are at greatest risk for cardiac toxicity following treatment with anthracyclines.

[Slide.]

So the easy answer to this would be, while there is increased risk of toxicity, you just need to reduce the dose. But there are at least some examples of these younger children also being at increased risk for treatment failure. The two I will describe to you are for rhabdomyosarcoma and for ALL.

[Slide.]

For children with rhabdomyosarcoma, the Kaplan-Meier curve for event-free survival is shown here. The top curve is for the one-to-nine-year group. The lowest curve, less than one year, the infants, have an event-free survival that is only 55 percent, much lower than that for children 1 to nine years of age.

If you were really paying very close attention, you will recall that these infants are the ones who get the half dose of chemotherapy agents. One question would be is this dose reduction that, in part, is to ameliorate toxicity, but is this somehow reflected in a lower failure-free survival for these infants.

Let's get all of the curve here.

[Slide.]

The second example is provided by the

Children's Oncology Group and by Dr. Sather, the statistician. This is looking at two recent COG--actually CCG--trials and the risk of treatment failure is greatest among children one-year of age--that is, 12 to 24 months--compared to older children, either to two to five-year-olds, or six-to-nine year olds. The grey, what should be grey and red bars, are two different clinical trials. The relative risk for infants is almost double that for children that are two-to-five-years of age.

The possible explanations; leukemia cell biology is certainly a possible explanation but things like the MLL gene rearrangement that occurs in the very youngest children are not that common in the one-to-two-year olds. So it is not clear what the leukemia-cell-biology explanation might be. The other would be some pharmacologic explanation, the latter being one that is potentially addressable by better dosing paradigms.

[Slide.]

Another point to emphasize is that the way we use these drugs in children is variable now. This is illustrated by The Rule of 30 that I will explain and how it is variably applied.

[Slide.]

The Rule of 30 is a rule that allows the conversion of any body-surface area from milligram-per-meter squared-based dosing to milligram-per-kilogram dosing. You use a factor of 30 to go from one to the other.

It has the effect of essentially being a reduction in dose when you go from dosing by body-surface area to by-weight dosing. So you get a dose reduction in the youngest children when you use dosing by milligram-per-kilogram. But this rule is variably applied in terms of when it is applied, milligram-per-kilogram dosing may be used for some treatments in less than 12 months, for others, less than-3 years.

When a weight parameter is used, it may be less than 10 kilograms, less than 12 kilograms, less than 30 kilograms. What is the basis for this and can we have more, better-data-supported, rules. Sometimes, we use 50 percent dose reductions as in the case of rhabdomyosarcoma for the children less than 12 months and for Wilms' tumor.

[Slide.]

So the Rule of 30 does lead to lower doses for younger children, having the effect of reducing

toxicity, potentially also reducing efficacy. But when you look at the Rule of 30, it really--this conversion is--the 10-to-11-year old is the one for which the Rule of 30 converts from the same dose by weight, by body-surface area.

Depending on whether you apply body-surface-area dosing or per-kilogram dosing, you can get doses that differ by a factor of 50 or 60 percent, particularly at the extremes of the youngest and oldest children.

[Slide.]

This illustrates the variability in dosing prescribed for one drug, that being vincristine, looking across the transition from nine months of age to 15 months of age. The points, without going into details about the different tumor types and why they might be different, but you notice a threefold difference in dose and you notice that, for some tumors, there is a step function at one year of age. For some tumors, that step is a doubling in dose. For some, it is an increase by 30 percent in dose. And, for some, it is a smooth transition.

Again, what is the best way to do it. Can we do it better?

[Slide.]

So it gets to the issue of the scaling of doses of anticancer drugs. The ultimate goal is to reduce variability in drug effect which is a function of drug exposure and tissue/tumor sensitivity. Fixed dosing, which is becoming the rule for adults, obviously, can't be extrapolated to dosing.

[Slide.]

So, in children, we need to understand the relationships between drug clearance and body measurements in order to provide the most appropriate dosing, so, the contribution of pharmacologic data to these off-patent drugs, where insufficient data exists, to determine the relationships between drug clearance and body measurements for younger and older children, use these data in concert with toxicity data to develop data-drive rules for dosing chemotherapy agents in younger children, and, in the absence of excessive toxicity, attempt to achieve the same exposures in younger children as those that are achieved in older children.

[Slide.]

In making the point about a need for

additional understanding of the pharmacologic behavior of these off-patent drugs in younger children, I show the age incidence profile for cancer in children. The highest incidence for cancer is in the youngest children, the infants, one-year-olds, two-year-olds.

Most of our pharmacologic data in phase I studies comes--the median age in those studies is often nine to ten or eleven years of age. So, for the group where there is the highest incidence, we actually have a least pharmacologic rationale for the dosing that we use.

[Slide.]

How can we correct this deficiency? We suggest that a way to do that is to build upon ongoing clinical trials.

[Slide.]

In terms of studying off-patent oncology drugs, there would be limited enthusiasm, I think, if FDA or some other body said, you have to do a phase III evaluation of this particular off-patent drug. Typically, the new phase III trials, to the extent possible, are looking at the newer treatments, new mechanisms of action, the topotecan being an example from rhabdomyosarcoma, a new

topo-1 inhibitor. Does this increase outcome for children with rhabdomyosarcoma.

However, ongoing trials use off-patent agents that have been inadequately characterized across the entire pediatric age range and children enrolled in this trials could participate in studies to evaluate the pharmacology of specific off-patent agents. You could use population PK methods, and Dr. Adamson will talk more about this in the next presentation, to limit the burden for individual study participants and, perhaps, make those studies more feasible in the youngest-age population.

[Slide.]

The advantages to this approach; one, to NIH is that it reduces costs. The study participants are already identified from--the ongoing clinical-trial data-collection procedures are already in place at the treating institutions and the central data-collection methods are already in place.

You are building on clinically important standard treatment regimens and so the data that you collect have inherent applicability.

[Slide.]

Now to turn to the question of what off-patent agents should we focus on and to the question that this committee is being asked to address in terms of prioritizing--this was not supposed to come up one-by-one. But I will just click through. This is on the handout that each of you have. This is half the list of the drugs, the potential off-patent drugs that this committee and NIH can consider.

[Slide.]

The other half of the list is shown here. So there is a substantial list. Of this list, there are probably only about a fourth of them that are actually used in any major way within current childhood cancer treatments.

[Slide.]

The two agents that I would draw your attention to for prioritization, at least initially and not to say that others wouldn't be prioritized subsequently, but the two agents are one, vincristine, which is widely used in the youngest-age population, used in Wilms' tumor, rhabdomyosarcoma, medulloblastoma, low-grade gliomas, acute lymphoblastomic leukemia, hepatoblastoma, so a very broadly used agent.

Then dactinomycin, or actinomycin D, used in Wilms' tumor, used in rhabdomyosarcoma, and one where, clearly, the youngest children are at increased risk of toxicity.

[Slide.]

So these two agents, first of all, they are important in treating the cancers in infants and young children. Second, as I illustrated, particularly for vincristine, there is substantial variability in dosing for infants and young children in current pediatric protocols. For two of the tumor types, rhabdomyosarcoma and ALL, gave evidence that the younger children are, in fact, at increased risk of treatment failure.

Then we have limited pharmacologic rationale on which to base our dosing decisions or to try to improve them.

[Slide.]

Those familiar with the literature will say, well, there are a number of papers about vincristine pharmacology in children and there are--Bill Crom and the group at St. Jude published in 1994 a paper of pharmacokinetics of vincristine in children and adolescents with ALL. Then several subsequent papers, the most recent being published

this year looking at--arguing that there is no pharmacologic rationale for dose reduction in adolescents based on vincristine pharmacology.

[Slide.]

When you look at the populations studied in these papers, and this shows the vincristine clearance versus age normalized to body-surface area and weight, from the report from St. Jude in 1994, very few of the youngest children in the study.

[Slide.]

Similarly, the report, the most recent report, by Frost and DeGraf's group, again, no infants and few young children in this study. So there is a gap in terms of our understanding of the pharmacology of this particular agent in the younger children.

[Slide.]

So, to close, and to allow Dr. Adamson to talk more about population PK and how that might be applied, infants and young children are at increased risk for some drug-related toxicities and for treatment failure for some types of cancer. There are limited data concerning the pharmacology of many off-patent drugs, especially in infants and

young children.

An increased understand of the pharmacology of these drugs in infants and young children could lead to guidelines for dose that reduce the variability in drug effect.

[Slide.]

Population PK studies incorporated into ongoing childhood cancer clinical trials may provide the data needed to develop more rationale dosing guidelines for off-patent drugs used in treating infants and young children. These dosing guidelines, new dosing guidelines, could lead to increased survival and diminished toxicity for infants and young children with cancer who are treated with off-patent drugs.

So I turn the podium over to Dr. Adamson.

DR. SANTANA: Thanks, Malcolm.

Population Pharmacokinetics in Childhood Cancer Drug Development

DR. ADAMSON: Steven and others, thank you for the invitation to speak a little bit about population pharmacokinetics and its potential role in childhood cancer drug development.

[Slide.]

Clinton Stewart, who is at the table, is

really one of the pediatric leaders in this field and I am sure won't hesitate to correct me but, more importantly, will be available, I think, to address some of these issues during the question period.

[Slide.]

So what is population pharmacokinetics? I think the most important take-home message about population pharmacokinetics is that you are doing the studies in a population that is representative of the target population. It is not a highly select group, but is a real-world population.

It recognizes variability as an important feature that should be identified and measured and, as importantly, it explains that variability by identifying demographic, physiologic, developmental or drug-related factors and is able to quantify the magnitude of the unexplained variability.

[Slide.]

Like any method, there are pros and cons. First, let's compare it to what we have done traditionally in pediatric oncology which is a traditional pharmacokinetics or two-stage method. In the traditional method, we do extensive sampling. That might mean anywhere from eight to

twelve samples in an individual child. These are usually small studies. As people know, in phase I, when we do these, we are talking 20 to 30 patients maximum.

The population is relatively homogeneous. In pediatric oncology, we rarely study drug disposition in young children. The median age, as Malcolm said, is approximately ten years. When one wants to do correlations between drug disposition and effect, pharmacokinetics, pharmacodynamics, one essentially can study one factor at a time with these methods. In general, these studies tend to use noncompartmental analyses.

In contract, population PK/PD sparse sampling is involved, usually two to three samples, sometimes as few as one. Certainly the more the better, but you don't need extensive sampling. You can perform a single large study or you can actually look across study at pooled data There is a very diverse patient population.

One can study several factors looking for PK/PD relationships at the same time and, in the end, you have a complex data analysis that results in what will hopefully be a useful model that can later be applied.

[Slide.]

The approach that is taken is as follows. One determines the pharmacokinetic, and I will use pharmacokinetic and, parenthetically, pharmacodynamic, because, more often than not, you attempt to address both in these models. You develop a structure for the population. You can then estimate the typical or mean population parameter as well as the interindividual variability.

Not only do you do it for the entire population, there are methods, then, to make estimates for any individual within that population. It allows one to estimate the residual as well as interoccasion variability and then it identifies measurable sources of variability in pharmacokinetic or pharmacodynamic factors and describes the relationship to these parameters.

The power of population modeling is it can do all these things in the intended patient population.

[Slide.]

In practice, what does this mean? Well, if one were to look at individualized clearance estimates from a population not only do you

determine the mean, you will also quantify the variability as well as understand the factors that lead to the wide variation that we often see in individual clearance estimates.

[Slide.]

There are certainly advantages to this approach. As I have said, this usually involves less than intensive samplings but it allows for variations in dosing regimens as well as sample collection. It can utilize unbalanced data, study a broader spectrum of patients. In addition, it has a potential to start screening for drug interactions and, as I said earlier, it can pool data from multiple sources.

[Slide.]

There are, however, disadvantages to the approach and limitations. In general, these are slower than standard phase I PK studies in establishing an initial dosage.

Now, as Malcolm has alluded to, that is not what we are really after here when we are looking at off-patent drugs. Random samples, if you leave it entirely up to random drawing of samples, may not always be adequate and you may have to apply some structure to obtaining samples.

As you have seen, primarily with vincristine, age effects are usually nonlinear. It is not that you start low and continue up throughout childhood and adolescence.

As vincristine has shown us, you might start with high clearance. It might lower during early childhood only to increase again during adolescence. The QA of data entry is more difficult. When you are doing larger studies, keeping control of this data is more difficult.

Now, sometimes one of the more informative points is the six or eight-hour point. But, again, if you leave this up to random drawing, in reality, that rarely happens. If a child is dosed sometime in mid-morning, the six or eight-hour time point is in the evening and most children are no longer in clinic at that point.

Ultimately, these methods, in fact, can't rescue bad data. You can't have collected all this data and say, ah-ha, let me do a population analysis. No; you have to do this prospectively if you want to have an interpretable outcome.

[Slide.]

Population modeling usually uses what are called mixed-effects models. This allows for

simultaneous estimation of parameters relating to fixed effects and random effects to observe data. Fixed effects are observed or measurable variables. These include the dose, the time of the dose, the weight of the patient, if you know, the GFR, things that you can actually quantify.

And then there are random effects which then it goes to explain the unexplained random variability both interindividual variability or the residual error.

[Slide.]

There are a number of software applications that are in use today. Probably NONMEM in industry is most commonly used. But there are a lot of applications that can undertake a population approach. What I would say is, first off, the interface to these applications makes the windows interface look attractive.

These are not for the light of heart. In fact, it takes specialized training actually just to operate these programs. Interfaces are improving, but this is really a highly specialized field where one needs a great deal of training and expertise and time to perform the analysis. The approaches that are used are often Bayesian in

nature.

[Slide.]

Steven asked me if I could pull examples from the literature. There are a number of examples where population approaches have been undertaken during pediatric phase II or phase III trials. One of the more recent ones is a study of zidovudine in preterm infants, studies undertaken by the Pediatric Aids Clinical Trial Group, PACTG.

[Slide.]

The study, which was led by Edmund Caparelli, looked at 37 HIV-exposed preterm infants. They stratified by gestational age. The regimen was based on data from term infants. It allows for initially a lower dose and increases, or a higher, dose over a very short study period of six weeks.

Pharmacokinetic evaluations took place during two windows, during the first week at Days 4 to 7, during later in the second week, Days 12 to 16. And then Days 24 to 30.

[Slide.]

If one looks at the data from the same group in term infants and looks at the clearance with IV dosing or the apparent clearance with oral

dosing, one sees that, over the first few days of life, there is a very steep increase in clearance over time.

The first thing I can tell us is that a population model can take advantage of the this. It is not restricted to studying one route of administration at a time. When Caparelli and colleagues looked at the preterm infants who were greater than 30 days in gestational age, the data was relatively well predicted by the data in term infants. There was an increase over time, a rapid increase over time, again, not surprisingly, the parent clearances were higher than true clearances.

However, when they looked at micro-premies, infants less than 30 weeks of gestational age, the term model no longer held and was no longer applied.

[Slide.]

One can basically extrapolate these types of findings to realize that you can't simply use a model that is derived in one age population and assume it is going to apply across the age populations. The power of population modeling is that one can look at this and develop a model that tries to look at factors that explain this

variation.

[Slide.]

It not only gives you population estimates for variables such as volume of distribution in clearance and bioavailability as well as absorption-rate constants. It can then look at factors and the relative magnitude of the impact of those factors. So renal function is measured by serum creatinine.

The post-natal age turns out to probably be the most important factor, how old these children are relative to birth, not just their gestational age, and so on and so forth, to explain not only the mean variation but what are some of the variables that go into the variability between patients of the same post-natal age.

You see here that there is an interaction with furosemide on clearance. One can't assume that is truly a drug interaction. Whether this is a surrogate for something else going on in the preterm infant could not be determined from the study. But, in the end, you have a model that examines several factors simultaneously and is able to quantify the magnitude of the impact that these factors have on the ultimate drug disposition.

[Slide.]

Let's move from the jump-start that our colleagues, looking at antiretrovirals, have to what we could potentially use in drugs. The example that I have taken is the one that Malcolm has spoken about, actinomycin D. Probably the reason there is very little data on actinomycin D is, when you look at the structure, it starts off as a friendly enough small molecule and then it just happens to tack on two cyclic peptides onto this making this an extremely difficult molecule to quantify and, up until this month, there was no meaningful published method to do this. Gareth Ville, in the U.K. has now published LCMS method that will quantify actinomycin D in plasma.

[Slide.]

So, if we were to undertake a population PK approach, where would be start? Well, there is some data with radiolabeled actinomycin D in animal models, rat, dog and monkey, but there is really no data yet, meaningful data, in humans looking at metabolism, protein binding or elimination.

As I said, there is extremely limited PK data. One of the advantages of presenting actinomycin D when you have ten minutes is that you

can summarize all the human PK data in a single slide. So this is what we know. And this is in three adult patients with melanoma. They received tritiated actinomycin D. This was published a little over 25 years ago, but it is a starting place, although it is an NS3 and these are adults.

[Slide.]

If one were to undertake a pop PK approach, well, obviously, the objectives would be to describe the pharmacokinetics of actinomycin D in pediatric patients and then to estimate the population pharmacokinetic parameters and evaluate covariates. Those covariates could include, but would not necessarily be limited to, body size and composition, the cancer type, polymorphisms and drug-metabolizing enzymes, concomitant drug administration as well as the effect of age and gender.

It may well turn out that the debate about do we dose by body weight or body-surface area will pale in comparison to other factors that we may define in such a model that would really define the more appropriate method for dosing these infants.

[Slide.]

This clearly would be an open-label study.

You would obtain not only pharmacokinetic but as well as additional safety and tolerability data. As Malcolm said, this drug is used in rhabdomyosarcoma and Wilms'. Depending on additional preliminary data, this would take at least 100 children in order to get a meaningful model out of and probably double that number if we were to extensively study infants throughout their first year of life.

Now, I can point out that actinomycin, except for, I believe, a single dose during Wilms' tumor therapy, is almost always administered with vincristine. One could consider a study design that would look at these drugs simultaneously.

[Slide.]

Now, sampling strategies, as I said; leaving it up entirely to random sampling has its limitations. One could randomize to two simple schedules or one could randomize to schedules that have windows that take time points on the first day and then time points at later time points. Again, it is hard to know what the optimal sampling strategy is until we have additional preliminary data to make educated assumptions about where we should sample.

One could develop a model using NONMEM, build covariates to examine the sources of variations and, ultimately, determine individual predictive parameter estimates that you could use to explore the relationship between pharmacokinetic metrics as well as clinical outcomes, toxicities as well response.

So I will stop there and I think turn it back over to Dr. Santana.

DR. SANTANA: Thank you, Peter. I have just been informed that other members at the table have joined us since we started. So could those individuals please introduce themselves for the record.

DR. ROBERTS: Good morning. I am Rosemary Roberts. I am the Deputy Director of the Office of Counterterrorism and Pediatric Drug Development. I am very happy to share this morning with you.

DR. SANTANA: Thanks, Rosemary. I think there was a gentleman over there. Yes?

DR. MATTISON: I am Don Mattison from NICHD.

DR. SANTANA: Thank you.

Questions to the Presenters

DR. SANTANA: We now have an opportunity

to ask questions of the presenters. I am going to start with one question. When we have looked at the time lines for the drugs, the five oncology pediatric drugs that have been granted exclusivity so far, what has been the time frame from the initial request to the actual point in which the exclusivity was granted and, related to that, how do oncology drugs compare to other drugs that are out there that are going through the same process, some antibiotics and anticonvulsants? Are we in the same frame or are we different? Are we worse? Are we better?

DR. HIRSCHFELD: I could try to address that. The drugs that so far have been granted exclusivity were products that had preexisting data. So the time frame was relatively rapid. It was typically within 18 months of issuing the written request and the time period was utilized to obtain the data from the cooperative groups to format it, analyze it, and prepare the report.

That did not require do novo studies for these particular products. Now, in other cases, we have requested de novo studies but, because of the breadth of activity and the richness of the data collected, particularly by the cooperative groups

but also by other institutions, and the pediatric oncology community in general, it has not been a barrier to obtain data from studies that were well conducted.

In many cases, though, we have requested prospective studies. Particularly anyone that does the arithmetic can readily see that approximately half of our written requests are for products which are not yet approved. So we are anticipating that those data would come in but they won't come until the actual NDA submission arrives.

So that would be the broadest distinction. Now, relative to other written requests, I am going to make a comment and then I will defer to Dr. Roberts sitting to my left, if she would want to add some other comments. But I would say that it is, again, highly variable in the other areas.

I have been attending the meetings of the Pediatric Implementation Team and the Exclusivity Board since they were first established, and we find some of the products have submissions that are fairly rapid and others which take several years.

As a general framework, when we issue a written request, we anticipate that it will take several years between the issuance of the written

request and the completion of the request, its studies and preparation of the report. "Several" is usually a number you can count on one hand.

DR. SANTANA: I think you made a very important distinction that I publicly want to acknowledge; that is, for these initial exclusivity determinations, we have a lot of data, like you suggested, like you confirmed, that have made it a very rapid process. But we should not go back and use those as benchmarks for the newer studies which I think probably will take a little bit longer.

So I think, publicly, we need to admit that we are in a good fertile ground right now but that may change as new requests come through and we have to do newer studies that may take longer. So the public perception should be that it will take longer, not shorter. We are not aiming for shorter because the benchmark is different.

Rosemary?

DR. ROBERTS: I would say that that is going to be true for the other areas, too. In products where we already had a lot of information and products that were being used and there was an anticipation by industry that they might seek some kind of--I mean, industry was aware that this whole

FDAMA idea was brewing. As a matter of fact, some of industry had already done their studies and were waiting for the President to sign the legislation.

There was nothing in the legislation that prohibited them from then submitting those studies if they were consistent with what we requested. So I think that, for new products where they have to start from the ground up in order to get the studies, then it is going to take longer. We have certainly seen, in some classes of agents where there are several different members of that class, that, in those sponsors who had already done, started some initial studies in the pediatric population, they had much less to do when they got their written request because they had some information, whereas others who had not studied the pediatric population at all ended up having to do all their studies after they got the written request. So they have lagged behind.

DR. SANTANA: Thanks. One more question, and then I will let others, so I can stop talking because of my voice. Anne, can you readdress with this the issue of the coordinating center? I didn't quite understand how that fits into this and how that is going to be run. Can you clarify that

for us?

DR. ZAJICEK: Absolutely. Don may want to pitch in, too. So, the NIH is going to fund studies, off-patent studies, based on the written requests. So the question was how to coordinate or how to monitor what is going on with these studies. So, for example, lorazepam, I guess, will, at some point, be contracted out. So someone needs to monitor how these studies are going, whether they are getting adequate enrollment, that kind of thing. Are they on time for some sort of deadline?

So the coordinating center is being funded to basically monitor the progress of the studies and to collect the data because the data will have to come back to the NIH and then be submitted to the FDA for a labeling update.

Does that answer your question?

DR. SANTANA: In part. So the coordinating center is at NIH?

DR. ZAJICEK: The coordinating center is not at the NIH.

DR. SANTANA: It is part of the study group.

DR. ZAJICEK: It is a contracted-out group.

DR. SANTANA: Contract?

DR. ZAJICEK: Yes; exactly. So the NIH will be monitoring the coordinating center but the coordinating center is not the NIH.

DR. SANTANA: Peter?

DR. ADAMSON: This is a question that actually may be best for you or for others at NICHD or the FDA. The off-patent mechanism is obviously a new mechanism for the pediatric community.

DR. ZAJICEK: Yes.

DR. ADAMSON: The contract mechanism, I should say, is relatively new for us. Can you tell us, when you develop, in conjunction with the FDA, a written request, what type of cost analysis is done? In other words, when you outline, sort of your ideal study, we want to gather all this type of information.

One analysis is done before the written request is issued to get an estimate of what would it actually cost. Certainly, for the on-patent, that is probably the first analysis that is done. We would all wish every oncology drug was a billion-dollar market but, as you get down to $100 million and $10 million, that is the analysis that drives are we going to respond to this.

Is there a similar process as far as truly costing out what is in the written request?

DR. ZAJICEK: I will send this over to Don.

DR. MATTISON: Yes; there is. We actually can't issue a request for proposals until we perform an internal NIH cost estimate for the studies. However, if I could sort of go beyond what may in your question, in the context of prioritization, we haven't been formally looking, up to this point, at cost estimates and population of children affected.

We are in the process of trying to develop a set of richer and more explicit data resources which allow us to look at questions like that for the prioritization process. But that is taking us some time to put in place. So the answer is yes, we do perform an internal NIH cost estimate. That is actually required before any RFP is published.

DR. ADAMSON: And as a follow up to that, can you--again without getting into specifics, because the contract mechanism is relatively foreign to people who write grants, when you get those proposals and the proposals go out with costs not really anywhere mentioned--and I understand, I

think, in the contract mechanism that is how it has to be.

The proposals you have received back, can you tell us, have the costs ranged by an order of magnitude? Have they been within a factor or 2 of what the internal estimates--at least, early on, how is the community doing, how is the NICHD doing, in estimating the costs?

DR. MATTISON: We have published four requests and have gotten back, and have had a chance to look at in detail, responses for three of those four. The areas where the cost estimates were the most variable dealt with funding for the coordinating center. It varied with the kind of resources and the cost of those resources that the coordinating centers thought they needed to provide.

There, I think, one of the estimates was as much as an order of magnitude greater than what we had anticipated in terms of internal costing. In the case of the drugs that we have gotten back and been able to analyze requests on, the disparity was much smaller.

DR. PRZEPIORKA: A question to CTEP and the FDA. Are there any guidance documents out on

using, or conducting population PK studies?

DR. HIRSCHFELD: There are some draft documents which are being circulated. They are available on the Internet. They outline the general principles but they don't go into the detail of stating which software or which kind of sampling methods, but address the issues of data quality and general principles.

DR. PRZEPIORKA: Thank you. Dr. Adamson did a great job introducing population pharmacokinetics and cited an example where the PK study, the pop PK study, showed a true difference by age. Has there been any example of validation of data that can be obtained from a population PK study?

DR. ADAMSON: I am not certain I know the answer to that. I mean, I do know, and Steven can tell me, there are a relatively significant fraction of labels that have been based on population PK submissions and not standard PK submissions, not just in oncology. I am thinking across the board.

So, as far as our pop PK methods an accepted and validated approach, I think the answer is yes to that but I may be misunderstanding the

question. Maybe Clinton can better address that than I.

DR. STEWART: What I was thinking of was this guidance in industry and the exposure-response relationships that is included in our reading. It definitely goes into some of that information in that in terms of the population PK software that is recommended for use there and the sort of guidelines that were recommended for use.

Specifically, what are you asking?

DR. PRZEPIORKA: Has there been any study performed that will in which a pop PK study was done on a drug with a narrow therapeutic index, such as an oncology drug, which then took those parameters and applied them clinically and showed that, yes, what we have learned was safe and effective.

DR. STEWART: No; not to my knowledge.

DR. HIRSCHFELD: If I may, I could just clarify. I don't think any of us at the table have specific numbers but my impression is it is actually relatively few applications come in with pop PK data. There haven't been very many. It is a growth area. The FDA has been looking at it for some time. We have actually been sent samples of

the software to test--some of the products that you listed on your slide, I have had the opportunity to get lost in.

There is, I think, an emerging technology. While pop PK has been evolved starting--and Clinton may correct me if I am mistaken--but I think the initial nest of pop PK was as UCSF in the 1980s. From there, it has been slow to gain general acceptance, particularly in the pharmaceutical industry, because of its high technical demands and the difficulties in doing the analyses that require a fair amount of expertise.

So there are relatively few centers that, I think, have a track record, although many people have been interested in the problem.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: In the interest of organization and time, Mr. Chairman, what I would like to do is just very rapidly, in a minute or two, go over a number of questions to the various people and then maybe they could put their comments or add their comments when they have a chance to speak. Otherwise, this can go back and forth and I don't want to monopolize everything.

I obviously congratulate Steve. I always

enjoy listening to your history. I wonder if somebody would tell me, either you or Dr. Cooper, when its his turn to talk, whether exclusivity really applies only to pediatrics or is it a general term that has other applications.

Does the foundation have any problem in getting access to the drug considering that it is non-patent, and how do yo get the drugs? I am interesting in knowing why you are prioritizing even oncology drugs. I am also interested in knowing why no one has ever mentioned steroids today? We don't have an idea on how to use steroids in oncology and in general in pediatrics. Should we cap the dose for big people?

This is something we have struggled with. We would also mention obesity, a big problem in the United States. We are talking about the infants. What about the obese child? I would like somebody, perhaps Anne or Steve, to handle that.

Of all your 169 drugs, some of the ones that were chosen, the three that you are choosing, other than maybe the antibiotic, has very little use--maybe Ativan has a little bit of use. Once you finish your contract, will the data be acceptable to the FDA because they have certain

criteria? And how are we going to move from your data to the FDA?

That also holds for all of us who do clinical studies, Malcolm. We have been doing clinical studies for decades. Yet, is it in the format that the FDA will accept? Better still, why won't the FDA accept our format because we know our format is the right way to study pediatric oncology?

For Peter, and for Malcolm, I mean, actinomycin D, I think, came in from Sidney Farber in 1956. Vincristine was 1960. If we are starting off, and I agree, we have to study those drugs, but if we start off with drugs that are over 50 years old, it is going to take us another 100 years to get the drugs that we are currently handling. So we need some kind of practical time line on how to handle this great challenge. Otherwise, the group that takes over from us five years or ten years from now will be discussing the same topic.

We do have one study that I can think of in acute lymphocytic leukemia, and Peter, you may want to comment, which is our 1991 COG study where, in actual fact, we increased dose to toxicity. That is sort of our practical clinical way to

trying to handle maximum dose.

Last but not least, if a counterterror person would like to tell us in about three sentences what they do for general information, I would appreciate it.

I yield, Mr. Chairman.

DR. SANTANA: That is a lot, Dr. Finklestein. I will allow Steve and Peter and Malcolm, I think were the three primary people that were mentioned in these questions, to go ahead and do their best.

DR. HIRSCHFELD: I am going to defer most of it to Rosemary Roberts. But I just want to touch on a couple of things and then I will let Rosemary certainly handle the counterterrorism part and maybe touch on some of the other more general questions.

So exclusivity is a regulatory and legal term which refers to a process where someone is given marketing rights where they are the only person that can legally sell that product for that intended use. The pediatric exclusivity is not something in isolation. There has to be exclusivity granted by a number of complex mechanisms which we don't need to go into now, but

there has to be preexisting exclusivity.

What pediatric exclusivity can do is that it can extend the preexisting exclusivity. As far as looking at the steroid question, Malcolm and I discussed this at some length. Here is where we ran into sort of a regulatory corner and that is that our charge was to identify drugs that are listed or catalogued as oncology products.

Even though some of the steroids have oncology indications, within the framework of the FDA, they also have multiple other uses and fell out of the purview of what we were charged with examining.

As far as formats go, I think the FDA is quite flexible with the format of data that comes in. As good data are good data, and inadequate data are inadequate data, I don't think any two NDA submissions or any two study reports submissions in response to written requests have been identical.

We have general guidelines but format, I don't think, has been a barrier. I will yield now to Dr. Roberts.

DR. ROBERTS: Let me just take up on the last question here. One of the things that the--actually, Steve has made us aware of, is that

in the United States, there is a very good system for studying children who have cancer. As a matter of fact, most children are in trials in this country. That is the standard of care.

He made it known to us that we don't want to disrupt this process as we try to figure out how to implement FDAMA and make it so that the oncology-drug industry could, indeed, benefit from the incentive and not disrupt the cooperative group process that exists in this country and that is the mainstay of care.

So we do recognize that the studies that you do are good-quality studies. In putting together a package for the on-patent products there is an entirely separate guidance for study of oncology drugs. That template is totally different. For the new products, one of the things that was very clear to us from the cancer advocacy groups as well as from the NCI and from the cooperative groups was that you all wanted to get drugs much earlier.

You didn't want to have them go through the adult pipeline, be approved and then you could access them for children. So, hopefully, with this oncology process that we put into place, you are

actually able to study drugs much earlier. Literally, a drug that is studied in a phase I type that you all would do, if it is so toxic that it really cannot even go further into phase II studies, that, alone, can qualify a sponsor of a new drug to get exclusivity once they bring in the studies for the adult.

If it is not so toxic at that point, and you can go into phase II, and you complete those studies and get some information as to what tumors these particular products might be advantageous for, then, at phase II, they can get the exclusivity.

Now, indeed, they have to submit the NDA and get it approved so they have something to hook that exclusivity onto. But there is no other group of drugs at the agency that has this innovative way to apply the FDAMA incentive, now that has been renewed through BPCA.

We told sponsors that you are to go through the cooperative groups. We don't want you independently setting up studies and competing with the cooperative groups. So we recognize that you do good-quality studies.

For products that are on patent, the

sponsor has to submit the data. So we are encouraging them to go through you, get that data and submit it. For the off-patent products, as far as how does that information get to the FDA, how does it get into a label, well, it is a much more laborious process.

One of the other functions of this coordinating center that the NIH has contracted out to is to put together the data in an application that is reviewable by the agency. So one of the criteria that these particular sponsors or research organizations has to show or demonstrate was they had some experience in putting together an FDA supplement because, essentially, unless that data comes in in a format that is reviewable, it is worthless to the agency.

So that is a key part of what they are to do. Once that data comes into the agency, that data is put up on a docket so it is immediately available to the public and the public can comment on it. The data is referred to the appropriate review division and, in this case, it is going to be the Oncology Division, to review the data, to look at those studies to see if, indeed, the studies obtained information on how to

appropriately use the product in the pediatric population, look at any comments that have come in, and then, in addition to taking an action, propose labeling.

So the division will actually propose labeling. Then they will have to negotiate that labeling with the innovator, if the innovator still exists in the market, or with the generic that has the greatest market share. So that is how the labeling will be done.

DR. SANTANA: Malcolm, did you want to comment?

DR. SMITH: I will say a couple of things and let Peter address it as well. The question about studying drugs that are from the '50s and '60s, that is the challenge here, is that the BPCA has these provisions for studying off-patent drugs and NIH has funds to study these off-patent drugs in children.

So our challenge is can we make--are there things that we don't know about these off-patent drugs that, if we knew, would benefit children with cancer. So that is the territory. These drugs that are from the '50s, '60s, '70s. I think the challenge to all of us is to identify what the most

important gaps in our information are that are addressed by additional research and then to try to see if we can't fill those gaps.

The two we suggested were for vincristine and dactinomycin. We are certainly open to other suggestions about important gaps from this list of off-patent drugs and ways that we could use them better.

Also, there are other types of drugs that are used for children as part of the supportive care for children with cancer and so steroids have multiple uses and other drugs for pain control and so on. So those are other areas that wouldn't necessarily be specific to oncology but which this committee might also want to consider if there are gaps in the off-patent drugs that are used for supportive care as well.

The final point I would make is that this, again, is about drugs that are from the '60s and '70s. We wouldn't want this to block studying--doing phase III trials, studying new drugs, new mechanisms of action, that are more scientifically and potentially more clinically relevant. So I think that is something that we would be very cautious about in terms of saying we

want to do something with the off-patent BPCA funds in oncology.

We should make sure that, when we do that, we are not blocking something that would actually be more contributory to improving outcome.

I think this proposal that you could kind of put together from my presentation and Peter's presentation wouldn't block the study of any new drugs because this is building into existing trials and the way we are using the drugs now in collecting more information.

I think a potential benefit of it is that it then provides a model or a paradigm for how we look at some of the new drugs as well because when we do our phase I studies of the new drug, the new inhibitor of this or that molecular target, again, we are looking in nine and ten-year-olds in getting PK the that population. Then when we move to phase II or phase III, we may be able to build in to those studies the kind of paradigm that we are talking about today with the population PK studies to actually learn from the start more appropriate ways for using the drugs across the entire age spectrum.

DR. SANTANA: Peter, were you going to say

something?

DR. ADAMSON: Yes, I was. I first wanted to jump back, if I can figure out how to do this, to Donna's question.

[Slide.]

This is a list that I happen to have on my laptop of drugs where there is population pharmacokinetics in the current label. This is probably a few months old now, so I think Steven is right, it is not a large number. But it does exist and this information does appear in the label. I think the agency, and I don't want to speak for them, a well-done population PK study is an acceptable form of gathering clinical pharmacologic data.

I want to echo what Malcolm said and just expand on a couple of issues because I think Jerry has really hit the point on the head here. We don't want to come back five years from now and realize that, you know, we are now only 35 years behind and not 45 years behind.

The paradigm that we have to develop drugs from phase I to phase II, phase III, will always leave us with large gaps in knowledge unless we change what we are doing. By that, I mean, we have

to extend pharmacology studies beyond phase I. We are never going to capture meaningful pharmacologic data in infants and young children on phase I. We are rarely going to capture it on phase II.

If we don't start doing it in phase III, twenty years from now, we are going to have the same thing and, up on the board, it is going to be irinotecan. How are we dosing irinotecan. It will be the same story all over again. So, with the new drugs, we have to clearly start changing how we are gathering this information.

Population PK is one way to do that. The problem, and the greatest challenge, is not the technological challenges anymore. We have the computing knowledge. We have the analytical methods to do it. The challenge is that physicians, nurses, staff that comprise a very productive network, are stretched to the limit on their capabilities with the funds they have.

The grant, as critical as it is to supporting these trials, when industry looks at--when we tell industry how we are doing this phase III trial that is gathering data for five years and what we are paying an institution, I think it is what, $1500 or $2000 or something like

that, for the whole study, they look at us like, well, there is no way the data is useful because you probably don't have it.

The reality is we have it. It is not up to industry standards in most cases. What falls by the wayside is, as we look at important correlative studies, and I would say pharmacology is an important correlative study, if we don't specifically fund those correlative studies, it is not going to get done in the way we need it.

A pop PK without accurate dosing time and sampling time and specimen handling is worthless. So you need qualified people. You need dedicated people who are going to explain studies to families, who are going to enroll children and who are going to make sure that all the data, even though it is limited data, if you are talking three time points, that data is "Q-A"ed and you can use it in the model because, if you don't, you are not going to have a model that is interpretable.

So I think the discussion that we are having for the off-patent, you can clearly put prospectively in the new drugs that we are studying. We have to figure out mechanisms to appropriately fund these studies. Certainly, BPCA

for off-patent for off-patent can help us go a long way and relative to other drugs, because we have an infrastructure in place, is probably going to be a bargain.

For new drugs, we have yet to figure out a mechanism for how are we going to extend these important studies beyond phase I into phase II and phase III.

I probably didn't address everything you asked, Jerry, but, hopefully, hit the high points.

DR. SANTANA: I think Dr. Reynolds had a question or a comment.

DR. REYNOLDS: First I would like to agree with Jerry. I think that, although I understand, Steve, your charge here is primarily antineoplastics, I think that agents that are used as antineoplastics in the pediatric population, as Jerry mentioned, in the steroids, I would add to that the retinoids, should be included in this as off-patent drugs that need to be studied and we need to learn more about.

I really specifically had a question for Anne. I was intrigued by the concept that you mentioned that, if there was the need for a pediatric formulation on an off-patent drug that,

somehow, that could be studied through this mechanism. The cost of doing that would be substantially greater than simply doing a PK analysis. I wonder is this program prepared to do that costs? Are they prepared to do the preclinical IND-directed toxicology that is necessary?

What is available here because there are some very substantial needs in that area?

DR. ZAJICEK: I think I would safely say this is probably the least explored area of the BPCA. I started life as a pharmacist so formulation problem is a big problem. Just to complicate things, if you are going to compare a formulation that already exists to a new formulation, then the FDA has requirements for exposure, Cmax, that kind of thing.

So I can't say we have explored that at any length, but it certainly is an issue. Don, do you want to add anything?

DR. MATTISON: It is clear if you look at challenges in treating pediatric patients that formulation represents one of the greatest challenges, probably one of the most significant causes of medication errors. I am telling you

folks things that you already know. The issue of making drugs appropriately usable by pediatric patients, I think, needs to be addressed.

We do have the resources, I think, to be able to do it in selected drugs. If folks from your home district that are serving in Congress are educated to the fact that this is a critical issue, then additional resources could be directed to it.

Kind of in response to the question that Dr. Adamson mentioned, we have to prioritize testing for drugs that are currently available in formulations that can be used. But that is kind of a backwards and not the world's best approach to drug development. So we would like very much, with the help of our various advisory groups, to identify a small group of drugs for which formulation changes will make a big difference and we will do our damndest to work with the FDA to get those formulations produced and marketed.

DR. REYNOLDS: One intermediate to this that you might want to consider is that there are probably some generally used extemporaneous formulations and, perhaps, formal study of those could be done as a less costly endeavor than developing a totally new formulation and would

allow for some product labeling that would give guidance on using some of these drugs that simply doesn't exist.

DR. ZAJICEK: It is a great idea. If, during this meeting, you want to mention specifics about what compounds you think we should consider?

DR. REYNOLDS: One that comes to my mind is--

DR. SANTANA: We will have time for that during the discussion of the questions.

DR. ZAJICEK: Good.

DR. SANTANA: I think we would do that. I think Rosemary or somebody had a comment over here, or Richard. I'm sorry.

DR. PAZDUR: The one point I would like to emphasize is let's not be guilty of age discrimination against drugs. Jerry. I love accusing Jerry of age discrimination of drugs. The issue here, just because a drug is old does not mean that it is not important to study. Remember, and I feel almost I shouldn't have to mention this in this group is that many of these drugs are being used in curative regimens. Therefore, I think it is especially important here that some of these older drugs be studied.

Remember, if we are really effective in the incentive program, there really shouldn't be this lag that exists for generations and generations of medical oncologists because the newer drugs should be studied under the incentive program and really the life span of this off-patent thing in oncology should be somewhat limited if we--and I think this is important--if we are truly successful in the incentive program because that lag should be a finite lag here.

DR. SANTANA: Steven, you had a comment, too?

DR. HIRSCHFELD: I was just going to say that if the legislation pending before Congress, which would give us also a mandate under particular circumstances, comes into passing, then that could also address the problem. This committee has formally identified areas where a pediatric rule type program could have an impact and benefit children with cancer.

DR. SANTANA: Dr. Boyett, last question to the presenters.

DR. BOYETT: Actually, I want to agree with Peter that I think it is appropriate to study PK in phase III settings where the drugs are

actually given and we don't know much from the phase I. I also think that applying nonlinear mixed-effects modeling to PK data is appropriate. However, I would like to point out it is not a free lunch. I got the idea from listening to you that we could solve just about every problem, that the modeling you talked about and the software you threw up there could handle any situation. And that is clearly not the case.

The issue you have is not with the software. What you need is to get statistical sciences involved whose areas of research are nonlinear mixed-effects modeling. Those are the people who write some of the better softwares that are up there and they understand it. So it is not a matter of using the tool. It is plugging it in.

I would point out that, in linear modeling, there is a "seat of the pants" rule that you need about ten patients per factor. Nonlinear mixed-effects modeling is much more complicated. I am not sure there is such a "seat of the pants" rule yet. But the study that you quoted, the zidovudine study, in my mind, is grossly underpowered.

I shuddered when you put up the number, we

need about 100, and then maybe you said 200, in, I forget, the rhabdomyosarcoma setting. Maybe you said actinomycin D. Statistical scientists need to look very seriously at it and help you decide what sample size you really need given all the factors that you are going to try to adjust for because, you know, it is worthless to do an underpowered study.

It may be more dangerous to the children to do an underpowered study and misinterpret it than it is to leave things the way they are. I also would disagree with the interpretation of the plot that you showed from the ZDV study for concluding that the term IV was a good fit for the preterm greater than 30-week CA. I don't think that fits it at all, and the PO doesn't look very helpful as well.

So I think we have to be very careful in interpreting the results from these studies. You can publish any study in some journal someplace.

DR. SANTANA: One last comment. Ms. Hoffman?

MS. HOFFMAN: I just wondered about a mechanism, I guess, if you do the population studies phase III and you are looking at possibly

increasing dosage in infants, then, counterbalanced to that, is looking long-term at toxicity results. So, if this coordinating center is going to be subcontracted out, what is the mechanism to protect that information? Companies come and go. Is there going to be some way to make sure that we have a very committed subcontract that is going to be watching these kids long-term to be able to see what the potential impact on increased dose in infants would be? They could be committed for ten years, 15 years, whatever. If they are not, then what is the mechanism to take that information back into the NCI or who is going to have access following?

DR. MATTISON: It is clear that, just like formulation is an issue, long-term safety is an issue in infants and pediatric populations. The current, the Best Pharmaceuticals for Children Act, expires in 2007. So we have got whatever funds we can sort eke out of Congress through that period of time.

Let me say, though, that, in collaboration with the FDA and with folks in the industry, it is clear that infant, childhood and adolescent toxicity and its developmental consequences are an

issue that we have to give substantial attention to. Just like we are looking at the development of methods for studying the off-patent drugs in terms of characterizing appropriate dosing and regimens, and so on, it seems to me that we could use these long-term safety studies as a model that might be useful in some of the new drugs as well.

Our hope is that we will be funded as long as is necessary to clear up the backlog. But that it not our decision. That is a Presidential decision.

DR. SANTANA: Do I dare ask the unspeakable which is currently what amount of money do we have to do this?

DR. MATTISON: Up until the beginning of this fiscal year, we had zero dollars for this. This is an act that was signed in January of 2002. We are currently authorized to spend $25 million in this fiscal year. The Secretary has said that $50 million would be available in Fiscal Year 2005.

My sense is that we can easily spend that money in pediatric clinical trials. The real question is getting advice to make sure that these clinical-trials investments yield substantial benefits for children.

DR. SANTANA: Thank you. Malcolm, one last comment. Dr. Blumer, did you have a comment? Since you haven't said anything before, I will let you go ahead.

DR. BLUMER: Thank you. I have one concern about the approach and it sort embodies several of the comments that were made. I think that Malcolm laid out a very important paradigm in talking about, number one, you have drugs that have been used for years and years and years. You have patient groups that have not responded at the level that they are expected to respond in terms of clinical efficacy.

And you also have, to some extent, unexpected adverse events occurring in the context of the these protocols. We have heard that. And then we heard presentations about pharmacokinetics. As a pharmacologist, that is always very exciting. But where we let you down is that we don't bring them together.

The worry I have, and it extends from two of the comments that I heard before, is that if we endorse this approach of integrating pharmacokinetic trials, we run the risk of simply collecting pharmacokinetic data. I am not sure

that we have targeted what is that purpose, what does it mean.

So I would just wonder and ask if we couldn't at least say okay, the reason for collecting this is either to determine why patients don't respond or why they have toxicity and use that as a target and then consider whether population PK is really the way to do that.

Coming from an historical perspective, our approach to pharmacokinetics was really individualization of drug therapy and therapeutic drug monitoring. That sort of went by the wayside. One of the inherent goals in population PK is to try and find a dose that, on average, works for everybody in a certain group.

But when you are dealing, as has been pointed out, with drugs with very narrow therapeutic indices, with life-threatening toxicities, maybe that is not the approach that we want to take. In fact, maybe what we wanted to know is what concentration or area under the curve or some pharmacokinetic characteristic is associated with some of these efficacy or toxicity paradigms and then should we, instead of a population PK approach, incorporate

individualization-of-therapy approaches.

I am just concerned I haven't heard that. I don't know what the right answer is, necessarily, but there hasn't been that balance here.

DR. SMITH: I was looking to Peter to answer that.

DR. SANTANA: We will have time to discuss that when we come back after the break. We will have plenty of time when we come back to answer the questions to carry the discussion further.

DR. SMITH: I think the one point to Ruth's comment that I would say is that we have been envisioning--it is this type of approach goes forward that it would be in the context of ongoing clinical trials where there are follow-up mechanisms for at least substantial periods of time so that at least some of the effects that would occur later after treatment could be recognized, so it wouldn't be dependent on necessarily the duration of a contract.

DR. SANTANA: Thank you. We are going to go ahead and take a fifteen-minute break, because we are running okay on time, and reconvene at 10:30. Please be back on time so we can get started. Thank you.

[Break.]

Open Public Hearing

DR. SANTANA: We now have an opportunity for public comments. If there is anybody in the audience that wishes to address the committee, please step forward.

If there is anybody that wishes to address to committee publicly, we do have a letter from a member of the committee, Dr. Reaman, who is unable to be with us today. He did send a letter to the FDA that he wanted publicly read and written into the record. So I will do that now.

It is dated October 3, 2003 and it addressed to Dr. Steven Hirschfeld.

DR. REAMAN: (Read by Dr. Santana) "As I am unable to attend the meeting on October 9, I would like to take this opportunity to provide input on the initiative to evaluate off-patent oncology drugs in the pediatric population supported by the FDA, the NCI and the NICHD in response to the Best Pharmaceuticals for Children Act.

"I applaud this effort to address a very serious gap in knowledge impacting the public-health needs of young children with cancer.

In light of information related to excessive therapy-associated toxicities, the variability of dosing recommendations which are oftentimes empiric or dependent on anecdotal experience, and the age-dependent discrepancies in outcome for common pediatric cancers for the potential contribution of additional age-specific and population-based pharmacology studies within the context of ongoing clinical trials of the Children's Oncology Group, to the health and safety of young children with cancer is enormous.

"Compromised outcome related to non-evidence-based dosage reductions and unanticipated life-threatening toxicities of conventional chemotherapy in young children, because of absent or incomplete pharmacology studies, are public-health hazards which could be avoided by such investigations of widely used agents in young children, specifically vincristine and dactinomycin. Other agents which should be considered for investigation include cisplatin, cyclophosphamide, doxorubicin and daunorubicin.

"Evaluating relationships between drug metabolism/clearance, body measurement and assessing systemic exposure and correlations with

toxicity and treatment outcome would be best accomplished by performing such studies within the context of controlled clinical trials. Utilizing the existing national infrastructure for pediatric cancer clinical trials would enhance efficiency and assure evidence-based rational dosing strategies for off-patent drugs used off-label in children with cancer.

"The positive impact of such studies in advancing the likelihood of cure and improving the quality of life of young children with cancer cannot be overestimated.

"Sincerely, Gregory H. Reaman, M.D., Professor of Pediatrics, The George Washington University School of Medicine, Chair, Children's Oncology Group."

So entered into the record.

Committee Discussion of Questions to the Subcommittee

DR. SANTANA: Let's go ahead and try to discuss the questions that have been put forth before us. I am not going to read the introductory bolded section because it defines what we are here to do this morning.

So I will go directly into the first

question; the BPCA of 2003 provides a mechanism to study to study off-patent medications in pediatric populations. Question No. 1; what factors should be considered in selecting off-patent drugs for study in children with cancer; these may include use in only a pediatric population, use in particular diseases, use in particular age groups or toxicity questions of particular concern?

So these are some examples that we have before us. Obviously, we could consider other examples or other criteria that should be used. So this question is now open for discussion.

I think one issue that I would like to add as one of the criteria is, since many of our children are now cured, I think one of the criteria for drug selection is if there is a particular drug that has a unique end-organ toxicity that would be relevant to the growth and development of the child. So the example that always comes to mind, because I use it a lot, is cisplatinum.

Cisplatinum is an effective drug. We really don't know a lot about its pharmacokinetics but certainly we know a lot about its toxicity. If we could use the end-organ toxicity as one of the criteria in this selection process, that would be

something that I would consider.

Donna?

DR. PRZEPIORKA: I was struck during the discussion earlier by two things. One is how incredibly important it is to dose drugs appropriately in the pediatric age group since their life span is huge. The other thing I was struck by was how little money we have to do this.

This is not too dissimilar to things that happen in the GNP lab where you have a very small budget and everybody is breathing down your neck. I have to put on my quality-management hat and essentially say, under those circumstances, how we choose what we look for depends on what is high cost and high risk.

So I would actually wonder if COG has a database that can tell us what are the drugs used most frequently in the pediatric population in the last five years and what are the drugs that have the most toxicity and in which age groups and hope that they would be able to share that information with the other institute that does the Herculean job of prioritizing which drugs to get funded.

DR. SANTANA: Malcolm?

DR. SMITH: In response to that, I think

we can provide estimates of the number of children treated with different drugs because they are standard treatments and we know the age distribution of children with different types of cancer and how many approximately are diagnosed each year. So it actually is a number that we could provide to NICHD and to FDA.

In terms of the risk--and one confounding factor is that the risk can be lower, the risk can be high, depending on how large the dose is and the patient population. If you look at carboplatin as one example used in the Good Risk Neuroblastoma Trial that COG is doing now, it is a lower dose. The risk is relatively small.

Then you look at that same drug when it is used in the high-risk population, in the transplant setting, and the dose is three or four times as much, then, obviously the risk is much higher. So it is a complicating thing to assess the risk because the risk is so modulated by the anticipated outcome of the patient and the risks that are perceived as appropriate to try to achieve cure.

DR. SANTANA: Peter?

DR. ADAMSON: This is going to be more of a tangential response to that and it comes back to

some of the earlier questions. I think, as we not only think about factors that should lead to a study of a particular drug, we have to look beyond what pharmacokinetics might be able to tell us.

What I mean by that is I don't think pharmacokinetics is necessarily going to always provide the answer. In fact, there are some examples where it clearly hasn't provided the answer. So the studies that we take forward have to look at factors in addition to what knowledge is already out there on PK. But that can't be the only factor that drives this.

There is a great example of a drug that we use in oncology that we probably know more about than any other drug but it hasn't helped us with dosing and that is 6MP. 6-mercaptopurine, we know its plasma pharmacokinetics in detail. We know polymorphisms and drug-metabolizing enzymes. We know active metabolites in the form of thioguanine nucleotides and we have studied this now for over twenty years.

Despite knowing all that, none of those turn out to be a good surrogate for toxicity and probably for response. The best surrogate we have for dosing that drug remains looking at the CBC.

So pharmacokinetics aren't always going to be able to provide the answers even when we do them well.

They are a surrogate. They are an important surrogate for most drugs. Getting to what Jeff said earlier for therapeutic drug monitoring, we are so far behind the antibiotic literature on this, we will never catch up. We don't know what effective exposures are. We don't know what toxic exposures are for virtually all drugs, except, perhaps, for methotrexate and toxicity.

So we don't know that in the adult population. We certainly don't know it in the pediatric population. It is a step towards, hopefully, more rational dosing and, hopefully, potentially towards individualized dosing, but we have to look at other factors. There are likely to be other factors other than plasma pharmacokinetics that might be better predictive of efficacy or toxicity be it polymorphisms and receptors that have yet to be described on down the line.

So, as we look at one of the factors that should go into that as far as what do we know, yes, we want to look at what do we know about the plasma pharmacokinetics but that, in and of itself, may be

insufficient knowledge and there are still going to be a lot of areas we don't know. I would second--as far as what we do know today, is we have a good description of what the short- and long-term toxicities are. We have a much harder time trying to refine what has the impact on efficacy been. Those should weigh heavily into the decision process as far as prioritization.

DR. HIRSCHFELD: If I may comment. I just want to build on what Dr. Adamson stated in that, even though there are limits to what is known, the approach, I think, is so critical. One of the historical facts is that there have been no approved drugs for pediatric oncology for a long period of time. Between the 1970s and the year 2003, there was only one drug that was approved.

Yet, without having new drugs approved through the systematic application of principles of evidenced-based medicine, in the context of an infrastructure, the survival and the outcome data have continued to improve.

So, just for the public record, I don't want--that there is the lack of knowledge means that the approach is not validated.

DR. SANTANA: Yes?

DR. BLUMER: Just to expand on that, I think that really is a key issue because I think, as you prioritize these off-patent drugs, in addition to the frequency of use and the safety profile that the drugs enjoy, two of the things that I mentioned before I do think have to help guide the process, and that is, given the favorable outcomes that so many pediatric-oncology patients now have, where you see drugs or drug regimens that are not working as well as expected, I think that should raise a red flag and move that drug to the head of the list, or somewhere in the upper echelon.

The same is true for unexpected toxicity. When you have an effective drug that, in a certain age group or a certain regimen, is leading to unexpected end-organ dysfunction, that, too, should trigger this.

I think the other thing that we haven't mentioned before, and it is interesting listening to people who focus on oncology talk about this all the time because it is glossed over, but as sort of a more basic pharmacologist, all of your regimens are multi-drug regimens. You are trying to close your eyes and pick the effects of that one drug out

of these regimens.

I think that the issues of drug-drug interactions have to come to the forefront here and be considered in part of what you are doing because you are, in fact, creating a very complex scenario. You are not just using 6MP but you are using 6MP and methotrexate or something else. Those things do count. It is not that you just want to focus on it.

Certainly, you may know that actinomycin D, for example, may, in and of itself, be hepatotoxic. But is there something about it in the context of these other--with vincristine, for example, that makes it more so in a certain age group because of the way that they handle vincristine, not the way they handle the actinomycin D.

I just think those things have to be considered as well.

DR. SANTANA: Alice?

MS. ETTINGER: In our historic phase I and in our phase I studies, we are always looking at pretreated patients who have other end-organ toxicities, albeit their numbers may look okay at the moment. But I think we have to consider that

that is how we have always looked at those things as well.

DR. SANTANA: Peter?

DR. ADAMSON: I think that the challenge of prioritizing is probably not as daunting as we think because, in reality, what we recognize as pediatric oncologists, we are really using a small family of drugs and just changing the order of the acronym.

So, in solid tumors, you are--really, for the vast majority of tumors, you can count on one hand the drugs and, for the others, you could expand to the second hand. With leukemia, again, you can count on ten fingers the drugs that are currently used and that has virtually complete overlap of the solid-tumor drugs.

So we are prioritizing probably--realistically talking about a list as short as ten drugs and, for the newer agents and uncommon drugs, you probably could expand it to fifteen. So it is not as daunting a task but it is certainly an important task.

DR. SANTANA: Jerry?

DR. FINKLESTEIN: I think Dr. Blumer obviously also hit the nail on the head because we

do everything in combination, as Peter mentioned. So I would ask the basic scientists and the statisticians, if we are going to do these scientific studies, should we not, at the outset, design them as combination-drug studies and figure out how we are going to analyze the interrelations because, doing them as single-agent studies is not in keeping with the way we manage children with cancer today.

I don't know enough about the statistical analysis nor the science to say more other than the interactions would be very important anyway from a clinical point of view.

DR. SANTANA: Malcolm?

DR. SMITH: I would just echo that. I think, to study these drugs outside of the context of useful combinations, the way they are actually used in the clinic, wouldn't be very contributory. So the challenge, then, is the appropriate study design that can include that data or else isolate the specific combinations.

DR. SANTANA: Any other comments? Let me try to summarize, then, what I have been hearing. Dr. Boyett?

DR. BOYETT: One of the ideas that you

might consider is that, obviously, you take leukemia, where you have a lot of drugs, and suppose there is a drug that you want to study that is used in a particular regimen. You might take the opportunity to consider--and suppose it is used in combination with another drug, just one other drug for simplicity--you might take the opportunity--in COG, you are going to register a couple thousand patients a year. You might take the opportunity on Day 1 to randomize patients to get the drug of interest with nothing else. The other alternative would be get the combination of that drug and the other drug which they would receive during whatever time of the regimen.

That gives you the opportunity to look at the PK data over one day or two days, whatever, a very short period of time. It wouldn't impact the outcome of the patients. These are active drugs. Also, then, you get the opportunity to pair that information within a patient when they actually get this same combination or a little different combination later, it gives you an opportunity to study drug-drug interaction and a potential impact of chronic treatment from the beginning to that particular point in time.

I think if we thought about those issues, we may be able, in some settings, to ferret it out. Now, in leukemia, there would be some differences because if you were studying 6MP and methotrexate, traditionally given in maintenance where there are no blasts. On Day 1, of course, there are blasts around and that might change some of issues, but you could learn some things, then, about outcome, as you mentioned, Jeffrey.

If you look at the impact of these drugs in the very beginning in circulating blasts or even if you could be so lucky as to get a bone-marrow a day or so after you gave these drugs, you would be able to see the impact of the efficacy as well.

DR. SANTANA: Pat?

DR. REYNOLDS: I think the flip side of the combination issue is that, in some of our combinations, we know what the contribution of individual drugs is because randomized studies have pointed towards that. In others, we don't. These combinations were empirically derived and the individual contribution of any particular drug to it may or may be defined.

I would suggest, then, the prioritization, that you might want to take into account those

drugs in which phase III studies have demonstrated conclusively that the individual drug contributes to outcome and use that as factoring the priority, if there are opportunities for potentially improving that outcome by understanding better how that drug is delivered.

DR. SANTANA: Let me see if I can try to summarizes what I hear the committee saying in relation to this question. I think what I am hearing is that there is no one unique factor that one can use to prioritize any one drug versus another and that it is a matrix of factors that will help us decide which drugs get studied up front.

The matrix that I heard goes from issues of addressing toxicity in drugs that may have a narrow therapeutic index but toxicity not only in the context of acute toxicity, like one would predict with actinomycin in terms of VOD but also issues of long-term toxicity for the majority of patients that are being cured and, related to that issue of toxicity, to also look at drugs that may have specific end-organ toxicities that may be relevant to patients that ultimately will be cured.

So I think that, in a nutshell,

synthesizes the toxicity issue in terms of how one could use it to prioritize.

The second issue that I heard was there has to be some sense of the frequency of use if you are going to have an impact on populations. So I think the comment that was made earlier of getting some sense of which drugs are out there, how are they frequently being used and in the context of what combinations, to then provide some idea of the appropriate templates of study designs in which one could then address these questions, whether they be in combination studies, in single agents early on, periods of time where they can be studied uniquely.

So I kind of heard that comment, that the frequency of use and how they currently fit into the clinical trials that are out there would be an important issue to try to help us prioritize.

We didn't really talk about cost because I suspect most of these drugs--well, the drugs we are talking about are off-patent but I think we do need to know what impact of cost it would have in terms of adding more costs to the current studies that we think could serve as templates to do these analyses or ask these questions on.

I heard some comments about special

populations. There was a lot of discussion about younger children and how unique they may be and so, if there are particular drugs that are used commonly in young populations, that we would use that as one of the tools to select the drugs we want to prioritize.

There was another special population that was not mentioned that I do want to mention as my own contribution which is the bone-marrow-transplant population. There are a lot of patients in pediatrics that are undergoing bone-marrow transplantation with very high doses of therapies. I think that will be true for the next five or six years until the phase III randomized studies are out.

So, bone-marrow-transplant-population patients particularly solid tumors, are a unique population in which, if there were drugs in that population that one wanted to prioritize, would be relevant because they are a unique population in terms of their prior history and what is going to happen to them after that.

I heard some comments about when drugs are prioritized for these off-patent studies, that we have to pay some attention to combination usage and

what opportunities we may or may not have to then, ultimately, get the answers that we want.

I heard some comments about drug-to-drug interactions and bringing that into the forefold of studies that we want to do so that if we are addressing issues of safety and toxicity, we will have the right answer at the end.

And then I heard some comments about how we really should be selecting drugs from the off-patent list in which there is a track record that they are efficacious. So, ultimately, if we get the answer that we want, it will improve the safety and will improve the efficacy and we won't be compromising anything for our patients.

So that was kind of my summary of the comments that I heard as people commented on. Other people can contribute to additional--yes?

DR. STEWART: Could you, perhaps, elaborate a little bit more on your selection, in terms of the special population. You indicated the bone-marrow-transplant population is a special population. Were you thinking of that from the perspective of those patients getting higher dosages, having prior therapy, organ dysfunction.

DR. SANTANA: All of the above. That

population of patients, to me, represents patients that historically have had very aggressive therapy early on in their treatment. They are now going to undergo another modality that, in most protocols, involves much higher doses of therapy, primarily the majority of them alkylator based.

They have unique toxicities to liver, to kidney, to CNS that we haven't really investigated very well. Some of those patients are being cured with that modality. I think that is a special population in which some of these drugs are being used in the context of clinical research and we really don't know very well how to use them.

Pat?

DR. REYNOLDS: Vic, I would just echo that. I think you raised a very good point, that the use of these drugs in the myeloblative setting is quite different than the use in the nonmyeloblative setting. By bone marrow transplant, I assume you mean self support.

DR. SANTANA: Yes; that is what I meant.

DR. REYNOLDS: Whether it is autologous, peripheral bloods or bone marrow or allogeneic. I think that is clearly a different population and probably needs to be considered differently from

the general population. The pharmacokinetics will be immensely different.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: Victor, I would like to hear from the pharmacologists. Although I mentioned obesity in terms of steroids, I would like to hear about whether they consider obesity as a challenge in terms of all our other oncologic drugs and whether that should be considered in the mix because we are well aware in pediatrics, obesity is a problem.

DR. STEWART: Victor?

DR. SANTANA: Yes?

DR. STEWART: I would certainly like to echo that that is especially a problem considering, I guess, some of the more recent reports that the adolescent population of the United States is starting to become more obese. Yeah; I would definitely think that is a population we would consider.

DR. SANTANA: Peter?

DR. ADAMSON: I would echo that. I think it has some very practical implications because, on a day-to-day basis, we actually don't know how to dose the obese child. Do you do ideal body weight?

Do you do actual body weight? It is a variable we are probably not tracking particularly well.

I think, as this discussion could probably go on for a while, we are going to uncover more and more of what we don't know. As far as drug interactions are concerned, I think the drug interactions of the cytotoxics--between cytotoxics--are the tip of the iceberg because what we don't ever consider are the antiemetics that we administer routinely with these cytotoxics.

That is probably having as likely an impact on their disposition as any of the other cytotoxics. We use corticosteroids almost with impunity not thinking about what impact it would have on efficacy. What struck me recently is aprepitant, a new antiemetic. In the label, it is specifically talking about CYP 3A4, CYP 3A4, 5, and drug interactions and data on specific drug interactions which is remarkable data for the label but what it really highlights is all the antiemetics--I mean, people, I think, are going to avoid that in certain situations but we shouldn't take comfort that using other antiemetics are, in fact, safer because we simply don't know the interactions that are taking place.

So, understanding drug interactions has to be a major component of any study we do and it is not just limited to other cytotoxics, something that we don't have any control over right now as far as gathering data. It is probably as much so the supportive-care medications that are administered concomitantly with the cytotoxics.

DR. SANTANA: Any other comments on this particular question? Okay, let's go on and move to the second question. Are there any comments, and I am sure there will be, on the proposed selection as discussed by the National Cancer Institute on the drugs actinomycin D and vincristine as priority choices and others to follow?

DR. HIRSCHFELD: May I just clarify the question here. The limitations are essentially resource limitations. So what this committee will do is make some recommendations or endorse some recommendations. Those will be carried forward into a master list for all of pediatrics.

What we anticipate is that, within that master list of prioritization, there will be some slots available for oncology-related drugs. But we don't have any assurance if and how many of the recommendations would go into the master list. So

we are going to operate on the assumption that we will have at least one, and potentially two, in there and the limitation, as Dr. Mattison pointed out, is the current-year funding.

But it doesn't mean that, in some subsequent framework, other drugs could also be part of the general mechanism.

DR. SANTANA: Steve, and the people from NIH maybe can help me, what is envisioned in the process if there are twenty drugs, let's propose, that ultimately make it to the list and there are only enough funds to study three? What happens to the other seventeen? Do they come up again for review in a year when more money comes up? Do we have to reprioritize those? Is there an allocation system of how we go down the line? Can you clarify that for us?

DR. MATTISON: The way that we have currently been operating, once a drug gets on the list, it is then available to us for exploring in a variety of ways including preclinical evaluations, clinical trials and so on.

We have tried to keep the list small so that we can operate in a reasonable way with the FDA in terms of looking at once a drug is listed,

what needs to be done in terms of filling data gaps to make that drug more appropriately useful in pediatric populations.

During that discussion phase, we sometimes discover information that puts a drug on a somewhat slower track for clinical trials. We may not be able to agree on what the endpoints for the trials should be. We may not agree on how the studies ought to be conducted. And so we need to bring in other folks to look at the drugs and help us think through the strategy for studying them.

If we are not able to get to a drug in a given year, we will continue to look at that drug until the data suggest that there is no further need for information about that drug. So, yeah; they will continue to be on a waiting list. We may get additional funds across the course of a year that we hadn't anticipated at the beginning of the year which would allow us to pop a drug into a study.

We may be able to negotiate with an institute like the Cancer Institute in terms of some sort of collaborative activity to study the drug. So all of the above, I guess, is the answer to that question.

DR. SANTANA: Malcolm, can you clarify for me a process issue? How do you envision--for the purpose of discussion, we say vincristine is the drug that we are going to push. How do you envision that in the current clinical research protocol scenario how you will get to the point of making sure that that drug gets studied the way we are recommending that it be studied?

There are going to be some process issues, some maybe regulatory issues. Have you thought that through, how that mechanism is going to help us get to where we want and what barriers we could be finding down the road?

DR. SMITH: I think the process issue goes, and probably Anne could address that, should address that, as well--the process would be an agreement that this drug should be prioritized, then the FDA's written request, NIH, NICHD preparing the RFP and then a response to the RFP. So there would be those steps along the way.

I think, in advising NICHD, we would want to make sure that the RFP that was being prepared was consistent with the priorities of the experts in childhood cancer in terms of the clinical trials that they are doing through the COG and would

really make the greatest contribution for our understanding of the drug selected.

But the process does go through the RFP and then, presumably, the Children's Oncology Group responding to that with a proposal. So there are multiple steps along the way to make sure we get it right.

DR. SANTANA: Can I clarify that? You are not excluding other groups like, for example if the Brain Tumor Consortium wanted to participate in one of these RFAs or two or three major institutions wanted to respond. How do you envision that?

DR. SMITH: I think it depends on the scope of the RFP. If we want to do the population PK study, if that really is the intent, and particularly if we are interested in young children receiving, or infants receiving, vincristine, it has got to be nationwide. Really, the only feasible way to do a study like that, if that is the study that needs to be done, is to build up on the nationwide clinical-trials mechanism, so I think the extent to which any RFP might be directed or not would really depend on the focus of the RFP.

DR. SANTANA: Jerry?

DR. FINKLESTEIN: While I recognize the

interest in actinomycin D and vincristine and, I guess, as a user for over forty years, it would be kind of fun to know a little bit more about them. On the other hand, actinomycin D has a very limited use in pediatric oncology today.

I think we understand a fair amount of vincristine in terms of the immediate toxicity. One of the drugs that was mentioned both by Greg, by our Chair and by other people, which I consider quite frightening as a user, is cisplatinum. If this question is asking us to prioritize or at least to give a view and what we would think should be really number one on the list, with due respect, Malcolm, I really think cisplatinum, which is used in just about in every child who has a brain tumor--the second most common cancer in pediatrics are brain tumors--is used in our patients who have bone tumors and a whole host of other diseases.

Considering we know very little about cisplatinum, I wonder if this committee and, perhaps, other individuals would comment on whether the prioritization should be looked at in terms of cisplatinum as our number-one choice.

DR. ADAMSON: I am going to have first a response to Jerry. I think cisplatin is certainly

on the list. It would be important to actually look at the patient numbers, I think, because I don't know where it would rank as far as utilization relative to vincristine and actinomycin. I think that is a number we can get, we can look at, but I don't know that.

As far as doing pharmacokinetic studies of cisplatin, I think we need to carefully look at the literature to see what the likelihood that that is going to potentially sort out the issue because there is free platinum pharmacokinetics which are very brief duration and whether we are going to actually be able to sort out, even if we do it, based on that, I am not certain.

But there may well be, and we have to look--there may be other questions we ought to be asking that can say what is the risk, what are the risk factors, for toxicities, what should we be looking at. It may be that plasma pharmacokinetics there has much less of a role, potential role, than others.

But I agree, as far as when it comes to dosing, what makes pediatric oncologists more nervous, cisplatin is probably at the top of the list when it comes to the concerns that you have as

far as long-term toxicity.

I did actually have a question, if I can remember it now, on the process. So the paradigm that we currently have in place with the coordinating center and proposals, I am assuming that that is not the only paradigm and, for cancer drugs, in fact, may not be the paradigm you would utilize. In other words, a separate coordinating center, if you are going to be doing studies on the backbone of an ongoing phase III trial, would not seem to be sort of a good use of resources. Am I correct in that assumption?

DR. ZAJICEK: I think that is correct. Again, we haven't talked about the nuts and bolts but it makes intuitive sense that if the NCI has their own coordinating center, that we wouldn't want to be reinventing the wheel here by having them report to another coordinating center.

DR. MATTISON: We have had a series of discussions with several of the institutes that have fairly extensive networks of clinical-trial studies and we are working out the mechanism by which we preclude duplication of effort and look at ways of developing efficiency in implementing and conducting these trials.

DR. ADAMSON: My other question I should know the answer to but when you are up to capacity, how many studies do you envision launching every year? Is it two to three? Is it five to ten?

DR. MATTISON: We are looking at probably something in the range of six to eight a year, maybe more initially. The issue is going to be staffing and the ability to continue to provide oversight to these tracking adverse events, dealing with the reporting requirements. So something like that, given the appropriate level of resources is what we would hope to achieve.

DR. ADAMSON: The appropriation, though, is then set aside--when you say you are going to do the study, that year's appropriation is set aside to complete that study or--

DR. MATTISON: We can use either mechanism. We can fund for actual costs or we can fund into the future through the completion of the study. Obviously, the first mechanism allows us to get more studies going and then potentially provides some leverage for our colleagues in Congress or for you to use.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: Actually, I have two

comments. First off, cisplatin, I definitely would move above actinomycin D, perhaps certainly not above vincristine. But it is an important drug in medulloblastoma and it is use is limited due to toxicity and maybe it is not because of the PK and maybe there are problems with studying it, but I haven't heard discussions about those technical difficulties with the other drugs. Maybe they exist. Maybe they don't exist. But I certainly think it should be considered.

The second has to do with the process. Obviously, if you are studying vincristine, COG--if you want to extrapolate to the population of children in the U.S. is the U.S., COG is the appropriate research tool to target. But then when you also say that you are going to make sure that--you are going to try not to duplicate effort with the coordinating centers, et cetera, you are really sole-sourcing and limiting, I think, your opportunity to be successful in your endeavors.

Maybe that is what you want to accomplish, but I think that you have to look at the efficiency of existing systems and things and how they might serve your needs for the future.

DR. MATTISON: Agreed.

DR. STEWART: I would just like to make a comment in regards to selection of the drugs. It is very difficult when you have a list of drugs to make a decision. Cisplatin, to speak to that in terms of it is a very important drug, a very important compound, for pediatric oncology. Obviously, it is used very extensively.

However, I can speak very directly to the pharmacokinetics of it and the methodological considerations. It is a very difficult compound to measure. There are a number of studies that are published with cisplatin in pediatrics. I am not sure that that is exactly the compound we need to be going after.

What I think you need to think about is what Jeff said a little bit earlier this morning and that is, when you want to think about what compound to study, you think about compounds that have--when you start losing efficacy or a compound starts demonstrating toxicity. That is exactly what happened with dactinomycin. It started demonstrating toxicity in a very young population.

That was sort of the stimulus for us to have the meeting that we had in May that Malcolm was talking about a little bit earlier and what

causes us to want to look into why is it that these kids are getting toxic. That sort of was the prompting that led us down that path and what caused us to want to propose to look at dactinomycin and subsequently vincristine.

So I would strongly urge the panel to consider studying those two compounds. They are two very important compounds in pediatric oncology and I think these are two compounds we need to be looking at.

DR. SANTANA: From a personal point of view, as an investigator, I would support those two drugs if somehow we could get both of them funded because I think these--like somebody mentioned earlier, the concern with both of these drugs, particularly in the younger population, they may have some interactive effects. It may not be the actinomycin. It may be the vincristine that they can't handle very well.

So this is an ideal pair of drugs to study if one is trying, for example, to address this issue of toxicity in the young age group. But I think separating them and competing one and the other is one comes first and the other one comes second. If there are not enough funds, then we may

not be able to get the real answer to at least one of the problems which is the issue of toxicity in the very young.

I think somebody over there was shaking their head.

DR. ADAMSON: This may be a situation where we really have to think out of the box because I think we can potentially do a single study with vincristine/actinomycin as a single study because actinomycin is always administered with vincristine.

As a single study--I mean, we should be able to figure out from the same specimens what is going on. Vincristine is used beyond that and so we have to it take into account, and it gives us an opportunity to look for an interaction because there is clearly a population that gets vincristine that does not get actinomycin.

But, in this case, we may be arguing over something we shouldn't be arguing because I think, if you are going to study one, you can almost, at the same time, study them both. So the discussion, perhaps, should be can we prioritize the combination vincristine/actino and cisplatin. I mean, I don't know if I would try to separate them

out simply because we don't admit--except for one dose on one protocol, actinomycin--I think that is right--is always given with vincristine.

DR. HIRSCHFELD: Although it wasn't specifically mentioned in your excellent summary of factors for prioritizing and for consideration, being practical and for the success of the program, I think feasibility is also a consideration. I would just want to, without reflecting any biases, state that if assays exist for one drug over another, or if conditions exist to favor the study of one drug over another, in order to establish the credibility of the program, that could be a consideration.

DR. SANTANA: I agree. Malcolm?

DR. SMITH: I was going to make the same point that Peter did. If, in fact, the pharmacologists think it would be feasible to, since they are always used together, to do both of those together, that would be a great use of resources in terms of kind of minimizing the burden all around.

One question that I would have, and I take the points about cisplatin, we haven't discussed the anthracyclines, particularly in the younger

population. If there is any sentiment that we should look at the effect--at something about the anthracyclines, particularly in the youngest population.

DR. SANTANA: Any other comments on that issue of anthracyclines? Peter?

DR. ADAMSON: I think the other population gets back to Jerry. Anthracyclines in the obese, I think, are a real big question of what to do. There is some data from the adult literature as far as changes in drug disposition in the obese, but it is really an unstudied area.

DR. SANTANA: Dr. Mattison?

DR. MATTISON: Could I ask for comments on another issue that came up earlier which is how should supportive care be prioritized against the active agents? Should we focus to any extent on some of the other therapeutic modalities that are used in this population? Should it be given higher or lower priority? Can you help us think through a little bit about how to deal with that issue?

DR. SANTANA: I think one of the problems in dealing with that, I have to admit that, for example, when it comes to supportive care issues of antiemetics, the practice is not as structured and

is not as adhered to as what we do with the oncology drugs.

So, even in my own institution, there are 50 different ways in which you can give steroids and ondansetron and Ativan and everybody has their own little recipe. So the problem with, for example, the antiemetic supportive-care issue in how to use this mechanism to do this is that I think we lack the rigor currently, in the current protocol structure that we have, to be able to approach that successfully early on in this process.

So, when I look at supportive-care issues in contrast to oncology drugs, I think we are a little bit ahead in oncology drugs of having a successful outcome with this initiative than we will be with, for example, antiemetics. That is just my general comment because the structure is just not as tight there.

If what we are looking is to advance the public-health needs, the structure already exists for the oncology drugs and we may be able to have some success after a few years. I think the others should be done but, in terms of priority, I don't think, right now, we have all that structure in

place to be able to do it effectively.

That is my own bias. Peter?

DR. ADAMSON: I think if you were to tell us realistically, keep your list to three, there wouldn't be an antiemetic on that list. I think, having said that, we should look, in the broader pediatric population where antiemetics are used for post-operative nausea and vomiting and, if we can impact on the priority of what antiemetics are going to be studied in the broader pediatric population, then I think it would make sense to say, well, which of these are being utilized more heavily in the oncology population.

But I would be interested if anyone thinks, if we had a list of n equals 3, that we would have an antiemetic as one of those three.

DR. SANTANA: Alice?

MS. ETTINGER: But if we were going to take a combination of vincristine and actinomycin or a platinum, we could build in a structured antiemetic regimen at that same time. I mean, just as combining it as well.

DR. SANTANA: My comment, Alice, was primarily because I heard Malcolm very astutely say that there already exists a clinical trial--there

already are clinical trials in which some of these questions can be "plugged in" without having to reinvent the wheel. So I was just responding from a strategy point of view that the advantage of some of these oncology drugs that we are discussing is that you could plug in the questions relatively easy.

I still will have to be convinced but the structure already exists that we may be able to do that more efficiently rather than having to design another new trial that will address these questions separately. I think the more drugs you add, the more complicated it gets.

But I do like the comment that Peter made. I think the group at the NIH obviously, in terms of supportive-care drugs, supportive-care drugs are used across different diseases in pediatrics. It is not only unique to oncology.

So if you guys get a sense that there is an interest from anesthesiologists in studying antiemetic in radiation therapists or use antiemetics, then one of those drugs potentially may make it to the top ten where there may be some funds to study. Then, certainly, we would find a way to plug it into our systems because I think it

would be appropriate.

MS. HOFFMAN: Adding onto that, Congress just mandated money through the M.D. Care Act for Muscular Dystrophy. Their main drug is prednisone. So it might be through NINDS or NIMS because they are actually just meeting about clinical trials and they don't have official clinical trials going. But it would be different. It is a male population. It is three and up. But it might be a good way to get prednisone with that as well.

DR. MATTISON: Yes. One of our colleagues in NICHD is responsible for that area and we have already begun a discussion with them about the potential of looking in that area.

DR. SANTANA: Dr. Roberts?

DR. ROBERTS: I would like to go back to Peter's comment about studying actinomycin and vincristine together because they are used together. From a regulatory perspective, we would really have to think outside the box to figure out how to do this process.

That doesn't mean it can't be done. But the written request is issued to the application holders of the approved products. That would be if there is any innovator left for vincristine and to

any generic houses that have vincristine for a vincristine written request. For actinomycin, it would be for the application holders of those approved products.

So you could--and I am thinking off the top of my head because we haven't had this, but it is a significant problem when you do a combination. If we, in conjunction with our colleagues at NCI-NICHD, and the Division of Oncology, could come up with a set of studies that would address how to label both of these products when used in combination, then you would issue the same written request to each of the sponsors.

But there would have to be ways to get information to ultimately label those individual products because that is what the goal is. So, throwing into the mix in the vincristine/actinomycin studies to study them in combination and now trying to study some antiemetics at the same time, there is just no way. It just logistically and from a regulatory point of view couldn't be done.

DR. ADAMSON: Just to clarify what I am thinking as far as antiemetics, I think you have to include antiemetics as a covariate. It is not

something that I would say you could study in the context of a single study. As far as the combination, this is a question for you, then. The written request, when it goes to industry, my guess is there won't be a stampede to respond for these two drugs.

Can the written request, when it then comes to the NIH, be different?

DR. ROBERTS: No. The written request that is issued to industry has to be identical to what we send to the NIH. Now, the reason is that industry, the industry that owns that product and owns the label, is going to look at that written request and they are going to look at the studies that are involved and say, as you have predicted--probably, they will say they aren't going to do them.

But at least they have received an outline of what those studies are. Once those studies are done under a contract and come back, if those studies don't look at all like what we asked industry to do, that is a real problem for us because we are going to ask them to put that information in the label and now they may have studies that they never even had a chance to say

they didn't want to do them.

So it is going to be problematic for us to get them to put that information into their label.

DR. SANTANA: I think Richard has a comment related to that.

DR. PAZDUR: Couldn't you have the two studies independently going out to each of the sponsors. When they come back to the NIH, could you then combine them together?

DR. ROBERTS: Well, what I was proposing--

DR. PAZDUR: If they are identical studies but you putting together.

DR. ROBERTS: If they are being studied together then I would assume that the group of studies would be identical. So the vincristine manufacturers would get X written request and the actinomycin manufacturers would get the same X written request. So, in essence, when they all turn it down, we will be sending a single written request to NIH.

DR. HIRSCHFELD: Just a point of information. I am positive there is only one source for actinomycin D and I believe there is only one source for vincristine, just as a point of information.

DR. SANTANA: NIH, I think, had their hands up over there, generically.

DR. MATTISON: Yeah; we have generic hands.

DR. SANTANA: Since we are talking off-patent; right?

DR. MATTISON: We have had a series of discussions with our colleagues at the FDA about this and we are still working through some of the interpretation of the law. But, Rosemary, it was my understanding that, after the written request was refused, we essentially become the sponsor and we can negotiate with you the studies that ultimately get performed. That was the agreement that we had at the retreat, at least.

DR. ROBERTS: I would say that this is not the forum for us to get into that. I think that we have had some difference--basically, the law indicates that the contract is to contain the elements of the written request. So I don't see how there can be negotiations of any significance since that is what the law says. I think that is what we discussed at the retreat.

DR. SANTANA: Malcolm, are you going to respond to that? If not, Jim has been having his

hand up.

DR. SMITH: I was going to respond to that. I don't know what the law is but I think it is, perhaps, a moot point because, if there are two requests, if there is one request that says, we want you to study dactinomycin. Here is what we want you to do. That's fine. And there is another request, we want you to study vincristine and here is what we want you to do. That's fine.

That request goes out. The fact is, the way it is functionally implemented, at the end user, can be one protocol that is going to study both of those, the same patients, one informed consent and so on. So, the request can still be as two. When the study actually done, the same patients are participating. The same samples are being used to test both.

The response back can give you the dactinomycin data. The data that you get can give you the vincristine data. I think we can work it out. The pragmatic issue that I was worried about earlier was whether you could do it, the same patients could be used for both drugs, if that can be addressed, and I think there is some way that we can find a way to make the RFP process work.

DR. ROBERTS: I think the key factor is the fact that FDA and NIH and the appropriate NCI and the people that are vested in these studies are going to work on that written request together to make sure that it contains appropriate information to label these products for us in this group of patients.

So, hopefully, Don, we have worked out that before we issue that written request to industry because, again, we can't change that written request because industry needs to look at it and to know what they are denying doing.

DR. SANTANA: Dr. Boyett? You withdraw your question? Any further comments. Let me see if I can summarize. Yes; I'm sorry.

DR. REYNOLDS: Just to address what Malcolm said, I think, of the practical natures that needs to be considered in this, since you are targeting, studying very young children, is the amount of blood you can obtain which IRBs will limit. It may not be possible if the blood requirements for particular assays are such to do both in the same patient. So that has got to factor into this as well.

DR. SANTANA: Yes; I think that fits into

the comment that Steve made about feasibility. I think he was talking about feasibility of assays but I think feasibility is much broader in terms of making sure that you have the right patients, the right amount of blood, all these other feasibility issues hopefully have to be considered in the prioritization of the drugs because it may be that if you are using an assay that requires a lot more sample, that it may not be feasible to do it in a 2-week-old or a 1-month-old.

So I think those issues, also, to me, encompass feasibility in terms of prioritization. Yes?

DR. FINKLESTEIN: I have a question for the FDA. Since most of the drugs we use in pediatrics are in combination, does that mean, and this has undoubtedly been discussed at other meetings but, perhaps, we could use a refresher or I can. Does that mean that labeling the drugs as drugs that are used in combination is something that you really can't do?

DR. SANTANA: And, kind of as a corollary to that because I have been thinking about this, so when a brand-new entity, a brand-new drug, is approved, I am thinking of when I used to

participate in the adult committee, anthracycline X is approved for the treatment of metastatic Y in the context of this regimen. Isn't that how it is approved? The drugs are not approved uniquely just sitting by themselves. They are usually approved in the context of a number of trials that have other drugs in them.

So why is this different?

DR. HIRSCHFELD: Rick might want to comment further but we have addressed this, as Jerry pointed out before, and it is the labeling reflects what the data support. If the data support its use in combination, and we have some very concrete examples of recent approvals, if I could mention a product, oxaliplatin was approved in combination with 5-fluorouridine and not as a single agent.

In fact, in that specific case, the single-agent data would not have supported an approved indication. So this is rather common.

Rick, did you want to add?

DR. PAZDUR: I think that is a good example. So, if the drug is studied in a combination, the label for the product that is being investigated will be labeled with that drug

that is was being studied. Now, that doesn't necessarily mean, for example, the 5-FU label was updated to reflect its use with oxaliplatin because, in order for that to happen, you must isolate that you definitely need that 5-FU and that brings us into study design here if there was a single-agent 5-FU arm, et cetera.

DR. SANTANA: Yes; I think in the context we are talking about is a strategy to study both of these drugs and then get information for a change for both labels in the context of using them in combination. Good.

Any other comments on Question 2 before I try to summarize? So I sense that there was some support from the committee in terms of prioritization of vincristine and actinomycin D because of some of the issues that were discussed before by Malcolm and others. But, in the context, if they could be prioritized equally, if the opportunity exists to do that in a reasonable study design, so that we could get two bangs for the same buck.

I got a sense that the committee was supportive of these drugs but far more supportive if there was a strategy in which we could study

them together and that probably could move us up in the last of drugs that could be studied.

Then I heard some discussion about cisplatinum. I didn't put my two-cents worth, but I guess it will come up with Question 2. We might as well open Question 3 which is, what are other drugs that could be studied and what would be the rationale.

I think we have talked about some variables that could be considered in prioritization and we really--at least I didn't come prepared to discuss cisplatinum in detail but I think there were some things about cisplatin that were mentioned that are relevant in terms of the populations at risk in which the drug is going to be used. End-organ toxicity is a major issue with cisplatinum.

Feasibility is a question of cisplatinum in terms of the assays and how pharmacokinetics predicts toxicity and/or efficacy. So, to me, cisplatinum, in response to Question 3, would be a drug that I think needs to go through the same rigorous process that you guys have already done for actinomycin vincristine and also, hopefully, come to the conclusion that it is a drug that

should be moved up in the priority list.

Peter?

DR. ADAMSON: Actually, I was going to ask Steve to clarify. When I read Question 3, I thought--my interpretation was are you talking about agents other than anti-cancer agents that should be studied in the population.

DR. SANTANA: Oh; was that the gist of that question?

DR. ADAMSON: Because I sort of thought we would agree that cisplatin would be high on the list if it were feasible. That was my sense.

DR. SANTANA: Let's clarify. Question 3 relates to this list of other off-patent drugs; right, oncology off-patent drugs?

DR. HIRSCHFELD: Right. Specifically, the oncology.

DR. SANTANA: Yes?

DR. ZAJICEK: We have an interest in that answer, too, though. If there are any other classes of drugs that you think should be studied, we would be very interested in discussing those.

DR. SANTANA: We can discuss it as a corollary to that question if people want to advise. Dr. Reynolds?

DR. REYNOLDS: I would add 13-cis-retinoic acid which is used as standard-of-care therapy for neuroblastoma and is not off-patent to that list as a nononcologic but it is used as an antineoplastic.

DR. SANTANA: I would support that but I want to make sure that we use the same model for all drugs, that we go through the exercise of asking the question, the population numbers, the usage numbers, the populations in which it is at risk, the issue of toxicity. I want to make sure of that.

I would agree with you, it is an important drug to study and, because of my own bias for that drug, I want it studied. But I want to make sure that we apply the same rigor to whatever drugs we advise that should be on the priority list.

So could you respond to that in retinoic acid?

DR. REYNOLDS: Yes. I mean issues of population, it is really restricted in pediatric oncology to high-risk neuroblastoma. So we are talking within the U.S,, what, approximately 200 patients a year would be getting the drug.

As far as toxicity, there hasn't been a whole lot of toxicities that one can point to with

this that would be life-threatening. Within our phase III study, we did have some uremic syndrome that may have been attributed to the drug in small numbers of patients.

But I think that it is an understudied drug in terms of the variability in terms of the metabolism and, in particular, in terms of the bioavailability. It is a suboptimal formulation especially for young children. So there is a great potential with this drug for there being underdosing and subtherapeutic dosing going on in a substantial number of patients.

Because, in a phase III randomized study, as a single agent, it is shown to contribute significantly to event-free survival in high-risk neuroblastoma. Then there are opportunities, if one could avoid underdosing those patients, to improve outcome.

DR. SANTANA: Pat, how do you respond to one of the concepts that was circulated earlier that one of the criteria for making it to the list would be a drug in which we have some evidence that we may be losing efficacy because of increased toxicity. How would you respond to that in the context of the retinoids?

DR. REYNOLDS: In the context, at least of 13-cis-retinoic acid, I would say that I don't know that we have evidence that toxicity is causing loss of efficacy. I think that we have some evidence accumulating that lack of appropriate dosing might be potentially leading to subtherapeutic levels. But I would have to say that we don't have the evidence on toxicity.

I would say that there may be that evidence for transretinoic acid in the setting of APL. But I would defer to Peter and Malcolm to comment on whether they think that is the case.

DR. SANTANA: Dr. Stewart.

DR. STEWART: I guess maybe I should ask this question of Dr. Hirschfeld, but in some part, Peter and Malcolm have come with their homework prepared in terms of numbers and what not. I am just wondering, is it possible that there be a committee or a subcommittee or some more formal mechanism by which this homework could be done to select other drugs, I guess is what I am trying to ask, so that these numbers and the detail that you are trying to get could be obtained.

DR. SANTANA: I guess what you are asking is now that we have advised the FDA and,

indirectly, the NIH in this forum of what criteria we would want for you guys to weigh on in the prioritization, who, now, does the homework to go out there and do this for this list of drugs. Is that what you are asking?

DR. HIRSCHFELD: It is done collaboratively between the FDA and, within the FDA, the Oncology Drug Division and the Division of Pediatric Drug Development and with other colleagues including the clinical pharmacologists and pharm-tox colleagues.

It is done in collaboration with colleagues in the NICHD and in the other relevant NIH institutes which, in this case, is the NCI. So the short answer is we don't have to appoint a new working group. We have a process in place but, because of limited time in our own sense, based on the meeting that you helped organize, we got a starting point.

So we took the discussion from the meeting earlier this year as a basis to proceed and we are taking now the discussion that would occur today as further basis to proceed. In that process, we are not shy about asking for help or outside consultation. We both formally and informally

request consultation in this area.

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

DR. PAZDUR: That is the point that I would like to make is just follow up from Steve. We could easily, instead of having a subcommittee, have external consultants before we make a decision. Whenever we make a decision, if we don't take it to ODAC, et cetera, generally we have always asked ODAC members or other consultants about NDA approvals, other details that we do. So a lot of that is behind the scenes but, nevertheless, has external input.

DR. SANTANA: Will this committee have an opportunity in the next year or two years from now to revisit this list? I was trying to get at that a little bit earlier in terms of process.

DR. PAZDUR: Yes.

DR. SANTANA: I didn't hear that clearly.

DR. PAZDUR: Yes.

DR. SANTANA: How is this going to a dynamic process?

DR. MATTISON: We are required to produce a prioritized list and publish it at least once a year on the anniversary of the Act. This year, we

actually published two lists and, from those two lists of drugs, have identified ten, one on-patent and nine off-patent, studies that are in the process of being developed for implementation.

We will continue this discussion around the listing process. We are actually transitioning the leadership of the listing process within NICHD to a new individual who is going to put the process in a two-year cycle. So there will be multiple opportunities including public comment periods to provide input from a variety of perspectives on the listing process itself.

In addition, after we get recommendations from groups like this, we ultimately will develop a list, as Anne said, of about 20-some drugs, 20 to 30, perhaps more, that will be reviewed again by external consultants to NICHD. Prior to those reviews, we actually create fairly detailed literature reviews of the drugs to help the external consultants understand issues like you have described; frequency of use, concerns about efficacy, a more detailed description of gaps in knowledge about dosing and safety to help us think through ultimately what will go into, as Rosemary indicated, the dialogue around the development of

the written request.

DR. ADAMSON: Just a comment on Pat's suggestion and to follow up on your comments, Victor, as interested as I am in the retinoids and wanting to know everything that Pat has mentioned, I actually don't think Accutane belongs on the list when we compare it relative to some of the other drugs right now.

It has a therapeutic index that is quite different from cytotoxic agents with toxicities that are usually readily reversible with discontinuation. As far as underdosing, it is an open question. We don't know. I agree it is a question but there are many drugs where we know that there is a dose-intensity-response relationship or potentially an exposure-response relationship. The anthracyclines fall into that class.

I would agree with what Greg put in his letter. The anthracyclines and alkylators that I think would be at the next level of what we ought to understand, cyclophosphamide, Iphosphamide, doxorubicin, daunorubicin. I think we have a lot to learn there and we do have varying degrees of data, certainly as far as toxicity, as well as

potentially as far as impact on efficacy with undertreatment.

DR. SANTANA: Another way to get around the issue of retinoids in terms of oncology is that retinoids are used in other patient populations that are also pediatric within our oncology patients.

DR. ADAMSON: But not the age group we are talking about.

DR. SANTANA: No; I am saying. But they are used in teenagers and so on and so forth so one could potentially, if one wanted to push the retinoids, there may be other disease categories that potentially could help us make it to the list and at the same time do oncology.

DR. MATTISON: We have to build it into Roche's care program in terms of the use of these drugs. In individuals of reproductive age, it represents a set of concerns that we would have to deal with. I really appreciate the discussion. I think it is very helpful. But we would have to think about how we would structure that.

DR. SANTANA: For the record, I want to point out that I did not mention a particular sponsor. I used retinoids generically.

DR. BLUMER: I just wanted to echo what Peter said, not in terms of the retinoids but in terms of the other groups. We have talked about anthracyclines. I think that the aklylating agents and, in particular, Iphosphamide as opposed to cyclophosphamide because you do seem to have a unique predilection to nephrotoxicity in younger kids which is something that we don't see that often so that that may make it something to focus on.

DR. SANTANA: Any other further advice on other drugs, Malcolm, before I open up a new question?

DR. SMITH: Another question?

DR. SANTANA: Yes; we have another question.

DR. SMITH: Oh, okay. Just for the record, another drug that is of interest is 6-thioguanine. It is the drug--we have one study now that suggests it may actually be beneficial in childhood ALL. But that study also found unexpected very serious toxicity in a small minority of patients. So I think one of the things that the ALL committee is considering is can one figure out ways to potentially take advantage of an

increased efficacy profile while minimizing the risk. Again, it is liver damage.

So it is another agent that, probably not this time, but is an agent that is off-patent for which there is active interest in one of the COG disease committees.

DR. SANTANA: Richard?

DR. PAZDUR: I just wanted to affirm that this will be an ongoing discussion with this committee. This is not a one-time event and I think that this is an excellent use of this committee to get your advice on specific drugs and probably one of the major intents of it.

DR. SANTANA: Good. So I think we have given you some advice on Question 3 without having to repeat all the drugs. We have kind of talked around the table.

During the discussion this morning, the issue of population PK was discussed to some degree. Dr. Przepiorka approached me and said, we really need to discuss this in the context of a question. So I will give her the microphone and maybe she can express her thoughts of maybe how the committee could further advise the FDA on this particular issue.

DR. HIRSCHFELD: I will just state that we would appreciate any input on designs as well as identification of products because the identification, while it is the first step, the next step is how does one approach it. So we are grateful to receive any comments related to study design.

DR. PRZEPIORKA: Actually, the question that I had posed to Victor which he thought was a good question and had an immediate answer for was are population PK studies an appropriate mechanism for determining safe and effective dosing for pediatric patients.

The immediate response that came to my mind was no because, in my mind, it is an hypothesis-generating study rather than an hypothesis-testing study and specifically for the reasons that Jim had brought up, that it simply doesn't have enough power.

If I were to be looking at data from such a study to determine whether or not it is adequate for labeling change, I would say, well, maybe two studies or three studies or four studies would have enough power in replication. But even if you had limited power or accepted a higher error rate, it

would still just be hypothesis-generating.

So, for the purposes of NIH funding, if I got this as a transnational research grant to review, I would say, well, this is a really nice, interesting, useful piece of information but it really won't change the practice of medicine. It has to be followed up with some small validation study to say what we learned in this big population study is actually true when we study it prospectively.

But what concerned me more, and I haven't had an opportunity to review the draft on the guidance for population PK studies, was hearing that it was largely--what was the computer program? I am, over the past several years, becoming more and more concerned about the amount of time it takes to get anything studied nowadays or getting grants approved. You have to keep going back in cycle after cycle.

Being a user of FDA guidance, I can tell you that, if it is well written, it really gets used. So I would hope that protocol design is considered as important as data analysis and that the guidance should include something about protocol design.

Just in what we have been talking about this morning, we talked about having, in the protocol design, the rationale for what is the population, what is the disease, what is the dose method, what is the age. If it is a limited age population that we are concerned about, why include all ages? Why not a smaller study with just that age group. The genetics; that can be done simultaneously.

Other chemotherapeutic regimens, other supportive care, timing of sampling and what do you measure; plasma samples, a PD. What? I think if the people who are going to be doing these studies either for the FDA or maybe even this should be in the RFP knew exactly what people were looking for when they are reviewing the protocols, it would help get protocols through a little bit faster.

DR. HIRSCHFELD: Thank you. I just would like to comment, just to help frame the discussion, it is not uncommon for FDA written requests to have staged studies. It is rare that there is a single study in the FDA written requests. In fact, they are often one, two, three, four, sometimes up to six studies that comprise--it is the package that is designed to elicit appropriate information.

These studies, again depending on the circumstances, can be either staged and there is a particular sequence and we are explicit in those cases that Study 1 must be done before Study 2 and the design of Study 2 should be, in turn, based on the results of Study 1. So that is a model that has been used before and may apply.

DR. SANTANA: Peter and Clinton, do you want to comment on the population PK?

DR. ADAMSON: Yes; I think I want to comment and I will yield to Jim on this. A population approach is not simply a hypothesis-generating approach. I think, at least the message I get from Jim and what I would agree with, you have to sufficiently power the study to answer the question, but you can answer questions, and this is a valid way to answer questions. They are not trivial studies to design.

We discussed this and we proposed this as a method that may be a very realistic method to address the problem of dosing in infants and young children. There is probably no other realistic method to begin to understand drug disposition in infants and young children when you think of the patient numbers, when you think of blood-drawing

requirements and when you think of the tremendous developmental changes that occur during the period of zero to 12 months and then zero to 36 months.

You can't simply understand it at one point in time. You really have to study infants and young children truly across an entire 36-month spectrum. A population method is probably a very reasonable method if it is well designed and if it is sufficiently powered to get answers and not simply generate hypotheses.

But, Jim, maybe you can expand on that.

DR. BOYETT: Actually, I hope my comments didn't kill it because I think it is a potentially useful tool. My only comment was that it does require careful thought in designing the study. Where you have factors that you can control, you should control those factors and that reduces the variability.

Given a particular situation, I could probably manufacture an hypothesis that the design would be there to test. But I think we know what the end result is that you would like to get out of it. So I think it is. I just sort of thought that it was a little bit--it is a much more complicated situation and there are statistical scientists who

devote their whole career to developing methodology for nonlinear mixed modeling.

It is a hard problem but it is not an unsolvable problem. There is methodology out there. I was remarking that the one I saw, I certainly thought was a little bit underpowered, or a lot underpowered.

DR. STEWART: I would just comment that the use of NONMEM, or the nonlinear mixed effects modeling, has been used extensively in the AIDS population especially in the neonatal population to learn a lot from that population. So I think that the use of population PK has been a real boon to that particular area and especially to learning how to use those type drugs in that population.

I think it is something that--one of the things that we wanted to do during this particular symposium that we had was to try to learn from that group of individuals and apply that particular approach in oncology. So I think that we really want to apply that but one of the things we have to be careful about is the things that Jim brought up. We have to be very careful about study design.

I think whenever Peter gave his presentation, he did a really nice job of giving

these provisos of population PK doesn't make bad data good. I would certainly, you know, echo that. The other point I was going to make, and I really didn't want to say too much bad about it because I am certainly a proponent of pop PK is that you can, if you are trying to come up with these covariates to explain clearance, you can do it as long as you design your study to collect the data for that covariate.

But if you don't design the study to collect that covariate, you will never figure it out. So you have to be very careful about what data you collect. So these studies have to be done right, and they have to be well thought out prospectively going into it.

Peter has a lot of experience doing this. We have a lot of experience. So I think that the population PK approach can be done and a lot of information about the disposition of drugs in these children can be learned from it. But that is only one part of it. That is the point Jeff brought up and that is where we need to carry it the next step.

What do you do with the disposition data? What do you do with the information about the

disposition of the drug in the kids? What does it really mean? What does it mean to efficacy? What does it mean to toxicity? I think that is the step we have got to really think out very carefully, how are we going to use that, how will we use that, information.

These are all things that we can do. You can do it in the context of a population analysis.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: One other comment. I think another appealing thing to it is, and I will probably get run out on a rail when I say this by my colleagues who have M.D.s--

DR. SANTANA: That has happened in this committee before, Jim.

DR. BOYETT: But I think what you have to have in defining doses is you have to have very simple rules to follow. I think the population-based approach would give you those types of rules on the average. If you look like this, this is the way you should get it. I don't think we would ever get to where an individual patient walks in and we check the color of their eyes and what day it is, et cetera, and we can tell you exactly how to dose this individual.

I don't think there are too many physicians out there could follow that. It has got to be very simple rules. And I think it gives you the opportunity to develop rules, I'll bet, within several subsets of populations of patients you would see. So that is another appealing thing to it, I think.

DR. SANTANA: Richard?

DR. PAZDUR: Just perhaps, in closing, if and when we get this data in, okay, this has to be the same rigor and scientific validity that anything that goes in the product label goes through as far as review and our scientific comfort that is a real and true finding here because, obviously, folks, we are not in that much of a rush here to relabel vincristine and actinomycin D that we would put things that we didn't feel comfortable with.

You know, the principles that you are talking about, adequate power of a study, adequate data collection, et cetera, are things that we want from any study, basically So I think we could basically have a whole session on population pharmacokinetics here and argue the pluses and minuses of it.

But, to address Donna's comment, I think Steve also already did it, if we really didn't feel comfortable that the magnitude of change that we saw in these population pharmacokinetic studies or pop-PK studies warranted, we could request other studies to look at it closer.

So I think that this isn't the end. It could be viewed as a start and, as with everything in the FDA, we have a kind of blanket statement; it will be a review issue when we get the data.

DR. SANTANA: Having said that, if there are no other further comments. Dr. Reynolds?

DR. REYNOLDS: I just wanted to say that I think we are missing one opportunity here, at least I haven't heard it said, and I know it is beyond the scope probably of what is envisioned from the funding of this which is to focus on PK, but a large component of the effort here, as Malcolm was mentioning, national efforts with large numbers of children are necessary to define this.

A large part of the effort will be actually going through IRBs, getting studies open and securing the blood specimens from the patients throughout the cooperative group. If we are going to go to that effort, I would hope that we could,

at the same time, maybe ask questions related to pharmacodynamics, if there are any, and pharmacogenetics especially if you can do it from the same sample where the plasma goes to the PK and the cells go to the other.

So I would encourage that to be incorporated into this in some fashion even if it is beyond the scope of the funding that is available.

DR. SANTANA: My sense was, during the discussion this morning, that there was some thought to that.

With those last comments, we will reconvene at 1 o'clock. I am advised by the Secretary that there is a designated area downstairs in the restaurant, that we could all sit and have lunch if you want to go eat lunch. If not, we will reconvene at 1 o'clock. Thank you so much for your discussion this morning.

[Whereupon, at 12:05 p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

AFTERNOON SESSION

[1 o'clock p.m.]

DR. SANTANA: We will go ahead and get started with the afternoon session.

As we are starting this new afternoon session, the issue that will be discussed will be the age-appropriate formulation changes as it relates to pediatric oncology setting. As, is customary, we will start by introduction of all the members that are here today.

So, if we could start with the people that are here. The gentleman sitting on my left. Please identify yourself by name and relationship.

DR. SHAW: Walt Shaw, Avanti Polar Lipids.

DR. FLANAGAN: Douglas Flanagan, the University of Iowa.

DR. ZAJICEK: Anne Zajicek, NCI--or, excuse me; NIH, NICHD. Excuse me would you.

DR. SMITH: Malcolm Smith, NCI.

DR. STEWART: Clinton Stewart, St. Jude Children's Research Hospital.

DR. BLUMER: Jeff Blumer, Case Western Reserve University.

DR. ADAMSON: Peter Adamson, Children's Hospital, Philadelphia.

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

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

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

DR. PRZEPIORKA: Donna Przepiorka, University of Tennessee Cancer Institute.

MS. ETTINGER: Alice Ettinger, St. Peters University Hospital.

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

DR. DINNDORF: Patricia Dinndorf, FDA.

DR. LOSTRITO: Rik Lostrito, FDA.

DR. HIRSCHFELD: Steven Hirschfeld, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. SANTANA: Thank you. Do either Richard or Steve want to have any introductory comments? If not, we will go directly into the items. Okay.

Open Public Hearing

DR. SANTANA: We have an opportunity for an open public hearing session. If there is anybody in the audience that wishes to address the

committee, this is the opportunity to do so. If there are no takes on that, we will go ahead and get started.

I think we will just go like we did this morning through all the presentations and then we will have an opportunity for questions, and then we will have the discussion of the item at hand.

So, Dr. Shaw.

Lym-X-Sorb

A Revolution in Oral Drug Delivery

DR. SHAW: Thank you for the opportunity to present our information here.

[Slide.]

What we are going to talk about is an oral drug-delivery system that is lipid based.

[Slide.]

It is a lipid-base but it is non-liposomal. It is made of three components but, when you mix the three components, it is monomeric. It transports the active drug components through the intestinal villae and into thoracic lymph. It is an organized lipid matrix consisting of lysophosphatidylcholine, monoglyceride and free fatty acids. These are the three components of lipid digestion.

It is this analogue of the lipid digestion that makes this unique because, once you have a drug in it, nothing in digestion can metabolize any of these components so they are stable. It has been used in a clinical trial in Montreal to deliver essential fatty acids to cystic-fibrosis patients. This was a two-year trial. The outcome of that trial was that the patients gained weight, they grew taller and they had better lung function.

[Slide.]

These components; this is the structure of the components. You can see there is a charged component to this. There is a negative charge on the phosphate, a positive charge on the nitrogen. There is a hydroxy for hydrogen bonding. Then there is a hydrophobic agent so you can have a charge-charge interaction, a hydrogen bonding and a Van der Waals interaction with the drugs. With the monoglycerides, you can have hydrogen bonding and the hydrophobic. The fatty acids, you have a charge-charge potential and a hydrophobic.

These components make this eutectic monomeric structure in the ratio of 1:4:2 to 1:3:3 and any ratio in between. So you can change the structure of this monomeric component by changing

the individual components.

[Slide.]

This is our representation of what goes on. We call this the glove. It is a lipid glove. The three components are the lyso PC, the fatty acid and the monoglyceride. The drug then would fit in this cavity. We do know that all drugs that we have tested with this, you have 1 mole of the complex with one mole of the drug. As soon as you exceed 1 mole of the drug, you exceed the capacity and the drug isn't taken up by the complex.

[Slide.]

This is a cartoon, although this is generated from a computer model where we put the components--and the drug is in yellow. This is fenretinide in yellow--and we let the computer come to the minimal energy. This is what the computer told us this complex looks like. We have no confirmation of this with real X-ray data. This is a cartoon.

The lipid glove, you can think of it as a first baseman's mit during the playoff season. You can pick your own team that this belongs to.

[Slide.]

The current liposome technology is that

you have a nonhydrated layer of lipids. They become hydrated. They swell and they spontaneously self-assemble to these multilamellar vesicles. You can put energy in the way of sonication and make small unilamellar vesicles or you can extrude and make large unilamellar vesicles.

This complex that we are working with fits into this scheme at this stage where we have a solid anhydrous lipid mix. You can put it in water and it will swell. Now, what it makes is not described in this scheme. There is no internal space. All these liposomes have internal space and what we make has no internal space so it is similar to liposome technology but different.

[Slide.]

The manufacture of this complex is made from phosphatidylcholine in the presence of monoglyceride and fatty acid. The phosphatidylcholine is a soybean source of phosphatidylcholine and it is represented in this beaker, large chunks of phosphatidylcholine. You react that with a phospholipase A2. This is a pancreatic phospholipase A2 and we have maximized the conditions so that, in five to six hours, this reaction is complete. You will go from

phosphatidylcholine to lysophosphatidylcholine, essentially 100 percent phosphatidylcholine.

The PLA2 does not react with the monoglyceride or fatty acid. These are cofactors of the reaction. What you get at that point is an oil, after you have dried this mixture, pulled off the water of the reaction for 18 to 24 hours. You get this oil which is in the gel phase at room temperature.

This is what we call Lym-X-Sorb, LXS. This is what you react with the drug to surround and complex the drug. If you work at 0.8 moles of drug, you can all the drug in if the drug is going to react with the complex.

You can use this as your final formula that you can homogenize with SlimFast or some other source to make a liquid drug-delivery system. We have also been able to make a powdered formulation of 25 percent of the Lym-X-Sorb drug in a powder.

[Slide.]

So the production of this is that we have a novel lecithin hydrolysis that, in five to six hours, gives us 100 percent lysophosphatidylcholine. At that point, the dried material you can mix with your drug. We can verify

this uptake of the drug by a polarized light microscopy study. The reaction is fully scalable. We have done this in--our usual reaction conditions are in a 5-liter reactor. We have done this in a 130-liter reactor and the reaction is perfectly scalable. The production of this is done in a Class 100,000 clean room facility.

[Slide.]

This is our test for uptake of the drug. At room temperature, the Lym-X-Sorb is in the gel stage. You heat the Lym-X-Sorb to 55 degrees and it melts. This is a polarizing light microscope look at the Lym-X-Sorb. Once you add the drug at 55 degrees, if the drug is taken up, the field that you are viewing does not look any different than the Lym-X-Sorb. If, however, you exceed the capacity of the Lym-X-Sorb with the drug--this is 1.2 moles of fenretinide with the Lym-X-Sorb. You can see crystals of the fenretinide.

You can also use this to screen, to look at other drugs of choice that you could put in the system to determine very quickly whether the drug is actually going to react with the Lym-X-Sorb. Not all drugs will react with the Lym-X-Sorb.

[Slide.]

This is the reactor that is used. The difference between this and the larger reactors is this bowl. You can extend that bowl out. Of course, it would take bigger motors. We have seen actual reactors that have 20,000-liter capacity. The 130-liter reactor is what you need to collect your data to scale up.

[Slide.]

The powder formulation; this is what the powder formulation looks like. It is formulated with flour, either a wheat flower or a rice flour, sugar, and you can put--this is 26 percent weight-weight of the Lym-X-Sorb with the xenobiotic. It is a free-flowing powder. There are a few aggregates that break up immediately upon stirring.

You can take this mix and put it in with oatmeal pudding or applesauce and the taste of this complex has been referred to as, this tastes like cookie dough. I don't like this in pudding. This has a texture to it. The taste--you don't have a bad taste in pudding, but you have this texture in a smooth pudding. You certainly want to stay with a textured food such as oatmeal or applesauce. There are probably other foods that would work well

with this.

[Slide.]

With the fenretinide, the study is, at present, being prepared through an NCI RAID grant with Barry Maurer. The Lym-X-Sorb and the fenretinide then are taken up through the intestine and it is assimilated, absorbed through the jejunum and delivered to the thoracic duct.

[Slide.]

The studies have been done in mice. This was done at Children's Hospital Los Angeles, in dogs at McNeil Labs, McNeil Pharmaceuticals, and in humans at McNeil Pharmaceuticals. The present study with NCI is going to include rats and additional human studies next year.

What we have produced is a drug that has more bioavailability and it has improved delivery to the plasma, liver, lungs, kidneys and brain.

[Slide.]

This is the data out of Los Angeles, Children's Hospital Los Angeles. The yellow and red bars represent Lym-X-Sorb in SlimFast and DI water. The blue and green bars represent Lym-X-Sorb dissolved in an oil and this oil is a corn oil and put into Slimfast in a high oil

content. In every case, in plasma, the Lym-X-Sorb has a much higher concentration in plasma, liver, lung, kidney and brain.

[Slide.]

The absorption of this--this is the data out of McNeil. On a time basis, the red is a corn oil at 200 milligrams--300 milligrams of drug. The yellow is the Lym-X-Sorb with the fenretinide at one-fifth the dose, 65 milligrams of drug. The reason that the study was done with one-fifth of the Lym-X-Sorb, and we don't see a high spike for the Lym-X-Sorb delivery, is of the night blindness associated with fenretinide.

From the animal studies, it was shown that the Lym-X-Sorb was five times better so the dose was reduced one-fifth and the kinetics certainly indicate a delay in the uptake which would indicate a thoracic duct and then a fall-off in the plasma with time.

[Slide.]

What all this means, from our perspective, is that we have a drug that is compatible with a large number of drugs. What you have is a complex that has available hydrophobic bonding, charge-charge interaction and hydrogen bonding, Van

der Waals forces and it self-assembles. So when you put the drug in, it will self-assemble to represent a glove in relation to the drug that is in it.

It protects the compound from oxygen, heat and light. The fenretinide is historically not stable in heat, light and oxygen. In the Lym-X-Sorb, it is very stable. It protects the drug in the acid and base conditions and in the stomach and intestine.

It minimizes the taste of the drug and minimizes the effect of food taken with it. The bioavailability of the oral Lym-X-Sorb; it is a readily absorbable delivery vehicle. It is absorbed in the upper intestine. Enhanced absorption of the drug, we see a fivefold increase and minimizes variation and bioavailability of the drug.

[Slide.]

This work was done--the complex was actually conceived by Dr. David Yesair and Avanti has contributed to the manufacture and the stabilization of this complex, and the complexing of the drugs and the Lym-X-Sorb.

Thank you.

DR. SANTANA: Thank you. We will hold the questions until we are done with all the presentations.

Dr. Flanagan?

Best Pharmaceuticals for Children

Best Formulation for Children

DR. FLANAGAN: Thank you. I appreciate the opportunity to speak with you today and I particularly appreciate the FDA awarding me two degrees that I don't have. My mother will be quite impressed.

Also, I have two purposes in coming to the Washington, D.C. area. One is to speak with you today and I was also given, by my colleagues, a big satchel to pick up the new twenty-dollar bills that are being issued today as I understand by the Bureau of Engraving and Printing. So, if somebody can direct me to where I should go, I would appreciate it.

[Slide.]

Anyway, I was contacted about eight weeks ago to attend this subcommittee meeting because of my particular interest in drug-formulation issues. I was aware of the Best Pharmaceuticals for Children Act but have become much more familiar

with the issues in the last two months. My particular parochial interests are in the realm of drug formulation.

[Slide.]

So I would say, for me, best pharmaceuticals for children should be our best formulations for children. I have read some of the transcript information available at the FDA website from previous meetings of this subcommittee and I have noticed a seeming lack of discussion of the formulation issue so I am very pleased to hear that that is coming to the forefront.

I also read the documents that were sent to me in preparation for this meeting. From my own particular point of view, what I took note of in the articles that were labeled PM1, PM2, PM3 were those related to formulation issues. So it is pretty easy for me to go through articles quickly because, in this area, there is very little emphasis, often, on the formulation aspects.

[Slide.]

The first one indicated that there are a lot of drugs that aren't available in suitable forms for children, that formulations, meaning, medications, are complex mixtures, contain a lot of

components and, over the last decade, there has been an effort to get new drugs simultaneously approved for children.

What I have highlighted is an optimistic statement about these efforts resulting in more appropriate formulations of new drugs for children. My comment is what about the off-patent or the old drugs?

[Slide.]

Dr. Nahata, in his article, discusses the extemporaneous formulation which is what we resort to when appropriate children's formulations are not available. He encourages an action plan involving government, academia, industry, U.S. Pharmacopoeia, professional organizations, everybody, to develop pediatric formulations which I think we all agree with.

[Slide.]

The third article was a specific one describing a particular drug being developed as a dispersible formulation that could be easily swallowed by children. Somebody indicated that, beyond just children, and this article indicates that geriatric patients or other patients that have difficulty swallowing normal oral dosage forms, so

there can be a potential for the pharmaceutical industry to gain more remuneration than just from the pediatric patients with such formulations that are easily ingested.

[Slide.]

I also learned about the Pediatric Rule that I really didn't know anything about. I was impressed that the FDA, from the source that I received, the information about the Pediatric Rule can actually require new formulations, or a new formulation if it is needed, for pediatric patients in an age group in which the drug is needed. But the FDA can't require off-label-indications studies.

This particular author indicated FDA seemed to have not used their full authority in this realm, though.

[Slide.]

In reviewing the guidance information, of course, FDA cites the need for timely development of pediatric medicinal products--

[Slide.]

--and provides information and encouragement for developing these formulations for accurate dosing and enhancing patient compliance.

I think we all know the kinds of formulations that we need.

[Slide.]

I might also highlight for injectable formulations, since these seem to be neglected from a reformulation or a new formulation point of view, that we probably need, for a lot of drugs that are given by IV or other injectable routes, appropriate drug concentrations that allow more accurate and safe administration of these drugs. Also a separate consideration that I will elaborate on a little more later is to reduce the number of steps in the handling of these cytotoxic drugs by health professionals who are regularly being exposed to these drugs as they administer them to pediatric patients.

Also, we know that there are certain additives or excipients that are inappropriate for certain age groups of pediatric patients like benzyl alcohol and there has also been the effort to reduce the use of alcohol in formulations. For those formulations that contain in appropriate excipients like benzyl alcohol, just diluting them down, then, for pediatric use is not appropriate if some other additive is toxic.

[Slide.]

I have also found some other article like Conroy this year discusses the use of unlicensed or off-label uses of oncolytic agents for acute lymphoblastic leukemia. This is, of course, in the U.K. These drugs were also used for other cancers.

[Slide.]

It also mentions, besides the extemporaneous preparation which immediately makes the product or the formulation or the prescription unlicensed, mentions special formulations that were prepared for named patients by pharmaceutical companies. So there were, or are, occasions where these might be prepared if they can be done simply by the pharmaceutical firm.

This author also indicated 40 percent of these cytotoxic prescriptions were involved in unlicensed formulation. The term "unlicensed" always sounds bad, but that means "needed to be modified."

[Slide.]

It concludes with it is disappointing that formulations suitable for children have not been licensed in all the years since many of these drugs, as we have discussed in the morning session,

have been around for 20, 30, 40 years.

[Slide.]

Another big issue gets to be compliance because many of these patients, of course, have to be treated on an outpatient basis. There are lots of factors that affect compliance in terms of palatability and ease of administration of the preparations. If the patient doesn't take the drug, they don't get the therapy.

[Slide.]

Conroy also mentioned a disappointing case of special formulation being withdrawn by the company without notifying health professionals, medical pharmacy professionals. So these things can happen. Drug companies can lose interest for one reason or another, mainly economic, but there could be other reasons, and drop these kinds of formulations.

[Slide.]

I had also come across that the Europeans have developed their own initiative to obtain better medicines for children.

[Slide.]

I look particularly for parts of their guidance or information about formulations. They

do make statements about the pharmaceutical industry tending not to develop specific pediatric formulations and go on to highlight other issues. They said one of their objectives is, in fact, encouraging the development of suitably adapted formulations for children.

[Slide.]

Conroy also had an article in 2000 about the general area of use of unlicensed and off-label drugs in pediatric wards and noticed that that is quite widely done in a number of areas.

[Slide.]

For this meeting, I also contacted a local clinical pediatric pharmacy specialist, Mr. Mark Sorenson, whose name is down at the bottom of the slide--he is also involved heavily with the Children's Oncology Group--to tell me about what they do in our University of Iowa hospitals and clinics with regard to treating pediatric patients.

So he mentions, for this particular disease, three oncolytic agents, one adjunctive-therapy agent that has to be extemporaneously prepared so that they can be ingested by pediatric patients.

[Slide.]

The problems that he highlighted were the lack of availability of these dosage forms for outpatients because even compounding pharmacies, those pharmacies that will come up with unique formulations, are reluctant to compound cytotoxic formulations. This leads to reduce compliance and negative cure rates.

The child goes home. The patient's family doesn't know where to get the particular drug and if the patient looks like they are in remission, which they, of course, may not be, the therapy ends.

Also, there are drug-supply shortages, especially for community pharmacists. Last, but not least, the topic of exposing healthcare professionals to these oncolytic agents was brought up by their repeated handling of them, needing either, at the lowest level, to do multiple transfers for diluting these adult-level doses down to pediatric dose levels or compounding or recompounding tablets or capsules into liquid formulations exposes healthcare professionals to more of these oncolytic agents.

[Slide.]

I just cite a couple of papers about

female pharmacists, pharmacy technicians, nurses, nurses aides, showing a significantly elevated odds ratio of self-reported infertility associated with handling these kinds of agents even though, for men, that didn't seem to happen and another paper, in 2003, indicating a variety of antineoplastic agents that were found in the urine of pharmacists and staffs of hospital pharmacies.

[Slide.]

So a separate concern is what are we doing to our health professionals that are having to handle these cytotoxic drugs on a daily basis and exposing them to possibly harmful low-levels of these agents.

So one possible solution, of course as we are pointing towards, is preparing unique pediatric oncolytic formulations that need no extemporaneous compounding and far less handling by health professionals and caregivers.

[Slide.]

So my modest proposal would be to use academic centers, since I have a particular interest in an academic center, that have capabilities to develop the formulations, study their stability and manufacture, clinical supplies

and also use academic centers that can test these formulations in pediatric patients to demonstrate efficacy and safety.

[Slide.]

Are there any such centers? Well, let's see. I think I know maybe one. This is now what I call the shameless commerce part of my talk which is the University of Iowa where I am employed, where we have an NIH-funded comprehensive care center in our hospital and we have an FDA-registered drug-manufacturing facility.

We also have a separate service facility that develops analytical methods and executes stability protocols. Last, but not least, I am part of the Pharmaceutics Division that has over 50 years total experience in industry or formulation-contract research with industry or government agencies.

[Slide.]

Our Holden Comprehensive Cancer Center has 166 open clinical trials for cancer patients and many of those are trials in pediatric patients.

[Slide.]

Our pharmaceutical service has operated for over 25 years as a contract manufacturer of

formulations for clinical trials. It has had over 25 years of NCI manufacturing contracts for investigational oncolytic agents. For those that might worry that academicians like me or just students are making formulations, I will indicate that there are 50 full-time employees that might have been students at one time but they are full-time employees that manufacture these formulations. Our separate service divisions provide support services for drug development, particularly analytical-methods development--

[Slide.]

--and stability studies which are an important part of any new drug or formulation development.

[Slide.]

Then we have ten faculty in our Pharmaceutics Division that have participated at various levels in everything from preformulation studies to formulation development, pharmacokinetics and pharmacodynamics.

Thank you.

DR. SANTANA: Thank you. Dr. Blumer?

Drug Formulation in Pediatrics

If It Tastes Bad, It Must Be Good For You

DR. BLUMER: Good afternoon.

[Slide.]

I was asked to give you some perspective on drug formulation from a clinical perspective of a pediatrician. I will try and do it. You have heard a lot of this and I am indebted to Steve Hirschfeld for sending me a copy of one of his presentations from which I borrowed liberally.

[Slide.]

So, in thinking about drug therapy for kids, I always start back here because there are three determinants of efficacy therapy. Talking about pharmaceutics and, in particular, formulation is one that we often talk about the least, in fact. Yet, it is one of the driving forces behind whether or not our patients, indeed, get the benefit of the therapy they received.

[Slide.]

We spend a lot of time waving this flag. In fact, in this area, children are, indeed, different because they are not, in general, capable of dealing with the dosage forms that are most commonly made available in the marketplace.

[Slide.]

But they are not Martians. They still

breathe oxygen. They metabolize glucose and they have some fundamental biologic characteristics that are very similar to adults.

[Slide.]

When we think about drug treatment, there are some challenges. The challenges largely fall into those pharmacokinetic and pharmacodynamic realms that do, then, lead us to focus on providing effective formulations. So when you look at pediatric patients, they are dynamic. They have changes in body composition, changes in developmental drug metabolism, changes in organ function.

When you begin to think about some of these things, some of the initiatives that we have heard about this afternoon and, in fact, this morning, begin to resonate. In fact, if you are going to give, and make, these different formulations, we have to take this into account. What happens if you take a dosage form that is a solid dosage form that has a set of bioavailability characteristics and make a liquid?

We learned the hard way very recently in doing that with a drug that was a hypnotic agent, that you really can dramatically change how that

drug is delivered and you change the overall pharmacokinetic profile.

[Slide.]

There are pharmacodynamic challenges as well. Receptor function and expression change over time. The children also have greater regenerative and recuperative potential. So we heard this morning that children tend to have a greater risk in some cases for toxicity but they also bounce back higher which is one of the nice things about being a pediatrician.

There are some unique disease processes that we have to deal with as well, and some of the things that we didn't talk about earlier were the fact that we are dealing, in many cases here, with tumors that often don't occur in adults and are very specific to pediatric patients and, therefore, need specific therapeutic interventions.

When we have patients with chronic diseases, and what I mean by chronic diseases here, diseases that not only may span a lifetime but may span a year or two. We are looking at patients who are going to dramatically change in terms of their drug requirements. That is a very different paradigm than we are used to in adults.

[Slide.]

That leads to some practical issues. When we dose children, we tend to dose on a milligram-per-kilogram basis, on a weight basis, for most drugs. In oncology, we probably need to add dosing in terms of meter squared or normalizing to meter squared and body-surface area. But, having said that, we also don't know when to stop.

Some of these things become problematic as we are looking at the changes in drug disposition over time. These dose requirements will change as the children grow and, as was alluded to just a moment ago, a lot of the parenteral dosage forms require some significant dilution prior to administration.

I will share with you some of the things that are derived from the neonatal population, but they do translate into older children as well. What happens when you do that?

Then we have this whole issue of oral dosing forms. There is this sense that, well, once we reach six years of age, the children ought to be able to swallow tablets. I don't know of many of you have kids, but, you know, it is like, "I will respect you in the morning." It is one of the

great lies of the modern world. They don't. In fact, some children never are able to swallow solid dosage forms.

That is reality. It is a reality we have to address especially when we are dealing with children who need chronic therapy for life-threatening diseases.

[Slide.]

There are complex solid dosage forms that are very, very revolutionary but they are not engineered, not only for pediatric GI physiology but, of course, as pediatricians, as soon as we see a solid dosage form, what do we do? We crush it. It is almost a reflex. As soon as you do that, you destroy all of the engineering that went into developing that solid dosage form and it becomes useless.

Another issue is that palatability is, indeed, the major determinant of compliance in our patients. We have the most wonderful medicine in the world but, if it is not palatable, and I was interested in hearing about sense of the grittiness and the texture, because palatability is not only flavor, but it also deals with the texture of the medication.

So oral liquids and chewable and dissolving dosage forms may be alternatives. Then, remember that our patients really do depend on someone else to give them the medicine. That has a lot of dynamic implications. First of all, we need to have families that remember.

All of you are familiar with the data even on training acute lymphocytic leukemia where the compliance with treatment, the recognition that these children, indeed, need to get their medicine every day is not always adhered to. You superimpose on that a child who looks like they are doing well and is fighting with their parents to take the medicine, the incentive to actually deliver the medication goes down exponentially.

So these are some real practical issues that, in thinking about developing pediatric dosage formulations, we need to take into account.

[Slide.]

We have lots of formulations available. We do have to spend a little bit of time talking about intravenous formulations. There are a whole bunch of different oral formulations and, as we heard today, there are more to come. Rectal administration, cutaneous creams, percutaneous

delivery systems, all of which offer some specific opportunities for enhanced delivery.

[Slide.]

Now, as I said, this is a slide that just sort of emphasizes this concept of dilutional intoxication. If you take a number of drugs that are used in the intensive-care unit on a fairly regular basis, look at the available concentrations that they come in and then calculate how the individual doses have to be delivered--this is, again, in the neonatal intensive-care unit.

We can go through the same calculation in the pediatric intensive-care unit. Remember that the most sensitive measurement that we can make in a clinical setting is a tuberculin syringe. So all we have is the tuberculin syringe. We don't have Mettler balances and things like that.

You end up with significant overdosing with many of these medications. We can just extend that on and on. So it is not only looking at formulations that are oral formulations for kids but we have to be sensitive to those situations where we need parenteral formulations as well.

[Slide.]

What is available? You have seen this

before. I just have a couple of comments to make on it. This was from one of Dr. Hirschfeld's slide. Yes; he rightly points out that we do have some pediatric formulations. We have drops and suspensions. I don't know how much experience all of you have with chewable tablets. It sounds like a great idea but when you watch children take chewable tablets, some of them think they are great. Some of them think they are god-awful and spit them out. It is not a particularly reliable way of getting medicine into children.

The whole idea of syrups is another one. It is always interesting to look at the flavors that some of the pharmaceutical companies come out with. My favorite was, long ago, when trimethaprim sulfate was being formulated and one of the iterations was a licorice-flavored suspension. They thought this was going to be great.

You would talk to them and they would say--I think was Roche--and you would say, children don't like licorice. Oh, yeah, yeah; it is great. We put it through our taste testing. Of course, it was a group like this. It just was awful. So we have to be sensitive to that.

We have talked a little bit this afternoon

about extemporaneous preparations. I will only say the following things. There are places like the University of Iowa that does an outstanding job and we have used their facilities in some of our studies. There are places like Ohio State where Dr. Nahata, whose work you have heard quoted, has spent a significant amount of time putting together at least recipes for extemporaneous formulations.

Now, the problem with that is, even when you are using national-formulary or USP-marketed vehicles, it is like using the Betty Crocker cookbook and everybody sort of adds their own twist to these things. If you take extemporaneous formulations from day to day, week to week, month to month, and actually just take them out of the pharmacy and analyze them, there are tremendous differences. No one is trying to do this maliciously, but when you are dealing with drugs with narrow therapeutic indices, where you are really trying to get the dose right, this is a problem.

It is a problem in some of the compounding pharmacies. We have a wonderful pharmacy in Cleveland where we had historically sent patients who needed drugs compounded for young children and

our hospital pharmacy wasn't interested in doing it any more. This particular pharmacist and his colleague embraced this and they really gave it their all. But the fact is that there was not great uniformity from day to day and from time to time, even with their best efforts.

Then you have this whole issue of food. All of the concerns about food, and you will see a quote later from Dr. Hirschfeld which I think will go down in the annals of pediatric pharmacology because I think it is true, but most of the data that we have on the effects of food on drug bioavailability are absolutely irrelevant to children.

I don't know any three-year-olds who eat fried eggs, slices of bacon, coffee with cream and toast and butter. It is not that. And I don't know of any drugs that have been studied with peanut-butter and jelly sandwiches, or Fruit Loops or Happy Meals. This is real life. So, do these things impact? Yes; we have studies in infant formulas and yes, we have studies in applesauce. We will have a comment on that.

[Slide.]

So what are the determinants of

formulation? I think we have talked about age and that is obvious. The ability to handle solid dosage forms and, really, it depends on what the solid dosage form is because there are many of them.

Then there is the disease and the disorder that we are talking about. That is key, as well. So there is a sense, and I think we will get to it, that when we talk about pediatric formulations, we want an oral liquid. That is what we are after. But that may not be the right formulation for all comers, for all diseases.

If you have chronic suppressive therapy, if you are taking drug over a long period of time, if you want to ensure that the patient is compliant and you can't get rid of the bitter taste, these are all considerations that may make a liquid not appropriate.

[Slide.]

What would I recommend? Well, until hearing some of the presentations today, I think certainly oral solutions are up there, suspensions. I think we ought to give more, or at least closer looks, to some of the rapidly dissolving tablets because at least, then, you can fake out these

little kids because, once they get it in their mouth, it is there and done and it gets in. That is important.

The transcutaneous delivery systems is another route that we haven't spent as much time working on. Certainly, with pediatric patients, every time someone gets to the point where they would like to look at it, they are unwilling to go through all of the formulation problems and dosing issues that, even if there is an adult formulation, like some of the opioid transcutaneous delivery systems.

Those are great and they have been licensed for adult patients, but there are different parameters that we have to deal with in terms of changes in the integument, changes in dosing strategy, et cetera, that are fairly expensive. Yet, for young children where you can put a patch somewhere where they can't get at it, this may be a very effective strategy.

The use of implantable reservoirs is something else that we may need to look at in kids. So I don't think we should eliminate those from our consideration.

[Slide.]

As I indicated, the pediatric holy grail some people think of as the oral liquid--again, I borrowed this. This is from the Pediatric Pharmacy Advocacy Group--that really sort of makes it our imprimatur to try and develop a liquid formulation.

[Slide.]

But I want to say, is that really what we want or need? I challenge this group to go back and say, okay, in certain contexts, this is wonderful, but this is not an area where one size is going to fit all and I think we have to start with what are we trying to treat, then look at who we are trying to treat and put those together and decide what the appropriate formulation may be.

[Slide.]

So the approaches we take, we have some proprietary ones that are liquids in suspensions. The extemporaneous ones still exist. As I said, our chief approach to solid dosage forms is to crush them.

[Slide.]

The downside of the oral formulations we have, the solutions often contain potentially toxic excipients. I want to underscore this. This is something that we haven't spent enough time looking

at and it is something that we do need--these are some of the silent problems that we have and we are not sure how significant they may be because we haven't looked at them.

The suspensions are my favorite because you take a suspension and you give it to the average mother and generally, when they start, especially if you give them a month's supply of it, for the first ten or twelve days, the children are either seizing or having arrhythmias or whatever it is that the medicine is for and then, for the last twelve or fifteen days, the children are toxic because you can never get them dispersed well enough.

This is not a reasonable strategy. It just doesn't work well. We also have to consider who is administered the drug and under what circumstances. As I indicated, palatability is key and that deals with both taste and texture. There are some very good-tasting drugs that children will shy away from, in some cases violently, because it is like taking a mouthful of sand. They just don't tolerate it.

The sprinkles and sachets have some advantages but they often have erratic absorption.

Some of that erratic absorption depends on what we are putting them in. Some of it just is inherent to the dosage form and, yet, if you are dealing with a drug that doesn't have a narrow therapeutic index, this, too, may be a very effective way to administer drugs to particularly young kids.

Then I have talked about transcutaneous delivery systems.

[Slide.]

The extemporaneous preparations, we have talked about these problems; stability, bioavailability, nonuniform composition, the variable effects of food.

[Slide.]

Now, are they important? Well, we know that food will affect bioavailability. It may not be clinically important. I think this is the key, though, and I think this will go down in the annals of pediatric pharmacology; not all applesauce is created equal. And it is not.

It is sort of like the old adage about delivering drug doses to kids in terms of teaspoons. If you go into a group of homes in any city and say, let me see your teaspoon, the sizes vary by a hundredfold. The same is true with the

contents of the applesauce.

For most drugs, the impact is small, especially with the foods that kids eat. That doesn't mean we should ignore it. We need to know, especially for a drug with a narrow therapeutic index, especially for a drug for a life-threatening illness, we need to know. But, at the end of the day, there haven't been a lot of drugs, especially those that we use in children, where food has been shown to have a clinically important impact. As I said, there are no studies that really deal with the foods that kids eat.

[Slide.]

To date, and, again I borrowed this and it is true; we have a number of bona fide pediatric formulations but I will talk about these in a moment. We have some extemporaneous preparations that are standardized. In his talk, and I didn't reproduce this, Steve showed the menu that you need to go through to make the extemporaneous preparation for Sotalol. That is accident waiting to happen. It really is. This takes major compounding time.

The sprinkle formulation, taking sprinkle with Montelukast, for example, where you have a

drug where you can give a whole elephantful of it and probably not hurt anybody, it does have advantages. I don't think we ought to dismiss that as a dosage form. It is not going to be as reliable as some others, but it may offer something.

[Slide.]

So then you get to these antivirals. Because of the tremendous interest in HIV infection, most of the antivirals have come out with some sort of oral solution. These are terrible formulations. They just sort of cut the mustard. They are liquid so you can take them if you can't take a solid formulation.

How reliable are they in terms of drug delivery to children and are we able to minimize the exposure to things like--you know, we want to dilute it in antifreeze or something like that, that is fine. I mean, these are problematic. So I am not sure that going to this kind of length to just sort of eke out something barely acceptable, even in a situation where we are dealing with a life-threatening disease like HIV infection, is the appropriate strategy.

I think we can do better and I think that

is where we need to put our mind set. So I just think there are some very real clinical issues that we have to consider. I don't think we should limit our focus to oral liquids and I think we need to explore both focusing not only on the age of the child or the fact that they are children, but what it is we are trying to achieve with the drug.

DR. SANTANA: Thank you, Jeffrey.

Questions to the Presenters

DR. SANTANA: We now have an opportunity to ask questions to the presenters. I want to start by asking a question regarding this Lym-X-Sorb technology. Do you need active bile salts to absorb it? Is it absorbed through the bile-salt intestinal transport system or is it absorbed uniquely by itself?

DR. SHAW: I don't have any data on that, absorption without bile salts.

DR. SANTANA: It just occurred to me. It is a lipid formulation; right?

DR. SHAW: It is lipid but the components are all the products of digestion. You have lysophosphatidylcholine which is the product of phosphatidylcholine digestion. You have monoglyceride which is a product of triglyceride.

And then you have free fatty acid. So you don't need any pancreatic lipase to act upon this to be digested. It is the end product of digestion.

DR. SANTANA: Dr. Stewart?

DR. STEWART: I had a few questions for Dr. Shaw. You mentioned that the bioavailability had been increased. I guess, since we are here at the FDA meeting, we should use the strict FDA definition. I did notice that the extent had been increased but I guess the strict definition includes rate also. I didn't really see how the rate had been increased. Does the rate of absorption also increase?

DR. SHAW: No; I would think not.

DR. STEWART: So it is really just the extent of absorption.

DR. SHAW: The extent, the amount.

DR. STEWART: The other question I was going to ask was you had mentioned that the variability decreased, the variability in absorption was decreased. I guess the one graph that you showed didn't really have error bars, the graph of--it was a study from CHLA. I didn't really see any measure of variability. Do you have an idea, can you tell us how much variability

is--how much it decreased the variability in absorption, because I think that is a very important point.

Based on the studies that we have been involved in at St. Jude, obviously, you want to increase the bioavailability but you also want to decrease the interpatient variability. That is a very important point in regards to oral drug formulation.

So if the formulation is able to do that, I think it is a very important contribution that it makes. Are you able to quantitate? Does it decrease it from 100 percent down to 10 percent, or 100 percent to 50 percent? Can you quantitate that?

DR. SHAW: I don't have any quantitative data. The clinical trial that was done in Montreal on the cystic-fibrosis patients, the Lym-X-Sorb complex was given as a unit. There was no drug associated with that. It was a delivery of the essential fatty acids that were in the complex.

That was a two-year study and the result of that was that the patients all gained weight and grew taller and had better lung function. But I don't have the data to show what the variability

per each patient was.

DR. STEWART: I just think it is real important for, whenever we do consider the formulation considerations that we consider variability as one of the aspects of it.

The other question I was going to ask you was, when you showed the tissue and plasma levels and you were showing the fenretinide, were you measuring, in your assay, the complexed drug, the glove, or were you measuring the fenretinide?

DR. SHAW: That was the fenretinide that was being measured.

DR. STEWART: So it released in the tissue?

DR. SHAW: Yes. Well, it was taken up in the plasma and then the tissue would take up the fenretinide from the plasma, or from the blood.

DR. STEWART: Okay.

DR. SANTANA: Peter?

DR. ADAMSON: I actually had three questions for you, Dr. Shaw, because I think, if the--and I am going to say "theory" but please tell me if I am wrong--if the theory is that absorption is virtually exclusively through the lymphatics, that actually has significant impact in that it

avoids first-pass metabolism.

DR. SHAW: Yes.

DR. ADAMSON: And so those studies, can you tell us a little bit about how you have proven that that is route of absorption?

DR. SHAW: I think the time of the drug presence in the plasma is delayed so that you could assume that it doesn't go directly to the hepatic system. It goes through this lymphatic system.

DR. ADAMSON: So you haven't actually sampled from the thoracic lymphatic duct.

DR. SHAW: No.

DR. ADAMSON: Again, I think that would be important to document because a lot of our drugs are probably limited, in good part, by first-past metabolism, and knowing that with certainty.

My next question is that this is useful for a large number of drugs. How many drugs have you actually studied in either preclinical or in humans?

DR. SHAW: There has been cyclosporine, which is a cyclic peptide, and fenretinide.

DR. ADAMSON: Those are the two?

DR. SHAW: Those are the two. Now, there have been many drugs that have been looked at to

make a complex with the Lym-X-Sorb that have never been put into animals or humans.

DR. ADAMSON: The last one, and, again, it, in part, is following up to Clinton again and, because we are at the FDA, I feel like we can throw this out on the table, although I believe it will increase bioavailability, I don't think your data support that. The reason I say that is that it is resting on the assumption that the pharmacokinetics are linear and not saturable.

I think the only way you can show increase is actually to study the same dose, albeit a lower dose, but, otherwise, if the absorption is saturable, you are not showing increased bioavailability. It might just be saturable absorption if it is no different. I tend to believe that you have increased it, but I don't think the data, and there may be more data there, but I don't think it demonstrates that.

DR. SHAW: Okay.

DR. SANTANA: Donna?

DR. PRZEPIORKA: For Dr. Shaw. It is a very interesting formulation and the moment you put up your first technical slides, I thought, my, this looks very familiar to somebody who has done gene

therapy in the past. My question is, do you know the charge of the pocket in the glove and will that actually complex with virus or nucleic acid?

DR. SHAW: We have not put a virus or nucleic acids in this complex. We have some people that are talking to us about doing that.

DR. PRZEPIORKA: The reason I ask that, of course, is because this is one of the routes that we use to transfect cells with genetic material.

DR. SHAW: Yes.

DR. PRZEPIORKA: If, in fact, your drug is not covalently complexed with the lipid, there may be some opportunity for mass action to move drug out and virus or nucleic acid in since it is going in via a non-sterile route.

Alternatively, if the drug is not totally complexed, or rather if your lipid formulation is not totally complexed with the drug, you would have, around the open glove--if you were going into a place that could pick up anything. I would be concerned about what the potential would be for transformation and long-term safety in these kids. So I would just want to raise that concern.

DR. SHAW: Thank you.

DR. SANTANA: Peter?

DR. ADAMSON: This is a question for either Jeff or Dr. Flanagan. I think, if we were to look at pediatric cancer therapy today as far as where is formulation, perhaps, going to have the greatest impact, I would potentially argue for the thiopurines for 6MP. That is a medication that is administered daily. It is administered daily for years and we know, from the extensive studies that we have done, that the inter- and intrapatient variability are extreme for this drug.

To me, because it is continuous administration, it is almost begging a transcutaneous route. How complicated is it to make a drug into a transdermal delivery system? Maybe, Dr. Flanagan, you can tell me that, or tell us that.

DR. FLANAGAN: Well, the transdermal delivery systems are rather complicated. At the simplest end would be some kind of topical, let's just say, ointment. If the drug is permeable through the skin, then possibly, if you could do this in a controlled fashion, applying an ointment or a topical formulation with the drug in it might work.

At the other end of sophistication, to

make something like the fentanyl patch or the nitroglycerine patches, that is a lot more technically involved and isn't something that usually people do. They don't do it on an extemporaneous basis. They don't do it in a hospital setting. It takes some rather sophisticated equipment, but if you can demonstrate that the drug can be delivered transdermally, then you could probably interest a transdermal delivery company in going further with it.

DR. ADAMSON: Because I think the greatest potential impact, if you look at standard risk ALL, the largest number of failures occur during maintenance therapy. Whether they are because of ineffective delivery of maintenance therapy, we don't know that. But both from a quality-of-life standpoint for medications daily as well as trying to decrease the extreme variability, that would seem to be a significant area of potential formulation development when it comes to pediatric formulations for children with cancer.

DR. SANTANA: Dr. Finklestein?

DR. FINKLESTEIN: As a follow up to Peter's question, is there any data to show how effective the transdermal application is correlated

to the age of the child's skin thickness? So then we would be back to square one.

DR. FLANAGAN: To my knowledge, that is not known.

DR. FINKLESTEIN: And is it important?

DR. FLANAGAN: Additionally, you don't get a lot of drug transferred through the skin. So if you are going to need many milligrams of drug, the skin isn't going to be the route to do that. But if pediatric doses are much reduced compared to adult, that is a possibility. But you are not going to get tens or twenty-fives of milligrams across the skin.

DR. BLUMER: But this is the kind of thing where you might want to consider changing the strategy and saying, okay, if you had an implantable pump to continuously deliver 6-mercaptopurine, would that not get rid of some of your variability? That is why I say, these are things that we shouldn't abandon, again, looking for liquid formulations and things like that.

There may be alternatives that will give us more reliable delivery.

DR. SANTANA: Jeffrey, can you comment on--you kind of touched on it very lightly in your

presentation. But can you give us more detail how industry decides when they need to rethink about a new formulation or a new vehicle of giving a drug. Is it empiric? Is it all market driven? Is there any science to the madness because I got a sense from you that it was the later.

DR. BLUMER: I think that there is certainly science to the madness because some of these things get quite complex. But I think it is still market driven and I don't know that pediatric patients will ever be the kind of market that will drive that without some significant incentives. So I just can't see going out there. What we are lacking, while there are a number of small pharmaceutical companies today, boutique firms that are looking to reformulate drugs and patent new dosage forms, most of them are looking at liquids or something else. They are not looking at some of the more complex dosage forms.

So I think I would be pretty pessimistic that some of the large pharmaceutical companies are going to embrace this without some significant--

DR. SANTANA: Can I take that further? How does the maker of the biggest analgesic decide that they want to do a cherry flavor or a chewable

and they want to do another one? How is that process? Who decides that? What information is brought into that decision?

DR. BLUMER: I think the flavoring is done--to me, it has been a mystery, quite frankly, because, when you work with these companies in the beginning of the development of an oral dosage form, and one that we were just involved with, one of the things that did determine it ultimately was the flavorings, one of the flavorings, did, in fact, dramatically affect the stability of the suspension.

So I guess there are some of those. But why they start out and say, well, we really believe that lemon creme is going to mask the flavor of this better than banana nut. There doesn't seem to be any real rhyme or reason to that.

DR. SANTANA: Dr. Stewart?

DR. STEWART: This is actually a comment that I was thinking of. I am going to wear my hat as a parent now. I was thinking during Jeff's talk about what kind of formulation could I come up, or could I think of, that would give my ten-year old to take medication and I started thinking, well, if I came up with the ideal formulation, that might be

actually sort of a drawback because then you start thinking about, if you get such a good formulation, you have to worry about kids wanting to take it and poisonings.

So I think one of the things--maybe it sounds a little absurd, but you do have to worry about kids getting into medications and taking them and the poisonings. Maybe I am going a little bit overboard, but I am sounding a note of caution, I think, in terms of medications being too tasty and too much like candy and kids getting into them. I think that is a concern we have to think about.

DR. BLUMER: I think it is a legitimate concern. At this point, we do have some experience with that. Fortunately, it hasn't been a bad experience. When the ability to really flavor liquid medications became a commercially viable entity, so you could go into your pharmacist and say, yeah, I want my child's amoxicillin to taste like Welch's grape juice or something. They can now do that.

I think one of the concerns that maNy of us had is just what you were articulating, Clinton. But it has turned out that, after a number of years, that hasn't been a big issue. So, while I

echo your note of caution, I think we now have some real-life experience to show that that hasn't contributed significantly. Running one of the poison centers around the country, that certainly--in fact, I can't think of a time where that has been a problem.

DR. REYNOLDS: I have a question for Jeff. Your point about flavor, I think, and palatability is extremely key in this whole situation with the oral medications. We have been frustrated with trying to find, in the literature, any kind of body of literature, even single papers, dealing with how this flavoring is done.

I hear through the grapevine that it was a tour de force to disguise the taste of Tylenol in the oral McNeil preparation, yet there is nothing on that. It seems to be a trade secret. I was wondering if you could comment on whether there is some literature that I am just missing or whether there is some opportunity to get together in some place a body of such literature which would not only be useful for extemporaneous formulations the pharmacist might do but would be extremely useful for those of us trying to develop pediatric formulations for specific use in the future.

DR. BLUMER: I know that a literature exists, and Dr. Flanagan probably has a better sense of that than I do. It is not something that I generally read. But the medicinal chemists certainly do this. Most of the pharmaceutical companies have people who do nothing but deal with flavoring.

DR. FLANAGAN: A lot of the information is proprietary, but there is a publication for compounding pharmacists or health professionals interested in compounding that has a lot of material about flavoring. Sometimes, I am reluctant to recommend some of these things because there is a kit of flavors that pharmacists can purchase and just add whatever flavor they would like into a product viewing a flavor as not a chemical entity but just something that changes the taste and you never know what it does to the stability or the bioavailability of the drug. But there are flavor kits available.

DR. REYNOLDS: Just to follow up on that comment, then would you think it is safe to say that one of the issues that we do need to study, then, is the impact of these and develop a scientific basis for what flavors an what compounds

used to flavor do affect drug bioavailability.

DR. FLANAGAN: Sure.

DR. SANTANA: Alice?

MS. ETTINGER: I, after twenty-five years of being a nurse and getting meds into kids, don't think that there is any one flavor or any one anything that is going to get any kid, even the same kid five minutes later, to take a medication. That is a real problem. The applesauce isn't the applesauce.

I have a compounding pharmacist where we are. He has used every flavor kit not nailed down for one particular kid. And then the next kid liked one of them and that one went right in. So I think we are spinning wheels here in terms of every single solitary kid trying to take every medication.

In the other hand, I liked the comment about the parent. I think that that is something that we cannot overlook and the impact that the parent has on having a child take a certain kind of a medication over the long haul.

DR. SANTANA: I was thinking about this, that there is a big piece missing in this discussion which is this whole issue of behavioral

medicine and modifying behavior of kids taking medications. It is no offense to anybody on the team here, but we really should have given some forethought about discussing that too, because that is important in terms of compliance.

But that relates more to compliance rather than to issues or formulations and things like that which is what the FDA wants us to discuss. But I agree with you. The issue of compliance is completely separate and the behavioral-medicine impact to that is something that needs to be addressed across all pediatrics.

DR. BLUMER: I would just emphasize that I think, at least for pediatric formulations, compliance is so intertwined that they can't be separated. So, as the FDA considers issues of pediatric formulations, that has to be something that has to be on the table and how do we do that. For example, a lot of the oral antibiotics have been put through so-called taste tests. Generally, children are not part of that.

Can you actually give them a taste test without exposing them to the medicine? These are real challenges.

DR. SANTANA: It will be interesting if

those studies have to go through the IRB, too.

DR. SANTANA: Ms. Hoffman?

MS. HOFFMAN: I guess, as a parent who had to try to convince my child to take chemochip chocolate ice cream unsuccessfully--she had learned to dissolve the ice cream in her mouth and spit out the pill that was all crushed up into minuscule little pieces. I mean, the ideal would be having a Mary Poppins scenario where, every time you poured out the bottle, it was a different flavor and a different magical color.

But we don't have that kind of world. I think the other factor in terms of compliance is, again, as a parent, these kids learn really fast. I take that medicine and I feel like shit and I am going to get sick in X number of--a half hour or hour. So it is not only a matter of not wanting to take the medicine because it tastes really yucky. I don't want to take the medicine because in a few minutes I am going to feel really, really even worse.

There are so many factors involved in making sure that they get the antiemetic beforehand so they don't feel nausea and all the associations.

DR. ADAMSON: I just wanted to follow up a

little bit about Jeff's comment as far as industry's interest in formulation. Rick, I will direct this to you, but you can sort of turf it. If I recall correctly, a formulation was developed for intrathecal Ara-C deposition that would seem--am I bringing up a bad topic?

DR. PAZDUR: Steve was the reviewer on that.

DR. ADAMSON: Okay. Maybe I will direct this to Steve. For people who don't know, it is a long-acting intrathecal Ara-C. When you think about the market there, children's cancer becomes an epidemic relatively speaking. So the question is what motivates industry, not big PhRMA, but could you give us some--what do you think motivates industry to develop a formulation for a small market.

DR. HIRSCHFELD: That is a very complex question. I couldn't even pretend to answer it thoroughly. But there are a number of factors and they have to do with establishing credibility as an entity with demonstrating something that is going to differentiate them from their competitors that, even though the sales may not be eye-popping, the stock price of the company can reflect either a

capability or a promise of not necessarily that product but maybe a technology.

And there are also grants that are available which, in some cases, are a very strong motivating factor. The FDA has grants, the Orphan Drug Program. The NIH and the NCI, in particular, have grants. There are some entities which essentially establish the credibility and are able to survive through funding mechanisms.

So all of those are motivating factors.

DR. PAZDUR: Very politically correct, but, Peter, the real answer is one and one only; profit. The issue is off-label use for the most part. That is where they see a niche. We get this so many times, people coming in for just, I want to approve this drug in fifth-line relapsed patients, knowing extremely well that that is not the market that they are going after. Or, we want to develop this drug for people on respirators that are getting acute leukemia. They are not developing that drug. That is one of issues.

Here, again, Steve is right. These are different areas. But one of the things that propels things, the market, in general, is can they use these drugs off-label. This is obviously a big

area in medical oncology.

DR. SANTANA: Peter?

DR. ADAMSON: I was just going to follow--for a drug like 6MP, if you were to extrapolate that, you might say get it labeled for children with leukemia and then use it in all the patients with inflammatory bowel disease. So I think there may be small companies you might be able to interest even though we can't--or, at least I couldn't envision the profit. It may be there when you put someone who has an MBA behind it.

DR. PAZDUR: I don't want to seem glib or something. There may be altruistic benefits, obviously, but, ultimately companies have to be viable. Will this have potentials? Will they be looking at this technology to export to different products down the line that may have larger markets trying to develop it in a small market first. That might be one situation that comes to mind.

But, ultimately, there has to be a market for a drug. When we see many of the pharmaceutical companies coming to us, although the niche market may be for the treatment of leptomeningeal disease from a particular rarer type of tumor, the larger market is for solid tumors from breast cancer, et

cetera, coming down the line. It tends to be an easier, perhaps, way to get the drug initially approved. But, given the fact that off-label use is common practice in oncology, that is a consideration.

DR. REYNOLDS: Are we done with this issue?

DR. SANTANA: I think we are done with this issue, yes.

DR. REYNOLDS: I just have a comment on this issue.

DR. SANTANA: If you have a comment on this issue, go ahead, Pat.

DR. REYNOLDS: If I could just ask you, Rick, what you are seeing here, basically profit is the motivating factor. Yet we see generic drugs made all the time. I am wondering is there some possibility for some of these kind of formulation issues to be--the cost of development born by the government and then handed off to generics as a model for getting around this.

DR. PAZDUR: That could be a consideration and if they wanted to partner with the NCI in developing these, this would have to be under discussion with the NCI. But that is not an

unheard of example, either for formulation--well, for new molecular entities, definitely--

DR. REYNOLDS: Here, I was just talking about for formulations.

DR. PAZDUR: But for formulations, that would have to be something discussed with the NCI.

DR. HIRSCHFELD: I will just add on the same topic that, depending on the extent and elaborateness of the new development, it could quality as a new product and, therefore, would be something entirely--be patent protected, et cetera, which would be a different model.

DR. LOSTRITO: My question is for both Drs. Blumer and Flanagan. Dr. Flanagan had mentioned--showed some interesting information about occupational-exposure hazards to formulating chemotherapeutic agents. The issue of percutaneous or transdermal dosage forms came up. I would like you both to respond to this briefly that, traditionally, the products that are marketed to date for transdermal systemic absorption usually employ anywhere from 5 to 10 milligrams extra in the device for every milligram you want absorbed as a dose.

That is to maintain a linear absorption

profile. To me, this poses a different type of toxicity issue in terms of familial handling of it and what is a huge dose relative to what the patient just absorbed left in the device at the time you throw it away. I would like your comments on that with regard to the patient population, family considerations and also exposure.

DR. BLUMER: I think your points are very valid and very important. What we have to balance here is the importance of delivering the medicine to these children and then what kind of safety precautions you can take at home. Over the years, we have changed how even over-the-counter medications are packaged to ensure safety in the home.

Obviously, if we were going to introduce, if it were feasible and it may not be for the some of the cytotoxic agents, to deliver them transcutaneously, we would have to set up the kind of safety situation in the home to do this.

When you think of all the therapies that have now been translocated out of the hospital into the home with home IV teams and all sorts of dressing changes and drug deliveries, it is probably not out of the question. I think the

first thing we need to do is figure out whether you can really effectively deliver these kinds of drugs that way and what advantage it holds.

But I am not as pessimistic about it, perhaps. But I think that those are very key questions in terms of rolling this out on a commercial level.

DR. FLANAGAN: I guess I agree.

DR. SANTANA: Any other comments? Malcolm?

DR. SMITH: We have had some experience with drugs coming through adult development. There are tablets. There is going to be a pediatric formulation. And then we end up using the crushed tablets and it just didn't work out. My question is a generic one. Is there a strategy that we--is there a generic strategy, generic in a different context, that we should be pursuing, kind of an off-the-shelf approach, that would be feasible for a range of therapeutics? Is that something that is tenable, whether it is for 6MP off-patent or the newest drug that is coming down the pike? Is there technology that is on the horizon that could do that for us?

DR. FLANAGAN: I am not aware of any

off-the-shelf technology that would work across a range of drugs. But you have your pharmacy specialists in the hospital that are often very good at compounding things and taking anecdotal information from the patients and going back to the drawing board to modify it.

DR. HIRSCHFELD: I was going to comment to Malcolm's point. This is something which we have been interested in for some years and have had discussions with some of the major corporations in America, not just pharmaceutical companies but others. If there were some general approaches that could be used to look at pediatric formulations, could they be somehow into fine particles and dispersed or something that would be stable and have all the properties that Jeff discussed in his talk.

The short answer is no one has come up with an approach that would be sort of the general starting point for it. We remain interested and keep inquiring but it hasn't appeared yet.

DR. SANTANA: No; there is no general approach and there may be a little bit of science to the madness, but the madness is very disorganized. It is unfortunate because that is

what I was trying to get to earlier in my question is is there a way that industry systematically approaches this that could be modeled into what we want to do in pediatrics.

DR. SMITH: Are there delivery systems that could be engineered that could incorporate, here is what we have in the delivery system that can be an oral suspension or a sprinkle or whatever does it. Just press the button and you have it. We don't have that right now.

DR. SANTANA: Ms. Hoffman?

MS. HOFFMAN: I just had one other comment, I guess, as a parent. When my daughter came out of BMT, you are given so many medications, different dosages and different ways to give it to them. But I actually found that to be an advantage, to have multi different formulations. I knew I gave the yellow liquid in this and I gave her this much instead of two blue pills. She had to have--it is a cyclosporine in the glass syringe at such-and-such a time.

I think it actually helped. If I had had everything as sprinkle, the probability of having it correctly given to her I think would go down greatly and this may be something to keep in mind.

You are dealing with parents that are overwhelmed. We don't have degrees in pharmacology. Even literacy in your parents isn't necessarily--it might be Grade 8 level of literacy.

So you don't read your label and go, okay, I understand that I need X milligrams of this. You go, okay, I need two blue pills. Just keep that in mind that multiple formulations can probably help.

DR. SANTANA: Jerry?

DR. FINKLESTEIN: I would like to go back to Peter's comment earlier this morning which had to do with the fact that maybe the best we can do in pediatrics is monitor the white count. As I am listening to the discussion this afternoon, pharmacists, in good faith, are putting drugs together to give to children with a variety of diseases, but we will talk about children with cancer.

We have no idea of the bioavailability, whether it is given as a liquid or crushed in tablets. We use survival as a guiding light and yet we know our infants don't do as well. Over my career, we have seen the survival rate of children with cancer improve so now we think 75 to 80 percent of children with cancer will be living

for five years.

We are looking at genetics as perhaps the reason that we are missing the last 10 or 15 percent, but maybe it is bioavailability of drugs. I don't know if this is commission of the FDA, but I am taking a message back here that the protocol I referred to this morning where we use the white count, where we maximize our dose until we figure out more sophisticated ways of handling drug dosage, may, in fact, be the way we should operated in pediatric cancer. And we really aren't doing this across the board.

DR. SANTANA: Comments or reactions to Jerry's comments?

DR. ADAMSON: I have one.

DR. SANTANA: Peter?

DR. ADAMSON: I think, for maintenance therapy in ALL, that is still the gold standard and I agree we may never improve upon the gold standard for maintenance therapy despite what we know. But for much of the rest of therapy, we don't have the white count to adjust our doses to. And we certainly, even in maintenance therapy, probably avoid toxicity but not necessarily do what we are supposed to do and that is maximize response by

increasing dose as frequently as we ought to.

So it works in maintenance therapy and we are lucky. We may never improve upon maintenance therapy beyond the white count. But it really doesn't, I think, carry over to the vast number of other agents that we utilize in pediatric oncology. We don't have a surrogate like that.

DR. SANTANA: I think it also begs the question that most of the drugs that we use in oncology and pediatrics are actually intravenous drugs. So when we move into the oral use of drugs, we have to demonstrate that there is a good rationale for doing it orally, that it does provide a different advantage, whether the advantage is compliance, absorption, end effect.

I think that, to me, is a criterion that needs to be incorporated when one makes a decision that maybe giving this drug orally is better. There may be many different things that make it better. It is just not the end result that the patient is cured because you could get that by giving it I.V. if you wanted to, if that is true. That is not true for all drugs.

So I think that also has to be part of the consideration that every disease and every drug is

a little bit different and we always have the advantage of giving it intravenously because most of them were developed intravenously.

I am advocating for oral drugs. I am just saying that, when one talks about oral drugs, one has to have a good rationale why one wants to use it orally. There has to be a reason for that.

DR. HIRSCHFELD: I would like to point out that the context for having this discussion is not restricted to the off-patent drugs that we talked about this morning but for all pediatric oncology drugs. Many of the products that Rick and Rik and I are seeing are now oral products with different types of targets.

What we would like to see is some type of anticipation that, if we could have, as a result of this discussion, some principles or some goals so that when we talk to companies developing these oral cancer therapeutics, that we could not only ask them if they are interested in pediatric formulation but that we could give them some specific advice and maybe even develop, as Dr. Przepiorka pointed out, a potentially useful guidance document to assist them.

Then we also all know, as the point has

been made before but I will just make it again, one aspect, and that is, if you develop a pediatric formulation, also geriatric population, handicapped population, chronically ill people, will benefit as well as people who just would like to have a choice in the modality of taking their medication.

DR. SANTANA: Richard?

DR. PAZDUR: I would like to respond to Jerry's comments because I hear a frustration and I feel it. It is not unique only to pediatrics but I could say the same thing in adult medications, that our knowledge of what is the correct dose to use of an oncology drug is tremendously limited in adult oncology.

We have bought into more is better, more is better, more is better and have adapted that. There is very little in the way of dose-finding studies in oncology. Once a drug is approved at the maximum tolerated dose, it is almost impossible to go backwards and say, can we use less of a dose in a particular disease. Those studies are very difficult to do.

This whole area of what is the correct dose, not only dose formulation but dose, whether one takes a look at a white count or whatever, is a

very, very difficult one throughout the whole field of oncology.

But I think, you know, what Steve is bringing up, we are seeing more and more drugs being developed in an oral-dosing formulation. One story I would like to share with you for a degree, perhaps, of pessimism about a field, if you take a look at the drug IV 5FU, it took us almost 40 years to come up with a commercially oral form of that--i.e. capesitabine--to be delivered from when that drug originally came out in the late 1950s to the approval of capesitabine in the 1990s.

That had a lot to do with looking and understanding the pharmacology and going back not just to formulation but to the understanding of the drug in a pro-drug formulation and really creating a new drug.

Giving the drug in an oral fashion also is not necessarily the same thing as an IV formulation. You may get better efficacy changing in toxicity profiles, et cetera, and can turn a relatively marginal drug into a much better drug by continuous exposure. As Steve pointed out, I think a lot of the pharmaceutical firms are getting away from the fear of developing oral medications.

There was a tremendous fear in oncology due to the reimbursement issues regarding oral medications, that this was considered really a taboo area even to touch. It was almost the third rail to develop an oral anticancer drug because of reimbursement and the acceptance of private-practice medical oncologist.

However, I think we are getting away from that as we learn more about the drugs and different targeted agents and the obvious need that these drugs are going to have to be administered on a chronic basis.

So I think several points that I want to bring out. A change in the science that is going to go toward more oral medications, as Steve pointed out, and also the fact that it may not even be just a formulation issue but thinking about kind of tricks to use in presenting the drug to the body as capesitabine, as a prodrug of the drug 5FU.

DR. SANTANA: Clinton?

DR. STEWART: So I would like to maybe pick up on some of the stuff that Rick is saying. You know, with some of the targeted therapies like the erbB inhibitors like Iressa and some of the other compounds that are coming out, obviously they

are being developed as oral therapies.

So we have been doing some studies with those compounds and, you know, we talk about the formulation of the compound. One of the things that I would like to see also come out is maybe the dosage size. I say that on the one hand. I will say, on the other hand, we have been very fortunate in the three studies that I am participating in, that even though we are using adult dosages, we have been able to come really very close to the protocol-prescribed dosage, but it would make it so much easier if we had a smaller pill size.

We don't have to change the formulation, but let's get us a pill size that is smaller. I think that would really help out a lot. So I think that is another thing we should give consideration to.

DR. SANTANA: Other comments? Yes?

DR. FLANAGAN: I guess I have a question on a simpler level. For even those drugs that are still given intravenously, do people feel that there might be a need for the pediatric population to have either a smaller volume in a vial so there is more room for dilution or to take the adult volume in concentration and put it in a bigger vial

to just make it easier to handle for diluting or use? Do people find any difficulties using the adult parenteral products?

DR. SANTANA: Peter? Comments?

DR. ADAMSON: I think probably pediatric pharmacists could better address. My sense is that, because the doses we tend to use intravenously in children tend to be large, it is not a major issue. I think when you start talking about infants in vincristine, you may start getting into that type of issue. But I think that is an issue that a pediatric-oncology pharmacist could probably more readily answer. But vincristine is the only one that jumps to mind and I might be wrong on that one as well.

DR. SANTANA: Donna?

DR. PRZEPIORKA: Actually, the other person who might address that is the geriatric oncology pharmacist because we ran into a similar situation with adults who are on multiple medications with multiple interactions which not infrequently require a reduction in dose.

Unfortunately, the way Medicare reimburses is if you have a single-use vial and you only use half the dose, Medicare only pays for half the dose

despite the fact that the practice has to throw away the other half of the dose. So it becomes a real cost issue.

DR. SANTANA: Alice?

MS. ETTINGER: I think it leave a lot of room for error in some of the formulations, as I guess you pointed out--someone pointed out in a very nice slide--that there is a lot of room for error. Getting back to actinomycin, I mean, if I have ever seen a drug that is downright dangerous in terms of how it is formulated, I think that that is certainly one. It is tiny, but the smallness is actually more of its danger in micrograms and milligrams. So I think there is some room there certainly for different strengths to be manufactured.

DR. SANTANA: Pat?

DR. REYNOLDS: Just going back to the oral comments from Clinton, I agree completely about the smaller pill size. I know of at least one pharmaceutical company that talked to us about potential pediatric applications and, after talking to us, said, oh; we are going to keep the smaller pill size. They were about to toss it out because, by the time they got to that point, they realized

that their MPD didn't justify it in adults.

I think if FDA, in their having their pre-IND discussions or whatever discussions, would just simply remind them of the potential for pediatric, they may keep in the hopper those smaller pill sizes they probably developed anyway. It is not a big cost and it would, I think, add a lot of flexibility.

DR. SANTANA: Jerry?

DR. FINKLESTEIN: I would like to answer Dr. Flanagan's question from one clinician's point of view. In actual fact, it is really the antibiotics that cause us the greatest problem when we are worried about fluid intake. Trimethaprim sulfa is one that comes to mind. The amount of fluid that it requires is quite a challenge sometimes to pediatrics. I don't think it is the actual anticancer agents that we run into a problem with on a day-to-day basis when we are worried about fluid intake in patients that we have to watch this very carefully and closely.

DR. SANTANA: Good point. Rik?

DR. LOSTRITO: Thank you. I just wanted also wanted to respond to Clinton's comment before about having multiple or smaller dosages. I think

your point is very well taken and so in Patrick's in response. I don't want to diminish that. But I can say that it is not a trivial matter for drug companies to develop these collateral strengths or smaller strengths, that quite a body of data is needed to support the marketing of that in terms of definitely stability, perhaps bioavailability, data.

So it is an offsetting and competing forces of cost versus utility. But I think your point is well taken but it is not a trivial matter. It is something that I am sure most firms put some thought behind before they pick a strength or two.

DR. HIRSCHFELD: I would just like a point of information to Dr. Reynolds' aspect, not just in oncology but in principle across all the FDA, whenever someone comes in with a new product for development, they are asked, routinely and repeatedly, what their pediatric plan is.

DR. REYNOLDS: If I could ask there, I know it is not trivial, but if you are talking about a half-milligram versus a 1-milligram tablet size, is that really that expensive an issue?

DR. LOSTRITO: It is perhaps maybe a little more expensive than you think. Firms have

to show that they can manufacture that strength. They have to provide data to do that. They have to provide stability data, shelf-life data, show the packaging presentation. So it is not double the cost to develop a second strength but then, again, it is not 1 or 2 percent of the total cost, either. It is somewhere in between.

How significant an expense it is, I couldn't answer but I do know, looking at the data I see routinely, that it is a fair amount of work.

DR. SANTANA: Thank you.

DR. SMITH: I would just second it as a big issue, though. We have had examples where the capsule or tablet is marketed as a certain large size but there happen to be smaller sizes that were used during the development. So those were done for pediatrics, but then those run out and what is left for further pediatric evaluation.

So, as more and more drugs are oral and given on a rather continuous basis, it will become more and more of an issue. When we talk with companies about it, it is very clear to us that it is not a trivial issue for them. I think it is a very important one to address and I think it will be hard to address.

DR. SANTANA: Richard?

DR. PAZDUR: Every time there is a change, there is a potential for a mistake. I will just share with you a story, and I won't mention the drug, but a manufacturer from the clinical-trial tablet just changed the shape of the tablet as well as adding I think it was some dextran to it. That led to the product being not bioequivalent to the drug that they studied, that they did their clinical trials, which really caused a tremendous amount and potentially a delay of really getting the drug approved for I think it was months, six months or so. It was relatively trivial. It was shape and, I think, color of the--and dextran.

DR. LOSTRITO: We would not have expected the minor changes that were made to have the impact they did. So you just never know what small changes can lead to big effects.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: I would just like to echo the pill size, especially you may not be able to change it, but when you are doing phase I trials in pediatric oncology, you really need to be careful about it because the tradition phase I trials, the pediatric oncologists use the 3 and 6 rule. So,

oftentimes--in fact, we have got a study in the Pediatric Brain Tumor Consortium that we would really have fooled ourselves what the maximum tolerated dose was and what dosing we were giving because of the size of the pills and the size of the kids. I think that is not paid attention to very much in pediatrics.

DR. SANTANA: Pat?

DR. REYNOLDS: Just to return to the problems of how much it would cost to do, I wonder if the tablets are encouraged to be at least scored, would that not allow you to have the same formulation and do everything for the adults with one tablet? But, at least if they are scored, ideally, in four parts but, if not, in two, then at least you would have some flexibility. It is not as ideal as a separate particular dosage, but it is better than crushing the thing and trying to measure it that way.

DR. LOSTRITO: You bring up a good point. It is a good compromise.

DR. SANTANA: I think we are done with our comments and presented session, so I want to go ahead and try to address the questions that the FDA wants use to help them with.

Committee Discussion of Questions to Subcommittee

DR. SANTANA: The first one, actually it is like--that is why I was asking the question earlier, is there anything out there that we can grab onto. So you are asking us to create a whole new set of principles here, so we will do our best of trying to answer this question which is what factors would be considered essential in the development of a formulation for children with cancer. So what things would we consider are important when we are thinking about developing different formulations.

Specifically, they want us to comment on any age, disease of pharmaceutical-specific considerations. I think one thing that I heard earlier this morning and again this afternoon is this whole issue of usage. So if it is a drug like 6MP, which is going to be used for a long period of time in a relatively, pediatrically speaking, large population, then, to me, that would be an impetus of considering whether you push to get a formulation developed for that particular drug. So that would be one consideration.

So there it is a little bit the disease but also the chronicity of the treatment going

together in terms of guiding you that this is an important formulation issue.

Peter?

DR. ADAMSON: I would just reemphasize what I think Jeff hit upon and that is yes, a liquid formulation is a step but we really need to start thinking about some of the newer potential formulation deliveries, rapidly dispersible formulation, as well as for long-acting medications, other route of delivery that liquid formulations, in and of themselves, often are too small a step toward a pediatric formulation.

Jeff, is that fairly paraphrased?

DR. SANTANA: Pat?

DR. REYNOLDS: I think that we have heard, over and over again, particularly from nurses and parents here about the need for having different ways of doing this, that the same way won't work for the same kid all the time and certainly won't work for different kids.

So I think, when one develops the formulations, I think having the flexibility to incorporate them into foods to get them into the child is, perhaps, one important point we should consider. Then I think that means that we are

going to have to study then, in the context of Dr. Hirschfeld's comment, that not all applesauce is equal, meaning that we need to have, then, a defined set of foods that it is studied with that we know are going to be safe and effective.

So it complicates the matter, but I don't see any other way around it.

DR. SANTANA: Let me see if I follow you. You are suggesting that there should be like a standard set of foods that should always be tested? Is that what you are hinting at and should applesauce always be one of the vehicles that is tested, I guess is where I am going.

DR. REYNOLDS: Many years ago, when I talked to Steve Hirschfeld about this, he said, if you are going to specify peanut butter, make sure you say--I won't say the brand, but whatever brand, because that is then a uniform product or at least fairly uniform.

So I think we need to think in those terms but I also think that if there was in the guidance, Vic, that what you are saying is a standard list of what should be tested, or potentially testing vehicles and that what would be considered by FDA to be fairly standard versions of such foods, that

would be very helpful.

DR. SANTANA: Clinton?

DR. STEWART: I would like to actually pose a question just to get some feedback that would help me, actually. When we do our oral studies, to avoid this issue of food, what we do is we actually ask the child, the parents to have the child to fast. So we just get away from that whole issue of food. But that is not real life. That is not the way the child is going to be taking the drug. But it gives a real clear understanding of the bioavailability of the drug.

We don't have the confounding issue of which brand of peanut butter they had or applesauce, whatever. But the issue is should there be studies in children like there are in adults which evaluate the effect of food and, if so, should they be standardized. If so, how should you standardize those. Those are my questions.

DR. SANTANA: Those are the questions the FDA wants us to ask, to help them with.

DR. PAZDUR: The adult food-effect studies are very difficult also, having participated in them to develop oral medication. They actually require--they have this breakfast--I call it the

Breakfast of Champions. I can't think of any cancer patient that could actually eat it. It is, like, three eggs, two pieces of toast, hash browns and four cups of coffee, or I don't know what it is. But it is an unrealistic breakfast for even a lumberjack, almost, let alone a 90-pound woman that has cancer.

So that is very problematic. Here, again, when most people are developing an oral medication, they generally do try to go to a fasting state because the first of the problem for most of the sponsors is they really have to show that the drug works. If they can't show that the drug works, the drug is dead and you don't want it be to the fact that we messed up because everybody ate--or the food absorption was erratic.

So you first have to answer, especially in an NDA process when the drug is first being tested, when they are getting their initial licensing application, does this really work, what is the most uniform situation that you could have. Nevertheless, we firmly support that drugs should be studied and labeled with the way that the drug will be used.

I think that having pediatric-specific

food studies would be very much important to address this issue. I couldn't underscore that more. But we do have problems even in the adult situation here which we really need to relook at and reexamine.

DR. HIRSCHFELD: I think, just to clarify the question, the issue about food, not as in Food and Drug Administration, but food with drug is if the formulation that is being anticipated is one that is intended to be delivered with food as some kind of carrier vehicle, then I think standardization would be beneficial.

That is a separate question from the food effects on a drug which already has some formulation.

DR. STEWART: I'm sorry; I don't mean to monopolize this, but I realize that we do put drugs on food for kids to take. But that, in itself, is problematic because what if the child doesn't eat all the food. Immediately, you have reduced the bioavailability right there just by virtue of doing that.

Maybe I am stating the obvious, but I think that is really very problematic, that whole issue of delivering drugs with food.

DR. HIRSCHFELD: It is not something that is necessarily endorsed or encouraged, but it is realistic that someone may have a sprinkle or some type of other formulation where you would deliver it. That would be the context for soliciting the advice.

DR. SANTANA: In answering this question, there has to be an element of practicality. I heard a little bit about this earlier in terms of when sponsors approach you guys, what they can and cannot do based both on cost and other factors.

So I think maybe thinking this through out loud, maybe the way to approach sponsors is to say, if this drug is going to be used in a pediatric population and we are going to first assume that it will be used across all age groups, then, first, there should be a pediatric formulation. I am not the one to tell you whether it should be a suspension, a sprinkle or whatever.

I am not the one to tell you, but one of the criteria would be that if you think this will be used in children, you have to come up with a formulation that is ethical to children. So that would be the first cut, as I see it.

The second cut is if the disease in which

this will be used, obviously, is unbalanced in terms of the ages, so the HIV story is a good one. Most of those kids cannot take capsules. So, if the company came to you and said, we want to develop an HIV drug for adults and our solution for pediatrics is to develop a capsule. That is irrational. That is not going to be practical. It is not going to be used that way.

You are going to have to develop something in a liquid formulation or some other vehicle to treat the neonates and to treat the two-year olds. So I guess what I am hinting at in terms of trying to answer this question is that there is no unique answer but there is a stepwise answer depending on, first, that if the drug potentially is going to be used in children, we should request that a formulation be derived, that we are not going to tell them what the formulation is, that they have to, then, consider the impact of that medication across different pediatric populations and then select the first formulation that they want to test.

DR. PAZDUR: Let me just ask you one question. Would you, as a practicing pediatric oncologist, be willing to delay the development of

drugs in children until a pediatric formulation is made? In other words, if a company comes to us and says, gee, you know, we are developing this drug in breast cancer and it is a tablet that you could cut in half, but we are going to take probably two or three years down the line and, perhaps, not until the NDA gets approved to taking a look at pediatric formulations here, which is a realistic situation.

DR. SANTANA: But I thought this committee is on the record of saying that we want parallel development.

DR. PAZDUR: But that is what I am saying is if they say, for example--if they say, we are willing to start our pediatric studies with an adult formulation, a pill, part of a pill or whatever, would you say that they should delay the development of that initiation of the pediatric study?

DR. SANTANA: I will let other people comment.

DR. ADAMSON: There is a one-word answer which I think is no.

DR. SANTANA: I agree. I just didn't want to monopolize--

DR. PAZDUR: But that is what we face in a

real-life situation. We have very little regulatory power to say, you must do a pediatric formulation.

DR. STEWART: Do they have to repeat those studies when they do come up with a pediatric formulation?

DR. HIRSCHFELD: No; they can do the--

DR. SANTANA: That will be Questions 2 and 3.

DR. HIRSCHFELD: Yes; in effect. But, in short, Clinton, there are mechanisms that, once you have a formulation that has demonstrated efficacy and safety, then it is just another pathway in order to alter that.

DR. BLUMER: But what is missing, though, is the carrot to do it. I think we heard that many of the companies come to you with, perhaps, the best of intentions and, perhaps, not. But they at least tell you that they are going to try. It was interesting in the last experience I had with this where a company said they were going to try and do this for pediatric clinical trials and then they sort of shrugged their shoulders after a year.

We went into the lab and made one and said, okay, here is something, and they got all

embarrassed and went out and made their own, of course. But it happened in very short order.

It wasn't for an oncology drug, but I think that this is--without any sort of incentive, I don't think that this is going to be a fruitful area. You are not going to misbrand drugs that don't have pediatric formulations. No one here is interested in delaying drug development until there is one. It is a Catch 22.

DR. PAZDUR: From a practical experience, having worked with companies in this area, do you feel that they give a 100 percent good college try to try and develop these pediatric formulations, or is it, well, we will kind of get to it maana, maana, maana, maana.

DR. BLUMER: It is very half-hearted. It really is, in general. One of the things that impresses me in this whole area of oncology, and I am going through this with our hospital, is running our quality-assurance group. Our oncology floor has put together--we have had no major medication errors in oncology in five years.

When I look at the gyrations that the staff has put together to ensure that there are no medication--I said, this is wrong. Now we have a

paradigm where even the caregivers are reluctant to change because it works. But it takes hours and hours of extra time and effort to ensure this because they don't have the right tools to do it.

It is just very wrong.

DR. REYNOLDS: I just want to expand on the resounding no a little bit and say, you know, it seems to me like this should be an evolving process, though. If somebody brings forward a new antioncologic, to wait until they get around the pediatric formulation, obviously, we don't want that delay. But, secondly, if you try it in the pediatric population with the adult formulation and you have got good pharmacokinetics yet you didn't get activity, why would they want to go through the expense, or why would you want to encourage them to do that expense.

But yet, on the same token, if you took whatever formulation was available and you saw activity and it was, perhaps, suboptimal, then that would drive the pediatric formulation. So I think it is an evolution, not a just cart-and-horse issue.

DR. FINKLESTEIN: I have a question for Rick. I would like to piggyback on the geriatric

concept that you used. Do you have data in what percentage of the population are geriatrics that would need a liquid or some other kind of formulation, either in oncology drugs or drugs in general? I mean gerontology is really increasing as a field. If, indeed, it is significant, could we, as pediatricians, piggyback upon your idea?

DR. PAZDUR: I am probably the wrong person to ask because I am not in geriatric medicine. I think people that probably study this more would have an example, or have the data that you are looking for. So I don't have the answer to your question.

DR. FINKLESTEIN: Obviously, I am thinking that they are a very organized group.

DR. PAZDUR: I know. You better believe it.

DR. FINKLESTEIN: Getting them on this bandwagon would not be difficult if, indeed, it would be a benefit to that patient population.

DR. PAZDUR: Hello, AARP!

DR. HIRSCHFELD: Jerry, this has been looked at. I don't have the data but I know that the data do exist because there are a few companies and other organizations that have examined this

same issue over the years to say it is not an age-dependent, it is a patient-dependent, question about having the alternative formulations.

The reason we are trying to bring it up here in the pediatric context, aside from that we feel the need, is that we have some regulatory tools. We can do it through the incentive program. We can make a formulation as part of a condition of receiving the exclusivity extension if we feel that that is required.

And we may have tool, in some pending legislation, to, in some cases, as I think Dr. Flanagan noted, the Pediatric Rule which was struck down a year ago, while this committee was meeting, I should add--

DR. SANTANA: We won't read the paper tomorrow to see what has happened today while we are meeting; right?

DR. HIRSCHFELD: --may be enacted into law. Law, of course, has greater authority than a regulation. Then we would have the leverage to also compel that, too. But, again, it is through the vehicle of pediatrics. So any efforts that are done for other populations, and there are large active organizations for handicapped patients and

geriatrics, et cetera, the same things we discussed earlier.

But they haven't been adequately motivated, at least to the moment. So our focus is on the tools that we would have at hand.

DR. SANTANA: I want to encourage you, that, as you use those tools, which everyone--you ultimately wind up selecting from, that a driving principle for this issue of formulations is practicality. We could sit here for three hours and say, ideally, this is what we should be doing and this is what we want, like our Christmas list; right?

But, in practicality, there are some issues that I think you have to resonate with the FDA as you approach the company so that we do get some formulations and they are done in parallel as the adult studies are being developed and not put them in a box where we won't get anything out of them.

DR. PAZDUR: I think there has to be an element of practicality here. I think there is a difference in asking somebody to do something and mandating them to do it are two different things. We have very limited power. Remember, even if the

Pediatric Rule comes back, there is a limited amount of extrapolatability here. Even if we use the exclusivity process, one could say, well, if we put too many barriers in front of people, they may start backing away from this.

We have really limited experience with that process. So there are a lot of things. It is very complicated issue that we face frequently behind closed door that people do not see with the negotiations with the pharmaceutical companies.

DR. SANTANA: Dr. Boyett?

DR. BOYETT: I was going to suggest exclusivity as a way to hang the carrot out there. So maybe what you do is you add another month of exclusivity if you have a pediatric formulation or something like that.

DR. PAZDUR: That has to be required by law.

DR. SANTANA: We will work--

DR. HIRSCHFELD: Right. But ideas like that have been entertained and the legislation will come up in 2007. Just to tell you another idea that, because it is harder to do studies in neonates and infants, there was some discussion about adding some extra--but, all that is

theoretical. But who knows? It could be practical in three years.

DR. SANTANA: I think we have given you all the help we are going to give you with Question No. 1. So I want to move on to Question No. 2; what types of testing or clinical-trial design would you recommend for establishing the efficacy and safety of a new formulation for an existing oncology drug that already has efficacy and safety demonstrated in the same population?

Peter?

DR. ADAMSON: Extremely limited, I think is how I would put it. I think, ideally, you would like to do bioequivalence studies in adults as a starting point. Again, because these are cancer drugs, you would have to do it in the adult cancer population which will make it harder. But, when you can do it adults and demonstrate bioequivalency, then I think consideration of doing a similar study in children would be reasonable.

I don't think it is reasonable for us, except in very limited circumstances, to undertake additional efficacy studies for bioequivalent formulations. We don't have those kinds of resources.

DR. SANTANA: That is otherwise bioequivalent.

DR. ADAMSON: That is otherwise bioequivalent. I think you would have to individual because there are some drugs where, if they have a very different absorption profile, you could predict that you actually have to look at safety and efficacy, antimetabolites and other cell cycle. But, for others, you might take the knowledge we know and say, well, to what degree do we have to look at differences in safety and efficacy given differences in the profiles. So it would have to be, I think, individualized to some extent on the nature of the drug.

DR. PRZEPIORKA: I was going to disagree just a little bit and say that if you stick to the letter of the question, it actually hadn't included pediatric versus adult. It just said what type of testing, the trial for developing a new formulation.

I would suggest that it would be in the same population, number one, and, number two, since it has already been shown to be safe and effective and theoretically had a surrogate endpoint to monitor before waiting ten years for outcome, use

the surrogate endpoint as your outcome rather than long-term survival.

DR. SMITH: I would urge caution. If the new formulation is similar and has bioequivalence, then that is one issue. But just the extreme issue of 6MP being an example of that that we have been talking about all day, it was an oral formulation, you give it every day. We had the great idea--we didn't have the great idea, but there was the great idea that you could give it intravenously and avoid all the variation and absorption and all and that that would be a much more effective drug.

So we sponsored several clinical trials to try to prove that point. You can't give the I.V. formulation and mimic the same PK profile that you can with the oral and the I.V. was inferior to the oral. So the new formulation, which had a very different PK profile, was, in fact, less effective than our good-old oral 6MP.

So I think you really do have to individual and, if it is a more convenient formulation with the same PK profile, it is one thing. If the PK profile is changing substantially, then I would be very cautious about just accepting them as equivalent in terms of their

clinical effect.

DR. ADAMSON: I guess to expand a little bit about that, we all recognize there are only a limited number of phase III trials we can do in the pediatric cancer population. I think we would hard-pressed to commit one of those trials to an equivalency study. There would have to be really overwhelmingly compelling arguments to do that.

DR. BOYETT: I would like to follow up on that. Not only--the phase III trials you typically do are not equivalency trials. So, when you undertake an equivalency trial, your sample size goes up astronomically to prove there is absolutely no--so you have got real problems if you think you have got to prove equivalency.

DR. SMITH: Both points are well taken. It would be very hard to do equivalence trials. The one thing you could do, just to provide some confidence, is use a factorial design. The question you are really most interested in is some new drug, and, by the way, you are asking in that same clinical trial a question about two different formulations.

So you don't expect there to be a difference and it is almost a freebie. So, if

there was a case where you had some reason to want to be cautious, it may be possible to use it as a second or even a third randomization in a trial that would otherwise be ongoing.

DR. REYNOLDS: Malcolm, what about--you are talking about drugs that might have vastly different pharmacokinetic profiles. But what about ones that have similar pharmacokinetic profiles. I agree with you, Peter, we only have so many trials we can do, but I am wondering if they have very similar pharmacokinetic profiles, couldn't your population-kinetics modeling be plugged into a phase III study just using the new formulation to replace the old formulation and validating that PK on a larger set of patients, therefore killing two birds with one stone.

DR. SANTANA: I kind of get a sense that Malcolm kind of agreed with that comment.

DR. SMITH: Again, it depends on how similar is similar. The further apart you get in the comparability of the two in terms of their PK profile, the more and more cautious you would want to be about it.

DR. SANTANA: What about question 3, which is the same question but now with a different

population. What type of testing or clinical-trial design would you recommend for establishing the efficacy and safety of a new formulation for an already existing oncology drug that already has efficacy and safety demonstrated in a different population?

Go ahead, Dr. Boyett.

DR. BOYETT: The efficacy question, I think, is simple. You have got to do an efficacy study. You haven't done it in that particular patient population in drugs that are disease specific.

DR. SANTANA: Other comments? So the sense there is that you at least would have to do some efficacy trials since it is truly a different population. Any other comments on this question? Any other comments on the session this afternoon? If not, I think we are done unless Dr. Hirschfeld or Dr. Pazdur have some concluding comments.

DR. HIRSCHFELD: I would like to thank everyone again for a very interesting and what has proven to be stimulation session. I think we have identified a number of issues, both in the morning and the afternoon, which had not been anticipated in our other discussions which is always the value

of seeking advice.

We will make a commitment to move forward on these. I would also like to report back to this committee that, as a consequence of the last meeting we had in July, that we have been able to make progress on both those issues, one with regard to the labeling or relabeling of 6-mercaptopurine. I know that a representative of Teva Pharmaceuticals came here today and they have been very interested in following through on that. We will report back to you what that final label will look like, but the advice was extremely valuable.

Secondly, the advice that the committee provided for multinational studies has resulted in interest in our European colleagues who organized a meeting last month to address some of these issues and there will be follow-through on trying to reduce and then equilibrate the regulatory burdens for doing multinational studies.

So I wanted to committee to know that its work is not only appreciated but is acted upon expeditiously.

DR. SANTANA: Thank you.

DR. PAZDUR: To follow up Steve's words, only one word, "Ditto." Bye.

DR. SANTANA: I think Dr. Reynolds has one concluding comment.

DR. REYNOLDS: I just have one question for either Rick or Steve. I asked this last time and didn't get an answer.

DR. SANTANA: Try again, Pat.

DR. REYNOLDS: I thought I would try one more time. In the Best Pharmaceuticals for Children Act, the FDA was mandated to give a report to Congress on availability of drugs on January of 2003. I wondered if that report was going to be made available to this committee to see if it had been delivered to Congress. It would be a very interesting report for us to consider. Is that going to be made available publicly at some point?

DR. HIRSCHFELD: The anticipation is that it will be made available to this committee and will be made available public. But we don't have a date yet as to when that report will be issued.

DR. REYNOLDS: Thank you.

DR. SANTANA: Thank you everybody.

[Whereupon, at 3:30 p.m., the meeting was adjourned.]

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